

## International Consensus Statement on Obstructive Sleep Apnea

## Authors

1. Jolie L. Chang, MD
2. Andrew N. Goldberg, MD, MSCE
3. Jeremiah A. Alt, MD, PhD
4. Lisa Ashbrook, MD
5. Dennis Auckley, MD
6. Indu Ayappa, PhD
7. Hira Bakhtiar, MD
8. José E. Barrera, MD
9. Bethany L. Bartley, MD
10. Martha E. Billings, MD, MSc
11. Maurits S. Boon, MD
12. Pien Bosschieter, MD
13. Itzhak Braverman, MD
14. Kara Brodie, MD
15. Cristina Cabrera-Muffly, MD
16. Ray Caesar, DDS
17. Michel B. Cahali, MD, PhD
18. Yi Cai, MD
19. Michelle Cao, DO
20. Robson Capasso, MD
21. Sean M. Caples, DO, MS
22. Lana M. Chahine, MD, MSCE
23. Corissa P. Chang, DDS
24. Katherine W. Chang, MD
25. Nilika Chaudhary, MD
26. Crystal S. J. Cheong, MBBS
27. Susmita Chowdhuri, MD, MS
28. Peter A. Cistulli, MD, PhD
29. David Claman, MD
30. Jacob Collen, MD
31. Kevin Coughlin, MD
32. Jennifer Creamer, MD
33. Eric M. Davis, MD
34. Kara L. Dupuy-McCauley, MD
35. Megan L. Durr, MD
36. Mohan Dutt, MD
37. Mazen El Ali, MD
38. Nabil M. Elkassabany, MD, MSCE
39. Lawrence J. Epstein, MD
40. Justin A. Fiala, MD
41. Neil Freedman, MD
42. Kirat Gill, MD
43. M. Boyd Gillespie, MD, MSc
44. Lea Golisch, MD
45. Nalaka Gooneratne, MD, MSc
46. Daniel J. Gottlieb, MD, MPH
47. Katherine K. Green, MD, MS
48. Arushi Gulati, BS
49. Indira Gurubhagavatula, MD, MPH
50. Nathan Hayward, FRACS
51. Paul T. Hoff, MS, MD
52. Oliver M.G. Hoffmann, MD
53. Steven J. Holfinger, MD, MS
54. Jennifer Hsia, MD
55. Colin Huntley, MD
56. Kevin C. Huoh, MD
57. Phillip Huyett, MD

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1002/alr.23079](https://doi.org/10.1002/alr.23079).

58. Sanjana Inala, MPH
59. Stacey Ishman, MD, MPH
60. Tarun K. Jella, MPH
61. Aesha M. Jobanputra, MD
62. Andrew P. Johnson, MD
63. Mithri R. Junna, MD
64. Jenna T. Kado, MD
65. Thomas M. Kaffenberger, MD
66. Vishesh K. Kapur, MD, MPH
67. Eric J. Kezirian, MD, MPH
68. Meena Khan, MD
69. Douglas B. Kirsch, MD
70. Alan Kominsky, MD
71. Meir Kryger, MD
72. Andrew D. Krystal, MD, MS
73. Clete A. Kushida, MD, PhD
74. Tomasz J. Kuzniar, MD, PhD
75. Derek J. Lam MD, MPH
76. Christopher J. Lettieri, MD
77. Diane C. Lim, MD, MTR
78. Hsin-Ching Lin, MD
79. Stanley Y.C. Liu, MD, DDS
80. Stuart G. MacKay, Bsc, MBBS
81. Ulysses J. Magalang, MD
82. Atul Malhotra, MD
83. Joachim T. Maurer, MD
84. Anna M. May, MD, MS
85. Ron B. Mitchell, MD
86. Babek Mokhlesi, MD, MSc
87. Anna E. Mullins, RPSGT, PhD
88. Eman M. Nada, MD, PhD
89. Sreelatha Naik, MD
90. Brandon Nokes, MD
91. Michael D. Olson, MD
92. Allan I. Pack, MBChB, PhD
93. Edward B. Pang
94. Kenny P. Pang, MD
95. Susheel P. Patil, MD, PhD
96. Eli Van de Perck, MD
97. Jay F. Piccirillo, MD
98. Grace W. Pien, MD, MSCE
99. Amanda J. Piper, MEd, PhD
100. Andrea Plawecki, MD
101. Mark Quigg, MD, MSc
102. Madeline J.L. Ravesloot, MD, PhD, MSc
103. Susan Redline, MD, MPH
104. Brian W. Rotenberg, MD, MPH
105. Armand Ryden, MD
106. Kathleen F. Sarmiento, MD, MPH
107. Firas Sbeih, MD
108. Amy E. Schell, MD
109. Christopher N. Schmickl, MD, PhD
110. Helena M. Schotland, MD
111. Richard J. Schwab, MD
112. Jiyeon Seo, MD
113. Neomi Shah, MD, MPH, MS
114. Anita Valanju Shelgikar, MD, MHPE
115. Isaac Shochat, MD
116. Ryan J. Soose, MD
117. Toby O. Steele, MD
118. Erika Stephens, BA
119. Carl Stepnowsky, PhD
120. Kingman P. Strohl, MD
121. Kate Sutherland, BSc, PhD
122. Maria V. Suurna, MD
123. Erica Thaler, MD
124. Sritika Thapa, MD
125. Olivier M. Vanderveken, MD, PhD
126. Nico de Vries, MD, PhD
127. Edward M. Weaver, MD, MPH
128. Ian D. Weir, DO,
129. Lisa F. Wolfe, MD
130. B. Tucker Woodson, MD
131. Christine H.J. Won, MD, MSc
132. Josie Xu, MD, FRCSC
133. Pratyusha Yalamanchi, MD, MBA
134. Kathleen Yaremchuk, MD, MSA
135. Yerem Yeghiazarians, MD
136. Jason L. Yu, MD
137. Michelle Zeidler, MD, MS
138. Ilene M. Rosen, MD, MSCE

## Author Affiliations

1. University of California, San Francisco
2. University of California, San Francisco
3. University of Utah, Salt Lake City
4. University of California, San Francisco
5. Case Western Reserve University, Cleveland
6. Icahn School of Medicine at Mount Sinai, New York City
7. Norwalk Hospital, Norwalk
8. Uniformed Services University, Washington D.C.
9. Harvard Medical School, Boston
10. University of Washington, Seattle
11. Sidney Kimmel Medical Center at Thomas Jefferson University, Philadelphia
12. Academic Centre for Dentistry Amsterdam, the Netherlands
13. Hillel Yaffe Medical Center, Hadera Technion, Faculty of Medicine, Israel
14. University of California, San Francisco
15. University of Colorado School of Medicine, Aurora
16. Stone Oak Orthodontics, San Antonio
17. University of Sao Paulo, Brazil
18. University of California, San Francisco
19. Stanford University, Palo Alto
20. Stanford University, Palo Alto
21. Mayo Clinic, Rochester
22. University of Pittsburgh
23. University of Pennsylvania, Philadelphia
24. Washington University, St. Louis
25. PENDING
26. National University Hospital, Singapore
27. Wayne State University and John D. Dingell VA Medical Center, Detroit
28. Faculty of Medicine and Health, University of Sydney, Australia
29. University of California, San Francisco
30. Uniformed Services University, Bethesda
31. University of Tennessee, Memphis
32. Uniformed Services University, Bethesda
33. University of Virginia, Charlottesville
34. Mayo Clinic, Rochester
35. Kaiser Permanente, Oakland
36. University of Michigan, Ann Arbor
37. University of Pittsburgh
38. University of Pennsylvania, Philadelphia
39. Harvard Medical School, Boston
40. Northwestern University, Chicago
41. University of Chicago
42. Stanford University, Palo Alto
43. University of Tennessee, Memphis
44. University Hospital Mannheim, Ruprecht-Karls-University Heidelberg
45. University of Pennsylvania, Philadelphia
46. Harvard Medical School, Boston
47. University of Colorado, Aurora
48. University of California, San Francisco
49. University of Pennsylvania, Philadelphia
50. Monash Health, Victoria
51. University of Michigan, Ann Arbor
52. University Hospital Mannheim, Ruprecht-Karls-University Heidelberg
53. Ohio State University, Columbus
54. University of Minnesota, Minneapolis
55. Sidney Kimmel Medical Center at Thomas Jefferson University, Philadelphia
56. University of California, Irvine
57. Harvard Medical School, Boston
58. Icahn School of Medicine at Mount Sinai, New York
59. University of Cincinnati, Cincinnati
60. Case Western Reserve University, Cleveland
61. Rutgers Robert Wood Johnson Medical School, New Brunswick
62. University of Colorado School of Medicine, Aurora

63. Mayo Clinic, Rochester
64. University of Toledo, Monroe
65. University of Pittsburgh
66. University of Washington, Seattle
67. University of Southern California, Los Angeles
68. Ohio State University, Columbus
69. University of North Carolina School of Medicine, Charlotte
70. Cleveland Clinic Head and Neck Institute, Cleveland
71. Yale School of Medicine, New Haven
72. University of California, San Francisco
73. Stanford University, Palo Alto
74. University of Chicago
75. Oregon Health and Science University, Portland
76. Uniformed Services University, Bethesda
77. University of Miami, Miami
78. Chang Gung University, Kaohsiung, Taiwan
79. Stanford University, Palo Alto
80. University of Wollongong, Australia
81. Ohio State University, Columbus
82. University of California, San Diego
83. University Hospital Mannheim, Ruprecht-Karls-University Heidelberg, Germany
84. Case Western Reserve University, Cleveland
85. University of Texas, Southwestern and Children's Medical Center Dallas
86. Icahn School of Medicine at Mount Sinai, New York
87. University of Chicago
88. Stony Brook University, New York
89. Geisinger Health System, Danville
90. University of California, San Diego
91. Mayo Clinic, Rochester
92. University of Pennsylvania, Philadelphia
93. University of Glasgow, United Kingdom
94. Paragon Medical Centre, Singapore
95. Case Western Reserve University, Cleveland
96. University of Antwerp, Belgium
97. Washington University, St. Louis
98. Johns Hopkins University, Baltimore
99. University of Sydney, Australia
100. Henry Ford Health, Detroit
101. University of Virginia, Charlottesville
102. OLVG, Amsterdam, the Netherlands
103. Brigham and Women's Hospital, Harvard Medical School, Boston
104. Western University, Canada
105. Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles
106. University of California, San Francisco
107. Cleveland Clinic Head and Neck Institute, Cleveland
108. University of Colorado, Aurora
109. University of California, San Diego
110. Icahn School of Medicine at Mount Sinai, New York
111. University of Pennsylvania, Philadelphia
112. University of California, Los Angeles
113. Icahn School of Medicine at Mount Sinai, New York
114. University of Michigan, Ann Arbor
115. Hillel Yaffe Medical Center, Hadera, Israel
116. University of Pittsburgh
117. University of California, Davis
118. University of California, San Francisco
119. University of California, San Diego
120. Case Western Reserve University, Cleveland
121. University of Sydney, Australia
122. Weill Cornell Medicine, New York
123. University of Pennsylvania, Philadelphia
124. Yale School of Medicine, New Haven
125. University of Antwerp, Belgium
126. Academic Centre for Dentistry Amsterdam, the Netherlands
127. University of Washington, Seattle

128. Yale School of Medicine, New Haven
129. Northwestern University, Chicago
130. Medical College of Wisconsin, Milwaukee
131. Yale School of Medicine, New Haven
132. University of Toronto, Canada
133. University of Michigan, Ann Arbor
134. Henry Ford Health, Detroit
135. University of California, San Francisco
136. Emory University, Georgia
137. University of California, Los Angeles
138. University of Pennsylvania, Philadelphia

Corresponding Author:

Jolie L. Chang, MD  
2233 Post St. Box 1225  
San Francisco, CA 94115  
[jolie.chang@ucsf.edu](mailto:jolie.chang@ucsf.edu)  
Phone: 415-353-2757

Short Title: International Consensus on OSA

Key words: obstructive sleep apnea, sleep disordered breathing, evidence-based medicine, systematic review, positive airway pressure, outcomes, sleep surgery.

Funding Source: None

Word Count: Pending

## Abstract

**Background:** Evaluation and interpretation of the literature on obstructive sleep apnea is needed to consolidate and summarize key factors important for clinical management of the OSA adult patient. Toward this goal, an international collaborative of multidisciplinary experts in sleep apnea evaluation and treatment have produced the International Consensus statement on Obstructive Sleep Apnea (ICS:OSA).

**Methods:** Using previously defined methodology, focal topics in OSA were assigned as literature review (LR), evidence-based review (EBR), or evidence-based review with recommendations (EBR-R) formats. Each topic incorporated the available and relevant evidence which was summarized and graded on study quality. Each topic and section underwent iterative review and the ICS:OSA was created and reviewed by all authors for consensus.

**Results:** The ICS:OSA addresses OSA syndrome definitions, pathophysiology, epidemiology, risk factors for disease, screening methods, diagnostic testing types, multiple treatment modalities, and effects of OSA and treatment on the multiple comorbidities. Specific focus on outcomes with positive airway pressure (PAP) and surgical treatments were evaluated.

**Conclusion:** This review of the literature in OSA consolidates the available knowledge and identifies the limitations of the current evidence. This effort aims to highlight the basis of OSA evidence-based practice and identify future research needs. Knowledge gaps and opportunities for improvement include improving the metrics of OSA disease, determining the optimal OSA screening paradigms, developing strategies for PAP adherence and longitudinal care, enhancing selection of PAP alternatives and surgery, understanding health risk outcomes, and translating evidence into individualized approaches to therapy.

**Key Words:** Obstructive sleep apnea, consensus, treatment outcomes, sleep, evidence-based medicine, positive airway pressure, screening, polysomnography, home sleep apnea testing, PAP adherence, sleep surgery, uvulopalatopharyngoplasty, hypoglossal nerve stimulation, surgical outcomes, cardiovascular event, hypertension, atrial fibrillation, mortality, cerebrovascular disease, dementia, neurocognitive function, motor vehicle accidents, sleepiness, perioperative management.

## Table of Contents

<b>I. Introduction .....</b>	<b>19</b>
<b>II. Methods.....</b>	<b>20</b>
<b>II.A Topic Development .....</b>	<b>20</b>
<b>II.B Iterative Review .....</b>	<b>21</b>
<b>II.C ICS:OSA Statement Development.....</b>	<b>22</b>
<b>II.D Possible Adverse Effects of OSA Interventions .....</b>	<b>22</b>
<b>III. Definitions and Classifications Related to OSA.....</b>	<b>24</b>
<b>III.A Sleep Disordered Breathing .....</b>	<b>24</b>
III.A.1 Respiratory Event Definitions .....	24
III.A.1.a Apnea .....	24
III.A.1.b Hypopnea .....	24
III.A.1.c Respiratory Effort Related Arousal (RERA) .....	25
III.A.2 Summary Metrics.....	25
III.A.2.a Apnea Hypopnea Index (AHI) .....	25
III.A.2.b Respiratory Event Index (REI).....	25
III.A.2.c Respiratory Disturbance Index (RDI) .....	25
III.A.2.d Oxygen Desaturation Index (ODI) .....	25
III.A.3 Considerations in sleep study scoring and data interpretation.....	26
<b>III.B OSA and Subtype Definitions .....</b>	<b>28</b>
III.B.1 Obstructive Sleep Apnea Syndrome (OSAS) .....	28
III.B.2 Positional OSA.....	28
III.B.3 REM-related OSA .....	29
III.B.4 Primary Snoring .....	30
III.B.5 Upper Airway Resistance Syndrome (UARS).....	30
III.B.6 Obesity Hypoventilation Syndrome .....	31
<b>IV. Epidemiology and Contributing Factors in OSA.....</b>	<b>31</b>
<b>IV.A Prevalence .....</b>	<b>31</b>
IV.A.1 OSA Prevalence and Risk Factors .....	32
IV.A.2 OSA and Cardiovascular Disease .....	32
IV.A.3 OSA and Metabolic Disease.....	33
IV.A.4 Environmental factors and OSA .....	33
<b>IV.B Economic Burden of OSA .....</b>	<b>33</b>
IV.B.1 Costs of treating OSA.....	34
<b>IV.C Risk Factors for OSA .....</b>	<b>35</b>
IV.C.1 Sex .....	35
IV.C.2 Obesity.....	41
IV.C.3 Craniofacial Anatomy .....	48
IV.C.4 Genetics.....	56

<b>V. Pathogenesis of OSA.....</b>	<b>57</b>
<b>V.A Contributory Factors for OSA: Anatomy .....</b>	<b>57</b>
V.A.1 Nasal Airway .....	57
V.A.2 Pharyngeal Airway .....	59
V.A.3 Craniofacial Structure .....	61
V.A.4 Upper Airway Fat.....	61
<b>V.B Contributory Factors for OSA: Physiology.....</b>	<b>62</b>
V.B.1 Ventilatory Stability/ Loop Gain .....	62
V.B.2 Neuromuscular Control .....	63
V.B.3 Arousal Threshold.....	64
<b>VI. Diagnosing OSA.....</b>	<b>66</b>
<b>VI.A Questionnaires for OSA .....</b>	<b>66</b>
V1.A.1 Screening Questionnaires.....	66
V1.A.2 Functional Status Measures and Health-Related Quality of Life Questionnaires .....	67
<b>VI.B Screening for OSA .....</b>	<b>71</b>
VI.B.1 Primary Care Setting.....	71
VI.B.2 Perioperative Setting.....	75
<b>VI.C Symptoms Associated with OSA.....</b>	<b>86</b>
VI.C.1 Snoring, Gasping, Daytime Sleepiness.....	86
VI.C.2 Nocturia .....	91
VI.C.3 Caffeine Intake.....	91
<b>VI.D Physical Exam Findings Related to OSA .....</b>	<b>92</b>
VI.D.1 BMI .....	92
VI.D.2 Neck Circumference .....	92
VI.D.3 Nasal Exam .....	95
VI.D.4 Oral Cavity and Oropharynx Exam .....	96
VI.D.5 Mallampati Classification and Friedman Tongue Position .....	96
VI.D.6 Laryngoscopy.....	98
<b>VI.E Imaging Findings Associated with OSA .....</b>	<b>98</b>
VI.E.1 Lateral Cephalometry .....	98
VI.E.2 Cone-Beam CT.....	99
VI.E.3 Other Imaging Types.....	99
<b>VI.F Diagnostic Testing for OSA .....</b>	<b>102</b>
VI.F.1 Types of Sleep Studies .....	102
VI.F.2 Home Sleep Studies .....	104
VI.F.3 In-Lab Studies.....	114
VI.F.4 Oximetry .....	120
<b>VII. Comorbidities Associated with OSA.....</b>	<b>130</b>
<b>VII.A Comorbidities Associated with OSA: Cardiovascular Disease .....</b>	<b>131</b>
VII.A.1 Cardiovascular and All-Cause Mortality .....	131
VII.A.2 Coronary Artery Disease.....	131
VII.A.3 Myocardial Ischemia.....	138
VII.A.4 Hypertension .....	145



VII.A.5 Atrial Fibrillation .....	148
VII.A.6 Congestive Heart Failure .....	158
VII.A.7 Cerebrovascular Disease .....	163
<b>VII.B Comorbidities Associated with OSA: Pulmonary Disorders .....</b>	<b>168</b>
VII.B.1 Primary Pulmonary Hypertension .....	168
VII.B.2 Chronic Obstructive Pulmonary Disease (COPD) .....	170
<b>VII.C Comorbidities Associated with OSA: Obesity .....</b>	<b>173</b>
<b>VII.D Comorbidities Associated with OSA: Insulin Resistance .....</b>	<b>175</b>
<b>VII.E Comorbidities Associated with OSA: Cognitive Impairment and Dementia .....</b>	<b>176</b>
<b>VII.F Comorbidities Associated with OSA: Cancer .....</b>	<b>184</b>
<b>VII.G Comorbidities Associated with OSA: Nasal Disorders .....</b>	<b>186</b>
VII.G.1 Allergic Rhinitis .....	186
VII.G.2 Nasal Obstruction .....	188
VII.G.3 Chronic Rhinosinusitis .....	193
<b>VII.H Comorbidities Associated with OSA: Gastroesophageal Reflux Disease .....</b>	<b>196</b>
<b>VII.I Comorbidities Associated with OSA: Pregnancy .....</b>	<b>220</b>
<b>VII.J Comorbidities Associated with OSA: Other Sleep Disorders .....</b>	<b>203</b>
VII.J.1 Sleep Movement Disorders .....	203
VII.J.2 Narcolepsy .....	217
VII.J.3 Insomnia .....	203
<b>VIII. Medical Treatment for OSA .....</b>	<b>221</b>
<b>VIII.A Medical Management of OSA: Positive Airway Pressure (PAP) Therapy .....</b>	<b>221</b>
VIII.A.1 Types of PAP for OSA .....	221
VIII.A.1.a Types of PAP: Continuous Positive Airway Pressure (CPAP) .....	222
VIII.A.1.b Types of PAP: Auto-titrating Positive Airway Pressure (APAP) .....	225
VIII.A.1.c Types of PAP: Bilevel PAP .....	227
VIII.A.1.d Types of PAP: Adaptive Servo Ventilation .....	228
VIII.A.2 PAP Use: Mask Interfaces .....	229
VIII.A.3 PAP Titration Paradigms .....	235
VIII.A.4 PAP Adherence .....	236
VIII.A.4.a Measurement of PAP Adherence .....	236
VIII.A.4.b Predictors of PAP Adherence .....	239
VIII.A.5 Optimization of PAP Therapy .....	245
VIII.A.5.a Educational Interventions for PAP Adherence .....	245
VIII.A.5.b Supportive Interventions for PAP Adherence .....	249
VIII.A.5.c Behavioral Interventions and PAP Adherence .....	256
VIII.A.5.d Aerophagia Management and PAP Adherence .....	260
VIII.A.5.e Claustrophobia Management and PAP Adherence .....	260
VIII.A.5.f Humidification and PAP Adherence .....	262
VIII.A.5.g Nasal Obstruction and PAP Adherence .....	264
VIII.A.5.h Treatment Emergent Central Sleep Apnea (TECSA) .....	267
VIII.A.5.i Insomnia Treatment and PAP Adherence .....	270
VIII.A.5.j Long Term PAP Adherence Assessment .....	272

<b>VIII.B Efficacy of PAP for Symptoms and Comorbidities .....</b>	<b>274</b>
VIII.B.1 PAP and Daytime Sleepiness .....	274
VIII.B.2 PAP and OSA Severity .....	276
VIII.B.3 PAP and Mortality Risk .....	277
VIII.B.4 PAP and Cardiovascular Outcomes.....	280
VIII.B.4.a PAP and Control of Hypertension .....	280
VIII.B.4.b PAP and Control of Atrial Fibrillation .....	284
VIII.B.4.c PAP after CVA .....	290
VIII.B.4.d PAP for Heart Failure.....	296
VIII.B.4.e PAP and Cardiovascular Events .....	304
VIII.B.5 PAP and Cognitive Measures .....	309
VIII.B.6 PAP and Insulin Resistance .....	316
VIII.B.7 PAP and Motor Vehicle Accidents .....	318
VIII.B.8 PAP and Work Productivity.....	322
VIII.B.9 PAP and Insomnia .....	326
VIII.B.10 PAP and Obesity and Hypoventilation Syndrome .....	327
VIII.B.11 PAP in Overlap Syndrome (COPD) .....	328
<b>VIII.C Medical Management of OSA: Oral Appliances.....</b>	<b>332</b>
VIII.C.1 Tongue Retention Devices .....	332
VIII.C.2 Mandibular Repositioning Devices (MRD).....	334
VIII.C.2.a MRD Efficacy versus CPAP .....	338
<b>VIII.D Medical Management of OSA: Behavioral and Adjunctive Therapies .....</b>	<b>340</b>
VIII.D.1 Positional Therapy for Positional OSA.....	340
VIII.D.2 Weight Management for OSA .....	345
VIII.D.3 Sedative Medications and Effect on OSA .....	352
VIII.D.4 Nasal Obstruction and Sinusitis Management for OSA Treatment .....	353
VIII.D.5 Nasal Dilators for OSA .....	357
VIII.D.6 Surfactants for OSA Treatment .....	360
VIII.D.7 Supplemental Oxygen for OSA Treatment .....	362
VIII.D.8 Myofunctional Therapy for OSA.....	365
<b>IX. Surgical Treatment for OSA.....</b>	<b>368</b>
<b>IX.A Surgical Candidacy .....</b>	<b>368</b>
IX.A.1 Evaluation of PAP Failure Prior to Surgery .....	368
IX.A.2 BMI Criteria for Surgical Candidacy .....	372
IX.A.3 Surgery as Primary Treatment for OSA.....	377
<b>IX.B Perioperative Management of OSA.....</b>	<b>381</b>
IX.B.1 Anesthesia Considerations in OSA and Upper Airway Surgery .....	381
IX.B.2 Perioperative CPAP Use and Sleep Surgery .....	388
IX.B.3 Postoperative Disposition After Sleep Surgery .....	390
IX.B.4 Opioid Use for Pain Control After Sleep Surgery .....	394
<b>IX.C Surgical Planning: Level of Obstruction Assessment.....</b>	<b>398</b>
IX.C.1 Physical Examination for Surgical Planning.....	398
IX.C.2 Drug Induced Sleep Endoscopy (DISE) .....	404
IX.C.2a DISE Methods .....	404
IX.C.2.b DISE Findings Inform Surgical Outcomes.....	408
IX.C.2.c DISE for Treatment Planning and to Improve Outcomes .....	411

<b>IX.D Surgical Treatment for OSA .....</b>	<b>412</b>
IX.D.1 Sinus Surgery .....	412
IX.D.2 Nasal Surgery .....	415
IX.D.3 Tonsillectomy .....	418
IX.D.4 Soft Palate Surgery .....	422
IX.D.4.a Uvulopalatopharyngoplasty (UPPP) .....	422
IX.D.4.b Expansion Palatopharyngoplasty .....	426
IX.D.4.c Lateral Palatopharyngoplasty .....	432
IX.D.4.d Transpalatal Advancement Pharyngoplasty .....	435
IX.D.4.e Radiofrequency Palatoplasty .....	437
IX.D.4.f Pillar Implants .....	442
IX.D.4.g Palate Suture Suspension .....	448
IX.D.5 Tongue and Hypopharyngeal Surgery .....	453
IX.D.5.a Tongue Base Radiofrequency Ablation .....	453
IX.D.5.b Genioglossus Advancement .....	456
IX.D.5.c Tongue Suture Suspension .....	459
IX.D.5.d Hyoid Suspension .....	461
IX.D.5.e Lingual Tonsillectomy .....	464
IX.D.5.f Epiglottis Surgery .....	466
IX.D.6 Maxillary and Mandibular Surgery .....	466
IX.D.6.a Maxillary Expansion .....	466
IX.D.6.b Maxillomandibular Advancement .....	469
IX.D.7 Hypoglossal Nerve Stimulation (HNS) .....	473
IX.D.7.a Candidacy for HNS .....	473
IX.D.7.b Efficacy of HNS .....	474
IX.D.7.c Titration of HNS .....	483
IX.D.7.d Adherence in HNS Therapy .....	485
IX.D.8 Multilevel Surgery .....	488
IX.D.9 Durability of Surgery: Long Term Results .....	496
IX.D.10 Tracheotomy .....	500
IX.D.11 Bariatric Surgery .....	502
<b>IX.E Surgical Efficacy for OSA Symptoms and Comorbidities.....</b>	<b>506</b>
IX.E.1 Surgery and Daytime Sleepiness and Quality of Life.....	506
IX.E.2 Surgery to Improve OSA Severity.....	515
IX.E.3 Surgery and Mortality Risk.....	522
IX.E.4 Surgery and Hypertension Improvement .....	524
IX.E.5 Surgery and Cardiovascular Outcomes .....	526
IX.E.6 Surgery and Cognitive Measures .....	530
IX.E.7 Surgery and Cerebrovascular Disease.....	532
IX.E.8 Surgery and Work Productivity .....	534
<b>X. Pediatric OSA: Differences in Evaluation and Management.....</b>	<b>535</b>
<b>X.A Evaluation for Pediatric OSA.....</b>	<b>535</b>
<b>X.B Adenotonsillectomy as First-line Treatment for Pediatric OSA .....</b>	<b>537</b>
<b>XI. Knowledge Gaps and Research Opportunities .....</b>	<b>542</b>
<b>XI.A Phenotypes and Metrics of Disease .....</b>	<b>542</b>

<b>XI.B OSA Screening and Diagnosis .....</b>	<b>544</b>
<b>XI.C OSA Therapy .....</b>	<b>544</b>
XI.C.1 Benefits of PAP .....	544
XI.C.2 PAP Adherence .....	545
XI.C.3 Surgery and Definitions of Success .....	546
XI.C.4 Surgical Outcomes .....	546
<b>XI.D Longitudinal OSA Care .....</b>	<b>547</b>
<b>XI.E Patient-Centered Models of Care .....</b>	<b>547</b>

### List of Abbreviations Used

AAOHNS	American Academy of Otolaryngology-Head and Neck Surgery
AAP	American Academy of Pediatrics
AASM	American Academy of Sleep Medicine
AD	Alzheimer's disease
AF	atrial fibrillation
AHI	apnea hypopnea index
AI	apnea index
APAP	auto-titrating positive airway pressure
AR	allergic rhinitis
ARI	arousal index
ASA	American Society of Anesthesiologists
ASV	adaptive servoventilation
ATS	American Thoracic Society
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BPAP	bi-level positive airway pressure
BUR	auto-backup rate
BVS	bilevel ventilatory support
BVS-S	spontaneous bilevel ventilatory support
BVS-ST	spontaneous-timed bilevel ventilatory support
BVS-VTPS	volume-targeted bilevel ventilatory support

CAD	coronary artery disease
CAHI	residual central AHI
CBCT	cone beam computed tomography
CBT	cognitive behavioral therapy
CBTi	cognitive behavioral therapy for insomnia
CCC	complete concentric collapse
CEA	cost effectiveness analysis
CHAT	CHildhood Adenotonsillectomy Trial
CHF	congestive heart failure
CI	confidence interval
CIH	cyclical intermittent hypoxia
CIMT	Carotid artery intima-media thickness
CMS	Centers for Medicaid and Medicare Services
CO <sub>2</sub>	carbon dioxide
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CRS	chronic rhinosinusitis
CSA	central sleep apnea
CT	computerized tomography
CV	cardiovascular
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DISE	drug induced sleep endoscopy
DM	diabetes mellitus
DOME	Distraction Osteogenesis Maxillary Expansion
ECG	electrocardiogram
EEG	electroencephalogram
EF	ejection fraction
EMG	electromyography

EOG	electro-oculography
EPAP	expiratory positive airway pressure
ESP	expansion palatopharyngoplasty
ESS	Epworth sleepiness scale
FOSQ	functional outcomes sleep questionnaire
FSS	Friedman scoring system
FTP	Friedman tongue position
GDM	gestational diabetes mellitus
GERD	gastroesophageal reflux disease
GLP-1 RA	glucagon-like peptide-1 receptor agonists
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HGNS	hypoglossal nerve stimulation
HNS	hypoglossal nerve stimulation
HR	hazards ratio
HRQOL	health-related quality of life
HRV	heart rate variability
hs-CRP	highly sensitive C-reactive protein
HSAT	home sleep apnea test
HST	home sleep test
ICU	intensive care unit
IFL	inspiratory flow limitation
IPS	inspiratory pressure support
LAUP	laser-assisted uvulopalatoplasty
LES	lower esophageal sphincter
LOE	level of evidence
LP	lateral pharyngoplasty
LSAT	lowest oxygen saturation
LVEF	left ventricular ejection fraction

MA	meta-analysis
MAD	mandibular advancement device
MAP	mean arterial pressure
MARPE	Micro-Implant Rapid Palatal Expander
MC	Mallampati classification
MCI	mild cognitive impairment
MCI	multichannel intraluminal impedance
MI	myocardial infarction
MLS	multilevel surgery
MMA	maxillomandibular advancement
MP-H	mandibular plane-hyoid
mPAP	mean pulmonary arterial pressure
MRD	mandibular repositioning device
MRI	magnetic resonance imaging
MSLT	multiple sleep latency test
MT	myofunctional therapy
MWT	Maintenance of Wakefulness Test
NHANES	National Health and Nutrition Examination Survey
NO	nitric oxide
NPV	negative predictive value
NREM	non-rapid eye movement
NT	narcolepsy type
OA	oral appliance
ODI	oxygen desaturation index
OHS	obesity hypoventilation syndrome
ONF	oronasal fistula
OP	oropharynx
OR	odds ratio
OS	overlap syndrome
OSA	obstructive sleep apnea

OSAS	obstructive sleep apnea syndrome
OSLER	Oxford Sleep Resistance Test
P-SAP	Perioperative Sleep Apnea Prediction Score
PACU	post-anesthesia care unit
PAH	pulmonary arterial hypertension
PAP	positive airway pressure
PAT	peripheral arterial tone
PCI	percutaneous coronary intervention
Pcrit	upper airway critical closing pressure
PH	pulmonary hypertension
PLMs	periodic limb movements
POSA	positional obstructive sleep apnea
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROM	patient reported outcome measure
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
PT	positional therapy
QALY	quality-adjusted life year
QOL	quality of life
QSQ	Quebec Sleep Questionnaire
RBD	REM sleep behavior disorder
RCT	randomized control trial
RDI	respiratory disturbance index
REI	respiratory event index
RERA	respiratory-event related arousals
RF	radiofrequency
RFA	radiofrequency ablation
RFS	Reflux Finding Score
RLS	restless leg syndrome



RME	Rapid Maxillary Expansion
RR	relative risk
RSI	Reflex Symptom Index
SaO <sub>2</sub>	oxygen saturation
SAQLI	Sleep apnea quality of life index
SARPE	Surgically Assisted Rapid Palatal Expansion
SBP	systolic blood pressure
SD	standard deviation
SDB	sleep-disordered breathing
SF-36	short form health survey
SGA	small for gestational age
SHHS	Sleep Heart Health Study
SMD	standardized mean difference
SNA	sella, nasion, A point angle
SNB	sella, nasion, B point angle
SR	systematic review
SRBD-PSQ	Sleep-Related Breathing Disorder scale of the Pediatric Sleep Questionnaire
STAR	Stimulation Therapy for Apnea Reduction
STEMI	ST-segment elevation myocardial infarction
T&A	adenotonsillectomy
T2DM	Type 2 diabetes mellitus
T88	time spent with oxygen saturation less than 88%
T90	time spent with oxygen saturation less than 90%
TBRF	Tongue base radiofrequency
TBT	tennis-ball technique
TCRFTA	temperature-controlled radiofrequency tissue ablation
TECSA	treatment emergent central sleep apnea
TIA	transient ischemic attack
TMD	temporomandibular disorder

TMJ	temporomandibular joint
TORS	transoral robotic surgery
TPA	transpalatal advancement pharyngoplasty
TRD	tongue retention device
TS	tongue suspension
TST	total sleep time
UA	upper airway
UARS	upper airway resistance syndrome
UAS	upper airway stimulator
UES	upper esophageal sphincter
UPPP	uvulopalatopharyngoplasty
VAS	visual analog scale
VP	velopharynx
VPI	velopharyngeal Insufficiency
WAI	Work Ability Index
WHO	World Health Organization

## I. Introduction

Obstructive sleep apnea is a complex and multi-faceted disease with multiple associated symptoms and comorbidities. The last decade has contributed to expanding knowledge of disease incidence, new approaches to diagnosis, and novel improvements in therapeutic options. OSA was first defined in 1965.<sup>1,2</sup> For many years, the only therapy was tracheotomy tube placement to bypass upper airway obstruction. Continuous positive airway pressure therapy (CPAP) was introduced in 1981<sup>3</sup> and marked a pivotal discovery in OSA treatment. Since that time, growth in the literature and understanding of OSA as a heterogeneous and complex chronic disease has been exponential. Our abilities to diagnose OSA and to determine its far-reaching consequences have advanced significantly. OSA is currently recognized as a common and important major health issue, imposing a large cost on health systems around the world.

This International Consensus Statement on Obstructive Sleep Apnea (ICS:OSA) was created to summarize the best available evidence into a format that allows clinicians to examine diagnosis and management options for adult OSA, to understand the quality of evidence, and to translate the findings and recommendations into evidence-based care of the OSA patient. Contributions came from more than 130 international authors from various OSA specialties including neurology, pulmonology, sleep medicine, otolaryngology, oral-maxillofacial surgery, dentistry, anesthesiology, psychiatry, cardiology, and sleep physiology. The specialists contributing to this statement represent a diverse set of expertise that encompass the far-reaching and complex needs of understanding and treating obstructive sleep apnea. Topics on OSA were assigned to experts who utilized a structured review process to evaluate and interpret the evidence related to OSA. The ICS:OSA recommendations for diagnosis and management of OSA rely directly on the reviewed evidence with delineations of the benefits, harms, and costs that were considered for each recommendation.

This document highlights the current understanding and impact of OSA in adult patients. The ICS:OSA utilizes an evidence-based format defined by the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis in 2016 (ICAR-RS-2016)<sup>4</sup> which was adapted from a framework<sup>5</sup> that uses a blinded iterative review process. This method has been used for other subjects including allergic rhinitis, skull base surgery, and olfaction. For ICS:OSA, experts in the fields of sleep medicine and sleep surgery contributed to its creation as both section authors and blinded reviewers of other sections. Each section attempts to emphasize published, peer-reviewed evidence where available and identify gaps in knowledge of the disease.

The ICS:OSA is not a clinical practice guideline (CPG) and does not employ the steps of a CPG creation. The ICS:OSA includes meta-analyses and other systematic reviews when available for specific OSA topic areas but does not perform separate or new meta-analyses on the data summarized. This document aims to summarize and consolidate the best available knowledge on the diagnosis and treatment of OSA and provide a standardized format to display the evidence and allow for alternative interpretations.

Recommendations exhibited in the ICS:OSA are based upon the best available evidence, but for many topics the level and quality of evidence are variable or weak. Summary recommendations should be assessed in the context of the evidence on which they are based and the populations of the studies themselves especially when attempting to translate the data for individualized recommendations. Recommendations in the ICS:OSA do not define standard of care or medical necessity and cannot dictate

care of an individual patient. Variability in the presentation, symptoms, treatment responses and tolerance levels of therapy is appreciated for all complex diseases and OSA is no exception.

The best evidence-based practice utilizes shared-decision making approaches that incorporate evidence with individual patient factors, values, expectations and goals in creating individualized clinical decisions and recommendations. New and future research in OSA should aim to fill the knowledge gaps and strengthen the evidence that moves us towards optimal care of the OSA patient. As new and stronger evidence is examined, summary recommendations will require reevaluation and updates.

## II. Methods

### II.A Topic Development

The ICS:OSA document focused on incorporation and summarization of the published literature. The methodology for ICS:OSA followed that of prior International Consensus in Allergy and Rhinology documents<sup>4,6,7</sup> which involved a process adapted by Rudmik and Smith.<sup>5</sup> The approach aims to maximize impact of published evidence by systematically evaluating the literature, grading the evidence, and creating evidence-based recommendations.

The ICS:OSA was divided into over 150 topics, each topic was assigned to a senior author who is a recognized expert in care of obstructive sleep apnea patients. Topic generation spanned definitions of respiratory events in polysomnogram testing, controversies in different scoring definitions, epidemiology of disease, economic burden, risk factors, contributory factors for pathogenesis of OSA, diagnosis and screening tools, diagnostic testing modalities, medical comorbidities, medical management and surgical management for OSA. A focus of the ICS:OSA included the many cardiovascular, cognitive, and metabolic comorbidities associated with OSA which impact OSA screening and management. Separate sections were created to examine the evidence on the effects of PAP and surgical therapy for improving OSA-related symptoms and comorbidity risks.

A few topics based on disease definition or background information were assigned as literature reviews (LR). Certain topics were not appropriate or lacked sufficient evidence and were assigned as evidence-based reviews (EBR). Other topics had evidence to inform clinical recommendations were assigned as evidence-based reviews with recommendations (EBR-R).

For each topic, authors were asked to perform a systematic review of the literature using Ovid MEDLINE (1947-December 2019), EMBASE (1974-December 2019) and Cochrane Review databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standardized guidelines<sup>8</sup> were used to inform the systematic reviews. Randomized controlled trials (RCTs), meta-analyses, systematic reviews and published guidelines were first identified to provide the strongest level of evidence if available. When these were not available, observational studies were used. Identified studies were included to ensure relevant studies were captured. The majority of studies included were written in English. If the authors felt a non-English study should be included, the paper was translated and summarized. Important evolving topics did include papers after December 2019 if the paper significantly contributed new understanding or influenced the recommendations.

For EBR and EBR-R sections, relevant studies were displayed in a standardized format with quality of each study graded using the Oxford Level of Evidence (LOE level 1a to 5).<sup>9</sup> Next an aggregate grade of evidence (A to D) was determined based on guidelines from the American Academy of Pediatrics

Steering Committee on Quality Improvement and Management (AAP SCQIM)<sup>10</sup>(see Table II.A.1). When appropriate, a recommendation was written using the AAP SCQIM (Table II.A.2). Each recommendation was based on the aggregate level of evidence along with an assessment of benefit, harm, and costs related to the specific topic.

**Table II.A.1** Aggregate grade of evidence

Grade	Research Quality
<b>A</b>	Well-designed RCTs
<b>B</b>	RCTs with minor limitations Overwhelming consistent evidence from observational studies
<b>C</b>	Observational studies (case control and cohort design)
<b>D</b>	Expert opinion Case reports Reasoning from first principles

**Table II.A.2** AAP defined strategy for recommendation development<sup>10</sup>

Evidence Quality	Preponderance of Benefit over Harm	Balance of Benefit and Harm	Preponderance of Harm over Benefit
A. Well-designed RCT's	<i>Strong Recommendation</i>	<i>Option</i>	<i>Strong Recommendation Against</i>
B. RCT's with minor limitations; Overwhelmingly consistent evidence from observational studies	<i>Recommendation</i>		
C. Observational studies (case control and cohort design)			<i>Recommendation Against</i>
D. Expert opinion, Case reports, Reasoning from first principles	<i>Option</i>	<i>No Recommendation</i>	

## II.B Iterative Review

Following the development of each ICS:OSA section in LR, EBR, or EBR-R formats, the section underwent a two-stage iterative review process using at least two independent reviewers. The purpose of the

Accepted Article

reviews was to evaluate the completeness of literature identification, determine accuracy of the grade of evidence, and ensure the recommendations were appropriate. Most sections were reviewed across disciplines. Following the review process, changes were agreed upon by both reviewers and initial author(s).

## II.C ICS:OSA Statement Development

After review and edits were completed, the principal editors (JLC, ANG, IR) synthesized all sections into the ICS:OSA statement. The document draft was then reviewed by all contributing authors. Once consensus was achieved on literature completeness and final recommendations, the final ICS:OSA statement was produced.

As each topic was authored by individuals, search results may vary and this document does not present every study published on every topic. Most sections do not include an exhaustive list of all studies ever performed and authors were given the ability to select the most relevant evidence. For certain topics, the literature is extensive and the section focused mainly on high-quality studies or systematic reviews. The editors also made an effort to ensure recommendations aligned with recent published society guidelines.

## II.D Possible Adverse Effects of OSA Interventions

Throughout ICS:OSA, possible side effects or risks of testing or interventions were considered. In order to standardize a collection of these possible side effects and adverse effects, Table II.D defined typical adverse effects for a variety of OSA interventions both immediate and long term. Risks for these effects should be considered when determining policy level recommendations. Each intervention has the additional risk of insufficient improvement of symptoms and continued OSA disease. Table II.D may not include all possible risks.

**Table II.D** Risks, side effects and adverse effects of common obstructive sleep apnea interventions\*

Intervention	Possible side effects and adverse effects
Home sleep study testing	False negative result, diagnosis delay, sensor discomfort or failure, , skin irritation (from adhesives).
In-laboratory sleep study testing	Discomfort, skin irritation (from adhesives), sensor discomfort or failure.
Continuous positive airway pressure therapy or automatic positive airway pressure therapy	Discomfort, nasal complaints, oral dryness, skin irritation, allergy to mask materials, poor sleep quality, aerophagia, claustrophobia, mask leak, epistaxis, dizziness.
Bilevel positive airway pressure therapy	Discomfort, nasal dryness, oral dryness, skin irritation, poor sleep quality, aerophagia, claustrophobia, mask leak, epistaxis, dizziness.
Oral appliance	Discomfort, occlusal changes, jaw or temporomandibular joint pain, tongue irritation, excessive salivation, mouth dryness, damage to teeth
Drug induced sleep endoscopy	Excessive sedation, desaturation, laryngospasm, risk of anesthesia, <sup>†</sup> loss of airway, need for intubation, epistaxis.
Tonsillectomy	Acute post-operative pain or swelling, sore throat, temporary

	dysphagia, post-operative bleeding, infection, risk of anesthesia <sup>†</sup>
Soft palate surgery (ie. UPPP, ESP, LP)	Acute post-operative pain or swelling, dysphagia, taste change, post-operative bleeding, infection, temporary or permanent velopharyngeal insufficiency, long term globus sensation, pharyngeal dryness, oronasal fistula, risk of anesthesia <sup>†</sup> , death. UPPP surgery associated with 1.6% major complication rate and 0.09% mortality rate.
Genioglossus advancement	Acute post-operative pain or swelling, mandibular fracture, neurosensory changes, mandibular fracture, dental injury or dental pulp necrosis, post-operative bleeding or floor of mouth hematoma, infection, risk of anesthesia. <sup>†</sup>
Hyoid suspension	Acute post-operative pain or swelling with airway instability, temporary dysphagia, infection, post-operative bleeding, infection, risk of anesthesia <sup>†</sup>
Base of tongue surgery or lingual tonsillectomy	Acute post-operative pain, post-operative bleeding, infection, dysphagia, globus sensation, taste loss or change, tongue numbness, pharyngeal scarring, risk of anesthesia. <sup>†</sup>
Epiglottis Surgery	Acute post-operative pain, post-operative bleeding, infection, dysphagia, changes in speech, aspiration, globus, risk of anesthesia <sup>†</sup>
Nasal and Sinus surgery	Acute post-operative pain, post-operative bleeding, infection, orbital injury, septal perforation, cosmetic changes, lacrimal system injury, hyposmia/anosmia, vision changes or blindness, intracranial injury, cerebrospinal fluid leak, risk of anesthesia <sup>†</sup>
Jaw Surgery	Occlusal changes, facial neurosensory deficits, cosmetic changes in facial profile and structure, infection, bleeding, subcutaneous emphysema, malunion or nonhealing of the mandible, temporomandibular related pain, risk of anesthesia <sup>†</sup>
Hypoglossal Nerve Stimulation Surgery	Acute post-operative pain, post-operative bleeding, infection, tongue stiffness, tongue abrasion, transient tongue hemiparesis, lip weakness, device malfunction requiring revision surgery, device migration, pneumothorax, discomfort with use, risk of anesthesia <sup>†</sup>
Tracheostomy	Acute post-operative pain, post-operative bleeding, infection, tube obstruction, tube displacement, tracheoesophageal fistula, pneumothorax, tracheal stenosis, trachea-innominate fistula, thyroid injury, recurrent laryngeal nerve injury, risk of anesthesia <sup>†</sup>
Bariatric Surgery	Acute post-operative pain, post-operative bleeding, infection, nausea, vomiting, gastroesophageal reflux, mucosal ulcers, gallstones, anastomotic leak, chronic malnutrition, dumping syndrome, hernia, need for revision surgery, risk of anesthesia <sup>†</sup>

\*May not include all possible risks of listed interventions. Surgical risks include common expected postoperative symptoms and rare long-term risks.

<sup>†</sup>Includes risk of sore throat, nausea, vomiting, damage to teeth, laryngospasm, aspiration, anaphylaxis, hypoxia, respiratory failure, cardiovascular collapse, or death

### III. Definitions and Classifications Related to OSA

#### III.A Sleep Disordered Breathing

Sleep-Disordered Breathing (SDB) refers to a range of sleep-related breathing disorders that includes primary snoring, obstructive sleep apnea (OSA), central sleep apnea, Cheyne-Stokes respiration, and sleep-related hypoventilation. The risk factors and underlying pathophysiological mechanisms for these disorders have overlapping as well as unique features. Each is associated with impaired ventilation during sleep and sleep disruption, although they differ in the underlying severity of gas exchange abnormalities, anatomic obstruction, and degree of underlying ventilatory control abnormality.

OSA is the most common sleep disorder in adults that is evaluated at sleep centers. It is defined on the basis of nighttime and daytime symptoms as well as objective data from a sleep study. Objective sleep testing, with use of a home sleep apnea test (HSAT) or full polysomnography (PSG) records multiple channels of physiological data that allows identification of the key respiratory-related events that are used to assess SDB: apneas, hypopneas, and RERAs, patterns of oxyhemoglobin saturation, sleep-state related parameters (PSG only), and body position.

The American Academy of Sleep Medicine (AASM) publishes and regularly updates the guidelines that specify the technical requirements for sleep study data acquisition and scoring.<sup>11</sup> Since 1999, these have been updated to address advances in technology (e.g., use of nasal pressure signals for airflow detection) as well as changes in hypopnea definitions (reflecting both updates to the evidence and pragmatic issues in operationalizing alternative definitions).

##### III.A.1 Respiratory Event Definitions

In 2012, the AASM updated the 2007 respiratory event scoring rules,<sup>12</sup> which continue to be clarified.<sup>11</sup> Note that the scoring of some events (e.g., hypopneas, RERAs) remain controversial, resulting in Recommended and Acceptable definitions and Optional recommendations. Definitions of relevant respiratory event subtypes are largely based on expert consensus and are summarized:

###### III.A.1.a Apnea

A drop in peak signal excursion by  $\geq 90\%$  of pre-event baseline for  $\geq 10$  seconds using an oronasal thermal signal (recommended sensor), Positive Airway Pressure (PAP) device flow, or an alternative apnea sensor. No requirement for a desaturation or an arousal.

###### III.A.1.b Hypopnea

Recommended definition (AASM definition): A drop in peak signal excursion by  $\geq 30\%$  of pre-event baseline for  $\geq 10$  seconds using nasal pressure (recommended sensor), PAP device flow, or an alternative hypopnea sensor, AND a  $\geq 3\%$  oxygen desaturation from the pre-event baseline OR the event is associated with an EEG (cortical) arousal.



Alternative definition: A drop in peak signal excursion by  $\geq 30\%$  of pre-event baseline for  $\geq 10$  seconds using nasal pressure (recommended sensor), PAP device flow, or an alternative hypopnea sensor, AND a  $\geq 4\%$  oxygen desaturation from the pre-event. This is the current definition used by Centers for Medicaid and Medicare Services (CMS).

### III.A.1.c Respiratory Effort Related Arousal (RERA)

Sequence of breaths lasting  $\geq 10$  seconds characterized by increasing respiratory effort or by flattening of the inspiratory portion of the flow signal leading to an arousal from sleep when the sequence of breaths do not meet criteria for an apnea or hypopnea. Scoring of this event type is considered optional. Of note, the revised recommended hypopnea rules allow hypopneas to be recognized if associated with an arousal, thus identifying many events that previously would have been missed without the RERA classification.

*Note:* Apneas and hypopneas require comparison of breathing amplitude relative to a “baseline.” The AASM 2007 and 2012 manuals operationalize baseline as: “mean amplitude of stable breathing and oxygenation in the 2 minutes preceding the onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the 3 largest breaths in the 2 minutes preceding onset of the event (in individuals without a stable breathing pattern).”

**III.A.2 Summary Metrics** Summary metrics of OSA severity tabulate the frequency of breathing disturbances to 1) use as thresholds for defining disease; and 2) assess disease severity, with higher indices considered to reflect more severe disease.

**III.A.2.a Apnea Hypopnea Index (AHI)** The AHI is calculated as the number of respiratory events (apneas, hypopneas) divided by the number of hours of sleep documented during a polysomnography study. It is important to distinguish if all respiratory events are included (central and obstructive) or only obstructive events. Ideally, a total AHI inclusive of central and obstructive events would be reported along with a separate total for central apnea index.

**III.A.2.b Respiratory Event Index (REI)** The REI is calculated as the number of respiratory events divided by the number of hours of *estimated* sleep using a home sleep apnea test. The recommended approach for estimating sleep time is by editing from the total recording time the periods when the participant is likely awake, as evidenced by artifact, movement, and characteristic changes in heart rate and breathing.

**III.A.2.c Respiratory Disturbance Index (RDI)** The RDI is calculated as the number of respiratory events (apneas, hypopneas and RERAs) divided by the number of hours of sleep documented during a polysomnography study.

**III.A.2.d Oxygen Desaturation Index (ODI)** This metric refers to the number of dips (3 or 4%; ODI3%, ODI4%) in oxygen saturation relative to a local baseline per hour of sleep from an overnight sleep study. Unlike the AHI, the ODI is almost always automatically derived using analysis software. Software programs utilize various algorithms for averaging oxygen saturation signals, defining local baseline oxygen saturation, requiring minimal durations of oxygen fall, and for identifying and excluding artifact.

**Table III.A.1. Adult OSA Severity Classification**

OSA Severity Classification	AHI (events/hour)
-----------------------------	----------------------

None	<5
Mild	≥ 5 to <15
Moderate	≥ 15 to < 30
Severe	≥ 30

### III.A.3 Considerations in sleep study scoring and data interpretation

**Event features:** There are 3 key features of event definitions that influence prevalence estimates of OSA: 1) Degree of associated oxygen desaturation, 2) Use of event-associated EEG arousal, and 3) Amplitude of breathing reduction (magnitude and duration). These dimensions relate to the prognostic importance of the features under analysis: oxygen desaturation captures the effect of reduced ventilation and increased work of breathing on blood oxygenation and resultant intermittent hypoxemia. Events with associated arousals provide information on whether the breathing disruption was sufficient to trigger central responses and fragment sleep. Magnitude of breathing reduction provides measures of airflow limitation amplitudes and airway collapsibility. Varying hypopnea definitions have mostly focused on the level of associated desaturation and presence/absence of an arousal and have not rigorously compared differences in approaches for quantifying flow limitation or ventilation.

**Alternative hypopnea definitions impact AHI values:** All of the summary metrics are highly correlated with one another but can vary tremendously in the absolute numbers of events detected. In one of the first and largest studies, a 10-fold difference in OSA prevalence estimates was reported to result from use of different definitions of hypopnea and application of various disease-defining AHI thresholds.<sup>13</sup> More recently, studies have estimated the reclassification of OSA severity that results from use of a “3% desaturation or arousal” hypopnea definition compared to a “4% desaturation” criterion. A series of calibration equations were published to allow imputation of AHI levels across definitions.<sup>14</sup> This analysis highlighted that the largest differences in mean AHI occurred at lower OSA disease severity, with convergence at higher levels of disease severity, underscoring how different hypopnea definitions may reclassify individuals with mild to moderate OSA. A meta-analysis of 11 studies comparing these definitions calculated a sensitivity of 82.7% (95% confidence interval 0.72–0.90) and specificity of 93.2% (0.82–0.98) for the two definitions.<sup>15</sup> The analysis estimated that an additional 20% of individuals would be classified with OSA using the “3% desaturation or arousal” hypopnea definition.

Comparisons of the prognostic utility of the various hypopnea definitions have not identified clear advantages to any single definition but have highlighted the need to adjust the thresholds used to define SDB disease severity (none, mild, moderate, severe) according to the AHI. In a cross-sectional analysis of the community-based general population, HypnoLaus cohort, adjusted thresholds for defining moderate and severe OSA were shown to associate with both hypertension and diabetes. Specifically, this study suggested that the thresholds for defining disease severity need to be reduced by approximately one half for hypopnea definitions using a 4% desaturation criteria compared to the AASM hypopnea definition.<sup>16</sup> In the Sleep Heart Health Study, the application of the current AASM recommended definition (3% desaturation or arousal) resulted in an approximately doubling of the number of individuals classified with moderate OSA (AHI>15). The group solely identified with use of the AASM definition had a high prevalence of hypertension as compared to the group classified using the more conservative 4% definition, supporting the importance of using more inclusive definitions for identifying individuals at risk for hypertension.<sup>17</sup> It is important to recognize that OSA is associated with other

comorbidities, in addition to hypertension and diabetes. The prognostic utility of different definitions may vary for sleepiness symptoms, other diseases, and mortality.

Population characteristics, such as age, gender, and obesity, also may influence the accuracy and prognostic value of alternative event definitions, requiring care in selecting definitions most appropriate for given populations. For example, women tend to have shorter apneas and experience less desaturation than men,<sup>18</sup> but with aging, may experience increased death and incident heart failure.<sup>19</sup> A study that utilized estimates of AHI based on different hypopnea definitions (from calibration equations) showed greater variation in effect estimates for cardiovascular disease when arousals were used in the hypopnea definition in the overall population but not in women, where an arousal-based definition appeared appropriate.<sup>20</sup> Hypopnea definition and subsequent AHI scoring also has implications for insurance coverage for various OSA therapies.<sup>21</sup>

**Scoring reliability:** Although there is active research developing automated tools for respiratory scoring, event identification is largely done by manual annotation by trained scorers. Accredited sleep laboratories need to document acceptable inter-scorer reliability using well-defined protocols. Consistency in scoring will vary according to the technician skill, quality of the underlying signals and severity of the disorder. Apneas are generally considered easier to consistently score as their recognition simply requires identification of absent airflow. However, distinguishing event subtypes (obstructive, central, mixed) is much more difficult, resulting in worse scorer reliability.<sup>22</sup> Identifying subtle changes in ventilation can be difficult as is needed for hypopnea detection, and one argument for requiring correlative data (desaturation, arousal) to identify a hypopnea is to provide additional signs of physiological disturbances over and beyond those identified through a non-calibrated estimate of breathing amplitude change, thus improving scoring reliability. In those cases, care is needed to ensure reliable arousal scoring, which is additionally dependent on the quality of the underlying EEG and EMG channels. For example, in the unattended PSGs in the Sleep Heart Health Study, events were more reliably scored when desaturation criteria alone were used in comparison to inclusion of the arousal criteria.<sup>23</sup>

**ODI vs AHI:** Given that hypopneas utilize oxygen desaturation criteria for event identification, it is not surprising that the AHI and ODI often are highly correlated, but dependent on the specific oximeter and AHI scoring definition used.<sup>24</sup> The ODI is automatically derived using only a single sensor, providing objectivity, simplicity, and scalability. High diagnostic accuracy has been reported.<sup>25</sup> A number of epidemiological studies and clinical trials have utilized the ODI for defining SDB eligibility criteria (e.g., SAVE<sup>26</sup>), or for characterizing risk of incident disease.<sup>27</sup> However, the ODI may be less appropriate as a screening or prognostic index in individuals less likely to desaturate with respiratory events, such as younger patients, non-obese individuals, and women. Conversely, the ODI may be particularly useful to identify hypoxia-related stresses, which have been related to metabolic disease.<sup>16</sup>

**Time Spent with Oxygen Saturation < 90% (T90):** Measures of hypoxemia such as oxygen saturation nadir and time spent with arterial oxygen saturation <90% (T90), may be important in assessments of OSA severity and health risk determinations.<sup>28</sup> It has been shown that more hypoxemia as measured by T90 and lower oxygen saturation nadir in those with similar AHI is associated with more inflammation (measured by C-reactive protein, platelet count, and endothelial stiffness).<sup>28-30</sup> Recently a retrospective study found that having moderate to severe OSA and T90 > 20% of sleep time can be associated with a higher risk of hypertension, type 2 diabetes, and five-year mortality compared to those with T90 <

20%.<sup>28</sup> In addition, an oxygen saturation nadir of < 75% correlated with increased risk of hypertension in this group.

### III.B OSA and Subtype Definitions

Obstructive sleep apnea (OSA) is a chronic disorder caused by repetitive collapse of the upper airway during sleep. Episodes of complete (apneas) and partial (hypopneas) cessation of airflow can lead to two main consequences: arousals from sleep and oxyhemoglobin desaturations. Apneas and hypopneas occur in all phases of sleep, but are more common in N1, N2 and rapid eye movement (REM) sleep stages than in N3 sleep.

#### III.B.1 Obstructive Sleep Apnea Syndrome (OSAS)

Obstructive sleep apnea syndrome (OSAS) diagnosis requires the patient to have<sup>31</sup> symptoms of sleep-related breathing disturbances (snoring, snorting, gasping, or breathing pauses), excessive daytime sleepiness, or fatigue that occurs despite sufficient opportunity to sleep and is unexplained by other medical problems; and<sup>12</sup> five or more episodes of predominantly obstructive respiratory events (obstructive or mixed apneas, hypopneas, or respiratory-event related arousals [RERAs]) per hour of sleep (AHI/RDI  $\geq$  5).<sup>31</sup> OSA also may be diagnosed in the absence of symptoms if the AHI is  $\geq$ 15 episodes/h.

If presenting daytime and nighttime symptoms or cardiometabolic comorbidities are caused by OSA, the term OSAS is used. However, the terms OSA and OSAS are often used interchangeably in the medical literature.

OSAS is recognized to be a heterogeneous syndrome<sup>32</sup>. The classification that is most commonly used in clinical practice is the one based on frequency of obstructive events based on AHI (Table III.A.1). Frequency of respiratory events influences several important clinical consequences (hypertension, stroke) in a dose dependent fashion.<sup>33</sup> Frequency-based OSA classification using AHI is utilized as an indication for therapy in current national insurance coverage guidelines in the United States.<sup>34</sup>

However, this classification based on AHI alone poorly addresses various phenotypes of the disease. An alternative classification based on presenting symptoms has been proposed which identifies three clusters of patients: those with predominantly sleep disturbance, daytime sleepiness and minimally symptomatic ones<sup>35</sup>. Several other classifications, based on pathophysiology<sup>36</sup>, comorbid conditions<sup>37</sup>, and clinical outcomes<sup>38</sup> have also been described. Current guidelines for the treatment of OSA typically take into account several factors including the AHI, presence or absence of symptoms and associated comorbidities.<sup>39</sup>

#### III.B.2 Positional OSA

Episodes of airway obstruction in OSA are more frequent and more severe in the supine compared to the non-supine body position in nearly all patients.<sup>40</sup> OSA patients who have an increase in breathing abnormalities while in the supine versus lateral position are considered positional patients who exhibit positional OSA (POSA). In non-positional patients, respiratory events appear in all positions of sleep. With POSA, changes in sleep position effect the overall AHI on a sleep study and account for night-to-night variability in sleep study results. The predominant sleep position and time in each position on the

night of the study can be considered when evaluating OSA severity.<sup>41</sup> Patients with POSA have lower BMI, smaller neck circumference, longer posterior airway space measurements and smaller lateral pharyngeal wall tissue volumes.<sup>41,42</sup>

Various definitions have been used to diagnose positional OSA. Cartwright's definition is commonly used, which describes POSA when AHI in the supine position is greater than two times higher than the AHI in non-supine sleep position. For a subset of patients with POSA, the airway only reaches critical collapsibility in the supine, but not in the non-supine position.<sup>43</sup> These patients exhibit supine-isolated OSA, who have respiratory disturbances exclusively in the supine position without abnormalities when non-supine. Supine-isolated positional patients has been described in 27% of patients with POSA.<sup>44</sup> POSA is associated with lower body mass index and lower total AHI in males, lower AHI and higher sleepiness in premenopausal females, and lower AHI and lower Mallampati score in postmenopausal females.<sup>45</sup>

Treatment of positional OSA takes into account differences in the critical closing pressure between supine and non-supine positions of sleep. These are usually reflected by differences in pressures that need to be generated by continuous positive airway pressure (CPAP) devices in different positions of sleep. Although not universally accepted, auto-adjusting PAP (APAP) devices may provide a better treatment option for patients with positional OSA than constant-pressure PAP, as they may produce higher pressures in supine, and lower pressures in the non-supine position of the body.

Treatment of patients with positional OSA may comprise of enforcement of non-supine sleep. Supine sleep can be avoided by employing the older tennis-ball-technique (TBT), which involves placement of a bulky object on the patient's back, or newer generation sleep position trainers (SPT) that include small, battery-powered devices attached to the neck or chest that provide vibrotactile feedback when in the supine position.<sup>46</sup> (See section VIII.D.1)

### III.B.3 REM-related OSA

A number of physiological effects uniquely predispose airways to collapse in REM vs NREM sleep. In REM the genioglossal muscle activity is lower,<sup>47</sup> the respiratory drive is lower,<sup>48</sup> and the autonomic drive is higher than in NREM.<sup>49</sup> These factors result in a longer duration of obstructive events and deeper hypoxemia in REM than in NREM.

The term "REM-related OSA" describes a condition where sleep disordered breathing is predominantly present in REM sleep. While definitions vary, most authors define REM-related OSA in terms of the frequency of sleep-disordered breathing events (AHI) in REM and NREM sleep, with AHI in REM being at least double the AHI in NREM. Some groups add a qualifier of requiring a NREM AHI of < 15 events/hour.<sup>50-53</sup> Depending on the definition used and the population examined, the prevalence of REM-related OSA varies from 13.5% to 36.7%.<sup>50,51,53</sup>

Clinically, REM-related OSA is more common in young female patients, in patients with mild to moderate OSA, and in African Americans.<sup>50,54,55</sup> Excessive daytime sleepiness is usually less prominent in REM-related OSA than in non-REM-related OSA.<sup>56,57</sup> Depression has been reported more commonly in patients with REM-related OSA than in non-REM-related OSA and it may significantly affect these patients' daytime sleepiness and quality of life.<sup>58,59</sup>

The clinical significance of the “REM-related OSA” entity is unclear, and some treat it merely as a mild form of obstructive sleep apnea. Similarly, large studies failed to detect significant differences in symptoms or clinical outcomes between patients with REM-related (or REM-predominant) vs non-REM-related OSA.<sup>50,60-62</sup> As a result, the current classification of sleep disorders does not list REM-related OSA as a separate entity.

### III.B.4 Primary Snoring

Isolated snoring, also known as primary snoring, describes a pattern of vibrational sounds related to narrowing of the upper airway during sleep without significant apnea or hypopnea events (AHI < 5) and without sleep-related daytime symptoms. Snoring is a reflection of partial collapse of the upper airway and increased airway resistance. The soft tissue that forms the upper airway is prone to collapse during sleep which is associated with turbulent airflow and pharyngeal tissue vibrations that create the sounds of snoring.

Airway collapsibility is higher in patients with sleep apnea than in primary snorers and healthy controls.<sup>63</sup> Isolated snoring, upper airway resistance syndrome (UARS), and obstructive sleep apnea (OSA) can thus be viewed as three manifestations of progressive intermittent upper airway obstruction that occur during sleep. With progressive degrees and frequency of airway collapse as well as other modifying factors present in a given individual (arousal threshold, preexisting hypoxemia), intermittent obstruction of the airway is clinically reflected as a spectrum of sleep disordered breathing that presents as: 1) isolated snoring, then 2) obstruction-related arousals or desaturations (upper airway resistance syndrome or UARS) and finally, 3) partial or complete cessation of airflow through the upper airway associated with desaturations and/or arousals (OSA). What determines a given individual’s propensity to move along the path of progression from isolated snoring to UARS to OSA is complex, but is likely affected by several factors including weight gain, gender, race, genetic factors and advancement of age.<sup>64,65</sup>

Occasional snoring (snoring on three or less nights per week) is almost universal in the population with a prevalence of 38-76% in different populations.<sup>66-69</sup> Habitual snoring, defined as snoring on most nights of the week, is present in as many as 12-25% of the population.<sup>66-69</sup> Both occasional and habitual snoring are more frequent in men than in women.<sup>66-68</sup>

Since snoring is the primary nocturnal symptom of obstructive sleep apnea (OSA), its presence should prompt direct questioning about other symptoms of OSA including pauses in breathing at night, unrefreshing sleep, and daytime sleepiness, especially when the presence of snoring is identified in a setting of OSA-related comorbidities.

### III.B.5 Upper Airway Resistance Syndrome (UARS)

Some patients have significant fragmentation of sleep due to obstructive events that do not meet formal criteria of apneas or hypopneas. In a polysomnography tracing, these patients usually display respiratory effort-related arousals (RERAs). RERAs are defined as > 10 second sequences of breaths with increasing respiratory effort or flattening of the inspiratory portion of the flow signal, leading to an arousal.<sup>70</sup> Guilleminault et al. have coined the term upper airway resistance syndrome (UARS)<sup>71</sup> to describe the clinical entity of nocturnal airway collapse leading to respiratory effort-related arousals that are associated with daytime symptoms, usually excessive daytime sleepiness. These events do not meet the criteria of obstructive sleep apnea.

Most of the clinical and polysomnographic characteristics of UARS patients are based on a limited number of retrospective studies.<sup>72-74</sup> The prevalence of UARS among members of a military academy was found to be 8.6%.<sup>75</sup> Similar to OSA, the majority of patients with UARS are men, with M:F ratio of about 3:1.<sup>74</sup> Patients with UARS tend to have lower BMI than those with OSA and the amount of weight gain in the years prior to diagnosis is typically less in UARS than in OSA patients.<sup>74</sup> Daytime impairment in functioning tends to be worse in patients with UARS compared to those with mild OSA.<sup>74,76</sup> On PSG, patients with UARS may have less N1 and N2 sleep than patients with OSA, but more N3 sleep.<sup>74</sup> Several groups have reported an increased frequency of non-specific or functional somatic complaints in patients with UARS, compared to OSA patients including irritable bowel, insomnia, difficulty concentrating, cognitive problems, depression, and poor psychomotor performance.<sup>77-79</sup> These features may be apparent on the initial presentation or may appear over time. It has been postulated that some of these associated symptoms may result from lack of specific therapy for UARS, as many insurers do not include UARS definitions in coverage policies for positive airway pressure therapy.<sup>80</sup>

The upper airway resistance syndrome is no longer recognized as a nosological entity by the current edition of International Classification of Sleep Disorders<sup>81</sup>, as its pathophysiology is the same as OSA. As much as the term UARS has fallen out of favor, the value of this designation lies in underscoring the importance of respiratory-related sleep fragmentation in causing symptoms of sleepiness and impaired daytime functioning that may not be reflected by the apnea-hypopnea index (AHI).

### III.B.6 Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OHS) is defined by awake hypercapnia ( $\text{PaCO}_2 \geq 45\text{mmHg}$ ) in obese individuals ( $\text{BMI} \geq 30\text{kg/m}^2$ ) that is not otherwise explained by restrictive lung disorders or neuromuscular disease. This disorder represents the extreme end of the sleep disordered breathing spectrum. The prevalence of OHS in the general population is unknown, but conservative estimates range between 0.15% to 0.4% amongst adults in the United States.<sup>82,83</sup> However, in obese individuals referred to sleep clinics, prevalence rate increases to 10-20%.<sup>84,85</sup> In approximately 70% of those with OHS, severe OSA (ie.  $\text{AHI} \geq 30/\text{hr}$ ) is present while in 10% the abnormality is non-apneic sleep-dependent hypoventilation only, particularly in REM sleep.<sup>86</sup> The exact mechanisms underlying why only some obese individuals with sleep disordered breathing hypoventilate are not fully understood, but appear to be the end result of a complex interplay between obesity, lung mechanics, respiratory drive and neurohumoral factors.<sup>87</sup>

## IV. Epidemiology and Contributing Factors in OSA

OSA is a common disorder in adults; its prevalence has increased with rising rates of obesity. OSA is strongly associated with cardiovascular and metabolic comorbidities; it is highly prevalent in populations with diabetes, hypertension, heart disease and stroke. Environmental factors also contribute to OSA risk. The epidemiology of OSA depends on the criteria used to define the disease including how respiratory events are defined, AHI cut offs and the manner of testing. The 4% desaturation criteria for hypopneas ( $\geq 4\%$  oxygen desaturation) may be associated with a more cohesive group epidemiologically – typically older, male, obese and with underlying cardiac disease (e.g. heart failure, coronary artery disease, atrial fibrillation) or diabetes. The AASM definition of hypopneas for OSA classification ( $\geq 3\%$  desaturation or arousal) is more inclusive and captures more variable sleep disruption phenotypes of OSA, seen in younger, nonobese, and women patients who tend not to desaturate as substantially.<sup>36</sup>

### IV.A Prevalence

General population based studies of OSA show a high prevalence of undiagnosed sleep apnea.<sup>88</sup> A systematic review of OSA prevalence studies worldwide found a wide range (13-33% in men and 6-19% in women), likely due to methodological heterogeneity such as differences in sampling of the population, AHI cut-off applied, sleep-study scoring criteria used and test type performed.<sup>89</sup> In the US, the Wisconsin Sleep Cohort study<sup>90</sup> and Sleep Heart Health study<sup>91</sup> sampled large non-clinical cohorts in the 1990s. These studies found a general prevalence of 24% in men, 9% in women using the alternative definition of hypopnea ( $\geq 4\%$  oxygen desaturation). A smaller subset, 3-7% in men and 2-5% in women, had OSAS based on AHI  $\geq 5$  with excessive daytime sleepiness.<sup>88,90,92</sup> Population based studies in Asia show similar prevalence to these estimates.<sup>93,94</sup> An updated estimate based on the Wisconsin data in 2013 indicated higher rates of OSA in 14% of men and 5% of women ages 30-70 in the U.S. over time, attributed to changes in population levels of obesity.<sup>95</sup> Prevalence of OSAS was found to be even higher in a population study of Sao Paulo.<sup>96</sup> A more recent population-based study in Switzerland found a very high prevalence: 23% in women and 50% in men.<sup>97</sup> Using rates of obesity, race/ethnicity data and age and regional country data on prevalence, it has been estimated that nearly one billion people have OSA worldwide, the vast majority undiagnosed.<sup>98</sup>

#### IV.A.1 OSA Prevalence and Risk Factors

Consistent across all epidemiological studies, the prevalence of OSA is associated with sex, obesity, and age. Prevalence is higher in men by 2:1, but rates increase in women after menopause and become nearly equal.<sup>99</sup> As BMI increases, the risk of OSA rises with an increase in prevalence of AHI  $\geq 15$  from 3.6% in normal weight to 56% in those with BMI  $\geq 40$  among men aged 50-70 years.<sup>95</sup> OSA incidence increases with age through age 60, although there also may be subsequent increased risk associated with aging.<sup>100</sup> Other risk factors of OSA include a family history of OSA,<sup>101</sup> and certain structural abnormalities of the viscerocranium, including reduced size of the mandible.<sup>102</sup>

Minority populations have lower rates of clinical diagnosis of OSA despite a higher prevalence than white US populations and greater burden of obesity, diabetes and cardiovascular disease.<sup>103,104</sup> Prevalence of OSA in relation to BMI differs by race/ethnicity in US studies, with Hispanic and Chinese American subjects having higher odds of OSA after adjustment for obesity.<sup>105</sup> Differences in prevalence by race/ethnicity may be related to a number of factors, many of which are not well characterized (e.g., environmental exposures.). In addition, variation of craniofacial features by ancestry background may be associated with OSA risk; for example, some studies indicate that some Asian populations may be at increased risk of OSA despite low BMI levels due to shorter midface and shorter cranial base measurements.<sup>106</sup> Additionally, there are likely genetic factors that determine the amount of soft tissue in the upper airway that are responsible for family clustering of OSA.<sup>107</sup>

#### IV.A.2 OSA and Cardiovascular Disease

The prevalence of OSA is higher in those with cardiovascular disease. A recent meta-analysis estimated 49% of subjects hospitalized with cardiac disease (heart failure, acute coronary syndrome and arrhythmias) had previously undiagnosed OSA.<sup>108</sup> There is a very high prevalence of OSA in those with coronary artery disease, hypertension, heart failure, arrhythmias, and especially atrial fibrillation.<sup>109-112</sup> Among subjects with resistant hypertension, OSA is highly prevalent (up to 85% in one series) and the most common secondary cause of hypertension.<sup>113</sup>

OSA is associated with a multitude of cardiovascular outcomes in observational studies, especially in studies utilizing the CMS definition of OSA, as most cardiovascular outcomes are thought to be associated with oxygen desaturation.<sup>111</sup> Cohort studies have found severe OSA to be associated with



higher odds of incident hypertension,<sup>114,115</sup> stroke<sup>116,117</sup> and cardiovascular death.<sup>118</sup> This is thought to be due to the increased nocturnal sympathetic activation, pro-inflammatory state due to cyclic hypoxemia, arousals and negative intrathoracic pressures with occluded upper airway.<sup>110,119</sup> Stroke has been consistently identified as a devastating outcome of untreated severe OSA, especially in middle aged adults.<sup>120</sup>

#### IV.A.3 OSA and Metabolic Disease

OSA is strongly correlated with diabetes, both of which are highly linked to obesity and increased waist/hip ratio. Obesity is the most consistent risk factor for both disorders, especially central adiposity.<sup>121</sup> Trials enrolling obese diabetics have found that 86% have some degree of OSA.<sup>122</sup> Weight loss trials show improvement in both diabetes outcomes and reduced sleep apnea severity.<sup>123</sup> Additional metabolic risk factors include excess testosterone, growth hormone and hypothyroidism.

#### IV.A.4 Environmental factors and OSA

Recent studies examining residential factors demonstrate an association between neighborhood features and sleep apnea. High density of fast-food outlets and lower mixed land use may foster OSA through promoting obesity. Neighborhoods with more parks, higher street connectivity and aesthetic features promote walking. Residing in less favorable walking environments has been associated with more severe sleep apnea especially in male and obese individuals.<sup>124</sup> Neighborhood disadvantage, living in poor residential areas, has been associated with childhood sleep apnea in several epidemiological studies.<sup>125,126</sup> A recent meta-analysis also identifies that the social gradient is associated with OSA.<sup>127</sup> This association may be related to obesogenic environments with limited options for recreation and healthy food<sup>128</sup> and greater pollution in disadvantaged neighborhoods.<sup>129</sup> Ambient air quality has also been associated with sleep apnea.<sup>130,131</sup> The odds of sleep apnea increased by 39% as nitrous dioxide levels increased by 10 parts per billion (ppb) in US study.<sup>130</sup> These environmental features may contribute to disparities in obesity and sleep health.

Obstructive sleep apnea is a highly prevalent disorder, with increasing worldwide incidence as rates of obesity rise and is a considerable public health burden.

#### IV.B Economic Burden of OSA

Obstructive sleep apnea (OSA) not only impacts health and functioning but also economic outcomes. Several economic topics related to OSA include: the costs of OSA due to its impact on health, attention, and productivity; the costs incurred in management; the cost effectiveness of diagnosis and treatment; and whether medical cost savings occur with treatment.

A 2016 AASM commissioned report estimated the economic impact of undiagnosed OSA in the United States (US) to be \$149.6 billion in 2015 based on the interview of opinion leaders, the scientific literature, survey of patients and CMS fee schedules.<sup>132</sup> Direct economic costs included OSA-related comorbidities such as high blood pressure, motor vehicle or workplace accidents, and compensating behaviors such as substance abuse. Indirect economic costs included decreased productivity at work, reduced quality of life, and stress on interpersonal relationships. The largest economic impact was assigned to lost productivity (\$86.9 billion) followed by medical comorbidities and reduced mental health (\$30 billion) and motor vehicle accidents (\$26.2 billion).

Patients with OSA have about twice the medical costs of controls prior to diagnosis.<sup>133,134</sup> For example, a study of health maintenance organization members found average total medical costs in OSA patients

prior to diagnosis was \$2720 versus \$1384 in age and gender matched controls (in 1996 dollars).<sup>134</sup> In the Sleep Heart Health Study (SHHS), 256 subjects with OSA (AHI >11 and sleepiness) had about 17% higher predicted healthcare utilization compared to subjects not meeting these OSA criteria after adjustment for age, gender, BMI and study site.<sup>135</sup> Similarly, in the Outcomes of Sleep Disorders in Older Men (MrOS) study, among 1316 elderly men, mean annualized total healthcare costs were 11.6 % higher in untreated subjects with moderate to severe SDB than in those without SDB.<sup>136</sup>

With regards to OSA and productivity, data from the Danish National Patient Registry found lower employment (60% in OSA patients vs 64% for age, sex and region matched controls) and higher rate of public transfer payments (18% vs 13% for controls). As a result, labor market income was 9.3% lower and social transfer payments were 18% higher in patients over the 8 years prior to and after diagnosis.<sup>133</sup>

Data from the National Safety Council and a meta-analysis of studies investigating collisions and OSA indicated that 800,000 drivers were involved in OSA related motor vehicle collisions at a cost of \$15.9 billion and 1,400 lives in the year 2000 in the United States (\$23.9 billion adjusted to 2020 dollars).<sup>137</sup>

#### **IV.B.1 Costs of treating OSA**

The AASM commissioned-report estimated that in 2015, \$12.4 billion was spent diagnosing and treating the 5.9 million US adults with diagnosed OSA.<sup>132</sup> Costs related to OSA management vary based on whether laboratory or home-based diagnostic and management strategies are used. Based on data from a multicenter clinical trial using the payer perspective, the mean cost per patient over 3 months using home-based management was estimated at \$1807 vs \$2424 using lab-based management. Some of the cost advantage with use of home sleep testing (\$167 vs \$782 for lab study) was offset by the need for additional testing in some patients who have failed or had non-diagnostic home studies.<sup>138</sup> Management costs are highest at the time of diagnosis and tend to diminish over time. In a recent Australian cost effectiveness analysis (CEA), the average annual cost over 5 years for diagnosis and treatment of OSA using lab-based study was estimated at \$579 Australian dollars (AUD; \$495 US dollars).<sup>139</sup>

#### **Cost effectiveness**

Cost Effectiveness Analysis (CEA) compares interventions based on the differences in costs needed to provide an additional quality-adjusted life year (QALY) gained. A number of CEA have evaluated the value of managing moderate to severe OSA from a payer perspective: the estimated cost per QALY over 5 years has varied considerably but generally support its value when compared to other accepted interventions (<\$50,000 per QALY) (9). Some CEA have considered downstream medical cost (due to strokes, heart attacks, motor vehicle collisions) that could be prevented from OSA therapy. For example, Guest et al. estimated that cost savings exceeded the costs of treating OSA after 13 years (10). More recently, Streatfeild et al. estimated that from a healthcare system perspective, the estimated cost to treat OSA was \$12,495 AUD (US \$8746) per disability adjusted life year (equivalent to QALY gained).<sup>140</sup> They included the impact of estimated healthcare cost savings from reduced medical morbidity (\$76 AUD/year). From a societal perspective, there was net cost saving of \$326/year because of a projected \$783/year cost saving due to the reduction of financial costs (due to gains in productivity, fewer accidents and other savings).

#### **Cost Savings**

Observational studies are equivocal regarding whether medical cost savings occur with OSA treatment and their magnitude. Concern has been expressed regarding the adequacy of methodology in some of these studies because they do not include an appropriate control group, use a longitudinal cohort design, compare change in costs between groups (rather than relying only on costs in the post treatment period), measure treatment adherence, adjust for potential confounders and exclude costs of diagnosis and treatment (which naturally decline over time).<sup>141</sup> A recent high-quality study in an older population found costs during the 2 years following diagnosis increased relative to pre-diagnosis levels in individuals regardless of OSA diagnosis or PAP adherence status.<sup>142</sup> Medical costs increased about 8% less for the group fully adherent to CPAP relative to sleep apnea patients who did not receive therapy. It is likely that the impact of therapy on medical costs depends on factors such as the population characteristics (OSA severity and comorbidity), health system, effectiveness of therapy, and duration of observation.

In summary, untreated OSA is associated with substantial economic cost related to reduced productivity, medical comorbidity and motor vehicle and work accidents. Medical costs in clinically identified OSA patients are about twice that for age-sex matched controls prior to diagnosis. In contrast, when OSA is identified in community-based research cohorts cost differences are more modest (10-20% more than similar patient without OSA). Costs for managing OSA are substantial though the cost effectiveness for the treatment of moderate to severe OSA with CPAP is well established. It is reasonable to expect some cost savings long-term with CPAP therapy due to downstream benefits, though there is a need for additional high-quality studies to clarify this issue with regards to the magnitude of savings and variation with patient characteristics, models of OSA care and treatment adherence.

#### IV.C Risk Factors for OSA

##### IV.C.1 Sex

Most population-based studies show a 2-3 fold greater prevalence of OSA among men compared to women.<sup>18,45,90,93,96,99,104,143-155</sup> These findings span across a range of diagnostic modalities, hypopnea definitions, and AHI cutoffs. These findings are also consistent across ethnicities.<sup>45,93,96,145,147,148,152,156</sup> Even when matched for BMI and age, OSA occurs more commonly in men, and with greater severity.<sup>154,155</sup> Age and BMI are risk factors for OSA in both men and women, though the degrees of their impact varies between the sexes.<sup>146</sup> Weight loss or gain impacts AHI greater in men than in women.<sup>154</sup> The effect of BMI on OSA severity decreases with age for both sexes, and appears to be less for individuals older than age 60 years than in younger individuals.<sup>155</sup> In a prospective cohort population-based study, Tishler et al<sup>155</sup> demonstrated that the AHI increases by 140% per 10-years in women (OR 2.41) but by only 15% in men (OR 1.15). This results in a narrowing of the sex difference in OSA risk with increasing age. Sex hormones are implicated in the differential risk between men and women. Post-menopausal women, and particularly those not on hormone-replacement therapy, are at increased risk for OSA compared to pre-menopausal women, even when correcting for age.<sup>99,143,146,153</sup>

Clinic-based prevalence studies also show men to have greater AHI compared to BMI- and age-matched women.<sup>154,157-159</sup> The risk of mild OSA (AHI $\geq$ 5/h) is 2-fold greater in men than women, while the risk of severe OSA (AHI $\geq$ 30/h) is almost 8-fold greater. In a clinic population of 26,425 adults, 21-80 years old, age was less of a factor in AHI severity in obese men than in obese women.<sup>160</sup>

Polysomnographic features of OSA also differ between men and women. Men with OSA tend to have more frequent apneas (vs hypopneas), longer duration of apneas, and more severe oxygen

desaturations.<sup>157,161</sup> The distribution of apneas and hypopneas also differs between men and women. Women are more likely to have events during REM sleep.<sup>18,55,157,162-166</sup> Several studies show that women tend to have less NREM events, but similar or greater REM events compared to age- and BMI-matched men. The difference in the prevalence and severity of OSA between men and women are affected by AHI definitions. For example, Won et al.<sup>18</sup> showed defining respiratory events using lesser oxygen desaturation threshold levels and including arousals increased the relative proportion of women classified with OSA.

The reason for sex differences in the risk for OSA are not well understood but is thought to relate to several factors: 1) Facial anatomical distinctions, such as mandible position, impart different degrees of risk in men and women.<sup>167,168</sup> 2) Upper airway anatomy and function differ between sexes, with men demonstrating longer and more collapsible upper airways.<sup>169-172</sup> 3) Obesity<sup>173</sup> and fat distribution<sup>174,175</sup> differentially affect men and women's propensity for OSA. Lim et al<sup>175</sup> found that while waist-to-hip ratio predicted OSA in both men and women, neck circumference was only predictive of men with OSA. 4) Loop gain and other measures of ventilatory control have been measured in men and women, and in post- and pre-menopausal women, with some evidence to suggest sex differences in respiratory control.<sup>176-181</sup>

In summary, there are significant sex differences in the prevalence, polysomnography features, and risk factors for OSA. Men are in general at greater risk for OSA during NREM sleep, while men and women share similar risk during REM sleep. More studies are needed to understand the sex and sleep stage-dependence of OSA.

#### Sex as a Contributing Factor for OSA

Aggregate Grade of Evidence: C (Level 2b: 3 studies; Level 2c: 17 studies; Level 3b: 16 studies; Level 4: 19 studies)

**Table IV.C.1a: Population studies on prevalence or incidence of OSA in men and women**

STUDY	LOE	Study Design	Cohort	Sample Population	OSA Diagnostics/criteria	Conclusion
Young <sup>90</sup>	2c	Cross-sectional	Wisconsin Sleep Cohort 30-60 yrs N=602	Population-based	PSG AHI ≥ 5	Higher prevalence in men for all age groups Men 2 - 3.7 times greater prevalence
Bixler <sup>143</sup>	2c	Cross-sectional	20-100 yrs N=1741	Population-based	PSG AHI > 15	Prevalence greater in post-menopausal women, and in those not taking hormone replacement therapy
Shahar <sup>153</sup>	2c	Cross-sectional	Sleep Heart Health Study Women >50 yrs N=2852	Population-based	HST IV AHI > 15	Hormone use associated with less OSA, particularly among women 50-59 yrs old (adjusted OR 0.36)

Young <sup>99</sup>	2c	Cross-sectional	Wisconsin Sleep Cohort Study Women 30-60 yrs N=539	Population-based	PSG AHI $\geq 5$	Menopausal transition associated with OSA after controlling for age, body habitus, and several lifestyle factors Postmenopausal women 2.6 time more likely to have AHI $\geq 5$ , and 3.5 times more likely to have AHI $\geq 15$ , compared to premenopausal women
Quintana-Gallego <sup>182</sup>	3b	Case-control	Spain sleep clinic Women mean age $58 \pm 10$ yrs; Men mean age $53 \pm 11$ yrs N=1745	Clinic-based	PSG AHI $\geq 10$ or HST III RDI $\geq 10$	Prevalence: 4.9:1 men to women ratio
Gabbay <sup>160</sup>	3b	Case-control	Israel multiple sleep centers 21-80 yrs N=26,425	Clinic-based	PSG AHI $\geq 10$	AHI increased with increasing age for both non-obese men and women Obesity affected AHI in men aged 20-40 yrs, but AHI did not change after age 40 yrs in obese men
Huang <sup>146</sup>	2b	Prospective cohort	Nurses' Health Study (NHS)  Post-menopausal women who were free of known OSA  N=50,473 NHS N=53,827 NHSII	Population-based	Medical record  NHS: 12-yr incidence  NHSII: 20-yr incidence	Surgical menopause had 26% higher risk of incident OSA compared to naturally post-menopause, adjusted for age at menopause and other OSA risk factors.
Won <sup>18</sup>	2c	Cross-sectional	MESA cohort Mean 69 +/- 9 yrs N=2057	Population-based	PSG AHI $\geq 15$	Prevalence: 41% men, 22% women.

Table IV.C.1b.: Reasons for Sex differences in OSA

STUDY	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Anatomy and Anthropometric Traits					

Polese <sup>183</sup>	3b	Cross-sectional	Brazil N= 552 women N=450 men	Anthropometrics	Waist circumference and waist-to-height best predicted OSA in women.  Waist-to-height ratio and neck circumferences best predicted mild OSA in men, while BMI was associated with severe OSA.
Cho <sup>167</sup>	3b	Cross-sectional	Korea Suspected OSA  N=2016	Anthropometrics Cephalometry	Men with OSA had increased soft palate length compared to controls  Women with OSA had increased soft palate thickness and nasion angle than controls
Sutherland <sup>168</sup>	3b	Cross-sectional	Chinese and Australian sleep clinic  N=363 200 Chinese 163 Caucasian	Craniofacial features by face photography ethnicity	Women with OSA had different facial features compared to controls, such as greater face width to eye width ratio, and reduced mandibular plane.  Men with OSA had increased mandibular plane angle relative to controls.
Perri <sup>184</sup>	3b	Cross-sectional	Caucasian of European origin  Sleep clinic N=104 OSA N=85 healthy	Surface cephalometry	OSA patients had anthropometric and surface cephalometric phenotypes that differed in comparison with healthy subjects, however, sexual dimorphism levels (i.e. male–female ratios) were broadly similar in the two groups
Lim <sup>175</sup>	3b	Cross-sectional	Korean Clinic N=151	Anthropometrics	Neck circumference predicted OSA in men only, while waist-to-hip ratio predicted OSA in both men and women
Dancey <sup>185</sup>	3b	Cross-sectional	Canada sleep clinic N=3942	Neck circumference	Neck-to-height ratio predicted AHI, accounting for 19% of the variability, more significantly in men.
<b>Upper Airway Anatomy and Function</b>					
Brooks <sup>172</sup>	3b	Cross-sectional	Healthy volunteers  N=77 men N=98 women	Pharyngeal cross-sectional area during quiet breathing using the acoustic pulse technique	The men had a larger change in pharyngeal area with changing lung volume than the women
Segal <sup>171</sup>	2b	Cross-sectional	Chart review for those who have had PSG and	Upper airway length	Men with OSA were found to have longer upper airway length even when normalized to body height compared with OSA women

			CT neck N=24 (15 men, 9 women)		Correlation between upper airway length and AHI
Mohsenin <sup>170</sup>	3b	Cross-sectional	Sleep Clinic AHI $\geq 5$  N=71	Upper airway dimensions using acoustic reflectance while lower jaw was in the resting and retrusive posture	Men tend to have a larger but more collapsible airway during mandibular movement than women
Eckert <sup>186</sup>	3b	Cross-sectional	12 healthy, 8 OSA	Genioglossus electromyogram (GGEMG)	Reductions in GGEMG during REM sleep were not different between OSA patients and control subjects or between sexes.
Malhotra <sup>169</sup>	3b	Case-control	Healthy volunteers age and BMI matched  19 men, 20 women	MRI	Pharyngeal airway length and cross-sectional area, soft palate area, airway volume, was greater in men compared with women.
<b>Obesity and Fat Distribution</b>					
Simpson <sup>187</sup>	3b	Cross-sectional	Western Australian Sleep Health Study  Sleep clinic OSA patients (60 men, 36 women)	Obesity measures using dual-energy absorptiometry	In women, percentage of fat in the neck region and body mass index together explained 33% of the variance in AHI  In men, percentage of fat in the abdominal region and neck-to-waist ratio together accounted for 37% of the variance in AHI
Huang <sup>173</sup>	3b	Cross-sectional	Taiwanese Sleep center >18 yrs N= 2345 patients (339 females)	BMI	AHI was associated with BMI more strongly in men
Harada <sup>174</sup>	3b	Cross-sectional	Japanese Sleep Clinic 271 men, 100 women with OSA	CT scan measured visceral fat area	AHI was independently associated with visceral fat area only in men.
<b>Ventilatory Control</b>					
Sin <sup>176</sup>	3b	Cross-	Canadian	Hypercapnic	Elevated carbon dioxide and older age

		section al	sleep center N=219 (43 women, 176 men; 104 OSA, 115 no-OSA)	ventilatory response test (HCVR)	were significantly correlated with low HCVR in men, while BMI was associated with HCVR in women
Jordan <sup>178</sup>	3b	Cross-sectional	Healthy volunteers 12 men, 11 women at both their luteal and follicular phases	Post-stimulus ventilatory decline (PSVD)	There were no significant differences in PSVD between men and women in either luteal or follicular phases.
Syed <sup>177</sup>	2b	RCT	10 men and 7 women with OSA, with control 10 healthy men and 10 healthy women	Hypoxic ventilatory response augmentation (HVRA)  Ventilatory long-term facilitation (vLTF)	HVRA and vLTF were enhanced in the OSA group compared with control  Sex did not impact any measures  Exposure to intermittent hypoxia during sleep led to a corresponding increase in respiratory events compared with sham exposure, irrespective of sex
Pillar <sup>180</sup>	3b	Cross-sectional	8 normal women and 8 age and BMI-matched men, during stable NREM	Upper airway mechanics  Ventilation  Activation of two dilator muscles, genioglossus and tensor palatini were monitored during loading	Men developed more severe hypopnea in response to identical applied external loads than did women  Men and women had near identical minute ventilation responses to total load, implying no differences in central drive or load response  There were no significant increases in genioglossus or tensor palatini activation in response to loading in either sex
Zhou <sup>181</sup>	3b	Cross-sectional	8 men (25-35 yrs) and 8 women in the midluteal phase of the menstrual cycle (21-43 yrs)	Apneic threshold	In women, induction of a central apnea required an increase in tidal volume by $155 \pm 29\%$ , compared to men with an increase in tidal volume by $142 \pm 13\%$  Similarly, women required greater reduction in PETCO <sub>2</sub> compared to men, to general a central sleep apnea



			Repeated studies in 6 women during the midfollicular phase		There was no difference in the apneic threshold between the follicular and the luteal phase in women.
Jordan <sup>179</sup>	3b	Cross-sectional	11 men and 11 women were matched for severe OSA severity  second group of 12 men and 12 women were matched for body mass index	Loop gain (LG) measured using proportional assist ventilator  Critical closing pressure of upper airway (Pcrit) by progressive CPAP drop technique	In the BMI-matched subgroup, women had less severe OSA during NREM sleep and lower Pcrit, but similar LG compared to men.

#### IV.C.2 Obesity

Obesity is one of the most significant risk factors for sleep disordered breathing.<sup>95,155,188,189</sup> It is estimated that approximately 58% of adult OSA cases are attributable to obesity.<sup>190</sup> OSA is prevalent in 44.6% of men and 13.5% of women aged 30-49 years with body mass index (BMI) of 30-39.9 kg/m<sup>2</sup>, compared to 7% of men and 1.4% of women whose BMI is less than 25 kg/m<sup>2</sup>.<sup>95</sup> It is estimated that the prevalence of OSA in bariatric surgery patients is as much as 60-83%<sup>191,192</sup>, with weight loss after surgery resulting in significant reduction in AHI.<sup>191-194</sup> Furthermore, it has been shown that 10% increase in body weight is associated with an increase in apnea-hypopnea index (AHI) of approximately 30%.<sup>188</sup> Another study showed an increase in BMI by 1 standard deviation was associated with a 3-fold increase in risk of OSA.<sup>90</sup> However, this association with BMI decreases with age, and after age 60 years may be less significant.<sup>95</sup>

According to the U.S. National Health and Nutrition Examination Survey (NHANES), the prevalence of age-adjusted obesity (BMI>30 kg/m<sup>2</sup>) has increased from 30.5% to 42.4%, and of severe obesity (>40 kg/m<sup>2</sup>) from 4.7% to 9.2% since 1999 to 2017 (the prevalence of both obesity and severe obesity was highest in non-Hispanic black adults).<sup>195</sup> BMI correlates with body fat percentage, more so in women, but neither represents adipose tissue distribution nor differentiates between fat and lean tissue.<sup>196</sup> Fat distribution, particularly in the upper body rather than total body is the most important factor contributing to OSA.<sup>197</sup>

The mechanism by which obesity causes and progresses OSA is still unclear. Obesity, specifically central adiposity, increases pharyngeal collapsibility that causes recurrent episodes of upper airway obstruction in sleep apnea through both mechanical and neuromuscular effects.<sup>198-202</sup> Central adiposity increases the mechanical load on the upper airway, and decreases the compensatory neuromuscular response. This is thought to be mediated by adipokines that directly impact central nervous system activity.<sup>198</sup> A study by

Sands et al showed that obese patients with OSA compared to those without OSA have worse pharyngeal collapsibility with less active pharyngeal muscle response.<sup>203</sup> Despite the evidence of a link between obesity and central adiposity with OSA, there is variability in the prevalence and severity of OSA even in markedly obese patients suggesting there are likely other neuro-hormonal, anatomic, and genetic components involved.<sup>198</sup>

Although it is unclear whether a predominant mechanism of OSA in obesity is increased para-pharyngeal tissue, most studies suggest obese patients with OSA have a smaller upper airway cross-sectional area. Some studies suggest this is due to retropalatal fat deposition, while others suggest it is parapharyngeal fat or increased pharyngeal wall thickness that determines the development of OSA in obese individuals.<sup>199,201,204,205 206,207</sup> Recent studies evaluating dynamic changes have shown that parapharyngeal fat is associated with concentric obstruction in the retropalatal area. They have also shown that parapharyngeal fat deposition in the subglosso-supraglottic area is associated with increased OSA severity independent of BMI or neck circumference.<sup>208,209</sup>

Investigators have also shown that caudal traction by the mediastinal and ribcage muscle attachments to the upper airway improves airway patency, suggesting upper airway patency is proportional to lung volumes.<sup>210,211</sup> Caudal traction improves airway caliber by reducing transmural pressure and reducing compliance (i.e. increasing stiffness) of the pharyngeal muscles. In obese individuals, lung volumes are often reduced, which results in reduction in caudal traction, thereby contributing to upper airway collapse.<sup>210</sup>

It is not understood why some obese patients also have hypoventilation. Shimura et al showed higher levels of leptin in hypercapnic OSA patients compared to eucapnic OSA patients, even after correcting for BMI, fat distribution, AHI, and mean oxygen saturation. This suggests that leptin, an adipocyte derived hormone which is elevated in obesity, does not prevent hypoventilation in hypercapnic patients, despite it being a respiratory stimulant. It is possible that these obese individuals prone to hypercapnia have leptin resistance contributing to both obesity and hypoventilation.<sup>212</sup>

Further evidence that obesity is pathogenic in OSA for some individuals, is that weight loss results in marked improvement of OSA.<sup>122,213</sup> Since obesity confers additional cardiovascular risk to OSA patients, weight loss directly benefits cardiovascular health.<sup>214</sup>

#### Obesity as a Contributing Factor for OSA

Aggregate Grade of Evidence: C (Level 1: 5 studies; Level 2: 11 studies; Level 3: 13 studies; Level 5: 2 studies).

**Table IV.C.2 Obesity as a Contributing Factor for OSA**

STUDY	Year	LOE	Study Design	Study Groups/Age /N	Clinical End-point	Conclusion
-------	------	-----	--------------	---------------------	--------------------	------------

Hoffstein <sup>21</sup>	1984	3b	Case-Control	Obese subjects; OSA versus non-OSA N=19 Age=28-68	1. Cross sectional area of pharynx 2. TLC (Total lung capacity) to RV (Residual Volume)	In obese patients with OSA, pharyngeal cross-sectional area is small and varies considerably with change in lung volume (and this change in size with change in lung volume was significantly different in the 2 groups)
Katz <sup>197</sup>	1990	3b	Cross-sectional	Canada Sleep clinic N=123	PSG AHI ≥ 5	External, internal neck circumference and degree of obesity are important predictors of OSA
Mezzanotte <sup>200</sup>	1992	3b	Case-control	Denver Veterans Affairs Hospital OSA and normal controls N=25 Age=40-46 yrs	1. Supraglottic resistance 2. Genioglossal EMG 3. Minute ventilation 4. End tidal CO <sub>2</sub>	Neuromuscular compensation present during wakefulness from genioglossus may be lost during sleep in apneic patients
Shelton <sup>204</sup>	1993	3b	Case-Control	Univ of Virginia Sleep clinic and control from community N=30 Age=23-65	MRI for adipose tissue volume	Adipose tissue is deposited in pharyngeal area in OSA patients, and the volume of this tissue is related to presence and degree of OSA
Young <sup>90</sup>	1993	2c	Cross-sectional	Wisconsin Sleep Cohort study N=602	PSG AHI ≥ 5	1. Prevalence of OSA is 9% in women and 24% in men 2. Male sex and obesity strong risk factors 3. Increase in BMI by 1 SD is associated with 3-fold increase in risk of OSA
Schwab <sup>199</sup>	1995	3b	Cross-sectional	Sleep Clinic at University of Pennsylvania N=68	1. MRI 2. PSG RDI > 15	1. Lateral pharyngeal wall is larger in apneic patients 2. Wall thickness explains the largest part of variance in airway caliber
Peppard <sup>188</sup>	2000	2b	Prospective cohort	Population based N=690	1. Percent change in AHI on PSG 2. Odds of developing moderate to	1. 10% weight gain predicted an approximate 32% increase in AHI, with 6-fold increase in odds of developing moderate to severe SDB 2. 10% weight loss predicted a 26% decrease in AHI.

					severe SDB, with respect to change in weight	
Stanchina <sup>202</sup>	2002	3b	Cross-sectional	Healthy individuals in Boston N=15 Age=24-32	During NREM sleep: 1. Genioglossus EMG 2. Epiglottic pressure 3. Airflow under different conditions	Genioglossus muscle responds well during NREM sleep when hypercapnia is combined with resistive load, but is less responsive to either chemical stimuli (hypoxia, hypercapnia) or inspiratory resistive load alone
Young <sup>189</sup>	2002	2c	Cross-sectional	Sleep Heart Health Study N=5615	In home PSG AHI $\geq$ 15	Male sex, age, BMI, neck girth, snoring and repeated breathing pause frequency were independent, significant correlates of AHI $\geq$ 15
Schwab <sup>206</sup>	2003	3b	Case-Control	Penn Center for sleep disorder and control from community in same neighborhood N=96 Age=24-66	MRI of upper airway	Volume of lateral pharyngeal wall, total soft tissues and tongue larger in OSA than normal subjects
Tishler <sup>155</sup>	2003	2b	Prospective study	Cleveland family study N=286	HST AHI $\geq$ 10	5-year incidence of OSA--7.5% for moderate SDB and 16% for mild to moderate
Shimura <sup>212</sup>	2005	3b	Cross-sectional	Japanese sleep clinic patients N=185 Age=22-72	1.PSG AHI $\geq$ 5 2.CT scan for visceral and subcutaneous fat accumulation 3.Lung function 4.Leptin levels	1. Location of body fat does not contribute to hypoventilation 2. Circulating leptin levels does not maintain alveolar hypoventilation in hypercapnic obese patients with OSA
Kairaitis <sup>210</sup>	2007	5	Animal study	Male NZ white rabbits N=20	Upper airway extraluminal tissue pressure in lateral and anterior pharyngeal walls	Decrease in upper airway collapsibility due to lung volume related caudal traction
Foster <sup>122</sup>	2009	1b	RCT	16 US centers (Overweight	1. BMI 2. Waist and neck	1. The intensive lifestyle intervention (ILI) group lost more weight at 1 year than Diabetes support and education

				/obese with DM and OSA) N=264	circumference 3. HbA1c	2. ILI was associated with an adjusted decrease in AHI of 9.7 events/hr
Flegal <sup>196</sup>	2010	2c	Cross-sectional	NHANES (National Health and Nutrition Examination Survey) population N=5555 Age>20 yrs	BMI	In 2007-2008, the prevalence of obesity was 32.2% in men and 35.5 women
Ashrafian <sup>191</sup>	2012	2a-	SR(with heterogeneity) of cohort studies	Studies with metabolic intervention -33 Studies with lifestyle intervention -24	1.BMI 2.AHI	Metabolic surgeries offer significant reduction in symptoms and measures of OSA by both weight dependent and independent mechanisms
Dixon <sup>193</sup>	2012	1b	Individual RCT (Bariatric surgery vs conventional weight loss)	Australian Hospital-Obese patients (BMI of 35-55) and <6 mths diagnosis of OSA (AHI>20) N=60	1.PSG(baseline to 2 yr change in AHI) 2.Weight 3.CPAP adherence 4.Functional status	In obese patients with OSA, bariatric surgery compared with conventional weight loss therapy did not result in a statistically greater reduction in AHI despite major differences in weight loss
Li <sup>201</sup>	2012	3b	Case-control	Chinese Han population (Otolaryngology Head & neck surgery dept.) N=28	1. MRI 2. Pharyngoscopy under general anesthesia	OSA patients have more fat tissue adjacent to pharyngeal cavity, and the fat-deposition correlated to collapsibility
Peppard <sup>95</sup>	2013	2c	Cross-Sectional	Wisconsin Sleep Cohort Study N=1,520	PSG AHI >=5 and ESS>10	Prevalence of SDB is increasing in the population (relative increases of between 14% and 55% depending on the group)

Chirinos 214	2014	1b	Individual RCT (Randomized to CPAP, weight loss and combined CPAP with weight loss)	Obese, moderate to severe OSA and CRP >1 mg/l N=181	1. CRP 2. Insulin sensitivity 3. Lipid levels 4. Blood Pressure	1. No difference in CRP level reduction 2. Weight loss provided incremental reduction in insulin resistance and TG level when combined with CPAP
Jang 208	2014	3b	Cross-Sectional	OSA patients from Korean Sleep Center N=33 Age=31-54	1. Facial CT 2. DISE (Drug Induced Sleep Endoscopy)	Parapharyngeal fat pad is associated with concentric narrowing of the retropalatal pharynx
Kim 207	2014	3b	Case-control	University of Pennsylvania Center for Sleep and Circadian Neurobiology N=121	MRI upper airway	Increased tongue volume and fat deposition at tongue base in OSA compared to controls
Pahkala 205	2014	1b	RCT	Kuopio University Hospital, Finland N=60	1. PSG 2. CT scan of upper airway	1. Pharyngeal fat pad area was significantly larger and hyoid bone to cervical spine area longer in OSA than habitual snorers 2. Weight loss by lifestyle intervention-based program led to improvement in OSA by reducing both central obesity and pharyngeal fat pad
Sands <sup>203</sup>	2014	3b	Individual Case control studies	Overweight/obese without apnea (AHI<15/hr), overweight/obese with OSA (AHI>=15/hr) and normal weight/non	1. Pcrit (Pharyngeal critical closing pressure) 2. Pharyngeal muscle (greater genioglossus) EMG	Overweight/obese without mod/severe OSA have increased (three times greater) pharyngeal muscle EMG activity during sleep responsiveness.

				apneic N=54		
Ashrafian <sup>194</sup>	2015	2a-	SR (with heterogeneity) of cohort studies (?but also has some RCT)	19 surgical (n=525) and 20 non-surgical (n=825) studies	BMI and AHI before and after intervention	Surgical patients achieved a significant 14 kg/m <sup>2</sup> weighted decrease in BMI with a 29/h weighted decrease in AHI. Non-surgical patients achieved a significant weighted decrease in BMI of 3.1 kg/m <sup>2</sup> with a weighted decrease in AHI of 11/h
Ng <sup>213</sup>	2015	1b	RCT	Prince of Wales Hospital, Hongkong OSA patients with AH $\geq$ 15/hr N=104	1. HST AHI 2. ESS 3. SF-36 (Short Form Health) survey 4. BMI	Lifestyle modification program (LMP) was more effective in reducing AHI from baseline (16.9% fewer events in LMP vs 0.6% more events in control group with usual care).
Peroma <sup>192</sup>	2017	2b	Prospective cohort	Bariatric OSA patients who underwent bariatric surgery N=132	1. PSG (12 months after surgery) 2. BMI 3. Neck and waist circumference	Prevalence of OSA decreased from 71% at baseline to 44% at 12 months after surgery (p < 0.001).
Chen <sup>209</sup>	2019	3b	Cross-sectional	Taiwan Hospital (Otorhinolaryngology dept.) N=41 Age=34-48	1. PSG AHI $\geq$ 5 2. Drug induced Sleep CT 3. BMI 4. Neck circumference	Subglossosupraglottic parapharyngeal fat pad area, independent of BMI and neck circumference influenced severity of OSA.
Hales <sup>195</sup>	2020	2c	Cross-sectional	US census from 2000	BMI	1. In 2017-2018, the age adjusted prevalence of obesity in adults was 42.4% 2. No significant differences between men and women 3. Severe obesity prevalence higher in women at 9.2%

OSA, Obstructive Sleep apnea; BMI, Body mass index; AHI, Apnea-hypopnea index; SD, Standard deviation; PSG, Polysomnography; Pcrit, Pharyngeal critical pressure; EMG, Electromyography; MRI, Magnetic Resonance imaging; CT, Computed Tomography; DM, Diabetes Mellitus

### IV.C.3 Craniofacial Anatomy

There are significant craniofacial differences among OSA subjects when compared to healthy controls. Craniofacial analysis within the literature has primarily been based on cephalometric measurements obtained through lateral plain film cephalograms. Jamieson et al first brought craniofacial morphology into OSA pathophysiology by examining cephalometry on sagittal plain films among 155 OSA patients and 17 non-OSA controls showing that OSA patients had a more acute cranial base angle and greater retroposition of the mandible.<sup>215</sup> Numerous studies have since been published examining a variety of cephalometric measures among OSA patients obtained through lateral cephalograms as well as craniofacial measurements obtained through other modalities including computed tomography (CT) and magnetic resonance imaging (MRI).<sup>216-227</sup> A systematic review and meta-analysis of 25 studies comparing lateral cephalometric measurements in OSA<sup>228</sup> showed the strongest cephalometric measurements associated with obstructive sleep apnea with the least variability and heterogeneity among studies were (see Figure IV.C.3):

- Increased anterior facial height
- Inferiorly and posteriorly positioned hyoid

Additionally, the following cephalometric measurements are suggested to be associated with OSA:

- Short anterior cranial base angle
- Decreased cranial base length
- Shorter maxillary length
- Shorter mandibular length
- Increased mandible rotation
- Retroposition of the mandible
- Decreased posterior facial height

However, there was greater variability and heterogeneity among studies for these measurements with some noting non-significant differences, while others did not measure all values in their cephalometry.<sup>228</sup>

In addition to lateral cephalometry, studies have also looked at transverse craniofacial features. Chi et al compared both sagittal and coronal three-dimensional cephalometry obtained from MRI among OSA patients showing that both an inferiorly positioned hyoid as well as a smaller and shallower mandible was associated with OSA risk.<sup>223</sup> Seto et al measured interdental widths and showed that OSA patients had decreased inter-molar widths as well as higher palatal indexes which suggests a higher, deeper arched palate.<sup>229</sup> Johal et al measured maxillary widths and found that OSA patients did not have shorter interdental widths but did show an association of OSA with increased palatal heights.<sup>230</sup> Kuzucu et al reported that OSA patients have decreased distances between the pterygoid hamuli along the posterior maxilla.<sup>231</sup>



Common craniofacial physical exam findings that are associated with OSA risk include: retrognathia, micrognathia, high arched palate, larger thyromental angles, and shorter thyromental distances.<sup>218,229,232-235</sup> Dental findings may also be suggestive of underlying craniofacial deficiency and include: open bite, overbite, overjet, and proclination of the mandibular incisors.<sup>218,233,236</sup>

BMI is a confounding factor for craniofacial influences on OSA. OSA patients, when compared to BMI matched controls, showed craniofacial differences including a lower positioned hyoid, shorter mandibular body length, retroposition of the mandible, decreased mandibular ramus height, increased lower anterior facial height, and shorter cranial base length.<sup>237-240</sup> Furthermore, comparing OSA among different ethnicities, studies have shown that Asian subjects have shorter cranial base angles, shorter maxillary lengths, shorter mandibular body lengths, greater mandibular ramus lengths, greater maxillary widths, and shallower maxillary depths while Caucasian subjects tend to have higher BMI and larger tongue volumes.<sup>150,241</sup> In contrast, African Americans tend to have larger tongues than Caucasians and were less likely to be brachycephalic, a craniofacial form that is associated with reduced anterior-posterior facial dimensions.<sup>242,243</sup> These studies suggest that craniofacial dimensions are a risk factor for OSA even when controlling for BMI and that different ethnicities may carry different OSA risks based on the contributions of BMI and craniofacial form.

In summary, there is a large body of evidence suggesting there are associated craniofacial factors in OSA. However, there is heterogeneity among studies regarding which specific craniofacial measurements are associated with OSA. All studies were also skewed heavily toward male patients and none focused primarily on female patients, making gender-based differences less clear. Increased anterior facial height and lower hyoid position were the most strongly associated with OSA while there is more mixed evidence regarding cranial base, maxillary, and mandibular measurements. These measurements appear more pronounced on non-obese patients suggesting that craniofacial factors play a greater role in OSA among thin patients.

#### **Craniofacial Anatomy as a Contributor for OSA**

**Aggregate Grade of Evidence: C (Level 3a: 1 study, Level 3b: 21 studies, level 4: 3 studies)**

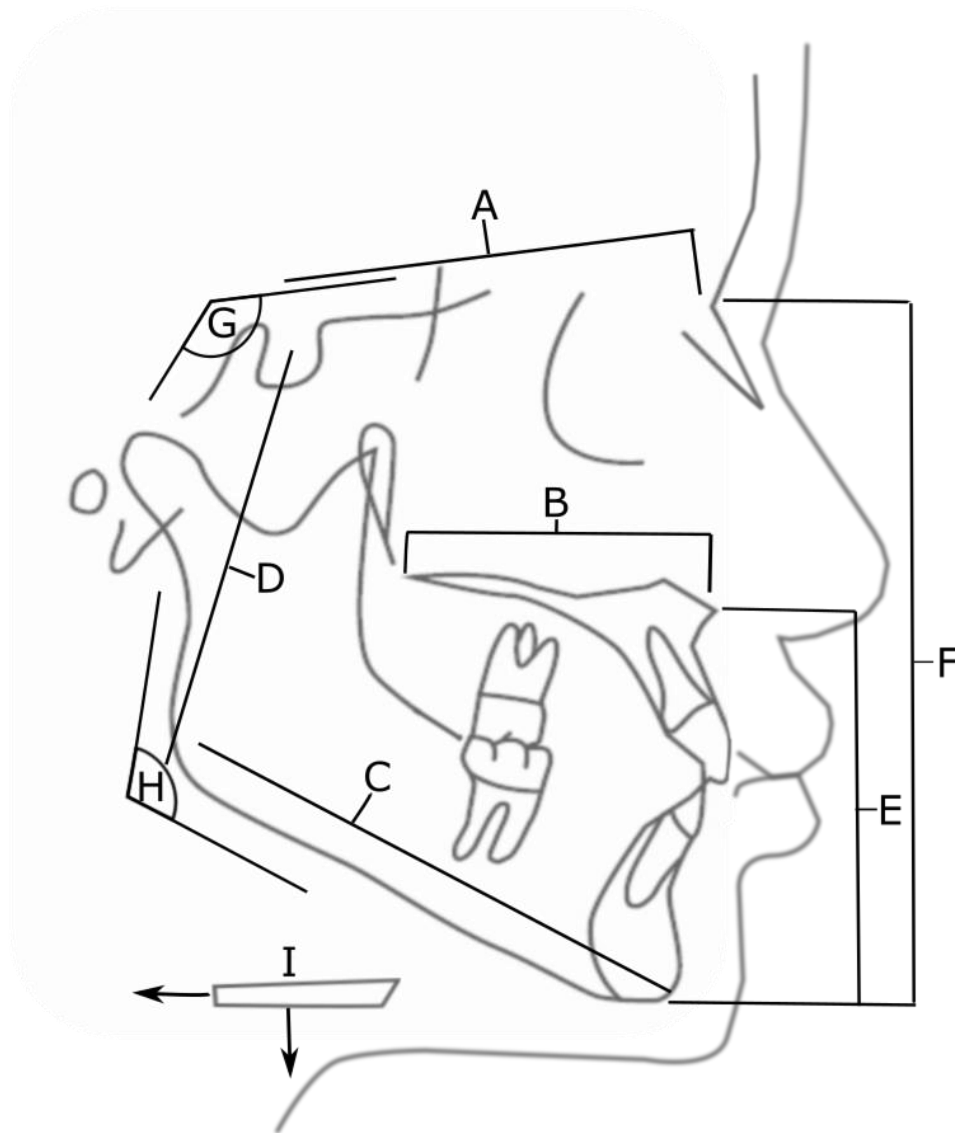


Figure IV.C.3: Common sagittal cephalometric findings associated with OSA: A- decreased cranial base length, B- decreased maxillary length, C- decreased mandibular length, D – decreased posterior facial height, E&F- increased anterior lower facial height and total facial height, G- decreased cranial base angle, H- decreased gonial angle (posterior rotation of mandible), I- inferior and posterior displacement of the hyoid bone.

**Table IV.C.3: Evidence for Craniofacial Anatomy as a Contributor to OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusions
Jamieson et al <sup>215</sup>	1986	3b	Case-Control Study	Adult OSA patients (n = 155) and non-OSA controls (n = 17)	Lateral cephalometry	OSA patients had greater retroposition of the mandible and a more acute cranial base angle.
Hochban and Brandenburg <sup>216</sup>	1994	3b	Case-Control Study	Adult OSA patients (n = 403) and non-OSA controls (n = 88)	Lateral cephalometry	OSA patients had longer facial type, retroposition of the mandible, more dorsocaudally positioned hyoid bone, and an anteroposterior narrowing of the posterior airway space.
Frohberg et al <sup>217</sup>	1995	3b	Case-Control Study	Adult OSA subjects (n=30) and Adult chronic snorers (n = 20)	Lateral cephalometry	OSA group had retroposition of maxilla and lower positions hyoid.
Lowe et al <sup>218</sup>	1995	3b	Case-Control Study	Adult OSA subjects (n=80) and non-OSA controls (n=25)	Cephalometric measurements obtained from CT	OSA subjects have higher upper and lower facial heights, elongated maxillary and mandibular teeth, and proclined lower incisors.
Battagel et al <sup>219</sup>	1996	3b	Case-Control Study	Adult OSA patients (n = 35) and healthy non-OSA controls (n = 24)	Lateral cephalometry	OSA patients had shorter cranial base length, shorter mandibular body length, enlarged soft palate.
Tsai et al <sup>220</sup>	2007	3b	Case-Control Study	Asian adult non-obese severe OSA patients (n = 46) and non-obese, snoring controls (n = 36)	Lateral cephalometry	Severe OSA patients had increased soft palate length and lower positioned hyoid bone compared to snorers.
Riha et al <sup>221</sup>	2005	3b	Case-Control Study	Adult patients with OSA (n = 22) and non-OSA sibling controls (n = 22)	Lateral cephalometry	OSA patients had shorter mandibular body length and lower positioned hyoid compared to non-OSA

						siblings.
Johal et al <sup>230</sup>	2007	3b	Case-Control Study	Adult OSA patients referred for oral appliance (n = 78) and gender matched healthy non-OSA controls (n=78)	Lateral cephalometry	OSA patients the following differences compared to non-OSA controls: low set hyoid, reposition of the mandible (SNB angle), increased soft palate length, thickness, and area.
Gungor et al <sup>224</sup>	2013	3b	Case-Control Study	16 Turkish adults with OSA and 16 Turkish non-OSA controls	Lateral cephalometry	OSA subjects had shorter midface length, protrusion of upper incisors, and lower positioned hyoid bone.
Banhiran et al <sup>225</sup>	2013	3b	Case-Control Study	Adult OSA patients divided into mild (n = 43) and moderate/severe (n = 98) categories compared to non-OSA controls (n = 47)	Lateral cephalometry	Moderate/severe apneics had inferiorly positioned hyoid, shorter anterior cranial base angle, and longer soft palate compared to controls. There were no statistically significant differences between mild OSA patients and non-OSA controls.
Costa et al <sup>226</sup>	2013	4	Case Series	Portuguese Adult OSA patients (n = 171)	Cephalometric measurements stratified by BMI	Caudally positioned hyoid, rotated mandible, and decreased hypopharyngeal airway caliber were associated with increasing AHI severity.
Sakat et al <sup>227</sup>	2016	3b	Case-Control Study	Japanese adult severe OSA patients (n = 30) and BMI matched non-OSA controls (n = 10)	Craniofacial measurements on sagittal CT versus OSA	Retroposition of maxilla (SNA angle), reposition of mandible (SNB angle), inferiorly positioned hyoid, shorter mandibular length were associated with OSA.

Neelapu et al <sup>228</sup>	2017	3a	Systematic review and Meta-analysis	Adult OSA patients and healthy non-OSA controls (n = 26 articles)	Lateral Cephalometry	Significant weighted mean difference with insignificant heterogeneity was found for the following parameters between OSA patients and non-OSA controls: greater anterior lower facial height, lower position of hyoid bone, and decreased pharyngeal airway space. Significant weighted mean difference with significant heterogeneity was found for the following parameters between OSA patients and non-OSA controls: shorter cranial base and angle, decreased mandible, increased mandible rotation, decreased maxillary length, increased tongue area, increased soft palate area, and increased upper airway length.
Chi et al <sup>223</sup>	2011	3b	Case-Control Study	Adult OSA patients(n=55) and healthy non-OSA controls matched for age, sex, and race (n = 55)	Cephalometry based on MRI	Significant mean differences between OSA patients and non-OSA controls: Inferiorly and posteriorly displaced hyoid is associated with OSA.
Seto et al <sup>229</sup>	2001	3b	Case-Control Study	Adult OSA patients (n = 29) and non-OSA controls (n = 21)	Lateral Cephalometry, maxillary width and height on dental exam	OSA patients had shorter mandibular body length and lower positioned hyoid compared to non-OSA patients. On maxillary width, OSA patients showed decreased inter-molar widths and increased palatal index.

Johal et al <sup>222</sup>	2007	3b	Case-Control Study	Adult OSA patients referred for oral appliance (n = 78) and gender matched healthy non-OSA controls (n=78)	Lateral cephalometry	OSA patients had the following differences compared to non-OSA controls: low set hyoid, retroposition of the mandible (SNB angle), increased soft palate length, thickness, and area.
Kuzucu et al <sup>231</sup>	2020	4	Case Series	89 Adult OSA subjects	Craniofacial measurements on CT	Narrower interpterygoid distance and smaller interpterygoid to velopharyngeal length ratio was associated with increasing AHI.
Lam et al <sup>235</sup>	2005	3b	Case-Control Study	Asian adults (n = 164) and White adults(n = 75)	Craniofacial measurements on physical exam obtained with patient sitting upright with head in neutral position	OSA subjects had; larger thyromental angle, neck circumference, BMI and Mallampati scores.
Ferguson et al <sup>237</sup>	1995	4	Case Series	Adult OSA patients divided into three groups based on neck circumference (n = 161)	Lateral cephalometry	Larger neck circumference apneics had lower hyoid bone positions, smaller neck circumference patients had smaller maxillary and mandibular lengths.
Tangugsorn et al <sup>238</sup>	2000	3b	Case-Control Study	Obese OSA patients (n = 57), Non-Obese OSA patients (n = 48), and healthy non-OSA controls (n = 36)	Lateral cephalometry	Significant differences observed between OSA patients and non-OSA controls for the following parameters: Inferiorly positioned hyoid, shorter cranial base, increased gonial angle, increased lower anterior facial height, decreased posterior facial height, large tongue, and large soft palate associated with OSA compared to non-OSA controls. Significant differences observed

						between non-obese and obese OSA patients for the following parameters: shorter mandibles, greater posteriorly displaced and rotated mandibles, greater anterior facial height, decreased posterior facial height.
Paoli et al <sup>239</sup>	2001	3b	Case-Control Study	Obese adult OSA patients (n = 46) and non-Obese adult OSA patients (n = 39)	Lateral cephalometry versus Obesity	Retroposition of mandible (SNB angle), shorter cranial base, shorter mandibular ramus in non-obese OSA patients versus obese OSA patients.
Yu et al <sup>240</sup>	2002	3b	Case-Control Study	Asian adult obese n = (33) and non-obese OSA patients (n = 29) and non-obese, non-OSA snoring patients (n = 13)	Lateral cephalometry	OSA patients have longer soft palates and lower hyoid position compared to snorers.
Lee et al <sup>106</sup>	2010	3b	Case-Control Study	Caucasian adult OSA patients (n = 74) and Chinese adult OSA patients (n = 76)	Lateral cephalometry	Chinese OSA patients had shorter cranial base angle, shorter maxillary length, and shorter mandibular body compared to Caucasians. Chinese OSA patients had greater severity of OSA and lower BMI compared to Caucasians.
Xu et al <sup>241</sup>	2020	3b	Case-Control Study	Icelandic adults (n = 108) and Chinese adults (n = 57) with OSA defined by ODI > 10 matched for age, gender, and ODI	Craniofacial dimensions as measured on MRI	Chinese subjects had bigger ANB angle, shorter mandibular corpus length, longer mandibular ramus length, and a wider and shallower maxilla.

Cakirer et al <sup>243</sup>	2000	3b	Case-Control Study	Caucasian adults (n = 364) and African American adults (n = 165) and BMI <32	Cranial and facial indices measured using calipers	Caucasians with AHI > 5 had lower cranial and facial indices compared to those with AHI <5 while African Americans had similar cranial and facial indices between the same groups.
------------------------------	------	----	--------------------	--	--	--

#### IV.C.4 Genetics

It has been known for over two decades that obstructive sleep apnea aggregates in families. This is shown in the Cleveland Family Study in the United States<sup>244</sup> and also in studies in Scotland<sup>245,246</sup>, Iceland<sup>247</sup>, and Israel<sup>248</sup>. The family aggregation is not explained by obesity<sup>244</sup>. Individuals with a first-degree family member with OSA have approximately a two-fold increased risk of having the disorder<sup>244</sup>. Structural risk factors for OSA—both soft tissues<sup>107</sup> and craniofacial<sup>249,250</sup>—also aggregate in families. Moreover, characteristics of the sleep study in OSA such as apnea-hypopnea index, event duration, and measures of oxygen desaturation during sleep are heritable<sup>251</sup>. Heart rate response to arousal is also heritable<sup>252</sup> as is cardiopulmonary coupling<sup>253</sup>, a measure of sleep depth<sup>254</sup>. Extreme phenotypes have been demonstrated<sup>255</sup>. Individuals with high phenotype risk scores but not OSA are extreme controls, while individuals with low phenotype risk scores but severe OSA are extreme cases. This suggests that there are likely to be rare genetic variants leading to these extreme phenotypes.

While family aggregation has been shown, progress on identifying relevant gene variants has been slow. There are different pathways to disease, such that OSA is a heterogeneous disorder. Obesity plays a major role<sup>90</sup>. There are both soft tissue<sup>107</sup> and craniofacial<sup>249,250</sup> risk factors. There are also multiple physiological traits that determine risk for the disorder<sup>36,256,257</sup>. The initial approach to identifying genes was linkage analysis<sup>258,259</sup>, and most recently linkage has been used in conjunction with sequencing data to narrow windows of analysis to improve power,<sup>260</sup> and applied to quantitative traits related to overnight oxygen saturation. However, candidate gene studies have been underpowered and largely have not been replicated<sup>261</sup>. More recently, progress has been made using genome-wide association studies<sup>262-264</sup> or use of a special SNP panel<sup>265</sup>.

Genome-wide studies<sup>262-264</sup> have largely focused on quantitative variables obtained from the sleep study to characterize sleep-disordered breathing that were shown to be heritable<sup>251</sup>. Based on primarily the Hispanic Community Health Study, a variant in GPR83 was found to be associated with AHI<sup>262</sup>. However, the variant in GPR83 was specific to Caribbean background and data were unavailable for replication.

A larger genome-wide association study using data from multiple cohorts in both men and women looked for association with AHI in NREM sleep and REM sleep independently<sup>264</sup>. While there were several suggestive associations, only one reached genome-wide significance, i.e., a variant in *RAI1* with NREM AHI in males (but not females)- a gene that has also been shown to show sexual dimorphism for cardiac disease and for adiposity traits in model organisms. Haploinsufficiency of the gene is implicated in the Smith-Magenis syndrome<sup>266</sup>. Individuals with this syndrome have craniofacial abnormalities and circadian rhythm disturbances<sup>267</sup>. Notably, significant sex by gene variants for sleep apnea were detected for multiple genes, supporting the importance of considering sex-specific genetic effects.



Studies have also focused on association with oxygen desaturation measures. Variants in the interleukin 18 receptor and hexokinase genes were associated with oxygen desaturation measures during sleep<sup>268</sup>. This is based on a large multi-ethnic sample with replication. A later linkage-sequencing study also implicated multiple rare variants in the GTPase-activating protein *DLC1*<sup>260</sup> with oxygen desaturation measures, with findings replicated in independent samples and supported by multiple sources of information, including genetic variants, gene expression, and methylation.

Admixture mapping has also been applied<sup>269</sup>. This is an analytical tool that is applied to recently admixed populations where ancestors came from isolated continents<sup>270</sup>. Novel variants were associated with AHI as well as oxygen desaturation measures. Notably, local African ancestry was shown to have a protective effect on the AHI and associated with shorter duration events. A region on chromosome 18q21 that included 20 variants on *NARS/FECH* was associated with both AHI and percentage time  $\text{SaO}_2 < 90\%$ , with 12 associations that replicated in independent cohorts. Evidence for a causal role in OSA was supported by finding that *FECH* expression was increased in association with lower nocturnal  $\text{SaO}_2$ . These findings suggested a novel for iron metabolism in pathway influencing OSA phenotypes.

A genome-wide study that specifically examined both common and rare variants by whole genome sequencing<sup>263</sup> identified novel rare variants associations with measures of desaturation, i.e., *ARMCX3*, *MRPS33*, *C16orf90*.

A Phenome-wide association study (PheWAS) study sought to determine support for previously identified variants<sup>271</sup>. A PheWAS seeks association between gene variants, the diagnosis of OSA in the electronic health record<sup>272</sup> or association with quantitative traits from sleep studies done clinically<sup>271</sup>. For most of the previously described gene variants, there was no evidence of association with OSA diagnosis or with quantitative traits from the sleep study with findings from community-based cohorts which underwent standardized sleep apnea phenotyping.

Thus, studies of genetic variants in OSA are evolving. Recently, large biobanks have begun analyzing genetic associations with snoring and ICD-based OSA diagnosis.<sup>273</sup> Future advances are expected as data from large clinical cohorts are combined with data from more deeply phenotyped research studies that also include data on gene function (expression, methylation).

## V. Pathogenesis of OSA

### V.A Contributory Factors for OSA: Anatomy

#### V.A.1 Nasal Airway

The nasal cavity accounts for half of upper airway resistance.<sup>274</sup> Several recent reviews indicate that nasal obstruction from septal deviation, inferior turbinate hypertrophy, nasal valve collapse, polyposis and/or inflammation is common in patients with sleep disordered breathing, but the role of nasal obstruction as a contributing factor in the pathogenesis of obstructive sleep apnea (OSA) and sleep disordered breathing (SDB) is controversial.<sup>275-277</sup>

#### Pathophysiology

Nasal breathing serves important physiological functions, including humidification, heating and filtration of inhaled air.<sup>274</sup> Nasal breathing is often decreased during sleep due to increased nasal mucosal congestion when recumbent<sup>278</sup> and circadian variation in nasal resistance.<sup>279,280</sup> Several physiologic mechanisms have been reported to explain the relationship between nasal airflow and breathing during sleep.

The first of these mechanisms is the Starling resistor model, which views the upper airway as a hollow tube<sup>281,282</sup> with a collapsible pharyngeal segment bounded by the nasal and tracheal airways. The flow of air through the collapsible pharynx is influenced by upstream nasal, downstream tracheal, and transmural pressure gradients. For example, when the nasal airway is obstructed, nasal resistance increases. In order to maintain stable maximum airflow from the nasal passages through the pharynx, the pharyngeal pressure drops, leading to increased collapsibility at the pharynx. In addition, by Pouseille's Law, airway resistance is proportional to the length of the airway and inversely proportional to the fourth power of the radius.<sup>283</sup> Thus, even a small change in nasal airway patency can significantly increase airway resistance.<sup>284</sup>

The second reported mechanism is high nasal resistance promoting mouth breathing, which can predispose patients to SDB. During sleep, airway resistance is higher when breathing through the mouth compared to through the nose.<sup>285</sup> Mouth breathing during sleep has been associated with up to 2.5 times higher airway resistance.<sup>286</sup> This increased airway resistance can narrow the pharyngeal lumen leading to more frequent obstructive events, as demonstrated by Fitzpatrick et al who found worsening of OSA severity when mouth breathing compared to nose breathing.<sup>286</sup> Similarly, another study demonstrated that jaw opening during sleep, associated with posterior tongue displacement, is greater in patients with OSA than those without OSA.<sup>287</sup>

A third proposed factor is the nasal ventilatory reflex, which states that decreased nasal airflow can result in decreased activation of nasal receptors leading to decreased pharyngeal muscle tone and central respiratory drive and worsening of apneic events.<sup>288,289</sup> This is supported by studies that have applied local anesthetic to nasal mucosa in healthy subjects resulting in significant increase in central and obstructive sleep apnea events.<sup>290,291</sup>

Finally, it is postulated that nitrous oxide (NO) may play a role in maintaining pharyngeal muscle tone, spontaneous breathing, and sleep regulation.<sup>292</sup> NO is produced in the nasal cavity and sinuses, and the total inspired quantity of nitrous oxide varies with nasal airflow.<sup>293</sup> Despite these studies, its role in OSA development and regulation is still not completely understood.<sup>294</sup>

#### Clinical Relationship Between Nasal Obstruction and SDB

Several studies demonstrate that patients with SDB have increased rates of nasal obstruction. A recent study by Magliulo et al<sup>275</sup> demonstrated that 70% of patients with OSA had nasal obstruction confirmed by clinical examination and rhinomanometry. Another study of 49 OSA patients found that 45% reported subjective nasal obstruction.<sup>295</sup>

Data are conflicting regarding patients with nasal obstruction and risk of SDB. A study of 541 snorers who underwent posterior rhinomanometry concluded that nasal obstruction is an independent risk factor for OSA.<sup>296</sup> The Wisconsin Sleep Study showed that those with self-reported nocturnal congestion had a threefold increased incidence of habitual snoring.<sup>69</sup> Conversely, a study by Miljeteig et al<sup>297</sup> divided 683 patients referred for polysomnography into three groups based on severity of nasal resistance and found no difference in apnea or snoring severity between groups.

#### Allergic Rhinitis and SDB

A recent consensus statement on allergic rhinitis (AR) summarized the literature regarding the relationship between AR and sleep. The authors concluded that AR is associated with snoring, sleep fragmentation and decreased sleep quality of life, and successful treatment of AR can improve sleep

quality. Many small studies with polysomnogram (PSG) data indicate that AR is associated with worsening PSG parameters, in terms of sleep efficiency, oxygen desaturation, and sleep architecture metrics, although results are mixed between studies.<sup>6</sup>

#### Nasal Packing and SDB

Clinical studies and studies of normal subjects with artificially-induced nasal obstruction have consistently demonstrated a greater predisposition to SDB.<sup>298-303</sup> These studies obstructed the nasal cavity via the following measures: inflated balloons<sup>302</sup>, petroleum jelly-soaked gauze<sup>299-301,303</sup> or tape around the nares<sup>298</sup>. Likewise, many studies have shown that the application of nasal packs during the management of epistaxis and post-nasal surgery can result in worsening sleep quality and increased apneic episodes.<sup>304-309</sup>

In summary, the literature suggests that nasal obstruction, either artificially- or disease-induced, is associated with sleep symptoms such as snoring and poor quality sleep. Among those with SDB, nasal obstruction is highly prevalent. There does not appear to be a direct correlation between degree of nasal obstruction and SDB severity by AHI or oximetry.

#### **Relationship between Nasal Obstruction and OSA**

Aggregate Grade of Evidence: C (level 2b studies: 1, level 3b studies: 20, level 4 studies: 9, level 5 studies: 7)

#### **V.A.2 Pharyngeal Airway**

Anatomic sites of airway obstruction during sleep have been assessed with a variety of techniques including pharyngeal pressure catheters placed at various sites in the upper airway (UA), cine fluoroscopy, sleep endoscopy, computerized tomography, and MRI.<sup>310</sup> Airway pressure monitoring studies have demonstrated that airway collapse is confined to or initiated in the oropharynx in the majority of patients.<sup>311</sup>

#### Pharyngeal Shape

Several studies have identified differences in the pharyngeal lumen shape between patients with sleep disordered breathing (SDB) and those without. Compared with normal subjects, habitual snorers have a generalized narrowing of the pharyngeal region.<sup>312</sup> A normal pharyngeal lumen is elliptical in shape, with the long axis in the lateral dimension.<sup>313</sup> In contrast, the lumen of snorers and obstructive sleep apnea (OSA) patients is circular or elliptical, with the long axis in the anterior-posterior dimension.<sup>313</sup> This change in shape is likely a result of obstruction from the lateral pharyngeal walls. Studies have shown that the pharyngeal shape changes are most prominent at the retropalatal level<sup>199</sup> and during sleep.<sup>314</sup>

In addition to shape, the length of the pharynx may also play an important role in OSA. Cephalometric studies demonstrate that lengthening of the pharynx is related to the severity of OSA.<sup>315</sup> Similarly, increased rate of OSA in men may be primarily a result of a longer pharyngeal airway compared to female counterparts.<sup>316</sup>

#### Soft Tissue Factors

Several soft tissue factors can lead to pharyngeal narrowing or pharyngeal shape changes in adults with OSA including hypertrophy, inflammation, and/or edema.<sup>310</sup> Thickened and collapsible lateral pharyngeal walls are a well-recognized factor in the pathophysiology of adult OSA.<sup>199,206,317</sup> MRI studies confirm soft tissue enlargement in the UA leading to reduced size of the retropalatal airway, specifically, in OSA patients compared to control subjects.<sup>199,206,318</sup> Lateral pharyngeal wall edema and enlarged lateral pharyngeal fat pads have been identified via tissue specimens and imaging in OSA patients.<sup>199,204,319-321</sup> Lateral pharyngeal wall edema has been hypothesized to result from multiple factors including vascular congestion, inflammation secondary to trauma from snoring vibration, or pulmonary hypertension from recurrent hypoxic pulmonary artery vasoconstriction.<sup>322</sup> An MRI study demonstrated that thickness of the lateral pharyngeal wall musculature was the predominant anatomic factor causing lateral airway narrowing in OSA patients as opposed to enlarged pharyngeal fat pads.<sup>199</sup>

Soft palate changes have also been noted in OSA patients including thickening of the soft palate<sup>323</sup> and enlargement of the uvula.<sup>324</sup> Soft palate position may also be related to OSA severity.<sup>310,315,317,325</sup>

Many studies have assessed the relationship of tonsil size (both grade and volume) and OSA. The most recent study by Jara et al studied an adult heterogeneous OSA population in the United States and found that increasing tonsil grade was significantly associated with increasing OSA severity with adjusted data showing that every increase in tonsil grade as measured by the Brodsky classification system correlated to an increase in AHI of approximately 14 events/hour.<sup>326</sup> They also found that tonsil grade was more predictive of OSA than tonsil volume indicating that the actual tonsil volume may be less important than the proportion of space that they occupy within the oropharynx.<sup>326</sup> Other groups have studied the relationship between subjective (grade) or objective (volume/weight) tonsil evaluation and AHI and reported a trend toward significance<sup>327</sup> or a significant association<sup>317,328-333</sup>. To further support the role of enlarged tonsils in OSA, Camacho et al performed a systematic review and meta-analysis of 17 studies evaluating tonsillectomy alone as treatment for adults with enlarged tonsils and OSA. They found a significant improvement in OSAS with a mean AHI decrease from 40.5 to 14.1 and a mean ESS decrease from 11.6 to 6.1.<sup>334</sup>

Other groups have assessed a relationship between narrow fauces (posterior pillars of the tonsillar fossae) and OSA. Anatomically, the width of the fauces is generally defined as the diameter of the palatopharyngeal arch from oral view using a pharyngeal grading system.<sup>234</sup> The grading system is based on the location of the palatopharyngeal arch intersection with the tongue. The presence of narrowing at the fauces has been previously defined as impingement of greater than 25% of the pharyngeal space by the peritonsillar tissues, excluding the tonsils.<sup>317</sup> Studies report that the presence of narrow fauces is predictive of the presence of OSA.<sup>234,331,333</sup> Woodson et al found that smaller endoscopically measured oropharyngeal spaces were correlated with elevated AHI.<sup>335</sup>

In summary, the oropharynx is a common location of airway obstruction in subjects with SDB, and many anatomic factors have been identified as potential contributors to SDB including pharyngeal lumen size/shape, thickened lateral pharyngeal walls, elongated soft palate, enlarged uvula and/or tonsils, and narrow fauces.

### Oropharynx Anatomy and OSA

Aggregate Grade of Evidence: C (level 2a studies: 1, level 3b studies: 22, level 4 studies: 4, level 5 studies: 3).

### V.A.3 Craniofacial Structure

Craniofacial differences are present among OSA patients when compared to non-apneic controls.<sup>228</sup> There are few studies examining how these anatomic factors contribute to the mechanism of upper airway collapse. A comprehensive review of the literature revealed 5 studies evaluating craniofacial measurements and physiologic factors that contribute to adult OSA. Sforza et al measured critical closing pressures (Pcrit) among 54 OSA patients and compared this to cephalometry. They found an association between greater Pcrit values (indicative of greater airway collapse) and longer soft palate length as well as with an inferiorly positioned hyoid.<sup>336</sup> Genta et al studied 34 Japanese-Brazilian men with OSA and also found an association between greater Pcrit values with an inferiorly and posteriorly positioned hyoid.<sup>337</sup> Verin et al compared upper airway resistance and cephalometry among OSA patients, snorers, and controls and found that an inferiorly and posteriorly positioned hyoid was associated with greater upper airway resistance among OSA patients.<sup>338</sup> Watanabe et al examined pharyngeal closing pressures at the velopharynx (VP) and oropharynx (OP) among 54 Japanese OSA patients.<sup>339</sup> Patients were stratified to either VP or VP+OP collapse which were the only two types of collapse patterns seen in their study. They found that patients with multilevel collapse (VP+OP) had a lower BMI, smaller maxillary and mandibular lengths, and a lower positioned hyoid compared to non-apneic controls while patients with only VP collapse had a larger BMI, and a lower positioned hyoid compared to non-apneic controls. No other cephalometric differences were seen among the groups. Comparing upper airway collapse among different ancestry background groups, Schorr et al compared cephalometric measurements and Pcrit among Japanese-Brazilian OSA (n=39) patients and Caucasian-Brazilians (n=39).<sup>340</sup> They found both groups had similar Pcrit values but that Japanese-Brazilian group had smaller cranial base angles, mandibular and maxillary lengths while the Caucasians-Brazilian group had greater BMI, tongue volume, and tongue length.

The studies to date suggest an association between several cephalometric values including: low hyoid position, short maxillary and mandibular length, short anterior cranial base length, and acute cranial base angles with higher Pcrit values, increased upper airway collapsibility, and greater upper airway resistance. Craniofacial influences may also be associated with increased risk for multilevel upper airway collapse. Furthermore, comparing OSA patients of different ethnic backgrounds have shown similar Pcrit values despite differences in BMI, tongue size, and craniofacial metrics suggesting that all these factors play a role in upper airway collapse. However, most studies had relatively small sample sizes. Therefore, larger studies controlling for BMI, soft tissue size, are needed to better elucidate the contributions of craniofacial metrics to OSA pathophysiology.

### V.A.4 Upper Airway Fat

Tongue fat appears to play an important role in linking obesity and OSA risk. The pattern of fat deposition rather than BMI may be more indicative of OSA risk. There are only a handful of studies examining this relationship. Brennick et al showed that among obese rats, there was greater deposition of fat within the tongue compared to non-obese rats.<sup>341</sup> Kim et al. compared MRIs of the tongue between 90 obese OSA patients and compared them to 31 obese subjects without OSA. They showed that tongue fat volume calculated from the MRI was greater among the obese OSA patients versus obese subjects without apnea.<sup>207</sup> Wang et al. compared tongue fat volumes among 67 obese OSA

patients before and after a medical or surgical weight loss regimen.<sup>342</sup> A reduction of tongue fat through weight loss correlated strongly with AHI reduction and was the primary upper airway mediator of the relationship between reductions in weight and AHI.

Although there is evidence that tongue fat is increased in obesity and that greater tongue fat is associated with OSA, how tongue fat influences the pathophysiology of OSA has not been well studied. There are no studies examining how tongue fat influences upper airway resistance, tongue muscle properties, and upper airway collapsibility. Future studies are needed to better understand the role of tongue fat in the pathogenesis of OSA.

## V.B Contributory Factors for OSA: Physiology

### V.B.1 Ventilatory Stability/ Loop Gain

“Loop gain” is an engineering term used to define the stability (“low” loop gain) or instability (“high” loop gain) of a negative feedback control system<sup>179,343-346</sup>. Control of breathing is a negative feedback system in which chemoreceptors (e.g. in the carotid body; “controller”) and the lung (“plant”) try to maintain a PaCO<sub>2</sub> at roughly 40 mmHg. In this setting, a high loop gain leads to large fluctuations in carbon dioxide. A useful analogy comes from consideration of room temperature in which a negative feedback control system tries to maintain a relatively constant temperature, for example at 20 C. If the thermostat (controller) were too sensitive, then any minor drop in room temperature would start the furnace (plant) and thus cause frequent fluctuations in room temperature. By analogy the CO<sub>2</sub> levels are expected to fluctuate markedly if the chemoreceptors are too sensitive to minor CO<sub>2</sub> perturbations. The temperature analogy is also helpful when one considers a plant that is too powerful. For example, if the room temperature were to fall to 19C and in response the thermostat were to blast the temperature to 40 C, then the result would be major oscillations in room temperature. By analogy, if an individual were to respond to an increase in PaCO<sub>2</sub> from 40 to 45 mmHg with hyperventilation lowering the PaCO<sub>2</sub> down to 10 mmHg, then major fluctuations in CO<sub>2</sub> would occur<sup>347-349</sup>. Mathematically, loop gain is defined as the response (i.e. the increase in PaCO<sub>2</sub> or room temperature) divided by the disturbance (i.e. initial drop in PaCO<sub>2</sub> or room temperature): a major response to a minor disturbance (i.e. *high* loop gain) is considered destabilizing.

Loop gain has several components which are sometimes referred to as controller and plant gain. Controller gain can be thought of as chemoresponsiveness, which is the amount that ventilation changes for a given change in CO<sub>2</sub>. High loop gain due to a high controller gain (i.e. overly sensitive thermostat in the analogy above) can be seen in clinical situations such as high altitude or heart failure<sup>350,351</sup>. Plant gain on the other hand is a measure of the efficiency of CO<sub>2</sub> excretion (i.e. too powerful furnace, or a very small room in our analogy), and is the amount that CO<sub>2</sub> changes for a given change in ventilation<sup>352,353</sup>. High loop gain due to high plant gain is clinically less common, but situations in which the lung volume decreases (e.g. supine sleep)<sup>354</sup> can increase overall loop gain. Another component which is less often discussed is the so-called mixing gain which is a function of circulatory time and other factors<sup>355</sup>. The overall loop gain is the product of the various gains, principally determined by the controller and the plant.

Clinically a high loop gain can express itself as periodic breathing e.g. at high altitude<sup>356</sup>, or in congestive heart failure<sup>357,358</sup>. In OSA, the contribution of loop gain to OSA pathogenesis is less clear, but many believe it plays an important role<sup>344-346,359,360</sup>. Several studies have shown an elevated loop gain in OSA

compared to controls, although some debate is ongoing as to whether the observed abnormalities are a cause or effect of the disease<sup>361</sup>. In theory, a high loop gain could manifest as fluctuations in output from the central pattern generator in the brainstem. This output would affect the diaphragm as well as the upper airway muscles. When output from the central pattern generator is at its nadir, the upper airway would be vulnerable to collapse in those who are anatomically susceptible based on the low output to the upper airway dilator musculature. Of note, because loop gain is considered a response over a disturbance, a spontaneous respiratory event e.g. a hypopnea may be destabilizing if a patient experiences a marked response to such a respiratory disturbance. Some have coined the expression “apnea begets apnea” based on the self-perpetuating nature of the control system abnormalities.

From a surgical perspective, elevated loop gain may be important since it has been found to predict failure of sleep apnea surgeries, at least in some cases<sup>362-364</sup>. Given the variability in OSA pathogenesis, the strategy to improve pharyngeal anatomy/collapsibility surgically may be prone to failure in the subset of patients in whom OSA is primarily caused by abnormal ventilatory control<sup>36</sup>. In theory, interventions lowering loop gain (e.g. acetazolamide or oxygen)<sup>365,366</sup> may be considered rescue strategies for such patients who have residual OSA despite upper airway surgical intervention<sup>367</sup>.

It may be possible to quantify loop gain directly from in-lab or home sleep studies.<sup>368-370</sup> More research is needed to test on reproducibility and if prospective measurements of loop gain allows identification of surgical responders, and if loop gain lowering interventions may be useful for (a subset) of patients with an incomplete response to sleep apnea surgeries.

### V.B.2 Neuromuscular Control

Patients with obstructive sleep apnea (OSA) typically have an anatomical compromise of the upper airway predisposing them to pharyngeal collapse.<sup>206,371</sup> Through protective upper airway dilator muscle reflexes, the activity of the muscles is increased during wakefulness in OSA compared to matched controls.<sup>200</sup> However, with sleep-onset there is loss of upper airway motor output leading to collapse of the vulnerable airway.<sup>372</sup> Brainstem control of upper airway dilator muscles has been the subject of intense investigation.<sup>373,374</sup>

The upper airway in humans includes 23 pairs of muscles which support its patency. The genioglossus is an important, major upper airway dilator muscle. The genioglossus is a large muscle comprising the substance of the tongue and maintains patency of the retroglossal airway.<sup>349,353,375</sup> Notably, the hypoglossal motor nucleus in the medulla of the brainstem provides the input for the genioglossus muscle. Additionally, it is a complex muscle which has both tonic activity (i.e., present throughout the respiratory cycle) as well as phasic activity (i.e. bursts with each inspiration).<sup>376,377</sup> The phasic activity of the genioglossus is thought to be representative of other phasic upper airway dilator muscles; thus the study of genioglossus motor control may be reflective of other phasic muscles (e.g. palatoglossus and hyoglossus).<sup>378</sup> The genioglossus has been shown to have state dependence i.e. has activity during wakefulness which is attenuated at sleep onset. Indeed, there is a marked fall in genioglossus activity at the alpha-theta transition which may be important in compromising pharyngeal mechanics.<sup>372,379,380</sup> Lastly, hypoglossal nerve stimulation has been shown to be effective for treatment of OSA.<sup>381-383</sup> Hypoglossal nerve stimulation likely acts via tongue protrusors from the medial branch of the hypoglossal nerve i.e. largely through genioglossal stimulation.<sup>384-386</sup>

The genioglossus' behavior is influenced by a number of important factors:

- a) A negative pressure reflex (NPR) exists whereby a sub-atmospheric (negative inspiratory or suction) pressure leads to a robust activation of the genioglossus muscle.<sup>387-389</sup> This reflex is thought to be important in modulating upper airway patency since it serves to restore pharyngeal patency in the face of a collapsing perturbation. The NPR has been mapped using neurochemical techniques and is thought to be regulated by cholinergic systems in the brainstem, e.g. the peri-obex region which is heavily cholinergic.<sup>390</sup> Pharmacological studies indicate manipulation of the cholinergic system may influence this reflex, recognizing the complex role of acetylcholine throughout the brain and systemically.<sup>391</sup> A recent pilot study showed potential benefits of the combination of oxybutynin and atomoxetine on the apnea hypopnea index.<sup>392</sup> A larger multicenter trial recently completed enrollment, but the results are not yet reported (NCT03919955).
- b) Chemoreflexes are also thought to be important since hypoxia and CO<sub>2</sub> may serve to activate the genioglossus muscle. CO<sub>2</sub> stimulation may have differential effects on the diaphragm vs. the upper airway dilator muscles. The combination of negative pressure plus CO<sub>2</sub> may serve synergistically to activate the upper airway dilator muscles.<sup>202,316,393-395</sup>
- c) The arousal response also has a major impact on genioglossus activity. When an individual awakens from sleep, there is a robust activation of the genioglossus muscle which is thought to restore pharyngeal patency.<sup>289,396,397</sup> On the other hand, if sleep is maintained following upper airway collapse, then the accumulation of respiratory (CO<sub>2</sub>, negative pressure) stimuli may activate pharyngeal dilator muscles and thus restore pharyngeal patency without the need for repetitive arousal from sleep. Thus, the arousal threshold has become an important therapeutic target, but its manipulation is a double-edged sword: drugs (hypnotics, sedatives) which delay arousal may allow some stabilization of breathing but may also lead to severe hypoxemia prior to arousal.<sup>398-400</sup> Consequently, patient selection becomes a critical factor in designing appropriate studies.<sup>376,401</sup> At present, no randomized controlled trials have shown improvements in hard clinical outcomes, despite some potential physiological benefits.
- d) A number of neurochemical influences can affect hypoglossal motor control. Monosynaptic projections from various brain structures have been shown in animal models including locus coeruleus (adrenergic), lateral dorsal/pedunculopontine tegmentum (cholinergic), and hypothalamic (orexiner) and raphe neurons (serotonergic) among others. These neurochemical targets may allow augmentation of hypoglossal motor output and effect genioglossus activity.<sup>374,402-404</sup>

Other muscles are likely important, e.g. the tensor palatini which receives its output from the mandibular branch of the trigeminal nerve.<sup>405-408</sup> Of note, the neurobiology and control of different motor nuclei differ substantially from the standpoint of premotor inputs and neuropharmacology. The tensor palatini has primarily tonic activity (i.e. constant activity throughout the respiratory cycle) and thus has less in the way of respiratory modulation than the genioglossus or other phasic muscles.

Neuromuscular control is an important factor in upper airway patency. It can potentially be manipulated either pharmacologically or via electrical stimulation. Further study regarding underlying mechanisms and clinical trials focused on hard outcomes would be encouraged.

### **V.B.3 Arousal Threshold**



The arousal threshold refers to the propensity to wake up from sleep. Some people have a low arousal threshold meaning they wake up easily – or with minimal stimulus – whereas other people have a high arousal threshold – meaning they require considerable stimulus to arouse.<sup>396,409</sup> The arousal threshold is thought to be important in OSA pathogenesis since roughly 1/3 of OSA patients are found to have a low arousal threshold and may wake up prematurely.<sup>397,410</sup> The accumulation of respiratory stimuli during stable sleep has been shown to activate pharyngeal dilator muscles, which in many patients is both necessary and sufficient to stabilize breathing.<sup>393,395</sup> Stanchina et al.<sup>202</sup> showed a combination of carbon dioxide and negative intrapharyngeal pressure could lead to robust activation of the upper airway dilator muscles during stable sleep. Thus, patients with a low arousal threshold may not experience sufficient accumulation of respiratory stimuli to activate the dilator muscles and thus repetitive airflow limitation is predicted. In contrast patients with a high arousal threshold could get sufficient magnitude of respiratory stimuli for adequate duration to activate pharyngeal dilator muscles and thus stabilize breathing. The observation that even severe OSA patients have some periods of spontaneously occurring stable breathing has yielded discussion regarding potential therapies to manipulate the arousal threshold.<sup>397,411</sup> Some view the arousal threshold as a double-edged sword. That is, therapies to increase the arousal threshold may be beneficial if this intervention allows dilator muscle activation and stabilization of breathing.<sup>412</sup> On the other hand, an agent which raises the arousal threshold may yield substantial hypoxemia and hypercapnia which could impact end organ function.<sup>413</sup> Thus, agents such as sedatives or hypnotics which can raise the arousal threshold may be beneficial at least in theory for select patients. However, the existing data suggest that any improvements in apnea which occur with these agents are relatively modest.<sup>399,400</sup> Consequently, combinations of therapy may well be required to eliminate apnea using this approach.<sup>414</sup> Another consideration is that these pharmacological agents have risks and benefits like all interventions and thus carefully performed outcome-based studies will be needed before any clinical recommendations can be made.

One strategy which has been discussed in the context of combination therapies is that of surgical rescue. Some data suggest that a low arousal threshold may be a risk factor for failure of upper airway surgery to achieve a surgical cure.<sup>362,363,415</sup> In theory, the elevation of the arousal threshold may be a therapeutic target whereby an agent (e.g. trazodone or eszopiclone) could be used to elevate the arousal threshold in patients who have residual apnea e.g. following uvulopalatopharyngoplasty.<sup>398</sup> Such strategies would need to be studied carefully in the context of patient reported outcomes and hard endpoints.

Regarding the assessment of the arousal threshold, several techniques have been employed. The ‘gold standard’ measurement was considered either esophageal manometry or intrapharyngeal pressure catheter measurements.<sup>409</sup> However, Edwards et al. reported a regression formula which has considerable value in estimating the arousal threshold using clinically accessible data, such as the degree of hypoxemia, the arousal index, the apnea hypopnea index, and the occurrence of apneas vs. hypopneas.<sup>410</sup> Using this approach more than 60% of the variance in the arousal threshold can be predicted. In addition, Sands et al. developed a technique using signal processing of the polysomnographic recordings which can also estimate the arousal threshold using clinically available data.<sup>369</sup>

One important consideration is the fact that the arousal threshold is not a fixed trait but rather a dynamic phenomenon which changes with treatment.<sup>416,417</sup> For example, many patients with a high arousal threshold with sleep apnea will experience a lowering of arousal threshold over time on therapy. This observation leads to speculation that the elevated arousal threshold seen in some OSA patients

may be an adaptive phenomenon whereby elevation in the arousal threshold may allow the accumulation of respiratory stimuli, which could ultimately help to improve sleep to some extent.<sup>417</sup> Another extension of this logic is that CPAP treatment in some patients may lead to insomnia since the lowering of arousal threshold may be associated with worsening of sleep quality.<sup>418</sup> The same argument could be made for non-CPAP therapies as well. Further study is clearly required to determine the importance of arousal threshold in OSA pathogenesis and its importance in treatment of OSA both adjunctively (e.g. with CPAP)<sup>419</sup> and as a rescue strategy (e.g. following failed UPPP).

## VI. Diagnosing OSA

### VI.A Questionnaires for OSA

In-laboratory polysomnography (PSG) is the gold standard for diagnosis of OSA, but can be expensive, inconvenient, and difficult to access. This is particularly true when considering screening in the general population or perioperatively. Additionally, PSG may not be readily available to all clinicians. Validated questionnaires are easily administered in all clinical settings and offer a rapid point-of-care tool to risk-stratify patients. Equally important is the assessment of the quality of life (QOL) impairment in patients with OSA as physiologic sleep measures are poor descriptors of QOL.<sup>420</sup> Patient-reported outcome assessment is especially important when evaluating changes in QOL after treatment or over time. This review is based on more than 20 studies with reports ranging from level 1a to 2b (overall grade C evidence) (Table VI.A.1).

#### VI.A.1 Screening Questionnaires

Clinical questionnaires validated to assess the risk of OSA include the Berlin,<sup>421</sup> STOP-BANG,<sup>422</sup> and NoSAS<sup>423-427</sup> screening tools.<sup>428-430</sup> The Berlin questionnaire contains a total of 10 items divided into 3 categories: 1) daytime sleepiness 2) BMI and hypertension, and 3) height and weight, where a positive score in 2 categories indicates high risk for OSA.<sup>421</sup> The STOP-BANG is an 8-question survey including 4 subjective and 4 objective items with each positive item contributing 1 point for a maximum score of 8 points.<sup>422</sup> The NoSAS is a newer tool developed in 2016 in sleep clinic patients and includes 5 items assessing mostly objective data such as BMI and neck circumference with scores ranging from 0 to 17 and a score  $\geq 8$  denoting high risk for OSA.<sup>425</sup>

A clinically useful questionnaire that assesses OSA risk should be able to identify patients with clinically relevant OSA ( $AHI \geq 15$ ), where an increased risk of cardiopulmonary disease and mortality has been established (true positive)<sup>431-433</sup> and minimize the incorrect labeling of individuals without clinically relevant OSA as having the condition (false positive). The Berlin and STOP-BANG questionnaires have sensitivities of 82% and 94% respectively,<sup>421,422</sup> while the NoSAS has a sensitivity of 65-90% in identifying sleep clinic patients with clinically relevant OSA.<sup>423-430</sup> Additionally, the Berlin and STOP-BANG questionnaires have reported sensitivities of 79-82% and 91% respectively among surgical patients and 89% and 88% respectively among general clinic patients.<sup>421,422</sup> The ROC curves for the STOP-BANG at different OSA severity classes are shown in Figure 1. Using a STOP-BANG cutoff score of 5 had the best combination of sensitivity and specificity for moderate-severe OSA ( $AHI \geq 15$ ) in sleep (60%, 72%) and surgical populations (45%, 56%).<sup>422</sup> At this cutoff score, the STOP-BANG also has the best combination of sensitivity and specificity for severe OSA ( $AHI \geq 30$ ) in sleep clinic patients (66%, 66%) and surgical patients (56%, 74%).<sup>422</sup>

### V1.A.2 Functional Status Measures and Health-Related Quality of Life Questionnaires

It is well documented that, in general, patients with sleep apnea have limitations in daily activities and poorer QOL than normal healthy subjects.<sup>434</sup> Thus, assessment of functional status and QOL is highly important to evaluate in addition to physiologic sleep measures when assessing OSA patients. Validated functional status and QOL measures most used in the clinical and research settings include the Epworth Sleepiness Scale (ESS),<sup>435</sup> Sleep Apnea Quality of Life Index (SAQLI),<sup>436-440</sup> Functional Outcomes of Sleep Questionnaire (FOSQ),<sup>436,440,441</sup> and the Pittsburgh Sleep Quality Index (PSQI).<sup>442</sup>

Questionnaires can be divided into functional status questionnaires, which measure the ability to perform daily activities, and health-related QOL questionnaires, which capture the unique personal response to not being able to perform routine activities. Functional status questionnaires include the PSQI, ESS, and FOSQ. The PSQI was developed to measure multiple components of sleep quality and includes questions on sleep propensity (likelihood of falling asleep) over the past 1 month.<sup>442</sup> The ESS assesses likelihood of falling asleep across 8 scenarios on a scale of 0-3 with a higher score indicating more sleepiness.<sup>435</sup> The psychometric properties of the FOSQ suggest that it offers a unique self-report measure of functional status as it relates to the impact on daily activities.<sup>441</sup> The FOSQ has 30 questions in 5 domains: activity, vigilance, intimacy and sex, general productivity, and social outcome.<sup>436,440</sup> The SAQLI is a health-related QOL questionnaire that is disease-specific and includes questions focused on evaluating functioning across daily aspects of life affected by poor sleep.<sup>436,438-440</sup> The SAQLI includes 35 questions across 4 domains: daily functioning, social interactions, emotional functioning, and symptoms and can be combined with a fifth domain that assesses negative impacts of treatment.<sup>436,438-440</sup>

When evaluating functional status and health-related QOL surveys, it is important to consider the reliability, validity, and responsiveness of these measures. Reliability of these questionnaires were reported in terms of internal consistency, the degree to which individual items on a survey are related as measured by Cronbach's  $\alpha$ , and test-retest reliability, the consistency of scores for the same patient over time measured by the intraclass correlation coefficient (ICC). All 4 of the QOL questionnaires demonstrated acceptable internal consistency ( $\alpha \geq 0.7$ )<sup>435,442</sup> while the FOSQ and SAQLI demonstrated excellent internal consistency ( $\alpha \geq 0.9$ ).<sup>436,437,439,441</sup> The FOSQ and SAQLI demonstrated excellent test-retest reliability (ICC  $\geq 0.9$ )<sup>438,439,441</sup> while this test characteristic was not clearly assessed for the ESS and PSQI. Four studies assessed this factor in the ESS, but results of the test and retest populations are not comparable due to a long time interval between administrations or due to a change in test conditions.<sup>435</sup> The data on test-retest reliability in the PSQI is limited to 3 studies that either did not include patients with a sleep disorder or had a long time interval between test administration.<sup>442</sup> Measurement error, the error in a measurement that is not due to true differences in the construct being measured, was not reported for any questionnaire.

The validity of QOL and functional status instruments were measured in terms of convergent, divergent, and discriminative validity. Convergent validity measures the degree to which scores of a questionnaire correlate with other questionnaires with related constructs. The PSQI had strong correlations ( $r \geq 0.7$ ) with other questionnaires measuring sleep quality.<sup>442</sup> The SAQLI showed moderate correlations ( $0.3 \leq r < 0.7$ ) with related domains of general health-status questionnaires such as the 36-item Short Form (SF-36) and the Global QOL Scale.<sup>436-440</sup> The FOSQ showed moderate correlations with related domains of the SF-36 and the Sickness Impact Profile.<sup>436,440,441</sup> The ESS showed a moderate correlation to the

Maintenance Wakefulness Test and poor correlation ( $r \leq 0.3$ ) with the Multiple Sleep Latency Test, both of which are objective daytime sleepiness measures.<sup>435</sup> PSG measures (AHI, minimum O2 saturation) were either poorly or not significantly correlated with any of the questionnaires.<sup>435,436,440,442,443</sup>

Divergent validity assesses whether instruments with unrelated constructs in fact have low correlations with one another. Divergent validity was reported for the PSQI, which had non-significant correlations with unrelated instrument measures of bladder dysfunction and psychopathology.<sup>442</sup> No other questionnaires reported on this measure. Discriminant validity refers to the ability of an instrument to distinguish between patients with sleep disorders and normal subjects. Discriminant validity was present for the ESS, PSQI, and FOSQ, but was not reported for the SAQLI.<sup>435,441,442</sup>

The ability of an assessment to measure change over time is important especially if the instrument is used in treatment effectiveness studies. The SAQLI and FOSQ both demonstrated the ability to detect change over time after treatment initiation.<sup>436-439</sup> Both showed large effect sizes ( $d \geq 0.8$ ) after CPAP treatment in patients with OSA.<sup>436,438</sup> In one study, the FOSQ showed a larger improvement in scores in patients who used >4 hours of CPAP nightly while there was no difference in scores for the SAQLI.<sup>436</sup> (Table VI.A.1) An important limitation of this review is the heterogeneity of studies reporting on both screening and QOL questionnaires. Definitions of hypopnea and method used to detect OSA varied between studies resulting in wider ranges of reported sensitivity and specificity. Additionally, several studies used translated versions of the questionnaires that were not previously validated in those languages. Another limitation is the lack of high-quality validation studies for all QOL measures. Future research should focus on using uniform definitions of hypopnea/apnea and utilize the gold standard PSG in validating OSA questionnaires and to further validate QOL surveys to estimate their adequacy as an outcome measure.

Overall, validated clinical questionnaires may be used as a tool to identify patients at high risk for OSA, monitor response to treatment, or evaluate the functional status and health-related QOL of patients. To screen patients suspected of sleep apnea in the clinic setting or preoperatively before planned surgery, we recommend using the STOP-BANG questionnaire with a cutoff score of 5. To measure functional status related to OSA, we recommend using the FOSQ as it is disease-specific, assesses the effect of sleepiness comprehensively across domains, and has the strongest evidence for all measurement properties.

#### Questionnaires for OSA Screening and QOL Evaluation

**Aggregate Quality of Evidence:** C (1a: 5 studies, 1b: 4 studies, 2a: 3 studies, 2b: 7 studies; Table 2)

**Benefit:** Validated questionnaires offer a simple, point-of-care option for screening in patients suspected of OSA to prioritize patients needing confirmatory testing with PSG and evaluating functional status and health-related QOL in patients with OSA.

**Harm:** Minimal to none.

**Cost:** No financial burden to patients. Clinic and patient time required to administer and collect responses are required.

**Benefits-Harm Assessment:** Preponderance of benefit over harm. Low risk of harm with additional PSG testing in patients with false positive responses. Low risk that a false negative response may lead to delay in testing and further management.

**Value Judgments:** Validated screening questionnaires can enhance diagnosis and treatment rates of OSA in a cost-effective manner. Validated functional outcomes and health-status QOL questionnaires serve as important tools in evaluating the behavioral and functional consequences of OSA and in measuring response to treatment.

**Recommendation Level:** Recommendation

**Intervention:** The STOP-BANG using a cutoff score of 5 may be used to screen patients for OSA and identify those needing confirmatory sleep study testing. The FOSQ may be used to assess both functional outcomes in patients with OSA and to follow change in status over time and after treatment.

**Table VI.A.1. Evidence for the role of validated screening, functional outcomes, and health-related QOL questionnaires for OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Nagappa <sup>422</sup>	2015	1a	Systematic review	1. Sleep 2. Surgical 3. General	Meta-analysis of STOP-BANG	STOP-BANG is adequate screening tool in sleep and surgical patients.
Abrishami <sup>428</sup>	2010	1a	Systematic review	1. Sleep 2. Surgical 3. General	Meta-analysis of OSA screening questionnaires	STOP-BANG & Berlin had similar sensitivities. Studies were heterogenous.
Amra <sup>429</sup>	2017	1a	Systematic review	1. Sleep 2. Surgical 3. General	Comparison of OSA screening questionnaires.	STOP-BANG had best sensitivity and specificity for moderate OSA
Chiu <sup>430</sup>	2016	1a	Systematic review	1. Sleep 2. Surgical 3. General	Meta-analysis of STOP-BANG, Berlin, STOP, & ESS	STOP-BANG most accurate at detecting OSA at all severity cutoffs.
Senaratna <sup>421</sup>	2017	1a	Systematic review	1. Sleep 2. Surgical 3. General	Meta-analysis of Berlin questionnaire	Berlin is adequate screening tool in sleep and surgical patients. Studies were heterogenous.
Billings <sup>436</sup>	2014	1b	Cohort	Sleep clinic	Comparing psychometric properties of SAQLI & FOSQ	Both demonstrate responsiveness to CPAP treatment. Comparable reliability and validity.
Coutinho <sup>423</sup>	2019	1b	Cohort	Sleep Clinic	Validate NoSAS as screening tool for OSA	NoSAS is an adequate screening tool for OSA

Marti-Soler <sup>425</sup>	2016	1b	Cohort	General	NoSAS derivation & validation. Comparison to other screening questionnaires.	NoSAS adequate screening tool compared with Berlin and STOP-BANG.
Silva <sup>440</sup>	2016	1b	Cohort	1. OSA 2. non-OSA	Comparison of SAQLI, FOSQ, SF-36 scores with OSA severity	Scores correlate w/OSA severity in females, but not males. All demonstrated convergent validity.
Abma <sup>443</sup>	2016	2a	Systematic review	1. Sleep 2. Non-sleep	Review of quality of PROMs for OSA	Most PROMs not adequately assessed due to low quality studies.
Mollayeva <sup>442</sup>	2016	2a	Systematic review	1. Sleep 2. Non-sleep	Meta-analysis of psychometric properties of PSQI	Adequate reliability & validity as QOL tool
Kendzierska <sup>435</sup>	2013	2a	Systematic review	1. Sleep 2. Non-sleep	Overview of psychometric properties of ESS	Convergent validity lower than expected. Few high quality studies.
Rong <sup>427</sup>	2019	2b	Cohort	1. OSA 2. primary snorers	Comparison of NoSAS to STOP-BANG	NoSAS and STOP-BANG had comparable sensitivities and ROC
Flemons <sup>438</sup>	2002	2b	Cohort	OSA	Evaluate psychometric properties of SAQLI	Adequate properties as a QOL instrument
Flemons <sup>437</sup>	1998	2b	Cohort	1. OSA 2. primary snorers	Derivation of SAQLI	Excellent internal consistency and responsiveness is present.
Hong <sup>424</sup>	2018	2b	Cohort	Sleep clinic	Comparison of NoSAS to STOP-BANG, ESS, & Berlin	NoSAS is an adequate screening tool for OSA
Lacasse <sup>439</sup>	2002	2b	Cohort	Sleep clinic	Validation of SAQLI	Adequate validity and responsiveness to treatment.
Peng <sup>426</sup>	2018	2b	Cohort	1. OSA 2. primary snorers	Comparison of screening questionnaires	NoSAS, Berlin, & STOP-BANG have comparable sensitivities
Weaver <sup>441</sup>	1997	2b	Cohort	1. Sleep 2. Non-sleep	Derivation of FOSQ	FOSQ had excellent reliability & demonstrated known-groups validity.

ESS = Epworth Sleepiness Scale, PSQI = Pittsburgh sleep quality index, FOSQ = functional outcomes sleep questionnaire, SAQLI = sleep apnea quality of life index, PROMs = patient reported outcomes measure

Table 2. Functional Status and Health-Related QOL Questionnaires

	Internal Consistency <sup>A</sup>	Test-retest reliability <sup>B</sup>	Measurement Error	Convergent Validity <sup>C</sup>	Divergent Validity	Discriminative Validity	Responsiveness
ESS	Acceptable	**	--	Poor to Moderate	--	Present	--
PSQI	Acceptable	**	--	Strong	Present <sup>D</sup>	Present	--
SAQLI	Excellent	Excellent	--	Moderate	--	--	Present
FOSQ	Excellent	Excellent	--	Moderate	--	Present	Present

-- not reported; \*\* not clearly assessed; <sup>A</sup> Based on Cronbach's  $\alpha$  values: Unacceptable ( $\alpha < 0.5$ ), Poor ( $0.5 \leq \alpha < 0.6$ ), Questionable ( $0.6 \leq \alpha < 0.7$ ), Acceptable ( $0.7 \leq \alpha < 0.8$ ), Good ( $0.8 \leq \alpha < 0.9$ ), Excellent ( $\alpha \geq 0.9$ ); <sup>B</sup> Based on Intraclass Correlation values: Poor (ICC  $< 0.5$ ), Moderate ( $0.5 \leq \text{ICC} < 0.75$ ), Good ( $0.75 \leq \text{ICC} < 0.9$ ), Excellent (ICC  $\geq 0.9$ ); <sup>C</sup> Reported as degree of correlation with questionnaires measuring related constructs: Poor ( $r < 0.3$ ), Moderate ( $0.3 \leq r < 0.7$ ), Strong ( $r \geq 0.7$ ); <sup>D</sup> Indicates presence of poor or non-significant correlations with unrelated questionnaires

## VI.B Screening for OSA

### VI.B.1 Primary Care Setting

Although a myriad of screening instruments exist for obstructive sleep apnea (OSA), the majority of the literature centers around four main questionnaires: (1) Berlin, (2) STOP, (3) STOP-BANG, and (4) Epworth Sleepiness Scale. The Berlin Questionnaire is composed of 10 items grouped into three domains to assess snoring severity, excessive daytime sleepiness, and history of hypertension or obesity.<sup>444</sup> The STOP Questionnaire is constructed in an even simpler format, with four yes or no questions corresponding to snoring, tiredness, observation (of apneas), and blood pressure.<sup>445</sup> The STOP-BANG questionnaire consists of the STOP items with an additional four questions for body mass index, age, neck size, and gender.<sup>446</sup> Lastly, the Epworth Sleepiness Scale (ESS) is an 8-item questionnaire asking participants to rate their likelihood of falling asleep during various daytime activities.<sup>447</sup> The convenience and low cost of questionnaires are well suited for the primary care setting.<sup>448-451</sup> The four questionnaires mentioned above are the most widely discussed with respect to OSA screening in primary care and have each been validated on multiple occasions across a wide range of demographics.

Several studies have evaluated the differences in sensitivity and specificity between screening questionnaires.<sup>421,452,453</sup> A recent multicenter prospective study enrolled 812 patients diagnosed with type 2 diabetes, obesity, heart failure, or resistant hypertension who completed multiple OSA screening questionnaires. Following a diagnostic sleep study, the STOP-BANG questionnaire (with "high-risk" set to 3 points or above) had a greater sensitivity than either the Berlin Questionnaire or the OSA50 questionnaire (95%, 75%, and 88% sensitivity respectively). After increasing the "high-risk" threshold to

5 or above on the STOP-BANG, it also had a greater specificity (69% compared to 38% for the Berlin and 21% for the OSA 50).<sup>454</sup>

The largest comparative study to date was a retrospective review by Silva et al. that included 4,770 patients from the Sleep Heart Health Study. For this cohort, the STOP-BANG had the highest sensitivity for moderate-to-severe OSA (87%). The 4-Variable screening tool (sex, BMI, blood pressure, snoring) had the highest specificity.<sup>455</sup> A separate cohort study of 212 patients in Beijing similarly found the STOP-BANG questionnaire to be of superior predictive value than the ESS, Berlin or STOP questionnaires.<sup>456</sup> Additionally, a recent meta-analysis confirmed the STOP-BANG possessed the greatest pooled sensitivity. The ESS questionnaire, however, was shown to have markedly higher pooled specificity compared to the STOP, STOP-BANG, and Berlin.<sup>430</sup> Although the STOP-BANG is the most sensitive screening questionnaire, the evidence is unclear as to which questionnaire is the most specific. In the primary care setting, a screening test with higher sensitivity may be preferred to ensure adequate diagnostic investigation and mitigate sequelae of untreated OSA.

There is very little evidence on the benefits of widespread screening for OSA in asymptomatic adults without comorbidities.<sup>428</sup> A 2017 systematic review supervised by the United States Preventive Services Task Force analyzed 110 studies with over 46,000 patients and found no information relating OSA screening to health outcomes.<sup>457</sup> To adequately assess the impacts of screening, a randomized trial assigning patients to screening and control groups- with adequate sample size and follow-up- would be required. With respect to costs, the general sentiment behind the creation of the STOP and STOP-BANG questionnaires was to simplify previous instruments and reduce the burden of measurement on survey participants.<sup>446,456</sup> Although there is no direct evidence describing the financial burden of implementing OSA screening, reports of other screening instruments have suggested minimal burden and disruption of the clinical workflow.<sup>445,458-460</sup>

In summary, the literature with respect to OSA screening in the primary care setting remains ambiguous. Support exists for the superior sensitivity and performance of the STOP-BANG as a screening tool, but no evidence has shown the long-term health impact of screening compared with no screening. Although the harms associated with screening appear limited, the precise cost-utility tradeoff of screening in the primary care setting has yet to be assessed.

#### Widespread Screening for OSA in the Primary Care Setting

Aggregate Quality of Evidence: C: (Level 2a: 6 studies, Level 2b: 6 studies, Level 2c: 1 study).

Benefit: Screening for OSA has the potential for earlier diagnosis and treatment which may be associated with reduction of symptoms.

Harm: Potential for unnecessary diagnostic testing. There is very little evidence on the benefits of widespread screening for OSA.

Cost: Low cost of screening and time required for screening.

Benefits-Harm Assessment: Balance of benefit and harm.

Value Judgments: Primary care screening may enhance diagnosis and treatment rates at the population level, although no evidence has shown the long-term health benefits of screening.

Recommendation Level: Option to screen for OSA in asymptomatic patients.

Intervention: Screening for OSA in the primary care setting is optional. Further studies are required to determine the long-term health impact of widespread screening and health risk prevention, which is not proven. STOP-BANG questionnaire has consistently higher sensitivity compared with other screening questionnaires.



Table VI.B.1: Evidence for Screening for OSA in the Primary Care Setting

Study (Authors)	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical Endpoints	Conclusion
Jonas et al. <sup>457</sup>	2017	2a	SR	110 studies (1994 -2016)	Association of OSA screening with health outcomes	Insufficient evidence for OSA screening among asymptomatic adults; no studies were found comparing screening to no screening.
Abrishami et al. <sup>428</sup>	2012	2a	SR	10 studies (1988 – 2008): 1 retrospective review, 9 prospective cohorts	Sensitivity and specificity values of the Berlin, STOP, STOP-BANG, Wisconsin, and SASDQ questionnaires	Reviewed OSA screening questionnaires show inconsistent predictive values.
Kee et al. <sup>454</sup>	2018	2b	Prospective multicenter cohort	Patients with diagnosed comorbidities (diabetes, obesity, resistant hypertension, and heart failure) and a baseline home sleep study who completed the STOP-BANG, Berlin, and OSA50 questionnaires	Sensitivity and specificity values	STOP-BANG had the best sensitivity for screening purposes in patients with diabetes, obesity, resistant hypertension, and heart failure.
Silva et al. <sup>455</sup>	2011	2b	Prospective multicenter cohort	Sleep Heart Health Study (SHHS) Participants who completed baseline PSG, 4-Variable Screening	Sensitivity and specificity values	STOP-BANG had the highest sensitivity while the 4-Variable had the highest specificity for moderate-to-severe OSA.

				Tool, STOP, STOP-BANG, and ESS questionnaires		
Luo et al. <sup>456</sup>	2014	2b	Prospective single center cohort	Patients both with and without OSA who completed the STOP, STOP-BANG, Berlin and ESS questionnaires	Sensitivity and specificity values	STOP-BANG had the highest sensitivity among the reviewed questionnaires.
Tan et al. <sup>453</sup>	2017	2b	Prospective multicenter cohort	Singapore Health Study 2012 (SH2012) participants who completed home sleep study and Berlin questionnaire	Sensitivity and specificity values	Berlin questionnaire possesses a high sensitivity and NPV for severe OSA.
Senaratna et al. <sup>421</sup>	2017	2a	SR and meta-analysis	35 studies (2008 – 2016): 26 prospective cohorts, 5 retrospective reviews, 4 cross-sectional analyses	Pooled sensitivity and specificity values of the Berlin questionnaire	Limited evidence to suggest utility of Berlin questionnaire in general population
Chiu et al. <sup>430</sup>	2017	2a	SR and meta-analysis	108 studies (1999 – 2016)	Pooled sensitivity and specificity values of Berlin, STOP, STOP-BANG, and ESS questionnaires	The STOP-BANG questionnaire is the most accurate tool for detecting mild, moderate, and severe OSA.
Tan et al. <sup>452</sup>	2016	2b	Prospective multicenter cohort	Singapore Health Study 2012 (SH2012) participants who completed home-based sleep study	Sensitivity and specificity values	STOP-BANG has moderate sensitivity and high NPV for moderate-to-severe OSA.

				and STOP-BANG questionnaire		
--	--	--	--	-----------------------------	--	--

### VI.B.2 Perioperative Setting

The prevalence of Obstructive Sleep Apnea (OSA) among surgical patients is 7–10% and approximately 70% in patients undergoing bariatric surgery.<sup>461-463</sup> The diagnosis of OSA is associated with increased risk for postoperative complications in general and increases cardiac adverse events,<sup>464-467</sup> respiratory failure, oxygen desaturation, and intensive care admission.<sup>466,468-476</sup> Moreover, these complications have increasingly resulted in malpractice lawsuits.<sup>477,478</sup> Data about postoperative mortality is mixed but generally shows no increased 30-day mortality, which is thought to be due to increased monitoring in this group of patients.<sup>467,471,479-484</sup> Identifying at risk patients is critical to perioperative planning given the increased risk of postoperative cardiopulmonary complications with OSA.<sup>485</sup>

As most surgical patients with OSA are undiagnosed, the Society of Anesthesia and Sleep Medicine Guidelines on preoperative screening and preparation of patients with OSA strongly recommends screening for OSA in the preoperative period.<sup>485</sup>

Screening will prompt practitioners to create a safer postoperative management plan, such as extended monitoring, the use of continuous positive airway pressure (CPAP) therapy, using less opioids and sedatives, and more regional anesthesia techniques whenever applicable. It also helps in deciding on the eligibility for ambulatory procedures.<sup>486</sup>

Sleep study testing is the standard for OSA diagnosis. However, it is not cost-effective or practical to screen patients using PSG in the perioperative setting due to its high-cost and inconvenience of requiring an overnight stay. There are often logistical issues of coordinating sleep study testing and surgery scheduling timelines. However, the preoperative assessment is a cost effective opportunity to screen for and select high risk patients who can then be offered sleep study and treatment for OSA.<sup>487</sup> In order to facilitate OSA detection, several predictive screening tools have been proposed. Using the questionnaires and clinical criteria is easy, inexpensive, and has an acceptable sensitivity. However, they should not be used as a diagnostic tool without confirmatory sleep study testing given the low to moderate specificity and the potential for misdiagnosis.<sup>445,463,485,488</sup>

#### Screening Components

It is best if the patient is seen a few weeks before surgery, so a proper diagnosis and treatment are initiated. Patients can be screened by their primary care physician, by their surgeon, or by the anesthesia care provider in the pre-anesthesia clinic. Screening may take place in the hospital, or on the day of the procedure.

#### Preoperative Screening

Preoperative evaluation of a patient for potential identification of OSA should include: medical history, screening questions, and physical exam. A focused review of history includes prior airway difficulty, hypertension, cardiovascular problems, craniofacial abnormalities, and any previous sleep studies. A physical examination should include evaluation of the airway, neck circumference, tonsil size, and tongue volume.<sup>489</sup>

## Screening Methods in the Perioperative Setting

Several pre-operative screening questionnaires are available. Only STOP-Bang, Berlin, American Society of Anesthesiologists (ASA) checklist, and perioperative sleep apnea prediction have been evaluated and validated in surgical populations.<sup>490</sup>

### STOP-Bang (SB) questionnaire

The questionnaire builds on the STOP questionnaire (snoring, tiredness, observed apnea, high BP) and adds the BMI, age, neck circumference and gender criteria (BANG). Each item in the questionnaire is scored as (yes/no) and is scored as (0-1) for a total score of 8. The STOP-Bang questionnaire has a high sensitivity where a score of  $\geq 3$  score is associated with an increased risk of moderate-to-severe OSA.<sup>469,491,492</sup> and a higher rate of perioperative complications,<sup>468,470,472,474-476,484,485,493-495</sup> On the other hand, the specificity ranges from 30- 43%, which may yield high false positive rates and may increase unnecessary testing.<sup>445</sup> The addition of serum  $\text{HCO}_3^-$  of at least 28 mmol/l to the STOP-Bang score improves the specificity but decreases its sensitivity.<sup>446</sup>

### Perioperative Sleep Apnea Prediction Score (P-SAP)

The P-SAP score includes the following: snoring, thyromental distance  $< 6$  cm, type II diabetes mellitus, high blood pressure, Mallampati class III or IV,  $\text{BMI} > 30 \text{ kg/m}^2$ , age  $> 43$  years, neck circumference  $> 40$  cm, and male gender. A diagnostic threshold P-SAP score of 2 or higher showed excellent sensitivity (0.939) but low specificity (0.323), whereas a P-SAP score of 6 or higher had low sensitivity (0.239) but excellent specificity (0.911).<sup>463</sup>

### American Society of Anesthesiologists (ASA) checklist

ASA OSA scoring checklist combines physical characteristics, history of apparent airway obstruction, and somnolence.<sup>496</sup> Physical characteristics include signs and symptoms suggestive of the diagnosis of OSA ( $\text{BMI} > 35$ , craniofacial abnormalities, neck circumference). Symptoms of apparent airway obstruction include: loud snoring, frequent snoring, observed pauses in breathing during sleep, and awakening from sleep with choking sensation. Somnolence is present if the patient reports fatigue despite adequate "sleep" or falling asleep easily in a non-stimulating environment. The ASA checklist was validated in surgical population with a moderate sensitivity (72-87%) which was comparable to both the STOP and Berlin questionnaires.<sup>488</sup>

**The Berlin Questionnaire**<sup>444</sup> This assessment tool focused on some risk factors for OSA. It includes questions about snoring, daytime sleepiness and fatigue. Patients are also asked to provide information on history of hypertension, age, weight, height, sex, neck circumference, and ethnicity. Its sensitivity is 68.9-87.2 in surgical patients<sup>488</sup>

**DES-OSA Score** is a morphologic OSA prediction Score; it takes into account the Mallampati score (MP), thyroid chin distance (DTC), BMI, neck circumference, and sex.<sup>497</sup> Patients with MP class II scores 2 points, and 3 points if they are class III or IV. They are awarded points based on their DTC, neck circumference, and BMI. Patients who score 5 or above are likely to have OSA diagnosis.

### Oxygen Desaturation Index (ODI)

Using overnight oximetry has been found to have a very good correlation with AHI on PSG in surgical patients.<sup>498</sup> ODI is defined as the number of desaturation episodes per hour. The ODI  $> 10$  demonstrated a sensitivity of 93% and a specificity of 75% to detect moderate and severe OSA.

### Screening for OSA in Perioperative Patients

**Aggregate Quality of Evidence:** C (level 2a: 1 study; level 2b: 11 studies; Level 3b: 1 study; level 4: 1 study).

**Benefit:** Preoperative screening for OSA can identify high-risk patients in order to guide perioperative management and prioritize patients needing sleep study testing.

**Harm:** Time required to implement screening system and the potential for over testing patients for sleep apnea (false positives on screening).

**Cost:** Low costs associated with screening patients for OSA using questionnaires but an increase in indirect costs for additional testing and monitoring may occur.

**Benefits-Harm Assessment:** Strongly favors screening for the diagnosis of OSA in the preoperative setting due to effects on perioperative management.

**Value Judgments:** The overall quality of evidence favoring preoperative screening of OSA solely for the planning of the perioperative period is generally strong.

**Recommendation Level:** Recommendation to screen for OSA in the preoperative setting.

**Intervention:** Patients who are undergoing surgery may benefit from preoperative screening for OSA. Based on the evidence reviewed, the STOP-BANG questionnaire is recommended as a screening tool due to its high sensitivity.

**Table VI.B.2 Association of OSA with Worse Postoperative Outcomes**

Perioperative screening using questionnaires and outcome							
Study	Year	LOE	Objective	Study design	Study groups	Clinical Endpoints	Conclusions
Khiani <sup>499</sup>	2009	3b	If the diagnosis of OSA using Berlin questionnaire will result in postoperative oxygen desaturation that needs supplemental oxygen following sedation for gastrointestinal procedures.	Cross sectional study	Berlin Questionnaire in patients undergoing sedation for GI procedures.	Rates of transient hypoxia, defined as a pulse oximetry measurement less than 92% requiring an increase in supplemental oxygen .	No significant difference in rate of transient hypoxia between the high- and low-risk groups (odds ratio 1.48; 95% CI, 0.58-3.80). suggesting that the majority of patients with no diagnosis of OSA can undergo conscious sedation for routine endoscopic procedures with standard monitoring

							practices.
Vasu et al. <sup>476</sup>	2010	2b	To determine whether high risk -OSA (HR-OSA) $\geq 3$ on preoperative Stop-Bang (SB) questionnaire correlated with a higher rate of postoperative complications.	Retrospective cohort study	Adults undergoing elective surgery at a tertiary care center who were administered the SB questionnaire. 135 patients were identified 56 (41.5%) had high risk scores for OSA.	Pulmonary complications: Hypoxemia, atelectasis, pulmonary embolism, or pneumonia. Cardiac complications: New-onset atrial fibrillation, systemic hypotension, or myocardial infarction.	Patients at high risk of OSA had a higher rate of postoperative complications compared with patients at low risk (19.6% vs 1.3%; $P < .001$ ). The SB questionnaire is useful for preoperative identification of patients at higher risk for complications.
Coté et al. <sup>470</sup>	2010	2b	To determine: The preoperative prevalence of OSA using SB questionnaire related to the need for airway maneuvers and sedation related complications.	Prospective Cohort study	231 consecutive patients undergoing advanced gastrointestinal procedures under sedation were identified by SB and were classified as high risk for OSA (score, $\geq 3$ of 8; SB+) or low risk (SB<3).	-Airway Maneuvers (AM): - defined as a chin lift, modified mask ventilation, nasal airway, bag-mask ventilation, and endotracheal intubation. -Sedation-related complications (SRCs) were defined as any duration of pulse oximetry less than 90%, systolic blood pressure less than 90 mm Hg, apnea, or early procedure termination.	The prevalence of SB+ was 43.3%. The frequency of hypoxemia was significantly higher among patients with SB+ than SB- (12.0% vs 5.2%; relative risk [RR], 1.83; 95% confidence interval [CI], 1.32-2.54). The rate of AMs was also significantly higher among SB+ (20.0%) compared with SB- (6.1%) patients (RR, 1.8; 95% CI, 1.3-2.4).
Pereira et al. <sup>474</sup>	2013	2b	SB score can predict the risk of a patient having OSA and to evaluate the incidence high risk OSA (HR-	Prospective Cohort study	A total of 340 adult patients after noncardiac and non-neurological surgery were admitted to	Postoperative respiratory complications; residual neuromuscular blockade (NMB); hospital length of	HR-OSA had: 1. More frequent hypoxia in PACU (9% vs. 3%, $p=0.012$ ). 2. Higher incidence of residual

			OSA) in surgical patients admitted to the Post-Anesthesia Care Unit (PACU).		PACU. 179 (52%) were considered HR-OSA. HR-OSA if SB score $\geq 3$ and Low-risk of OSA (LR-OSA) if SB score $< 3$ (LR-OSA).	stay.	neuromuscular blockade (NMB) (20% vs. 16%, $p=0.035$ ). 3. Longer hospital stays.
Chia et al. <sup>494</sup>	2013	2b	To analyze the association of pre-operative variables including SB score with postoperative ICU admission	Retro-spective cohort study	All patients were screened using the SB questionnaire. 5432 had elective surgery, 338 (6.2%) were admitted post-operatively to an ICU.	ICU admission	The odds ratios for ICU admission were: 2.2; 3.2, 5.1 for SB scores of 4, 5 and $\geq 6$ . SB score may be used to stratify the need for post-operative ICU admission. SB score $\geq 6$ associated with 5x higher rate of postoperative critical care admission.
Acar <sup>493</sup>	2014	2b	To evaluate if the HR-OSA by SB can predict difficult intubation	Pro-spective cohort study	200 patients undergoing surgery under general anesthesia. 83 with HR-OSA based on the SB score $\geq 3$ . Mallampati score and tonsil size, as well as demographic data, were recorded preoperatively for all patients.	Difficulty of intubation defined by Cormack & Lehane grade III or IV or the need of an intubation aid, or the need of three or more intubation attempts. 7% had difficulty of intubation.	Rate of difficult intubation was higher in HR-OSA patients than in LR-OSA patients. (13.3% vs. 2.6%. ( $p < 0.001$ ). A SB $\geq 3$ was seen more frequently in the difficult intubation patients (78.6% vs. 38.7%) ( $p = 0.009$ ).
Mehta et al. <sup>500</sup>	2014	2b	To identify the prevalence of OSA by using the SB	Pro-spective cohort	243 patients undergoing routine gastrointestinal	Airway interventions (AI): Chin lift, mask	48% with HR-OSA. An SB score $\geq 3$ was found not to be associated

			questionnaire and subsequent risk factors for airway interventions (AI) and sedation related adverse events (SRAE)	study	procedures under sedation. HR-OSA = SB $\geq$ 3score, low risk -OSA= SB score < 3	ventilation, placement of nasopharyngeal airway, bag mask ventilation, unplanned endotracheal intubation, hypoxia, hypotension, or early procedure termination.	with occurrence of AI (relative risk [RR] 1.07), or SRAE (RR 0.81, 95% CI, 0.53-1.2) after adjustment for propofol dose, BMI, smoking, and age. HR-OSA patients are not at higher risk for airway intervention or sedation-related adverse events SRAE.
Proczko et al. <sup>484</sup>	2014	2b	To determine if morbidly obese patients diagnosed by a PSG and using continuous positive airway pressure (CPAP) therapy have fewer and less severe perioperative complications and a shorter hospital stay than patients who have a medical history that meets at least three SB criteria and are not using CPAP therapy.	Retrospective Cohort Study	Three groups of morbidly obese patients undergoing bariatric surgery. Group A: 99 patients who were diagnosed with PSG and used CPAP therapy before and after surgery. Group B: 182 patients who met at least three SB criteria and did not use CPAP. Group C: 412 patients who scored 1-2 items on the SB.	Postoperative hospital stays and pulmonary complications.	Group B patients had a significantly higher rate of pulmonary complications, worse oxygen saturation, respiratory rates, and increased length of stay in hospital. There were also two cases of sudden death in this group.
Seet et al. <sup>475</sup>	2015	2b	Predict independent risk factors for intraoperative and early postoperative adverse events.	Retrospective cohort study	5,432 patients who underwent elective surgery were analyzed.	Adverse events: hypoxia, failed intubation or multiple attempts, dental injury, laryn-	7.4% had unexpected intraoperative and early postoperative adverse events. These events were



						gospasm, bronchospasm, arrhythmia, hypertension and hypotension, unanticipated surgical bleeding, hypothermia, nerve injury, drug adverse reaction, equipment failure, unplanned ICU admission, post-anaesthesia care unit (PACU) time > 2 hours.	greater in patients with SB scores $\geq 3$ Patients with SB scores $\geq 5$ had a fivefold increased risk of unexpected adverse events.
Chung et al. <sup>485</sup>	2016	2a	Does the diagnosis of OSA changes the postoperative outcome?	Systematic Review	Patients undergoing surgery either under general or neuraxial anesthesia or sedation	Pulmonary, desaturation, difficult intubation, atrial fibrillation, cardiac complications, resource utilization, mortality.	The presence of OSA negatively influences perioperative outcomes.
Gokay et al. <sup>472</sup>	2016	4	SB vs. Berlin OSA questionnaires for evaluating potential respiratory complications during the perioperative period.	Prospective Cohort Study	The study included 126 patients underwent laparoscopic cholecystectomy.	Perioperative respiratory complications.	Both questionnaires found statistically significant differences between the low- and high-risk groups.
Chudeau et al. <sup>468</sup>	2016	2b	To evaluate whether the SB is predictive of perioperative respiratory complications in urgent surgery	Prospective cohort study	The SB questionnaire was used. 104 patients were HR-OSA and 85 LR-OSA.	Perioperative complications: respiratory complications, cardiac complications, neurologic complications, hospital length of stay and mortality.	HR-OSA vs LR-OSA as diagnosed with SB had: Higher respiratory complications (21% versus 6%, $P < 0.002$ ), a prolonged length of hospital stay (6 [3-12]

							versus 4 [2-7] days, P=0.0002). SB score was independently associated with respiratory complications (OR 1.44 [1.03-2.03], P=0.03).
Setaro et al. <sup>501</sup>	2018	4	To determine if longer monitoring of patients with OSA in the PACU improves patient outcomes after general anesthesia	Retrospective cohort study	602 patients were evaluated. 68 patients (11%) had a confirmed and a presumptive diagnosis of OSA on chart review and screening STOP>1.	Oxygen desaturation <95 %, PACU length of stay	Most patients (96.5%) did not experience oxygen desaturation regardless of OSA diagnosis or a positive STOP score. Patients with OSA did not experience a higher incidence of respiratory symptoms while in the PACU.
<b>Diagnosis of OSA and Postoperative Morbidity</b>							
Memtsoudis et al. <sup>473</sup>	2011	2b	To analyze perioperative demographics and pulmonary outcomes of patients with OSA after orthopedic and general surgical procedures	Case-control study	2,610,441 entries for orthopedic and 3,441,262 for general surgical procedures performed between 1998 and 2007. Of those, 2.52% and 1.40%, respectively, carried a diagnosis of OSA.	Aspiration pneumonia, adult respiratory distress syndrome (ARDS), pulmonary embolism (PE), and the need for intubation and mechanical ventilation were the primary outcomes	OSA was associated with a significantly higher adjusted OR of developing pulmonary complications with the exception of PE.
Kaw et al. <sup>466</sup>	2012	1b	OSA is often undiagnosed before elective surgery and may predispose patients to	Systematic review	13 studies (n=3942). Studies without controls, involving upper airway surgery,	The incidence of postoperative desaturation, acute respiratory failure (ARF), postoperative	OSA was associated with significantly higher risk of postoperative cardiac events

			perioperative complications.		and with OSA diagnosed by ICD-9 codes alone were excluded.	cardiac events, and ICU transfers.	odds ratio (OR) 2.07; ARF OR 2.43; desaturation OR 2.27, and ICU transfer OR 2.81.
Opperer et al. <sup>467</sup>	2016	2a	The diagnosis of OSA has an impact on postoperative outcomes.	A systematic review	413,304 OSA and 8,556,279 control patients.	Combined complications of Cardiac, pulmonary, airway, mortality complications and resource utilization. Length of hospital stay and ICU admissions.	OSA patients had worse outcomes for pulmonary and combined complications, in-hospital mortality varied among studies; 9 studies showed no impact, 3 studies suggested a decrease in mortality, and 1 study reported increased mortality.

Chan et al. <sup>464</sup>	2019	2b	To determine the association between OSA and 30-day risk of cardiovascular complications after major noncardiac surgery.	Prospective cohort study	1364 patients recruited without prior diagnosis of OSA and undergoing major noncardiac surgery. Monitored with nocturnal pulse oximetry and measurement of cardiac troponin concentrations. OSA severity based on preoperative portable sleep monitoring.	Primary outcome was a composite of myocardial injury, cardiac death, heart failure, thromboembolism, atrial fibrillation, and stroke within 30 days of surgery.	Rates for composite complications: 30.1% for patients with severe OSA, 22.1% for patients with moderate OSA, 19.0% for patients with mild OSA, and 14.2% for patients with no OSA. OSA and risk for complications was significant only among patients with severe OSA (adjusted HR, 2.23 [95% CI, 1.49-3.34]; P = .001) and not among those with moderate or mild OSA.
<b>Diagnosis of OSA and Postoperative Mortality</b>							

Accepted Article

Lockhart et al, <sup>480</sup>	2013	2b	To determine whether a prior diagnosis of OSA, or a positive screen for OSA is associated with increased risk for 30 days and one year mortality.	Prospective cohort study	14,962 patients, of whom 1939 (12.9%) reported a history of OSA. All patients completed preoperative OSA screening combination of the Berlin and Flemons STOP , and SB scores.	30 day postoperative mortality and one-year mortality.	Screening tools identified a high prevalence of undiagnosed patients at risk for OSA (9.5%-41.6%).  Neither a prior diagnosis of OSA nor a positive screen for OSA risk was associated with increased 30-day or one-year postoperative mortality.
D'Apuzzo et al. <sup>479</sup>	2012	2b	To determine if patients with OSA have a higher likelihood of postoperative in-hospital complications or increased costs after revision arthroplasty.	Retrospective cohort study	Nationwide sample of 258 455 patients who underwent revision total hip or knee arthroplasty. Of these patients, 16 608 (6.4%) had been diagnosed with OSA.	In-hospital mortality, pulmonary embolism, and wound complications	OSA was associated with increased in-hospital mortality (odds ratio, 1.9; P = .002). Pulmonary embolism (odds ratio, 2.1; P = .001) Wound hematomas or seromas (odds ratio, 1.36; P < .001) Increased postoperative charges (\$61,044 vs \$58,813; P < .001).
Mokhlesi et al, <sup>483</sup>	2013	2b	To determine if sleep disordered Breathing (SDB) is associated with higher hospital mortality, longer hospital stay, higher cost, respiratory	retrospective Cohort study	Nationwide Inpatient Sample database of 91,028 adult patients undergoing bariatric surgeries	In-hospital death, total charges and length of stay, respiratory and cardiac complications	SDB was independently associated with decreased mortality (OR = 0.34, 95% CI = 0.23-0.50, p < 0.001), total charges (-\$869, p < 0.001), and

			and cardiac complications in bariatric surgeries				length of stay. SDB associated with significantly increased emergent endotracheal intubation, noninvasive ventilation, and atrial fibrillation).
Lyons PG, <sup>5</sup> 02	2016	2b	To investigate the association between OSA and in-hospital mortality rapid response team (RRT) activation, ICU admission, intubation, and cardiac arrest on the wards in a large cohort of surgical and nonsurgical ward patients.	Retrospective cohort	A total of 93,676 ward admissions from 53,150 adult patients' records were screened for the end points. OSA was identified in 5,625 (10.6%) patients.	Primary outcome is in-hospital mortality. Secondary outcomes included length of stay (LOS), RRT activation, transfer to the ICU, endotracheal intubation, cardiac arrest on the wards, and a composite outcome of RRT activation, ICU transfer, and death.	OSA patients had more frequent RRT activations (1.5% vs 1.1%) and ICU admission (8% vs 7%) than controls (P < 0.001), but a lower inpatient mortality rate (1.1% vs 1.4%, P < 0.05). OSA was associated with decreased adjusted odds for ICU transfer, cardiac arrest, and in-hospital mortality. OSA was not associated with clinical deterioration and was associated with decreased in-hospital mortality.
ICU: Intensive Care Unit, HR- OSA: High risk- OSA, Low risk-OSA: LR-OSA SB: Stop- Bang,							

## VI.C Symptoms Associated with OSA

### VI.C.1 Snoring, Gaspings, Excessive Daytime Sleepiness

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of partial and complete pharyngeal collapse. Accordingly, in patients with OSA, increased upper airway resistance from partial pharyngeal collapse may manifest as loud snoring. Complete pharyngeal collapse with cessation of

airflow may result in witnessed apneas. Individuals with OSA may report nocturnal episodes of choking or gasping, and/or symptoms of daytime fatigue, sleepiness, tiredness, or even insomnia. Bedpartners may be affected.

Large community studies have demonstrated habitual snoring (occurring most nights of the week) in 34-44% of the population, witnessed breathing pauses in 6-29%, and daytime hypersomnolence in 18-28% of individuals<sup>88,144,455</sup>. Recent data from a population sample in the United Kingdom has shown a significant increase in the rate of reported witnessed apneas in the community over the last 20 years concurrently with a rise in obesity<sup>503</sup>. The frequency of these symptoms is higher in those with OSA. Among individuals diagnosed with OSA, 38-80% report snoring, 10-67% report witnessed apneas, and 32-40% report excessive daytime sleepiness (ESS $\geq$ 11). In general, increasing frequency of each symptom occurs with increasing AHI and OSA severity<sup>88,455,504</sup>.

Findings from several population-based and retrospective studies have demonstrated that habitual snoring and witnessed apneas are predictors for OSA<sup>88,144,504,505</sup>. However, the most predictive symptom for identifying individuals with OSA may be nocturnal choking or gasping episodes<sup>506</sup>. A large Canadian population study in 2009 found that 4.3% of the population reported awakening suddenly with gasping or choking rarely or sometimes, and 1.5% reported this symptom occurring once a week or more<sup>507</sup>; of individuals diagnosed with OSA, 14.4% reported nocturnal choking or gasping episodes rarely or sometimes (OR 3.52, 95% CI 1.92-6.46), and 11.2% reported this symptom once a week or more (OR 7.92, 95% CI 3.74-16.74). Furthermore, a systematic review by Myers et al in 2013<sup>506</sup> demonstrated that nocturnal choking or gasping episodes had a likelihood ratio (LR) of 3.3 (95% CI 2.1-4.6) for the diagnosis of OSA (AHI $\geq$ 10), while snoring was found to be less predictive (LR 1.1, 95% CI 1.0-1.1).

Despite being common in the general population, snoring or apneas may not be routinely screened for or reported in the primary care setting<sup>508</sup>. Many validated questionnaires<sup>444,445,509</sup> include some or all of these symptoms and may help identify patients at risk for OSA.<sup>508</sup> Sex differences in reported sleep symptoms have been reported, with men being more likely to report snoring (34% vs 19%) and women being more likely to report hypersomnolence (22.6% vs. 15.5%)<sup>90</sup>. Shepertycky et al<sup>510</sup>, also demonstrated that women with OSA were more likely to report insomnia (OR 4.20, 95% CI 1.54-14.26) and less likely to report witnessed apneas (OR 0.66, 95% CI 0.38-1.12). These variations in OSA symptomatology are important to recognize not only for appropriate screening, but also may have broader implications for OSA treatment<sup>419</sup>.

#### **Patient Reported Symptoms Suggestive of OSA**

**Aggregate Quality of Evidence:** B (Level 1a: 1 study; Level 1b: 7 studies; Level 2b: 4 studies, Level 5: 1 study).

**Benefit:** Symptoms of snoring, gasping, and excessive daytime sleepiness are linked to OSA.

**Harm:** Potential for over-testing for OSA.

**Cost:** Minimal to none.

**Benefits-Harm Assessment:** Preponderance of benefit over harm.

**Value Judgments:** Patients can benefit from identification and treatment of OSA. Reporting of OSA symptoms may identify patients requiring further testing. Symptoms are not sufficient for diagnosis.

**Recommendation Level:** Recommendation.

**Intervention:** Patients reporting symptoms of snoring, gasping, and daytime sleepiness should be further evaluated for OSA.

Table VI.C.1 Evidence on the relationship between snoring, gasping, daytime sleepiness and OSA.

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Myers et al. <sup>506</sup>	2013	1a	Systematic review	Community-screened patients and patients referred for sleep evaluation	In-laboratory PSG	Nocturnal choking or gasping episodes most predictive symptom (LR 3.3, 95% CI 2.1-4.6) for the diagnosis of OSA (AHI $\geq$ 10). Snoring, reported apneas, and excessive daytime sleepiness were less predictive of the diagnosis (LR 1.1 [95% CI 1.0-1.1], 1.4 [1.2-1.5], and 1.3 [1.1-1.4], respectively).
Young et al. <sup>90</sup>	1993	1b	Prospective cohort	Wisconsin Sleep Cohort Study population (n=602)	In-laboratory PSG	In individuals with OSA (AHI $\geq$ 5), more men than women reported habitual snoring $\pm$ breathing pauses (34% vs. 19%), and more women than men reported hypersomnolence (22.6% vs 15.5%).
Johns et al. <sup>509</sup>	1993	1b	Cross Sectional Survey	Adult patients suspected of having OSAS by history of snoring (n=273)	Questionnaire (ESS) and in-laboratory PSG	Patients found to have OSAS (RDI $>$ 5) had significantly higher levels of daytime sleepiness (measured by ESS) than primary snorers; ESS scores and thus daytime sleepiness increased significantly with increasing OSAS severity.
Netzer et al. <sup>444</sup>	1999	1b	Cross Sectional Survey	Adult primary care patients (n=100)	Questionnaire (Berlin), in-home PSG	High-risk patients (in $\geq$ 2 categories) were more likely to meet criteria for OSAS (RDI $>$ 5). High-risk qualification by one symptom category did not predict RDI as



						well as composite score.
Young et al. <sup>88</sup>	2002	1b	Prospective cohort	Sleep Heart Health Study population (n=5,615)	Questionnaire, clinical examination, in-home PSG	Habitual snoring (OR 2.87, 95% CI 2.10-3.91), and breathing pauses occurring <3 nights/week (OR 1.78, 95% CI 1.34-2.37), or 3-7 nights/week (OR 4.03, 95% CI 2.87-5.67) were associated with moderate to severe OSA (AHI≥15).
Chung et al. <sup>445</sup>	2008	1b	Diagnostic accuracy	Adult Pre-operative Patients (n=177)	Questionnaire (STOP), in-laboratory PSG	Patients identified as high risk for OSA (≥2 'yes' answers) demonstrated a sensitivity of 65.6%, specificity of 60%, PPV 78.4%, and NPV 44.0% for OSA (AHI>5). The STOP questionnaire was more sensitive in detecting patients with moderate (AHI>15) to severe (AHI>30) OSA.
Silva et al. <sup>455</sup>	2011	1b	Prospective cohort	Sleep Heart Health Study population (n=4,770)	In-home PSG	Among individuals with moderate-to-severe SBD (RDI≥15,<30) and severe SBD (RDI≥30): 55.9% and 69.6%, respectively snore often/every night; 38.9% and 66.9% have witnessed apneas, and 32% and 40% have excessive daytime sleepiness (ESS≥11).
Johnson et al. <sup>505</sup>	2020	1b	Prospective cohort	Jackson Heart Sleep Study (n=719)	Questionnaire (Including, STOP-bang, ESS), in-home PSG	Among an adult African American cohort with moderate to severe OSA (REI≥15), 49.3% snore ≥3 nights/week (vs. 31.1% with mild or no OSA), 6.6% had witnessed apneas ≥3 nights/week (vs. 3.1%), and 22.4% had sleepiness (ESS>10) (vs. 19.5%)
Durán et al. <sup>144</sup>	2001	2b	Cross-sectional	Community sample	Structured interview, in-	Habitual snoring (OR 5.45) and breathing

				(n=555)	laboratory PSG	pauses during sleep (OR 13.4) are risk factors for moderate-severe OSA (AHI $\geq$ 15). Habitual snoring (OR 3.36) is also risk factor for mild OSA (AHI $\geq$ 5-14.9). Breathing pauses not significantly associated with mild OSA (OR 4.63). Daytime hypersomnolence is not associated with mild OSA (OR 1.37) or moderate-severe OSA (OR 1.05).
Shepertycky et al. <sup>510</sup>	2005	2b	Retrospective cohort	Population of patients diagnosed with OSAS (n=260)	Questionnaire, in-lab PSG	At the time of OSAS diagnosis, women were more likely to present with insomnia (OR 4.20, 95% CI 1.54-14.26) and less likely to report witnessed apneas (OR 0.66, 95% CI 0.38-1.12).
Ustun et al. <sup>504</sup>	2016	2b	Retrospective cohort	Clinical Sleep Laboratory Database (n=1,992)	In-lab PSG	Patients found to have OSA (AHI $>$ 5 or RDI $>$ 10) were significantly more likely to self-report snoring (79.7%) and witnessed apneas (43.8%) than individuals without OSA. A clinical prediction model for diagnosing OSA using medical history features was superior to model performance using symptoms alone.
Li et al. <sup>511</sup>	2019	2b	Cross-sectional observational study	Adult patients with snoring and suspected OSAS (n=134)	Questionnaire (ESS and Montreal Cognitive Assessment), in-lab PSG	Daytime sleepiness, as measured by ESS, worsens with increasing OSAS severity.
Epstein et al. <sup>512</sup>	2009	5	Guideline		Recommendations on the evaluation	A comprehensive sleep history in a patient with suspected OSA should

					and management of adult patients with OSA	include evaluation for snoring, witnessed apneas, gasping/choking episodes, excessive sleepiness not explained by other factors (including assessment of sleepiness severity by ESS), total sleep amount, nocturia, morning headaches, sleep fragmentation/sleep maintenance insomnia, and decreased concentration and memory.
--	--	--	--	--	---	--

### VI.C.2 Nocturia

Nocturia, refers to the need to urinate more than once per night<sup>513</sup>, affects greater than 60% of adults aged 70 and older and is more prevalent in women.<sup>514,515</sup> The prevalence of high risk for OSA (based on results from the Berlin Questionnaire), studied in a sample of female patients, in an urogynecology clinic was greater in patients with nocturia (61.7%) compared to those without (24.1%) (OR 2.9, 95% CI 1.29-6.52).<sup>516</sup> A recent meta-analysis demonstrated an association between OSA and risk of nocturia 1.41 (95% CI 1.26-1.59). Furthermore the authors' report that patients with severe OSA had a higher incidence of nocturnal urination in comparison to patients with mild or moderate disease (RR 0.82; 95% CI 0.72-0.94). In men there was a statistically significant association between OSA and risk of nocturia (RR 1.487, 95% CI 1.087–2.034), which was not the case in women.<sup>517</sup> To support the link between severity of OSA and nocturia, in a study comparing patients with and without nocturia, an increased oxygen desaturation index was associated with an increased probability of nocturia, in the multivariable model (OR = 1.03; 95% CI = 1.01-1.06).<sup>518</sup> The higher the ODI score, the greater the probability of nocturia.

A chain of physiologic effects leads to diuresis and nocturia in the setting of OSA. Increased intrathoracic negative pressures (needed to overcome a closed upper airway) lead to atrial stretch which triggers a signal of excessive fluid volume and the subsequent release of atrial natriuretic peptide inducing diuresis.<sup>519,520</sup>

Nocturia has significant effects on quality of life and in particular sleep quality, impacting total sleep time and sleep efficacy. In comparison to patients with OSA without nocturia, mean oxygen saturation, time spent in desaturation below 90% and ODI were worse in OSA patients with nocturia.<sup>515</sup> Treatment with CPAP has been shown to improve nocturia in patients with OSA.<sup>521</sup>

### VI.C.3 Caffeine Intake

Excessive daytime sleepiness is a common symptom of OSA. One of the reasons to consume caffeinated products is to counteract sleepiness. Caffeine is a natural psychoactive substance which blocks adenosine receptors in the brain 30-60 minutes after consumption. As adenosine builds up during the day, the sleeper we become. Caffeine blocks this process, and as a consequence we remain alert and vigilant.

Bearing this in mind, assessing caffeine use as a marker of sleepiness is recommended when taking patient history in patients suspected of OSA. Studies on patients with untreated OSA have demonstrated that increased caffeine intake is associated with less cognitive impairment<sup>522</sup> thereby indicating a potential therapeutic effect of caffeine and evidence for self-treatment of OSA. On the other hand, caffeine can delay onset of sleep and can interfere with our circadian rhythm.

Despite its common use, the prevalence of caffeine use in patients at risk for OSA is difficult to estimate. The Sleep Heart Health Study (SHHS) provides the most comprehensive assessment of caffeine use in OSA patients<sup>523</sup>. Women with sleep-disordered breathing have the strongest correlations between caffeinated soda and OSA. There was only an association between caffeinated soda and severe SDB in men<sup>523</sup>. Coffee and tea consumption were not associated with SDB.

Several trials were created to evaluate interactions among caffeine use, OSA, and cardiovascular risks. Bardwell and colleagues demonstrated that OSA patients consumed significantly greater caffeine than normal controls (295 mg/day vs. 103 mg/day of caffeine)<sup>524</sup>. Robinson and colleagues measured caffeine consumption before and after 4 weeks of CPAP. Although sleepiness improved after CPAP, caffeine intake did not change<sup>525</sup>. Such research has contributed to the concept that OSA has independent effects on hypertension and other cardiovascular markers which are separate from the impact of caffeine use.

#### VI.D Physical Exam Findings Related to OSA

Evaluation of patients with OSA includes standard physical exam that evaluates for age, BMI, neck circumference, assessment of craniofacial structures, and standard upper airway examination of the nasal cavity, oral cavity, and oropharynx. The ability of an individual physical exam finding to predict OSA alone is limited, but the entire physical exam can be considered in the context of the patient's history to provide a better assessment of OSA risk.

Some goals of the physical exam for OSA aim to: 1) incorporate exam findings for use in OSA screening tools in conjunction with patient symptoms; 2) determine potential causes of airway obstruction, 3) identify potential anatomic concerns that may limit PAP therapy, and 4) aid in determining potential therapeutic targets for sleep surgery (see Section IX.C.1).

This section evaluates the components of the physical exam relevant to OSA evaluation and summarizes the available evidence that associates particular exam findings with OSA. Evidence tables are provided for specific exam findings that have adequate data.

#### Components of the Exam

Not all components of the physical exam are routinely performed, and the examination should be tailored to each individual patient after completing a thorough history and symptom review.

##### VI.D.1 BMI

Obesity is a well-established risk factor for the development and progression of OSA. A BMI greater than 30 increases risk for OSA<sup>349</sup> and weight reduction is a treatment option that can improve OSA severity.<sup>188</sup> BMI level also has implications for surgical outcomes with higher BMI associated with persistent OSA after surgery<sup>526</sup>. BMI level should be included in the evaluation of OSA patients.

##### VI.D.2 Neck Circumference

Neck circumference (NC) or collar size is associated with OSA in adults.<sup>183,527-533</sup> It is standardly measured as the circumference of the neck at the superior border of the cricothyroid membrane. Larger neck circumference is related to elevated BMI. Fat deposition in the tissues of the neck results in a smaller and more collapsible upper airway, thus increasing the likelihood of OSA.

A systematic review and meta-analysis of facial phenotype in adult OSA found that adults with OSA had significantly larger NC compared to controls.<sup>534</sup> Neck circumference is associated with OSA severity.<sup>138,527</sup> Specifically, NC > 40 cm (16in) is associated with snoring and OSA.<sup>527,528,535-537</sup> Although it is positively correlated with OSA, NC alone is a poor predictor of OSA.<sup>538</sup> The sensitivity of NC alone is insufficient to identify patients with sleep apnea, but increases when combined with other clinical, anthropometric or cephalometric measures.<sup>536,539-541</sup> One screening tool that incorporates NC is the STOP-BANG which is used to identify patients at high risk for OSA<sup>445</sup> and uses NC or shirt collar size estimates with thresholds of 43cm (17in) for males and 41cm (16in) for females.

**Table VI.D Neck circumference (NC) measurement in the diagnosis of OSA**

Study	Year		Study Design	Study groups	Clinical endpoint	Conclusion
Agha et al <sup>534</sup>	2017	3a	Systematic review and meta analysis of predominantly case-control studies	Not applicable	Not applicable	Adults with OSA had an increased weighted mean difference in NC compared with controls, in five case– control studies. The pooled mean change was 1.26 mm (0.64–1.88), with large heterogeneity found between studies.
Kim et al <sup>138</sup>	2015	3b	Cross-sectional retrospective study	Cohort of snoring Asian patients	Neck circumference in Asian patients with OSA compared to individuals with simple snoring.	NC predicted OSA presence and severity.
Kushida et al <sup>536</sup>	1997	4	Prospective cohort study	Consecutive patients referred for evaluation of sleep disorders.	Evaluated measurements of the oral cavity with body mass index and NC, in predicting OSA.	A NC ≥ 40cm is associated with OSA sensitivity of 61% and specificity 93%.
Stradling et al <sup>532</sup>	1990	4	Prospective study	Men 35-65 years old GP	Registry study	NC was an independent predictor of nighttime

				registry		hypoxia events.
Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine <sup>512</sup>	2009	5	Guideline	Not applicable	Not applicable	Features that may suggest the presence of OSA include increased NC ( > 17 inches in men and > 16 inches in women) .
Ahbab et al. <sup>527</sup>	2013	4	Cohort Study	OSA adults.	Evaluate NC and metabolic syndrome parameters in OSA patients.	NC in severe OSA was significantly higher than in mild-moderate OSA.  NC was an independent risk factor for severe OSA (odds ratio [OR]: 1.55. 95% confidence intervals [CI]: 1.09–2.21. p=0.01).
Chang et al. <sup>528</sup>	2013	4	Prospective cohort	Cohort of Chinese patients with snoring complaints in sitting position.	Evaluate if snoring in a sitting position is a predictor of OSA in patients.	NC ≥40 cm as a predictor for OSA had sensitivity 48.6 %, specificity 87.8 %, and likelihood ratio 3.98.
Park et al. <sup>531</sup>	2014	4	Retrospective cohort	Non-obese Asian patients who underwent PSG	Evaluate association between body weight and obstructive sleep apnea even in patients who are not obese	AHI found to be positively correlated with the NC. NC is independently associated with OSA
Davies et al. <sup>529</sup>	1990	4	Prospective study	Cohort of patients	Importance of NC, obesity, and	NC of 42.5 cm (16.75 inch) for a 1.78 m (5

				referred for investigation of sleep disorders	radiographic pharyngeal dimensions for OSA.	feet 10 inch) man) is 77% sensitive and 82% specific for significant OSA with positive predictive value of 75%.
Yildirim et al <sup>533</sup>	2015	4	Prospective	Cohort of patients with a BMI $\geq$ 30 and OSA symptoms	Evaluate anthropometric measurements with OSA	Significant positive correlation between AHI and neck circumference.
Mirrakhimov et al <sup>530</sup>	2013	3a	Systematic review	Not applicable	Not applicable	Neck circumference is associated with OSA.
Santos et al <sup>541</sup>	2019	4	Cohort study	Cohort civil servants 35-74 years	Compare BMI, several surrogate markers of body fat (in isolation or combined) and validated questionnaires for screening OSA.	Age and gender-adjusted NC [AUC = 0.733 (0.711 - 0.755)] had moderate accuracy as predictor for OSA.
Yusoff et al <sup>537</sup>	2010	4	Prospective	Cohort randomly selected express bus drivers.	Identifying factors or conditions related with OSA.	NC (OR = 1.31, 95% CI 1.18–1.46) was significantly associated with OSA status.

### VI.D.3 Nasal Exam

Nasal obstruction is associated with sleep apnea and treatment of obstruction improves sleep quality and CPAP tolerance.<sup>295</sup>(see Section V.A.1) A thorough nasal examination includes evaluation of external nasal structures and visualization of the nasal cavity using a nasal speculum and/or nasal endoscope. The examiner should identify any external nasal deformity, internal septal deviation, inferior turbinate hypertrophy, nasal valve collapse, nasal cavity inflammation, and adenoid hypertrophy. The Cottle and Modified Cottle Maneuvers may be beneficial in assessing for internal nasal valve collapse.<sup>542</sup> The nasal

exam is focused and based on patient symptoms of nasal obstruction. Nasal obstruction has implications in PAP tolerance<sup>543</sup> and OSA-related symptoms.<sup>544</sup>

#### VI.D.4 Oral Cavity and Oropharynx Exam

Examination of the oral cavity and oropharynx is an important component of the OSA physical exam. Thickened and collapsible lateral pharyngeal walls and an enlarged uvula are well-recognized physical exam finding in adults with OSA.<sup>323,324</sup> Several studies also demonstrate that a narrow palatopharyngeal arch, or fauces, is predictive of the presence and severity of OSA.<sup>234,331,333,335</sup>

Tonsil size is commonly reported using the Brodsky tonsil grading scale: 0 = surgically absent; 1+ = 0%-25% oropharynx obstruction; 2+ = 25%-50% oropharynx obstruction; 3+ = 50%-75% oropharynx obstruction; and 4+ = 75%-100% oropharynx obstruction.<sup>545</sup> Tonsil size may predict severity of OSA, and a study of adults with OSA demonstrated that each increase in tonsillar size correlates to an increase in AHI of approximately 14 events/hour.<sup>326</sup> Identification of enlarged tonsils in patients with OSA also has implications in treatment decisions.<sup>334</sup>

#### VI.D.5 Mallampati Classification and Friedman Tongue Position

Common classification schema used for grading the oropharyngeal exam include the Mallampati classification (MC) and Friedman tongue position (FTP).

The MC was developed as a clinical indicator for difficult intubation and is performed by examining the seated patient with the mouth open and tongue protruded. Based on the visualized oropharyngeal structures (palate edge, uvula, tonsils), a classification from I to IV is assigned. Class I represents complete visualization of the soft palate and uvula, class II includes partial visualization of the uvula and complete view of the soft palate, class III involves view of the base of the uvula, and class IV view of the hard palate only.

The MC has since been modified several times most notably as the FTP, in which the airway is assessed with the tongue remaining inside the oral cavity instead of protruded with the original Mallampati Classification MC.<sup>546,547</sup> FTP was designed to grade the relative size of the tongue base and was used as a predictor for surgical success after UPPP. The modified Mallampati Classification also examines the oral cavity with the tongue at rest and is a variation of FTP.

Both the MC and FTP have been examined as predictors for the presence and severity of OSA, but conflicting evidence lends to uncertainty of their predictive values.<sup>546,548</sup> MC is associated with AHI but not among women.<sup>549</sup> Mallampati class IV is associated significantly with OSA.<sup>550</sup> FTP and AHI are positively correlated with higher FTP grade associated with higher AHI<sup>546,551,552</sup> however, low inter-examiner agreement in FTP scoring has been suggested.<sup>553</sup>

A recent review article concludes that MC and FTP may have limited predictive values for OSA when used independently, but they may play a role when incorporated into the overall patient assessment.<sup>547</sup>

**Table VI.D.5 Evidence for the Association between Mallampati Classification, Friedman Tongue Position and OSA**

Study	Year	LOE	Study	Study	Clinical Endpoint	Conclusion
-------	------	-----	-------	-------	-------------------	------------



			Design	Groups		
Friedman et al <sup>546</sup>	2013	3a	Systematic review	Adults with OSA	Systematic review and meta-analysis to assess the association between Mallampati and Friedman Tongue Position for OSA severity	Friedman tongue position and Mallampati classification were significantly associated with obstructive sleep apnea severity
Bins et al <sup>548</sup>	2011	3a	Systematic review	Adults with OSA	Systematic review to evaluate the diagnostic value of the Mallampati score in patients suspected of OSAS	No Evidence for Diagnostic Value of Mallampati Score in Patients Suspected of Having Obstructive Sleep Apnea Syndrome
Ruangsi et al <sup>550</sup>	2016	3b	Case Control Study	Group 1: OSA (N=78); Group 2: no-OSA (n=78)	Multivariate logistic regression analysis was used to identify the factors associated with OSA	Mallampati class IV was found to be significantly associated with OSA (adjusted odds ratio 5.040 (1.655, 15.358))
Amra et al. <sup>549</sup>	2019	3b	Cross sectional study	Adults with OSA	Evaluated anthropometric data and the Mallampati classification for predicting the severity of OSA	Mallampati classification was found to be associated with AHI indices, but not among women patients.

Study	Year	LO E	Study Design	Study Groups	Clinical Endpoint	Conclusion
Friedman et al <sup>546</sup>	2013	3a	Systematic review	Adults with OSA	Systematic review and meta-analysis to assess the association between Mallampati and Friedman Tongue Position for OSA severity	Friedman tongue position and Mallampati classification were significantly associated with obstructive sleep apnea severity
Banhira et al <sup>554</sup>	2014	3b	Cross sectional study	group 1 no OSA (n=66); group 2: OSA (AHI > 15/hr) n=217	Identify physical findings that may predict the presence of moderate to severe OSA in snoring patients	No significant difference was found in FTP between moderate to severe OSA and control patients (AHI < 5/hr).
Lin et al <sup>551</sup>	2019	4	Retrospective cohort	Adult habitual snorers and adults with OSA	Identify standard clinical parameters that may predict AHI and OSA severity.	FTP was found to be a reliable predictor of OSA (r=0.504, 95% CI: 0.417-0.580)
Subramanian et	2011	4	Prospective	Adult patients	Develop a novel screening tool for the detection of OSA,	FTP was found to be a reliable predictor of OSA

a <sup>552</sup>			cohort	being screened for OSA	combining self-reported historical factors with physical exam findings.	( $r=0.14, p=0.0019$ )
------------------	--	--	--------	------------------------	---	------------------------

### VI.D.6 Laryngoscopy

Laryngoscopy may be included in the OSA physical exam if indicated based on patient history. Laryngoscopy can be used to identify lingual tonsillar hypertrophy, to diagnose masses or lesions within the upper airway, and to determine the shape, size and position of the epiglottis. While lingual tonsil grade as defined by Friedman et al does not have a direct correlation with OSA, its presence may play a role in surgical planning.<sup>555,556</sup> A recent study demonstrated that presence of a mega-epiglottis on laryngoscopy is an independent predictor of moderate and severe OSA. This study also demonstrated that a modified Cormack-Lehane score of 2 or more as measured on laryngoscopy may predict OSA.<sup>557</sup>

### Physical Exam Summary

Specific physical exam findings may correlate to OSA risk and severity of disease however physical exam findings alone are insufficient for OSA diagnosis and severity estimations. Sleep study testing is required to achieve a diagnosis of OSA. The physical exam has a role in the evaluation for OSA specifically to: 1) incorporate exam findings into OSA screening tools for risk stratification; 2) identify potential anatomic concerns that may limit PAP therapy, and 3) aid in determining potential therapeutic targets for sleep surgery.

## VI.E Imaging Findings Associated with OSA

### VI.E.1 Lateral Cephalometry

X-ray cephalometry is a widely available and inexpensive imaging modality that assesses the craniofacial skeleton and its association with soft tissue of the upper airway. It was introduced in the 1980's as part of routine sleep surgical evaluation where cephalometric measurement of the length of the soft palate and the position of the hyoid bone were associated with severe OSA.<sup>558</sup> In a systematic review and meta-analysis, the following parameters significantly correlated with OSA: 1) A mandibular body length as measured from gonion to gnathion of less than 80 mm, 2) a sella, nasion, point A (SNA) angle of less than 75°, 3) an increased anterior lower facial height measured from the anterior nasal spine to the gnathion greater than 85 mm, and 4) hyoid bone more than 18 mm below the mandibular plane correlates strongly with OSA.<sup>228</sup> While this study provides the highest level of evidence, caution must be exercised in generalizing its conclusions. There are methodological differences in standardization of image acquisition, magnification of cephalograms, matching of controls, article selection bias, and quality of the constituent studies. Studies generally did not account for ethnic differences in craniofacial structures. Additional limitations to cephalograms include lack of three-dimensional (3D) assessment and low soft tissue detail. And despite the anatomic correlates, cephalograms can neither confirm nor exclude OSA. A meta-analysis linking adult OSA with cephalometric parameters failed to show a statistically significant difference when subjects with the disorder are compared to healthy controls.<sup>559</sup> Moreover, because they are done awake and in the upright position, they do not account for changes in the airway during sleep.

Correlation of cephalometric parameters with the apnea-hypopnea index (AHI) on overnight polysomnography has been inconsistent in the literature. Analysis of preoperative clinical screening tests for OSA revealed that cephalometry alone may miss a significant proportion of patients with OSA in

low-risk populations.<sup>560</sup> Therefore, it cannot be relied upon for OSA screening and should be considered as only an investigative modality for OSA evaluation. The main benefits of cephalogram are its low cost and low-risk nature in providing anatomic assessment for OSA. It is most useful in treatment planning for orthognathic surgery.

### VI.E.2 Cone-Beam CT

Cone beam CT (CBCT) has the benefits of three-dimensional volumetric assessment, which is more expensive than cephalogram, but increasingly available. High quality evidence supporting its use for OSA airway assessment is lacking. A systematic review of observational studies by Guijarro-Martínez et al. noted inconsistencies and discrepancies in the technique of imaging acquisition.<sup>561</sup> Most studies did not control respiratory phase, mandibular position, and/or tongue position, which influence airway dimensions. Also, the most widely available CBCT scanners acquire images in upright position, which impacts airway analysis for OSA patients. Conclusions from upright CBCT airway dimensions may not apply to supine cross-sectional imaging as the gravitational effect in response to the postural change leads to a smaller cross-sectional area of upper airway due to movement of the hyoid bone, the mandible, the tongue, and upper airway muscle. Hsu et al. showed that in the upright position, there is a significantly greater distance between the mandibular plane and the hyoid bone when compared to CBCT derived cephalometric images in the supine position among normal test subjects.<sup>562</sup> Chen et al. performed a systematic review of the most relevant upper airway anatomical parameters related to OSA by CBCT, conventional CT, and MRI.<sup>563</sup> On sagittal cross-sections, a soft palate measuring more than 38 mm in length and 10 mm in width, an oropharyngeal length measuring more than 70 mm, and tongue length more than 65 mm are correlated with OSA. That corresponds to a retropalatal cross-sectional area of less than 100 mm<sup>2</sup> and a retroglottal cross-sectional area of less than 150 mm<sup>2</sup> on axial views. Similar to cephalogram, CBCT can be of value as an adjunct in the anatomic evaluation of OSA and for surgical planning in orthognathic surgery.

### VI.E.3 Other Imaging Types

Cine CT (ultra-fast CT) provides dynamic airway examination, an advantage over CBCT and conventional CT. It does not reliably distinguish between patients with OSA and primary snorers. Somnofluoroscopy can distinguish snoring from apneas, but high radiation exposure and poor anatomical detail limit its utility. Sleep MRI provides superior soft tissue anatomical detail. Using sleep MRI, Liu et al. showed in multivariate analysis for subjects matched for age and BMI that severity of OSA can be predicted by the presence of lateral pharyngeal wall collapse and low hyoid bone position.<sup>564</sup> Limitations for the use of sleep MRI include lack of widespread availability, expense, and challenges involved in promoting sleep in an MRI scanner related to noise, sleep position and comfort. Awake ultrasonography is a promising imaging modality in diagnosing OSA. In a recent meta-analysis by Singh et al. showed in a meta-analysis a number of parameters with moderate to good correlation with OSA.<sup>565</sup> However, these parameters remain to be validated.

In the literature, there are only a few publications dealing with the evaluation of soft tissue and skeletal anatomy using MRI and lateral cephalometry with both control and OSA subjects. These studies utilized dynamic or ultrafast MRI sequences and cephalometric measures, but did not discriminate OSA from control subjects by sleep study or validated questionnaires as shown in our study.

The soft tissue landmarks in cephalometry are influenced by the superposition of all the structures present in the same plane, which makes some of the landmarks difficult to accurately and reliably identify. MRI provides unparalleled definition of soft tissue structures and their relationships in the upper airway, without exposing patients to the ionizing radiation. However, MRI offers a less precise bony contour definition. The bony landmarks could be harder to identify while analyzing the images. Because the enhanced soft tissue resolution of MRI affords greater measurement accuracy and allows for the determination of additional airway measures, which cannot be achieved through cephalometry (e.g., tongue volume, PAS area), MRI may be superior to radiocephalometry for assessment of anatomic measures in OSA patients.<sup>566</sup>

#### Use of Imaging for OSA Diagnosis

Aggregate Quality of Evidence: C (Level 2a: 5 studies, Level 2b: 3 studies)

Benefit: Imaging allows for visualization of the anatomical sites of obstruction. Imaging may be a potential diagnostic tool for OSA as PSGs are expensive and time consuming.

Harm: Unnecessary radiation exposure and poor diagnostic accuracy.

Cost: Cost and time to obtain imaging.

Benefits-Harm Assessment: Harms outweigh the benefits for OSA diagnosis.

Value Judgments: Lateral cephalometry is helpful for treatment planning in orthognathic surgery for OSA but not as a diagnostic tool for OSA.

Recommendation Level: Recommendation against use of imaging for OSA diagnosis.

Intervention: Routine imaging is not useful as a diagnostic tool for OSA. Imaging may aid in physician's specific treatment planning for the OSA patient.

**Table VI.E Evidence on Imaging and OSA Diagnosis**

Study	Year	LOE	Study design	Study groups	Clinical endpoint	Conclusion
Riley et al. <sup>558</sup>	1983	2b	Retrospective study	N=15 adult OSA patients, n=10 controls	Cephalogram	Length of the soft palate and the position of the hyoid bone serve as important cephalometric landmarks in OSA patients.
Neelapu et al. <sup>228</sup>	2017	2a	Systematic review, meta-analysis	25 studies	Cephalogram	Significant variables in OSA patients include increase in total anterior facial height, inferior hyoid bone position, and reduced pharyngeal airway space.

Armalaite et al. <sup>559</sup>	2015	2a	Systematic review, meta-analysis	11 studies	Cephalogram	The most reliable parameters in OSA subjects are MP-H and upper posterior pharyngeal space. However, the diagnosis of OSA cannot be made using cephalograms as the sole investigative modality.
Ramachandran et al. <sup>560</sup>	2009	2a	Systematic review, meta-analysis	26 studies	Multiple screening questionnaires, multiple history & physical examination elements, oximetry, cephalometry, and morphometry.	No ideal preoperative screening tool exists for OSA in the surgical population. Preoperative screening tools including cephalometry may not identify a significant proportion of patients with OSA.
Guijarro-Martinez et al. <sup>561</sup>	2011	2a	Systematic review	5 studies (relationship between upper airway and OSA)	CBCT	Statistically significant difference between OSA and non-OSA patients in the ratio of the airway cross-section area/square area.
Hsu et al. <sup>562</sup>	2019	2b	Retrospective study	n= 21 normal subjects (no OSA)	Cephalogram, CBCT	Cephalograms in the upright position had a significantly larger MP-H when compared to CBCT derived cephalometric images in the supine position.
Chen et al. <sup>563</sup>	2016	2a	Systematic review	8 studies	CBCT	The most significant anatomical characteristic related to the pathogenesis of OSA is the small cross-sectional area of the airway ( $CSA_{min}$ ). It is unclear how soft tissue structures interact to control upper airway dimensions.
Liu et al. <sup>564</sup>	2015	2b	Case control study	n=15 mild adult OSA patients, n=15 adult severe OSA patients	Sleep MRI	Based on sleep MRI, lateral pharyngeal wall collapse and low hyoid position are significant-

						ly associated with severe OSA.
Singh et al. <sup>565</sup>	2019	2a	Systematic review, meta-analysis	21 studies (3339 patients)	Ultrasound	Airway parameters correlated with OSA: neck circumference and retropalatal diameter shortening during MM, tongue base thickness during MM, resting tongue base thickness, tongue base width, and LPW thickening. Non airway: carotid plaque presence and carotid intimal thickening.

## VI.F Diagnostic Testing for OSA

### VI.F.1 Types of Sleep Studies

Traditionally, the standard way to diagnose obstructive sleep apnea (OSA) has been with polysomnography (PSG) which is an overnight test conducted when one is asleep in a sleep lab with a sleep technologist in attendance. PSG uses  $\geq 7$  channels to monitor sleep, respiration, and muscle activity. Monitoring of brain activity started in 1875 and evolved to the Sleep Research Society developing a standardization for the scoring of sleep in 1968 using the Rechtschaffen and Kales (R and K) manual.<sup>567</sup> R and K was the standard to score polysomnography until 2007 when the American Academy of Sleep Medicine (AASM) published a scoring manual<sup>568</sup> for scoring sleep studies that is followed by all accredited sleep centers and updated on an approximately annual basis. It describes types of sensors to be used, their placement, and how to score sleep, respiratory events, cardiac events, and limb movements. A standard PSG includes electroencephalography (EEG) with frontal, central, and occipital leads placed using the 10-20 international system, electro-oculography (EOG), chin electromyogram (EMG), lead II electrocardiogram (ECG), airflow monitoring via oral thermistor and a nasal pressure transducer, respiratory effort with inductance plethysmography, oxygen saturation via a pulse oximetry, and limb EMG.<sup>567</sup> Other monitoring that is typically done is snoring via a snore microphone, body position sensor, and video monitoring. A PSG report will contain information about the patient's sleep, limb movements, and the presence of sleep disordered breathing based on the apnea hypopnea index (AHI) calculated during the PSG.

In general there are 4 types of sleep monitoring devices (I-IV) (TABLE VI.F.1). Type I is a PSG described above and types II-IV are portable sleep monitoring (PM) or home sleep apnea tests (HSAT).<sup>567</sup> A type II study is portable monitoring done using the same channels as a type I device only it is unattended—meaning there is not a sleep technologist or sleep trained personnel with the patient while they are having the study done. Type III HSAT use 4-7 channels and type IV uses 1-2 channels with at least one being a pulse oximeter.<sup>567,569</sup> Most HSATs do not directly record sleep. Therefore, as opposed to an AHI,

HSATs report a respiratory event index (REI) which is the number of apneas and hypopneas per hours of recording time.<sup>570</sup> The American Academy of Sleep Medicine (AASM) recommends that HSATs record airflow, respiratory effort, and blood oxygenation.<sup>569,571</sup> Most literature reviews and recommendations focus on type III devices. Type II devices are not typically conducted in the clinical setting and not much data exists on their efficacy. Of note, the naming of sleep monitoring tests (Type I-IV) is non-descriptive and reflects a descending order of complexity/required channels. A separate mode of classifying sleep tests, the SCOPER criteria, have been proposed, but are not yet formally adopted. The Scoper criteria classify sleep tests by the parameters being assessed within a given individual test and is a reasonable alternative to the Type I-IV classification.<sup>572</sup>

A type III device that is FDA approved uses peripheral arterial tone (PAT) in combination with actigraphy, and pulse oximetry to diagnose OSA as opposed to the traditional combination of airflow, respiratory effort, and pulse oximetry used in other type III devices<sup>573</sup>. The algorithm correlates low oxygen saturation with sympathetic tone (determined by the peripheral arterial tone) to determine if low oxygen is due to an obstructive event (event with decreased oxygen saturation associated with high sympathetic tone) or central event (events with decreased oxygen saturation associated with low sympathetic tone)<sup>573-575</sup>. It also uses an actigraph to identify which potential events occurred in wakefulness or sleep. The device is worn around the wrist and has two finger probes. The actigraph is in the body of the device and detects movement of the arm to approximate sleep and wake. Obstructive events cause increased sympathetic activity which will lead to vasoconstriction of digital blood vessels resulting in attenuation of the PAT signal<sup>573,576</sup>. The device will report estimates of the AHI, sleep time, lowest oxygen saturation, REM percentage, and oxygen percentage<sup>573</sup>. Studies comparing PAT technology to PSG found a strong correlation of AHI and lowest oxygen saturation between the two study devices as well as reliable reproducibility with the PAT device results<sup>573-575</sup>.

**Table VI.F.1: Overview of the types of sleep testing, strengths, and associated limitations.**

	Type I	Type II	Type III	Type IV
Specifications	Full-attended polysomnography (≥7 channels)  EEG, EOG, EMG, ECG, airflow, effort, oximetry	Full-unattended polysomnography (≥7 channels)  EEG, EOG, EMG, ECG, airflow, effort, oximetry	Limited channel devices (4-7 channels)  ECG, airflow, effort, oximetry	1 or 2 channels with one typically being oximetry  Oximetry and other
Common examples	Routine Polysomnography	NA	Alice PDX Apnealink PAT	Pulse oximetry
Strengths	Gold-standard sleep staging and event scoring	Done at home  Diagnostic accuracy to rule in/out OSA	Done at home  Sufficient to rule in OSA	Done at home  Simple set up
Limitations	Requires subject to stay overnight	Requires technical expertise to set	High level of pre-test probability	Very limited data collected

	in the sleep lab and has greater associated costs	up and administer appropriately  Not appropriate for complex patients	required in order to accurately diagnose OSA	Additional testing often warranted
--	---	---	--	------------------------------------

### VI.F.2 Home Sleep Studies

A Home Sleep Apnea Test (HSAT) is recommended for the evaluation of patients with high clinical probability of OSA along with a comprehensive sleep evaluation<sup>577</sup>. Systematic reviews and meta-analyses of well-designed RCTs demonstrate that treatment outcomes and adherence are not statistically different between subjects diagnosed with HSAT or polysomnography (PSG).<sup>572,578</sup> Current guidelines recommend using polysomnography or home sleep apnea testing with a technically adequate device for OSA diagnosis.<sup>577</sup> These devices include type I-IV monitors (see section on Types of Sleep Studies). There is increasing evidence supporting the use of some home-based type III and IV type sleep studies to “rule-in” but not “rule-out”<sup>579</sup> moderate to severe OSA. Such devices may therefore prove useful in populations where there is high prevalence of OSA or when combined with validated sleep questionnaire(s) that enhance the pre-test probability of moderate to severe OSA<sup>580</sup>. A 18% false negative rate for HSAT in high-risk patients has been observed<sup>571</sup>, and therefore, if a single HSAT is negative, inconclusive, or technically inadequate, an in-laboratory, attended<sup>572,578</sup> PSG should be performed. In addition, a meta-analysis of laboratory versus HSAT concluded that they both provide similar diagnostic information, but HSAT may underestimate severity of AHI by around 10%.<sup>581</sup>

Meta-analyses have been conducted comparing type III portable studies and type I (PSG) studies in uncomplicated patients at risk for OSA<sup>582</sup>. The type III portable studies measured airflow, thoracoabdominal effort, oxygen saturation, and body position. The results showed that type III devices are both sensitive and specific for the diagnosis of OSA. In addition, as disease severity increases, there is increased specificity and decreased sensitivity. The technical failure rate is also higher for portable monitoring done at home as opposed to in the lab<sup>582</sup>. Therefore evidence supports that type III studies are useful to diagnose OSA in those with a high pre-test probability of having moderate to severe OSA<sup>138,572,578,581</sup>. Meta-analysis comparing one channel, two channel, and four channel HSATs, showed that the sensitivity is increased for devices using four channels compared to one or two channels.<sup>583,584</sup> Also sensitivity decreases and specificity increases when the AHI cut off was moved from 5 to 15 events/hour. It has been concluded that using type IV (1-2 channels) devices may lead to a higher number of false positives and negatives compared to type III devices but may have a role in screening for OSA in areas where access to type I and III studies are limited.

Subjects with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular conditions, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia, were excluded from most studies and therefore a PSG is recommended over HSAT in these cases.<sup>578</sup> However, there is emerging data from small RCTs that HSAT can be feasibly implemented after stroke or TIA or even patients in a stroke rehabilitation unit.<sup>585,586</sup> Therefore, this population could be considered for testing with HSAT.



On a practical level, the patient's insurance coverage may be the major determinant for which test is utilized. We recommend that if a single HSAT is negative, inconclusive, or technically inadequate, in-lab polysomnography be performed for the diagnosis of OSA.<sup>138</sup> More robust evidence based economic evaluation is needed to guide decision-makers about the cost and effectiveness of home-based testing compared to PSG. The gold standard diagnostic tool is polysomnography (PSG), yet the test is expensive, labor intensive and time-consuming. Home-based testing can broaden access to diagnostic services, in hopes to reduce the substantial economic burden related to OSA and provide consistent results signifying similar effectiveness<sup>138</sup>.

We recommend against home sleep testing for the routine assessment of isolated insomnia, restless legs syndrome or uncomplicated parasomnias if one of these conditions are considered the likely primary abnormality. HSAT may be considered if there is a high suspicion of overlapping OSA, as insomnia and OSA may co-exist in up to 30% of sleep clinic populations.<sup>587</sup> We recommend that if a HSAT is used to rule in OSA, there are clearly defined pathways for assessing the pre-test probability and co-morbidities. We recommend that if HSAT confirms diagnosis of OSA, there is no further need to confirm with in-lab PSG.<sup>457,578</sup>

#### Home Sleep Apnea Testing for Diagnosis of OSA

**Aggregate Quality of Evidence:** A (11 Level 1a studies; 13 Level 1b; 3 level 2a, and 14 Level 2b studies, 1 level 2c and 3 level 3b studies).

**Benefit:** HSAT with type III devices have good diagnostic accuracy in selected patients. HSATs are useful in populations with a high prevalence of OSA or when combined with validated sleep questionnaire(s) that enhance the pre-test probability of moderate to severe OSA.

**Harm:** Specificity of HSAT is lower in mild OSA patients. AHI, recording time, and sleep position affect the accuracy of HSAT. The moderate false negative rate seen with HSAT can potentially delay diagnosis and treatment.

**Cost:** A home-based diagnostic pathway for OSA is associated with lower costs than a laboratory-based pathway from insurance payer's perspective. There is substantial gap in the literature to guide home-based testing decision making and cost-benefit tradeoffs.

**Benefits-Harm Assessment:** In patients with high pretest probability of OSA, HSAT can diagnose OSA. The benefits outweigh the harms. HSAT is valued for testing convenience, potential cost savings and allows for increased access to testing. Certain populations may benefit from PSG over HSAT testing.

**Value Judgments:** Sleep study data represent only one component of the OSA diagnosis. Clinical history and examination are as important and are complimentary to the sleep study.

**Recommendation Level:** Recommendation

**Intervention:** Home Sleep Apnea Testing (HSAT) may be used for evaluation of patients with a high pre-test probability for obstructive sleep apnea. Inadequate or inconclusive results on HSAT may require PSG testing.

**Table VI.F.2: Home Sleep Study Testing Compared to PSG**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion

Kushida et al. <sup>577</sup>	2005	1a	Guideline	3464 studies	Standards of Practice: AASM indications for PSG for sleep disorders.	For patients with high-pretest-probability, type 3 sleep study may be an acceptable alternative to full-night PSG. In the unattended setting, or in patients without high pretest probability stratification, the data does not support the use of these devices.
Collop NA, et al. <sup>578</sup>	2007	1a	Systematic review	70 studies	Clinical Guidelines for the Use of unattended portable monitors in diagnosing OSA.	Portable monitoring for the diagnosis of OSA should be performed only in conjunction with a comprehensive sleep evaluation. In the absence of a comprehensive sleep evaluation, there is no indication for portable monitoring.
Collop NA, et al. <sup>572</sup>	2011	1a	Systematic review	27 RCTs	OOB testing with devices that measure Sleep, Cardiovascular, Oximetry, Position, Effort, Respiratory (SCOPER) parameters.	The literature is currently inadequate to state that a thermistor alone without any effort sensor is adequate to diagnose OSA.
Masa JF et al. <sup>579</sup>	2011	1b	Multicenter, randomized, blinded crossover study	366 patients suspected of OSA	Diagnostic and cost effectiveness of home testing compared with in-hospital PSG.	Home respiratory polygraphy is a cost-effective alternative to polysomnography for sleep apnea/hypopnea diagnosis. Telematic procedures may help patients with limited mobility and those who live a long way from the sleep center.

Masa JF, et al. <sup>588</sup>	2013	1b	Randomized control blinded trial	348 patients with suspected OSA	Diagnostic cost-effectiveness of a sequential HRP scoring protocol compared with manual HRP scoring, and with in-hospital PSG.	Manual HRP scoring had better agreement than automatic HRP scoring; The sequential HRP protocol is a cost-effective alternative to PSG; and the cost savings of the sequential HRP protocol is low in comparison to the manual HRP protocol.
Kim RD, et al. <sup>138</sup>	2015	1a	Economic analysis of RCT-home PAP	373 at risk for moderate to severe OSA	Cost-minimization analysis of home vs lab sleep study.	Per subject costs for the in-lab testing were \$1,840 compared to \$1,575 for home testing for the payer. Costs for the laboratory arm were \$1,697 compared to \$1,736 in the home arm for the provider.
Jonas D E, et al. <sup>457</sup>	2017	1a	Random-effects meta-analyses	110 studies	Review primary care-relevant evidence on screening adults for OSA, test accuracy, and treatment of OSA.	There is uncertainty about the clinical utility of all potential screening tools. Although screening with Multivariable Apnea Prediction, followed by home PM testing may have promise for distinguishing persons in the general population who are more or less likely to have OSA, current evidence is limited.
Abrahamyan L, et al. <sup>584</sup>	2018	1a	Systematic review and meta-analyses	24 full-text articles for final review	Systematically review the evidence on diagnostic ability of type IV PMs compared to PSG for OSA diagnosis.	Use of level IV PMs in clinical practice can potentially widen access to diagnosis and treatment of OSA, but evidence is not strong.

Corral J, et al. <sup>589</sup>	2017	1b	Multicentric non-inferiority RCT with two open parallel arms and a cost-effectiveness analysis	430 screened patients with sleep apnea suspicion	Long-term effectiveness of home versus lab PSG in patients with intermediate-to-high sleep apnea suspicion.	The home testing protocol was noninferior to the PSG protocol based on the Epworth scale. Home testing was the most cost-effective protocol, with a lower per-patient cost of 416.7€.
Douglas JA, et al. <sup>590</sup>	2017	1a	Guideline/position paper utilizing well designed RCTs.		Consensus statement on the indications and performance of sleep studies in adults.	There is increasing evidence supporting the use of some home-based type 3 and 4 type sleep studies to “rule-in” moderate to severe obstructive sleep apnea in high prevalence obstructive sleep apnea, and should be used under the supervision of an accredited sleep physician.
Kapur VK et al. <sup>571</sup>	2017	1a	Systematic review and meta-analysis	98 studies included in evidence based recommendations and 86 included in meta-analysis  Clinical Practice Guideline (AASM).	Guidelines on appropriate and effective diagnosis of OSA.	Polysomnography, or home sleep apnea testing with a technically adequate device, be used for the diagnosis of OSA in uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA. If a single home sleep apnea test is negative, PSG be performed for the diagnosis of OSA.

El Shayeb, et al. <sup>582</sup>	2014	1a	systematic review and meta-analyses	From 59 studies, 19 studies were included in the meta-analysis	Assess the diagnostic accuracy of level 3 testing compared with level 1 testing and to identify the appropriate patient population for each test.	Level 3 sleep studies are safe and convenient for diagnosing OSA in patients with a high pretest probability of moderate to severe forms of the condition without substantial comorbidities.
Rosen CL, et al. <sup>591</sup>	2012	1b	Randomized, open-label, parallel group, unblinded, multicenter clinical trial	7 AASM accredited centers recruited adults with high probability of OSA and ESS>12  Home PAP study	To test the utility of an integrated clinical pathway for OSA diagnosis and CPAP treatment using portable monitoring devices.	A home-based strategy for diagnosis and treatment compared with in-laboratory PSG was not inferior in terms of acceptance, adherence, time to treatment, and functional improvements.
Gabriela A, et al. <sup>592</sup>	2019	2b	Randomized, prospective, cross-over and single blind clinical trial	251 patients	Automatic validation of a new HRP system.	The automatic analysis of the HRP BTI-APNiA software presents a high validity in comparison to the AHI results measured by PSG. HRP BTI-APNiA is a valid alternative to PSG.

Flemons WW, et al. <sup>593</sup>	2003	1a	Systematic review	51	To assess the utility of portable monitors in diagnosing sleep apnea in adults.	High-quality studies of type 3 monitors in the sleep laboratory attended setting had low false-positive rates; most studies found a threshold that distinguished patients with sleep apnea from those without.
Chesson AL, et al. <sup>594</sup>	1997	2a	Systematic review	MEDLINE search; January 1966- April 1996	Indications for PSG.	22% failure rate of home based study to diagnose OSA.
Garcia-Diaz E, et al. <sup>595</sup>	2007	1b	Prospective randomized study with blinded analysis	62 patients with suspected OSA included	Utility and reliability of a respiratory polygraphy (RP) device with actigraphy in the diagnosis of sleep apnea-hypopnea syndrome.	HPR is an effective and reliable technique for the diagnosis of SAHS, although it is less sensitive than LRP. Wrist actigraphy improves the results of HRP only slightly.
Ayappa I, et al. <sup>596</sup>	2008	2b	Prospective study with blinded analysis	102 subjects recruited. 96 returned to lab	Validity of the Apnea Risk Evaluation System (ARES™) Unicorder, for the evaluation of sleep disordered breathing.	ARES™ Unicorder provides acceptably accurate estimates of SDB indices compared to conventional laboratory NPSG for both the simultaneous and in-home ARES™ data.

Garg N, et al. <sup>580</sup>	2014	1b	RCT crossover	75 urban African Americans with high pre-test probability of OSA, identified with the Berlin questionnaire	Feasibility of home PM in an urban population at risk for OSA compared to in-laboratory polysomnography (PSG) and patient preference with respect to home PM versus PSG.	Home PM for diagnosis of OSA in a high risk urban population is feasible, accurate, and preferred by patients. As home PM may improve access to care, the cost-effectiveness of this diagnostic strategy for OSA should be examined in underserved urban and rural populations.
Skomro RP, et al. <sup>597</sup>	2010	1b	Randomized trial	102 subjects	Compared subjective sleepiness, sleep quality, quality of life, BP, and CPAP adherence after 4 weeks of CPAP therapy in subjects diagnosed via lab versus home testing.	Compared with the home-based protocol, diagnosis and treatment of OSA in the sleep laboratory does not lead to superior 4-week outcomes in sleepiness scores, sleep quality, quality of life, BP, and CPAP adherence.
Abraham WT, et al. <sup>583</sup>	2006	2b	Prospective multi-center study	50 patients with NYHA III CHF (SEARCH Study)	Validity and clinical utility of home testing for SDB and arrhythmias in HF.	With CPS compared in in-lab PSG, the diagnostic accuracy was between 83-87% for OSA based on AHI of 5, 10 and 15.
Bravata DM, et al. <sup>598</sup> .	2017	1a	Randomized controlled intervention trial	225 randomized patients	Evaluate whether the intervention strategy improved sleep apnea detection and treatment,	The use of portable polysomnography, and auto-titrating CPAP in the patients' homes, improved both the diagnosis and the treatment for sleep apnea compared with usual care but did

					and hypertension control among patients with chronic cerebrovascular disease and hypertension .	not lower blood pressure.
Kotzian ST, et al <sup>585</sup> .	2018	1b	Single-blind, single center, randomized controlled trial	55 patients (HOPES Study)	Determine whether PAP adherence in patients who had a stroke with OSA can be improved by a PAP training strategy during in hospital rehabilitation combined with a telemedicine monitoring system after discharge.	Pre-results To our clinical experience, a severe SA in the screening PG remains a severe SA also in PSG. The diagnosis will not change. We think that patients who had severely affected stroke need a quick access to therapy.
Fitzpatrick M, et al. <sup>599</sup>	2020	1b	randomized, parallel, multicenter, single-blind, pragmatic controlled trial	233 patients (SIESTA Trial)	To evaluate the accuracy of the clinical diagnosis of OSA informed by the home sleep study with a Type 4 portable monitor versus Type 1 polysomnography	Home testing with portable devices plays a valuable role for diagnosing of OSA in a variety of settings.



Hui DS, et al. <sup>600</sup>	2017	1b	Prospective, randomized controlled CPAP parallel study	316 patients	Comparisons of home-based versus hospital-based approach in managing patients with suspected obstructive sleep apnea.	Home-based approach is non-inferior to hospital-based approach in managing patients with suspected OSAS, with shorter waiting time, and substantial cost savings
Mulgrew AT, et al. <sup>601</sup>	2007	1b	Randomized, controlled, open-label trial	68 patients	To test the utility of a diagnostic algorithm in conjunction with ambulatory CPAP titration in initial management of obstructive sleep apnea.	In patients with a high probability of obstructive sleep apnea, PSG confers no advantage over the ambulatory approach in terms of diagnosis and CPAP titration. The ambulatory approach may improve adherence to treatment. When access to PSG is inadequate, the ambulatory approach can expedite management of patients in need of treatment.
Guerrero A, et al. <sup>602</sup>	2014	1b	Randomized, blinded, crossover study	56 patients	Evaluate 3 night portable monitoring for OSA diagnosis.	3 consecutive nights of portable monitoring at home evaluated by a qualified sleep specialist is useful for the management of patients without high pretest probability of obstructive sleep apnea or with comorbidities.

Ferber R, et al. <sup>603</sup>	1994	2a	Systematic review	Literature review; MEDLINE (1966-1994)	Usefulness of portable Recording in the assessment of OSA.	No clear guidance for who is appropriate for home testing.
Morales CR et al. <sup>604</sup>	2012	2a	Prospective cohort study	452 participants	Assess utility of Home testing for the elderly with the complaint of daytime sleepiness	Unattended, self-assembled, in-home sleep studies recording airflow and respiratory effort are most useful along with a comprehensive sleep history, is accurate in identifying severe OSAS in older adults.
Pietzsch JB, et al. <sup>605</sup>	2011	1b	Decision-analytic Markov model using Tree-Age Pro 2009 Suite	Comparison of clinical health guidelines and health-economic studies	Benefits and cost-effectiveness of diagnostic tests	For payers, a home-based diagnostic pathway for obstructive sleep apnea with robust patient support incurs fewer costs than a laboratory-based pathway. For providers, costs are comparable if not higher, resulting in a negative operating margin.

### VI.F.3 In-Lab Studies

Traditionally, in-lab PSG has been the testing modality of choice to diagnose and assess the severity of OSA.<sup>577</sup> The 2017 American Academy of Sleep Medicine (AASM) Clinical Practice Guideline (CPG) recommended that polysomnography (PSG) remain the diagnostic testing modality for patients suspected of having OSA who had significant comorbidities or who failed an initial Home Sleep Apnea Test (HSAT), but that HSAT or PSG could be used to diagnose OSA for uncomplicated patients considered to be at risk of moderate to severe OSA.<sup>571</sup> This diagnostic testing section reviewed the literature and updated the indications for PSG in the context of the recent AASM CPG. Namely, it addresses new literature assessing the utility of PSG in patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular condition, awake hypoventilation, suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia.<sup>571</sup>

**Heart failure with reduced ejection fraction (HFrEF or congestive heart failure [CHF]):** HFrEF patients are at high risk for sleep disordered breathing (SDB), including both OSA and central sleep apnea (CSA). HSATs have been evaluated for the diagnosis of SDB in multiple studies of patients with HFrEF, including three level 1b studies, 1 level 2b study and one level 3b study.<sup>583,606-609</sup> In a study of 100 HFrEF patients

undergoing simultaneous home PSG and a 2 channel version of the ApneaLink™, accuracy for an AHI > 5 and > 15 was reported at 94%, though the PSG required a 4% desaturation to qualify as a respiratory event and the HSAT could not distinguish between obstructive and central events.<sup>608</sup> Aurora et al reported that adding an effort belt to the HSAT (ApneaLink™ Plus) yielded similar accuracy and could distinguish obstructive vs central events (obstructive AHI  $r=0.91$ , central AHI  $r=0.998$ ), though the study included only 57 inpatients with decompensated HFrEF.<sup>607</sup> In a prospective multicenter cross-sectional study, stable HFrEF patients (N=47 in the validation group) underwent simultaneous SleepMinder (a novel 2 channel touchless HSAT) and PSG.<sup>609</sup> The SleepMinder required a 50% reduction in airflow only for a respiratory event, while the PSG required 30% drop in flow and 4% desaturations. The SleepMinder had an area under the curve (AUC) of 0.85 but misclassified 19% of patients using an AHI cutoff of 15 to define SDB and was unable to distinguish obstructive versus central events. The nonlevel 1 studies in this group were downgraded due to small numbers and/or antiquated criteria used to define respiratory events.<sup>583,606</sup>

**Chronic obstructive pulmonary disease (COPD):** Patients with COPD are at risk for OSA, but also hypoventilation and nocturnal hypoxemia. Limited data is available to assess the utility of HSATs in the diagnosis of SDB in patients with COPD (one level 1b study and one level 3b study).<sup>610,611</sup> In prospective single center cross-sectional study of 90 outpatients with stable COPD and symptoms of OSA, Chang et al evaluated 1 night with a HSAT device (Nox-T3) and then an in lab PSG with simultaneous Nox-T3 within 1 week.<sup>610</sup> The best agreement was found when the studies were done on the same night, used a 4% desaturation criteria for respiratory events, and used an AHI cutoff of 15 to define SDB. Kappa values ranged from as low as 0.48 (different night, 3% desaturation criteria, AHI cutoff of 5) to 0.93 (same night, 4% desaturation criteria, AHI cutoff of 15). A small (N=33) prospective single center cross-sectional study of patients with stable Gold II and III COPD and symptoms of OSA compared a HSAT (WatchPAT™) to in lab PSG and found good sensitivity (92-96%) with moderate specificities (55-65%), and a concordance of 79% between the tests for an AHI > 15.<sup>611</sup> However, of note, this later study required only a 50% drop in airflow (no associated desaturation) to define a respiratory event on the PSG.

**Post-stroke:** Patients who have had a stroke have a roughly 60-70% risk of having OSA.<sup>612</sup> A single level 2b study compared a HSAT device (Embletta™) to simultaneous PSG within 3 days of an ischemic stroke.<sup>613</sup> In a prospective single center cross-sectional study, Chernyshev and colleagues found HSAT was accurate for diagnosing OSA (accuracy 1.0 and 0.95 for AHI cutoff's of 5 and 15). Both HSAT and PSG events were scored according to the 4% desaturation criteria. The main limitation to the study was that it included only 21 participants.

**Technically inadequate or normal initial HSAT:** A level 2b study performed as a retrospective single center review of patients with a high pretest probability of OSA who had a technically inadequate (N=111) or normal HSAT (N=127) but then a subsequent PSG, found OSA in 71% of the patients with technically inadequate studies and 24% of the patients with normal HSATs.<sup>614</sup> Older age and lower ESS were associated with OSA on the subsequent PSG.

#### Indications for In-Lab Polysomnogram vs. HSAT for OSA Diagnosis

##### Aggregate Quality of Evidence:

For patients with HFrEF: Grade C (*Level 1b: 3 studies; Level 2b: 1 study; Level 3b: 1 study*)

For patients with COPD: Grade C (*Level 1b: 1 study, Level 3b: 1 study*)

For patients following stroke: Grade D (*Level 2b: 1 study*)

For patients with technically inadequate or normal initial HSAT: Grade C (*Level 2b: 1 study*)

**Benefit:** Attended PSG can differentiate obstructive versus central events, which is important for HFrEF and post-stroke patients. PSG can also detect hypoventilation, essential for patients with COPD to provide accurate diagnosis of OSA that may be missed on HSAT.

**Harm:** PSG may limit accessibility for testing when compared to HSAT which may lead to delays in diagnosis.

**Cost:** PSG is more expensive than HSAT.

**Benefits-Harm Assessment:** Benefits outweigh the harms as PSG more accurately diagnoses OSA in patients with significant co-morbidities including HFrEF, COPD or stroke. PSG may be useful in patients with technically inadequate HSATs and in a minority of those with normal HSAT testing.

**Value Judgments:** Missed or delayed diagnoses of OSA will lead to adverse consequences particularly in patients with significant co-morbidities associated with OSA.

**Recommendation Level:** Recommend (in HFrEF, COPD, inadequate or normal HSAT). Option (stroke).

**Intervention:** PSG is indicated for the diagnosis of OSA in patients with HFrEF, COPD, or those with inadequate HSAT results. Patients with a high pretest probability and negative HSAT results should be offered repeat testing with in-lab PSG.

**Table VI.F.3: Diagnostic Testing: Indications for In-Lab Polysomnography**

Study	Year	LOE	Study Design	Study Groups	Clinical End point	Conclusion
CHF						
Abraham WT, et al. <sup>583</sup>	2006	2b	Prospective multicenter study comparing diagnostic accuracy of ClearPath System (CPS) vs. PSG.  Stable CHF with EF ≤35%	Night 1 did both in the lab and Night 2 (< 3 nights apart) was home CPS.  N=50	RDI as determined by 3% desaturations for respiratory events and “flow change.”	1)Same night: RDI>5 sens 92%, spec 52%, acc 73%, AUC NR  RDI>15 sens 67%, spec 78%, acc 75%, AUC NR  2)Different night:  RDI>5 acc 73% RDI>15 acc 77%
de Vries GE, et al. <sup>608</sup>	2015	1b	Prospective single center cross-sectional study in patients with chronic heart failure (stable CHF	Subjects underwent the ApneaLink (2 channel – airflow + oximetry) and simultaneous PSG at home.  N=100	AHI as determined by respiratory events required 30% drop in airflow and 4% desaturations.	AHI > 5 sens 98%, spec 60%, acc NR, AUC 0.94 AHI>15 sens 92.9%, spec 91.9%, acc NR, AUC 0.94  ICC 0.85 for categories  3) 29% CSA, 19% OSA, 13% mixed

			by clinical judgment).			4) Best accuracy at AHI 15. 5) Can't differentiate CSA vs OSA
Araújo I, et al. <sup>606</sup>	2018	3b	Prospective single center cross-sectional study in patients with chronic heart failure (stable CHF by clinical judgment).	Subjects were studied by the ApneaLink (2 channel - airflow+oximetry) and PSG simultaneously during in the sleep laboratory.  N=35	AHI as determined by respiratory events required 50% drop in airflow and 3% desaturations.	AHI > 5 sens 81.8%, spec 61.5%, acc 74.2, AUC 0.85  AHI>15 sens 83.3%, spec 91.3%, acc 88.6, AUC 0.93  AHI correlation r=0.79  Highest accuracy at AHI 15.  Can't differentiate CSA vs OSA  Downgraded due to small number and EF50%.
Aurora RN, et al. <sup>607</sup>	2018	1b	Prospective single center cross sectional study in hospitalized patients with decompensated heart failure (stabilized at the time of testing).	Subjects underwent concurrent ApneaLink Plus (3 channel - airflow, oximetry and effort belt) and PSG.  Recordings blindly scored for OSA and CSA.  N=57	AHI as determined by respiratory events that required a 50% drop in airflow and 3% desaturations (PSG allowed arousals).	AHI > 5 sens 95.8%, spec 80.0%, acc NR, AUC NR  Central AHI>5 sens 90.9%, spec 100%, acc NR, AUC NR  3) ICC 0.89 for categories, Obs AHI r=0.91, Central AHI r=0.99  58.5% central AHI > 5  4) Higher accuracy for central vs obstructive.  5) Can't differentiate CSA vs OSA.

Savage HO, et al. <sup>609</sup>	2016	1b	Prospective multicenter cross-sectional study. Stable CHF patients with an EF<45%.	Subjects underwent simultaneous Sleep Minder (airflow + movement via electromagnetic signals) and PSG. Development (D) (n=28) and validation (V) (n=47) groups were studied.  N=75	AHI as determined by Sleep Minder (SM) required 50% reduction in airflow only. PSG required 30% drop in flow and 4% desaturations.	AHI > 5 sens NR, spec NR, acc NR, AUC NR AHI <sub>≥</sub> 15 sens 70%, spec 89%, acc NR, AUC 0.85  AUC 0.85 for all, 19% misclassified (> <AHI 15) by SM  25%/34% (D/V) with OSA, 11%/9% with CSA  Best accuracy at AHI >30.  Can't differentiate CSA vs OSA.
COPD						
Chang Y, et al. <sup>610</sup>	2019	1b	Prospective single center cross-sectional study in outpatients with stable COPD and symptoms of OSA.	Subjects did 1 night with Nox-T3 and then an in-lab PSG with simultaneous Nox-T3 within 1 week.  N=90	AHI as determined by 2 different definitions for respiratory events: 1) Nox-T3 and PSG respiratory events required 30% drop in airflow and 4% desaturation, and 2) Nox-T3 and PSG respiratory events required 30% drop in airflow and 3% desaturation or, for PSG, an arousal.	Same night 4%: AHI>5 sens 96%, spec 84%, kappa 0.82 AHI>15 sens 95%, spec 98%, kappa 0.93  Different night 4%: AHI>5 sens 95%, spec 78%, kappa 0.75 AHI>15 sens 74%, spec 98%, kappa 0.74  Same night 3% kappa AHI>5 0.58, kappa AHI>15 0.88  Different night 3% kappa AHI>5 0.48, kappa AHI>15 0.70  Nox-T3 more often found hypoxemia (15 vs 5 with AHI < 5 and > 5 mins with sats <=88%.)
Jen R, et al. <sup>611</sup>	2020	3b	Prospective single center cross-	In random order, subjects underwent 1 night PSG and WatchPAT device in	AHI as determined by WatchPAT and PSG.	AHI>5 sens 96%, spec 55.6%  AHI>15 sens 92.3%,

			sectional study in outpatients > 40 yrs old with stable Gold II and III COPD and OSA symptoms.	the lab and another night with the WatchPAT at home.  N=33	WatchPAT uses PAT with either a 3% with "arousal" or 4% desaturation.  PSG required 50% drop in airflow without desaturation or arousals	spec 65.0%  3) Intraindividual AHI difference 78.8% concordance (AHI>15 and difference <10)
CVA						
Chernysh ev OY, et al. <sup>613</sup>	2015	2b	Prospective single center cross-sectional study of inpatients admitted for acute ischemic stroke. Studied within 72 hours of the CVA.	Subjects underwent a simultaneous PSG and HSAT within 3 days of their CVA.  N=21  BMI 33.1 (OSA) vs 23.8 (no OSA),  66.6% had an AHI>5,  48% had OSA, 19% had CSA	AHI as determined by HSAT and PSG. Respiratory events required 30% drop and 4% desaturation.	For OSA only:  AHI>5 sens 100%, spec 85.7%, acc NR, AUC 1.0  AHI>15 sens 100%, spec 83.9%, acc NR, AUC 0.95  Intraindividual AHI difference 1.5  Downgraded due to small number.
Failed HSAT						
Zeidler MR, et al. <sup>614</sup>	2015	2b	Retrospective single center review of patients referred for OSA evaluation who had a technically inadequate (N=111) or	All had a high pretest probability of OSA.  N=238	Respiratory events scoring criteria not defined for HSAT or PSG. OSA defined by an AHI > 5.	1) Technically inadequate HSAT:  71% with OSA: 38.7% mild, 32.4% moderate/severe  2) Normal HSATs:  24% OSA: 18.1% mild, 5.5% moderate/severe

			normal HSAT (N=127) but then had a subsequent PSG.			Older age and lower ESS were associated with OSA on PSG.
--	--	--	--	--	--	--

#### VI.F.4 Oximetry

**General population:** In the general population, two level 1b studies,<sup>498,615</sup> three level 2b studies,<sup>616-618</sup> and one level 3b<sup>619</sup> found reasonably good correlations between oximetry ODI and PSG AHIs, though primarily when the 4% desaturation criteria was used to score respiratory events. For example, in a study by Pataka et al, utilizing a 4% desaturation definition, there was good correlation between the ODI4% and the PSG ODI ( $r=0.95$ ), and for  $AHI > 15$ , ODI4% had a sensitivity, a specificity and a AUC of 82%, 94%, and 90%.<sup>615</sup> However, a number of these studies were downgraded for using the oximetry off the PSG as the comparison to the PSG derived AHI,<sup>616,617</sup> or for using highly selective populations.<sup>618</sup>

Two studies used acoustic devices to diagnosis OSA, one level 2b study<sup>620</sup> and one level 4 study.<sup>621</sup> In an exploratory study by Erdenebayar et al, there was moderate accuracy between in-lab PSG AHI and the piezo-electric sensor snoring index when worn at the same time as the PSG.<sup>620</sup>

**Heart failure with reduced ejection fraction (HFrEF or CHF):** The accuracy of oximetry in patients with HFrEF was assessed by two level 1b studies (Sharma et al, 2017 and Ward et al)<sup>618,622</sup> and one level 3 b study (Sharma et al, 2015).<sup>623</sup> The study by Sharma et al, 2017, was a prospective single center, controlled trial of 105 inpatients with acute CHF, where simultaneous HSAT with ApneaLink™ and a high-resolution pulse oximetry (HRPO) was performed for a single night.<sup>618</sup> The HSAT-derived respiratory event index (REI) was compared to the HRPO-derived oxygen desaturation index (ODI) using 30% drop in flow with 4% oxygen desaturations. The receiver operating curve (ROC) analysis showed an area under the ROC curve (AUC) of 0.89 for  $REI > 5$  events/h with 88% of the REI in the moderate-severe category being correctly classified. However, HRPO was unable to reliably differentiate between central and obstructive respiratory events. The second level 1b study by Ward et al was also a prospective, single center study of 173 CHF patients with simultaneous recording of unattended PSG, ambulatory electrocardiography and overnight pulse oximetry performed at the home or hospital per patient preference.<sup>622</sup> The results demonstrated that at the cutoff of  $>7.5$  desaturations/hour, the ODI3% had a sensitivity 97%, a specificity 32%, a negative likelihood ratio 0.08 and a positive likelihood ratio 1.42. The diagnostic accuracy increased using a cutoff of 12.5 desaturations/hour, with a sensitivity 93% and a specificity 73%. The ODI3% had an AUC of 0.92 (95% C.I. 0.88 - 0.96) for detection of SDB in CHF, at the cutoff of  $>7.5$  desaturations/hour. The third study, by Sharma et al, 2015, a level 3b study, was a prospective, single center, in patients admitted with acute decompensated heart failure patients with a high clinical suspicion of SDB and an ODI4%  $\geq 5$  on overnight photoplethysmographic signal recording who underwent PSG.<sup>623</sup> Among 86 patients who had oximetry, 68 underwent outpatient PSG within 4 weeks of discharge. Utilizing an  $AHI \geq 5$  to define OSA, the AUC was 0.82.

**COPD:** One each of level 1b, 2b and 3b studies met criteria for inclusion.<sup>624-626</sup> The study by Andrés-Blanco et al, a level 1b study, was a prospective single center in 193 COPD patients, where supervised portable oximetry was compared simultaneously to in-hospital PSG as well as to unsupervised portable oximetry at home.<sup>624</sup> A control group of 100 non-COPD patients was also included. An ODI4% cutoff was used for the oximeter. There were no significant differences between COPD and non-COPD groups



in both settings, particularly for severe OSAS. In a level 2b study, Scott et al compared overnight oximetry results to PSG in 50 COPD patients on long-term oxygen therapy.<sup>626</sup> Pulse oximetry tracing interpretation had a modest diagnostic value in identifying OSA in patients with moderate to severe COPD; the AUC was 0.57-0.64.

**Atrial Fibrillation (AF):** One level 2b study by Linz et al met criteria for inclusion.<sup>25</sup> It was a large prospective single center study in patients with documented AF (62% paroxysmal AF) who underwent PSG. Overnight oximetry from the PSG was used to determine the ODI and this was validated against the PSG AHI. In 439 patients with AF, the median AHI was 9.5 [3.6–21.0]/h and the prevalence of moderate (AHI 15–29/h) and severe SDB (AHI  $\geq$  30/h) was 17.3% and 16.6% respectively. The ODI4% was able to detect moderate-to-severe SDB with an AUC of 0.95 and only severe SDB with AUC 0.93. An ODI4% of 7.6/h yielded a sensitivity and specificity for AHI  $\geq$  30/h of 89% and 83%, respectively. However, oximetry was unable to distinguish between central or obstructive respiratory events.

**Post-stroke:** There were only two level 2b oximetry studies and one level 3b sonography study that were included in this analysis.<sup>627-629</sup> Lin et al performed a retrospective study in 254 acute stroke patients who underwent HSAT.<sup>628</sup> The ODI3% from the pulse oximetry channel was compared to respiratory event index (REI) obtained from HSAT devices. Nocturnal pulse oximetry had a high diagnostic accuracy in predicting moderate to severe SDB in patients with acute stroke and the ODI3% was accurate in predicting SDB at different REI thresholds (REI  $\geq$  5, REI  $\geq$  15, and REI  $\geq$  30 events/h) with AUCs of .965, .974, and .951, respectively. Aaronson et al also performed retrospective analysis of data obtained from 56 stroke patients who underwent nocturnal polygraphy and oximetry.<sup>627</sup> Sensitivity, specificity, and positive and negative predictive values for the ODI4%  $\geq$ 15 were, 77%, 100%, 100%, and 83%, respectively. Ryan et al reported on 23 patients who were post-stroke and had SDB.<sup>629</sup> Using a cutoff AHI of  $\geq$ 15 by PSG to diagnose OSA, in-lab use of the BresDx (single channel acoustic device) had a sensitivity of 90.0%, a specificity of 84.6%, and an overall accuracy of 87.0%. Bland-Altman plot showed close agreement, although a tendency for the BresDx device to slightly overestimate the AHI. The AUCs for PSG diagnostic AHI thresholds of  $\geq$ 5,  $\geq$  10, and  $\geq$ 15 were 0.90, 0.91, and 1.00, respectively. Comparing the home use of BresDx versus in-lab PSG, using an AHI threshold of  $\geq$ 15, the BresDx had a sensitivity of 100%, a specificity of 85.7%, and an overall accuracy was 91.3%.

### Oximetry for OSA Diagnosis

#### Aggregate Quality of Evidence:

For the general population: Grade C (*Level 1b: 2 studies; Level 2b: 3 studies; Level 3b: 1 study*)

For patients with HFrEF: Grade C (*Level 1b: 2 studies; Level 3b: 1 study*)

For patients with COPD: Grade C (*Level 1b: 1 study; Level 2b: 1 study, Level 3b: 1 study*)

For patients with atrial fibrillation: Grade D (*Level 2b; 1 study*)

For patients following stroke: Grade D (*Level 2b: 2 studies; Level 3b: 1 study*)

**Benefit:** Overnight oximetry is less costly intervention than PSG for the diagnosis of SDB and is readily available. The use of oximetry may allow early diagnosis of SDB and in turn may lead to more timely treatment of OSA with PAP.

**Harm:** Include risks of missed diagnoses and inability of overnight oximetry to differentiate obstructive vs. central events. Overnight oximetry is also unable to detect hypoventilation. Variability in interpretation of overnight oximetry between providers is recognized and may lead to inaccurate treatments. Small patient samples in some of the studies reduced generalizability of the results.

**Cost:** There was no formal cost assessment in the studies reviewed.

**Benefits-Harm Assessment:** Missed diagnoses with oximetry may lead to harm from undiagnosed OSA in patients with heart failure, atrial fibrillation, COPD or stroke. The inability to distinguish between ob-

structive and central events, coupled with variability in interpretation of studies can also lead to incorrect treatments. Combined, these harms outweigh the benefits of overnight oximetry to diagnose OSA. **Value Judgments:** Missed diagnoses of OSA will lead to adverse consequences of OSA as it would lead to incorrect or delayed therapy.

**Recommendation Level:** Recommend against (heart failure, atrial fibrillation, COPD, and stroke); Option (general population).

**Intervention:** Oximetry is not recommended for the diagnosis of OSA in patients with heart failure, atrial fibrillation, COPD or stroke. Oximetry may be an option for the general population without comorbidities, but more evidence is required.

**Summary**

This evidence-based review updated the review of the literature in the areas of diagnostic testing for patients with comorbid conditions and a moderate to high risk for OSA. While new data was found evaluating alternative diagnostic approaches, the weight of the evidence for each comorbidity did not support changing the 2017 CPG recommendations that in-lab PSG remains the diagnostic testing approach of choice for these patients.

Future research should account for several considerations. First and foremost, consideration should be given to the different definitions used to determine hypopneas as these differences will significantly impact the accuracy of testing that does not measure sleep and arousals, and as a result may affect long-term health outcomes in patients with OSA not associated with significant hypoxemia. Future work should also focus on the ability to predict patients likely to have false-negative HSAT or overnight oximetry testing results that may warrant follow-up testing, and what the impact of missed diagnosis may have on outcomes. Certain patient populations are at risk for complicated breathing disorders, including CSA and hypoventilation, and research is needed to advance technology for alternative testing devices that should take these factors into consideration. And finally, there is a lack of knowledge regarding the financial analysis of different approaches to diagnosing OSA in these specific high-risk patient populations.

**VI.F.4 Evidence for Oximetry for Diagnosis of OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical End point	Conclusion
CHF Sharma S, et al. <sup>618</sup>	2017	1b	Prospective single center, controlled trial -of patients admitted with CHF.	Simultaneous measurement of Apnea Link and high-resolution pulse oximetry (HRPO) for a single night  N= 105 61 (58%) M	HRPO-derived ODI (oxygen desaturation index) was compared with PM-derived respiratory event index (REI) using receiver operator characteristic (ROC) curve	1) ROC area under curve (AUC) was 0.89 for REI > 5 events/h. AUC ranged from 0.84 (REI ≤ 10 events/h) to 0.89 (REI ≤ 5 events/h and REI ≤ 20 events/h). 2) The Bland-Altman plot had good agreement 3) 88% of the REI in

					analysis and a Bland-Altman plot	moderate-severe category were correctly classified 4) Can't differentiate CSA vs OSA
Sharma S , et al. <sup>623</sup>	2015	3b	Prospective , single center cohort of consecutively admitted acute decompensated heart failure patients with high clinical suspicion of SDB .	Overnight (ON) inpatient oximetry (photoplethysmography) compared with outpatient PSG apnea hypopnea index (AHI).  N=105 subjects had ON oximetry and 68 underwent outpatient PSG within 4 weeks of discharge.	PSG defined hypopneas as some drop in flow with 4% oxygen desaturation compared with ON oximetry ODI of 4% desaturation  using ROC analysis and Bland-Altman plot	1) ODI correlated with AHI with AUC of 0.82 on ROC for AHI $\geq$ 5  2) The Bland-Altman plot had no major bias
Ward NR, et al. <sup>622</sup>	2012	1b	Prospective, single center cohort of CHF patients from cardiology clinics.	Simultaneous unattended PSG, ambulatory electrocardiography and ON pulse oximetry at home or hospital  N=173 86% M	Compared oximetry % ODI cutoff of >7.5 desaturations/hour to PSG AHI >15/hour. ODI used 3% desaturation. PSG defined hypopneas as 50% drop in flow with 3% desaturation or arousal.	1) At a cutoff of >7.5 desaturations/hour, the ODI3% had sensitivity 97%, specificity 32%, negative likelihood ratio (LR) 0.08 and positive LR 1.42.  2) At a cut-off of 12.5 desaturations/hour, ODI3% sensitivity was 93% and specificity was 73%.  3) The 3% ODI had an AUC under ROC curve of 0.92 for detection of SDB in CHF, at the cutoff of >7.5 desaturations/hour.
COPD						

Andrés-Blanco AM, et al. <sup>624</sup>	2017	1b	Prospective single center cohorts.	<p>Simultaneous portable ON oximetry at home and in- hospital PSG; and unsupervised portable ON oximetry at home</p> <p>Two independent validation datasets were analyzed: COPD versus non-COPD.</p> <p>N= 110 non-COPD test set (69% M) and 68 COPD test group (88% M)</p>	<p>A regression-based multilayer perceptron (MLP) artificial neural network (ANN) was trained to estimate AHI from portable oximetry recordings. Two independent validation datasets were analyzed: COPD versus non-COPD</p>	<p>1) Portable ON oximetry-based ANN reached similar ICC values between the estimated and actual AHI for the non-COPD and the COPD groups either in the hospital (non-COPD: 0.937, COPD: 0.936) and at home (non-COPD: 0.731, COPD: 0.788) setting.</p> <p>2) No significant differences in ROC between COPD and non-COPD groups in both settings</p>
Lajoie AC, et al. <sup>625</sup>	2020	3b	Prospective cohort recruited from an ongoing multicenter trial.	<p>Compared home ON oximetry and laboratory-based PSG in patients with moderate-to-severe COPD.</p> <p>N=90</p> <p>45 had OSA, 71% M</p> <p>45 did not have OSA, 87% M</p>	<p>ODI3% used for oximetry.</p> <p>AHI hypopnea definition not stated.</p>	<p>1) Oxygen desaturation indices obtained with nocturnal oximetry and during PSG were not correlated (<math>r = -0.27</math>; <math>p = 0.1</math>).</p> <p>2) Diagnosis of OSA in COPD should not be based solely on oximetry. OSA was confirmed in only 50% of subjects with oximetry tracings suggestive of OSA.</p>
Scott AS, et al. <sup>626</sup>	2014	2b	Consecutive chart review of the inpatient pulmonary rehabilitation service.	<p>Subjects with moderate-severe COPD who were clinically prescribed oximetry and PSG.</p> <p>N=59</p> <p>46% M</p>	<p>Criteria consisted of visually identified desaturation 'events' (sustained desaturation <math>\geq 4\%</math>, 1 hour time scale), 'patterns' (<math>\geq 3</math></p>	<p>1) 35 were correctly identified as having OSA / no OSA with accuracy of 59%, a sensitivity and specificity of 59% and 60%, respectively; AUC 0.57.</p> <p>2) Using software-computed desaturation events</p>

					similar desaturation/saturation cycles, 15 min time scale) and the automated oxygen desaturation index. Compared using AUC.	(hypoxemia $\geq 4\%$ for $\geq 10$ s) indexed at $\geq 15$ events/h of sleep as diagnostic criteria, sensitivity was 60%, specificity was 63% and the AUC 0.64.
<b>Atrial Fibrillation</b>						
Linz D et al. <sup>25</sup>	2018	2b	Prospectively single center cohort in patients with atrial fibrillation (AF) who underwent PSG.	Subjects with documented AF.  N=439 69% M	ON oximetry from the PSG was used to determine the ODI. ODI was validated against PSG AHI.  ODI4% used for oximetry, which came off PSG. PSG hypopnea definition was a 30% drop in flow for 10 seconds with either a 3% desaturation or an arousal.	1) ODI was able to detect moderate-to-severe SDB (AHI $\geq 15$ /hr) AUC: 0.951; severe SDB (AHI $\geq 30$ /h) AUC 0.932  2) An ODI cut-off of 4.1/hour had 91% sensitivity and 83% specificity in patients with and without AHI $\geq 15$ /h.  3) An ODI of 7.6/h yielded a sensitivity and specificity for AHI $\geq 30$ /h of 89% and 83%, respectively.  4) Can't differentiate CSA vs OSA
<b>CVA</b>						
Lin SH, et al. <sup>628</sup>	2018	2b	Retrospective chart analysis.	Subjects with acute stroke or TIA underwent ON oximetry and HSAT.  N=254 50.7% M 232 (91.3%) were ischemic or TIA	ODI from pulse oximetry channel were compared to respiratory event index (REI) obtained from HSAT devices.  ODI3% used for	1) ODI3% had correlation ( $r = .902$ ) and agreement with REI3%.  2) ODI3% was accurate in predicting SDB at different REI thresholds (REI $\geq 5$ , REI $\geq 15$ , and REI $\geq 30$ events/h) with AUC of .965, .974, and .951,

					oximetry. REI3% used for HSAT.	respectively. 3) An ODI3% $\geq$ 5 events/h rules in the presence of SDB (specificity 91.7%, PPV 96.3%). 4) An ODI3% $\geq$ 15 events/h rules in moderate to severe SDB (specificity 96.4%, PPV 95%) and an ODI3% $<$ 5 events/h rules out moderate to severe SDB (sensitivity 100%, NPV 100%).
Aaronson JA, et al. <sup>627</sup>	2012	2b	Retrospective study of stroke patients.	Compared polygraphy and oximetry from HSAT in stroke subjects.  N=56 62% male, 46% of the stroke patients had OSA. 69% with OSA were ischemic strokes.	Compared REI to ODI.  REI hypopneas defined as 50% drop in flow with a 4% desaturation. ODI used 4% desaturation.	1) Sensitivity, specificity, and PPV and NPV for the ODI4% $\geq$ 15 were, respectively, 77%, 100%, 100%, and 83%. 2) ODI4% predicted 87% of the variance in the REI. 3) Given a 46% prevalence of OSA in stroke, the PPV of oximetry was 100% with a NPV of 83%
Ryan CM, et al. <sup>629</sup>	2017	3b	Prospective cohort of patients with acute stroke in a stroke rehabilitation unit (SRU) .	Compared testing with BresoDx – a portable single-channel acoustic device - both simultaneously during attended PSG in lab and unattended on the SRU.  N=23 48% M 78% had OSA (defined by AHI $\geq$ 15) on PSG. 74% of subjects were	Compared PSG AHI to BresoDx AHI.  PSG hypopneas defined by a 30% drop in flow with 3% desaturation or arousal.  Determined AUC and Bland-Altman plot	1) Using cutoff AHI of $\geq$ 15 by PSG to diagnose OSA in-lab BresoDx had sensitivity of 90.0%, specificity of 84.6%, accuracy of 87.0%. 2) Bland-Altman plot: good agreement, but BresoDx overestimated AHI by 4.4. 3) The AUCs for AHI in lab Breos vs in-lab PSG at thresholds of $\geq$ 5, $\geq$ 10, and $\geq$ 15 were 0.90, 0.91, and

				ischemic strokes.		1.00, respectively 4) For home BresoDx vs in-lab PSG, at an AHI threshold of $\geq 15$ had a sensitivity of 100%, specificity of 85.7%, and accuracy of 91.3%.
<b>General</b>						
Pataka A, et al. <sup>615</sup>	2019	1b	Prospective study in a sleep clinic.	Compared sleep questionnaires (STOP-BANG (SB), Berlin (BQ), Epworth Sleepiness Scale (ESS) completed by subjects with home oximetry and in laboratory PSG, to determine predictive value of test for CPAP initiation.  N = 204 77.5% M	Determine correlations and accuracy. Compared PSG and oximetry values as well.  PSG hypopneas defined by a 30% drop in flow with 4% desaturation or arousal.  ODI used 4% desaturations.	1) Good correlation between oximetry ODI (ODIox) and PSG ODI ( $r = 0.95$ , $p < 0.0001$ ) and between ODIox and AHI ( $r = 0.811$ , $p < 0.0001$ ). - ODIox $\geq 15$ had sensitivity 89.3%, specificity 83.5%, PPV 87%, NPV 86.4% for CPAP initiation. 2) Among questionnaires, ESS had highest specificity (68.6%) and PPV (68.6%) and SB had the highest sensitivity (98%) and NPV (80%) but the lowest specificity (11%) for CPAP initiation. Oximetry was superior to questionnaires for predicting CPAP treatment initiation.
Christensson E, et al. <sup>616</sup>	2018	2b	Prospective, observational multicenter trial of sleep clinic patients.	Subjects underwent HSAT (Nox-T3), ON oximetry and STOP-BANG (SB) questionnaires.  N=449 subjects with suspected OSA	Compared REI to ODI. Compared REI to SB questionnaire scores.  HSAT hypopneas defined by 30%	1) Strong correlation between REI and ODI3%, Spearman 0.96 2) Positive correlation between SB score and ODI3%, Spearman $\rho = 0.50$ ; A SB score of $< 2$ almost excludes moderate to severe OSA, whereas

				61.5% M	drop in flow and 30% desaturation.  ODI used 3% for oximetry.	nearly all OSA patients with a SB score $\geq 6$ had OSA.
Sharma S, et al. <sup>618</sup>	2017	3b	Retrospective review of a large database of hospitalized inpatients.  Only those high ODI on ON oximetry were offered PSG.	Compared in-hospital ON HRPO to PSG post-discharge  N=1410 underwent in-hospital HRPO with 1092 having and ODI4% $\geq 5$ . Of these, 680 underwent PSG post-discharge. 54% M (of HRPO group)	Determined accuracy, AUC and Bland-Altman plot of HRPO-determined ODI vs AHI.  ODI used 4% for oximetry.  PSG hypopneas defined by a 30% drop in flow with 4% desaturation.	1) ODI4% $\geq 5$ had sensitivity 0.89 and specificity 0.48. 2) ODI4% $\geq 15$ had a sensitivity 0.65 and specificity 0.90 3) ODI4% $\geq 5$ had an AUC of 0.83 for an AHI $\geq 5$ and 0.76 for an AHI $\geq 15$ 4) Bland-Altman plot showed no significant bias when using ODI vs AHI to define SDB.
Hang LW, et al. <sup>617</sup>	2015	2b	Prospective study of sleep clinic patients undergoing PSG for suspected OSA.	Oximeter from PSG was used for ODI calculation without considering other PSG information.  N=699 (though only analyzed 544 with adequate TST and acceptable PSG signals) 77.1% M  PSG results:  20.6% had an AHI 5-15, 21.4% had an AHI >15-30, 46.3% had an AHI > 30	Compared accuracy and AUC of ODI from PSG oximetry to AHI from same PSG.  ODI used 3% and 4% desaturations.  PSG defined hypopneas as 30% drop in flow with a 4% desaturation.	1) For AHI $\geq 15$ , ODI3% had sensitivity, specificity and accuracy of 86.1%, 92.4%, and 89.5%. 2) For AHI $\geq 15$ , ODI4% had sensitivity, specificity, and accuracy of 85.7%, 89.7% and 87.8%; 3) AUC for severe OSA: 0.953-0.957; AUC of 0.921-0.924 for moderate to severe OSA patients. 4) Limitation due to removal of those with low TST on PSG.



Chung F, et al. <sup>498</sup>	2012	1b	Prospective study of patients presenting to presurgical clinic for elective surgery.	Subjects underwent unattended PSG and ON oximetry on the same night.  N=475 45.7% M	Compared PSG AHI and ON oximetry ODI.  Hypopnea definition was 30% drop in flow and 4% desaturation. ODI used 4% desaturation.	1) ODI4% > 5 had a sensitivity, specificity, accuracy of 0.96, 0.67, 87% for an AHI >5; and 0.99, 0.39, 61.7% for AHI >15 2) ODI4%>15 had a sensitivity, specificity, accuracy of 0.45, 0.98, 62.1% for an AHI >5, and 0.70, 0.93, 84% for AHI >15 3) The AUC for ODI to predict AHI >5, AHI >15, and AHI >30 was 0.908, 0.931 and 0.958, respectively.
del Campo F, et al. <sup>619</sup>	2006	2b	Prospective study of cohort of patients undergoing PSG for suspected OSA.	Oximetry and PSG done at the same time. Approximate entropy (ApEn) (a mathematical tool) was calculated off oximetry and compared with PSG data.  N=187 (22.5% had COPD) 79% M	Determined accuracy between PSG and ApEn.  PSG hypopneas defined by 30% drop in flow with a 3% desaturation.  ODI used 3% and 4% desaturations.	1) AHI correlated with ApEn ( $r = 0.607$ ; $p < 0.001$ ). 2) For AHI > 10, ApEn at 0.679 had sensitivity, specificity, PPV and NPV of 88.3%, 82.9%, 88.3%, and 82.9%, respectively.
Erdenebayar U, et al. <sup>620</sup>	2017	2b	Prospective cross-sectional study of patients referred to a sleep clinic.	Subjects underwent an in-lab PSG and piezo-electric sensor at the same time. The piezo-electric sensor detected snoring and heartbeat information, and snoring index (SI) and features based on pulse rate variability (PRV) analysis. A support vector machine (SVM) was used as a classifier to	Compared accuracy of piezo-electric sensor with PSG.  PSG scored per "AASM standards" but not defined further.	1) Mild OSA detection: sensitivity, specificity, and accuracy of 72.5%, 74.2%, and 71.5%; moderate OSA detection: 85.8%, 80.5%, and 80.0%; and severe OSA: 70.3%, 77.1%, and 71.9%. 2) Automatic snoring detection had sensitivity, specificity, and accuracy of 88.5%, 96.1%, and

				detect OSA events.  N=45  70% M		95.6%.  3) Heartbeat detection had sensitivity and PPV of 94.3% and 87.1%, all respectively.
Alakuijala A, et al. <sup>621</sup>	2016	4	Prospective cross-sectional study of patients referred to a sleep clinic.	Subjects underwent a HSAT (Nox T3) at home. Periodic snoring data was collected from the same HSAT.  N=211  61% M  There was no separate validation group.	Analyzed the percentage of periodic snoring during HSAT and compared to the AHI from the HSAT. Correlations and Bland Altman plot were analyzed.  The HSAT defined hypopneas by 3% desaturations.	1) AHI ranged from 0.1 to 116 events/h , and % of periodic snoring from 1% to 97%.  2) Positive correlation (r = 0.727, p < 0.001) between periodic snoring and AHI.  3) Sensitivity was 93.3%, specificity 35.1%, and NPV 75.0%.  4) Bland-Altman plot showed that periodic snoring percentage, and AHI agreed within range of various grades of OSA.
<b>Neuromuscular Disease</b>						
Aarrestad S, et al. <sup>630</sup>	2018	2b	Prospective cross-sectional study of patients followed for chronic respiratory failure due to neuromuscular disease, treated with chronic noninvasive ventilation (NIV).	All patients underwent the screening test panel (clinical evaluation, daytime arterial blood gas (ABG), nocturnal pulse oximetry (SpO <sub>2</sub> ) and data from ventilator software) , HSAT (Embletta Gold) and nocturnal transcutaneous CO <sub>2</sub> (while on their NIV).  N=67	Compared accuracy among the tests.  HSAT used 4% desaturation criteria. ODI3% used for oximetry.	1)Nocturnal SpO <sub>2</sub> and day-time ABG all failed to accurately detect nocturnal hypoventilation (NH) 2)ODI3% had a high sensitivity but low specificity for identifying obstructive events on NIV.

## VII. Comorbidities Associated with OSA

## VII.A Comorbidities Associated with OSA: Cardiovascular Disease

Obstructive sleep apnea (OSA) is highly prevalent in the general population and in individuals with cardiovascular disease. OSA is characterized by repeated episodes of upper airway collapse during sleep, resulting in intermittent hypoxemia and arousals.<sup>631-634</sup> The accompanying increase in sympathetic activity, inflammation, endothelial dysfunction, and elevated blood pressure is associated with increased risk for cardiovascular morbidity and mortality.<sup>633,635-637</sup>

Many observational studies have demonstrated an association between OSA and incident cardiovascular disease, such as hypertension, atrial fibrillation, coronary artery disease, congestive heart failure, myocardial infarction, stroke, and all-cause and cardiovascular mortality.

### VII.A.1 Cardiovascular and All-Cause Mortality

A recent meta-analysis by Fu et al. examined the relationship between OSA and all-cause and cardiovascular mortality in 27 cohort studies. OSA increased risk for both all-cause mortality (HR 1.86, 95 % CI=1.81–1.91) and cardiovascular mortality (HR 2.36, 95 % CI=1.22–4.57). However, when OSA was stratified by severity, there was no significant association between mild OSA or moderate OSA and all-cause and cardiovascular mortality. Only severe OSA was an independent risk factor for both all-cause and cardiovascular mortality.<sup>638</sup> On cluster analysis of the SantOSA cohort with moderate or severe OSA, the excessive sleepiness subtype was associated with an increased risk of incident cardiovascular mortality.<sup>639</sup>

### VII.A.2 Cardiovascular Disease

Compared to the general population, OSA is highly prevalent (38% to 65%) in patients with coronary artery disease (CAD).<sup>634</sup> Historically, evidence supports a significant association between OSA and CAD.

A large, population-based study was conducted to examine the cross-sectional relationship between OSA and cardiovascular disease (CVD). A cohort of 6,424 subjects aged 40 and older from the Sleep Heart Health Study (SHHS) underwent an unattended polysomnogram and categorized into quartiles of apnea-hypopnea index (AHI). The first, second, third, and fourth AHI quartile ranges were 0-1.3, 1.4-4.4, 4.5-11.0, >11.0, respectively. Of the 6,424 subjects, a total of 1,023 subjects reported at least one CAD outcome, as defined as myocardial infarction, angina, coronary revascularization procedure, heart failure, or stroke. Compared to the first and lowest quartile of AHI, the odds ratio (OR) of prevalent CVD for the second, third and fourth highest quartiles were 0.98 (95% CI=0.77–1.24), 1.28 (95% CI=1.02–1.61), and 1.42 (95% CI=1.13–1.78), respectively indicating that severe OSA is independently associated with CAD events with a dose response relationship after adjusting for demographic variables, tobacco use, cholesterol and hypertension variables.<sup>637</sup>

A secondary analysis of the SHHS cohort examined the prospective association of OSA and CAD. A subset from the SHHS cohort without CAD and heart failure at enrollment, and adequate data for analysis (4,422 subjects, 56.4% women), were followed for a median of 8.7 years for incident cardiovascular disease. After adjusting for other risk factors, OSA was significantly associated and predicted incident CAD events, defined as myocardial infarction, revascularization procedure, or coronary heart disease related death, however this was only observed in men aged 70 or younger (HR 1.10, 95% CI=1.00-1.21 per 10-unit increase in AHI). Severe OSA (as defined by AHI $\geq$  30 events per hour) conferred a stronger increased risk of developing symptomatic coronary artery disease (HR 1.68, 95% CI=1.02-2.76) again seen only in men aged 70 or younger.<sup>640</sup> However, another analysis of the full SHHS cohort has shown severe OSA to

be an independent predictor of death, and in particular death related to CAD. While this relationship was again strongest in men under 70 years of age (adjusted HR 2.09; 95% CI: 1.31–3.33), it was nonetheless seen across all patients with severe OSA in the study population (adjusted HR 1.46; 95% CI: 1.14–1.86).<sup>641</sup>

In addition to evidence supporting an independent link between OSA and incident CAD, there is evidence that OSA may be associated with recurrence of CAD events including restenosis after percutaneous coronary dilation and death among individuals with CAD and OSA.<sup>642</sup> Nakashima et al. conducted a prospective cohort study to determine whether moderate to severe OSA was associated with an increased risk of adverse cardiovascular events in patients who underwent primary percutaneous coronary intervention (PCI). The cohort was comprised of 272 patients who were admitted to the Nagasaki Citizens Hospital with acute myocardial infarction. Patients with moderate to severe OSA had independently and significantly increased acute coronary syndrome recurrence and major adverse cardiac events compared to patients with mild or no OSA.<sup>643</sup>

Participants in the other sentinel community-based prospective observational study of OSA, the Wisconsin Sleep Cohort, were significantly younger than those in the Sleep Heart Health Study. This may provide at least a partial explanation for the much stronger association seen between OSA and CAD in the former, wherein an AHI of  $\geq 30$  conferred a greater than two fold risk of incident CAD and heart failure events (adjusted HR 2.63; 95% CI: 1.13–6.10) over a period of approximately 18,000 person years.<sup>644</sup> The fully adjusted model for incident CAD only was not statistically significant (HR 2.4, CI 0.99–6.0).

The inevitable meta-analyses suggest that OSA confers an increased risk of incident clinically overt CAD in men, with an apparent weaker relationship between OSA and CAD in women.<sup>632,634,638</sup> A systematic review of untreated OSA and long-term adverse outcomes suggested that any negative effect of significant OSA on cardiovascular events was attenuated by female gender, age, a lack of daytime sleepiness, and obesity.<sup>636</sup> Overall, there is relatively strong, but not uniform, evidence from clinical and population studies to support an important role for OSA in promoting the evolution of CAD, particularly in younger male patients.

#### Screening for OSA in Patients with Cardiovascular Disease

**Aggregate Quality of Evidence:** C (Level 1b: 1 study; Level 2a: 3 studies; Level 2b: 16 studies, Level 2c: 1 study; Level 3b: 1 study).

**Benefit:** Earlier diagnosis and treatment of OSA may improve overall health and reduce the risk of all-cause mortality and cardiovascular morbidity and mortality.

**Harm:** Inconvenience of screening and testing.

**Cost:** Costs associated with screening and diagnosis for OSA.

**Benefits-Harm Assessment:** Moderately favors screening for OSA in patients with a history of cardiovascular disease.

**Value Judgments:** There is moderate quality evidence that OSA leads to cardiovascular disease, but low quality evidence that treatment with CPAP reduces this risk. The harm/costs of diagnosis and treatment are low and the benefits outweigh the harms.

**Recommendation Level:** Recommendation.

**Intervention:** Screen for OSA in patients with a history of cardiovascular disease.

Table VII.A.2: Evidence on Coronary Artery Disease and OSA

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Bauters et al. <sup>631</sup>	2015	2b	Review	Review to determine the association between OSA and cardiovascular disease and impact of CPAP treatment on cardiovascular risk factors and outcomes	Hypertension, stroke, ischemic heart disease, heart failure, atrial fibrillation, and cardiovascular mortality	Moderate to severe OSA is independently associated with various forms of CV disease.
Bouzerda <sup>642</sup>	2018	2a	Systematic Review	Review of pathophysiological mechanisms between OSA and cardiovascular disease and to determine prevalence of OSA in general population	Systemic and pulmonary arterial hypertension, heart rhythm disorders, coronary heart disease, heart failure and stroke	Recommend screening for clinical symptoms of OSA in patients with cardiovascular disease.
Campos - Rodriguez et al. <sup>645</sup>	2012	2b	Prospective Cohort Study	Cohort of 116 women consecutively referred to 2 sleep clinics in Spain for suspected OSA between 1998 and 2007 categorized into 5 groups: 1) control without OSA 2) CPAP treated group with mild/mod OSA 3) CPAP treated group with severe OSA 4) untreated group with mild/mod OSA 5) untreated group with severe OSA	Cardiovascular mortality, including death from stroke, myocardial infarction, heart failure or arrhythmia	Severe OSA is associated with cardiovascular mortality in women. Treatment with CPAP may reduce this risk.
Catalan-Serra et	2019	2b	Prospective cohort	Cohort of 1005 consecutive	Incidence of coronary heart	The incidence of stroke, but not

al. <sup>646</sup>			study	<p>patients referred to Sleep Units at 2 Spanish University hospitals who were ≥65 years. They were categorized into 4 groups based on AHI values from sleep studies and CPAP adherence:</p> <ol style="list-style-type: none"> <li>1) control group</li> <li>2) untreated mild-moderate OSA</li> <li>3) untreated severe OSA</li> <li>4) CPAP-treated OSA</li> </ol>	disease and incidence of stroke after adjusting for OSA group, age, BMI, HTN, sex, smoking, ESS, and afib	coronary heart disease, is increased in elderly patients with untreated severe OSA.
Drager et al. <sup>635</sup>	2015	2b	Review	Review of pathogenesis and association between OSA and cardiovascular disease	Cardiovascular disease including hypertension, autonomic dysfunction, insulin resistance, vascular dysfunction, lipid metabolism impairment, atherosclerosis	OSA activates multiple intermediate pathways that lead to cardiovascular disease
Fu et al. <sup>638</sup>	2016	2b	Meta-analysis	27 cohort studies with a total of 3,162,083 participants who were diagnosed with OSA by PSG	All-cause or cardiovascular mortality.	Severe OSA is an independent risk factor for all-cause and cardiovascular mortality. CPAP use significantly reduced both all-cause and cardiovascular mortality in patients with OSA.
Ge et al. <sup>632</sup>	2013	2b	Meta-analysis	6 cohort studies with a total of 9165 adults who had been diagnosed with OSA, of any	Cardiovascular mortality (defined as death from stroke, heart failure, myocardial	Severe OSA is a strong independent predictor for future cardiovascular and all-cause mortality.

				severity, confirmed by using a standardized polysomnography	infarction or arrhythmia), and all-cause mortality	CPAP treatment was associated with reduced risk of cardiovascular mortality.
Gonzaga et al. <sup>647</sup>	2015	2b	Review	Impact of OSA on cardiovascular disease and cardiovascular benefits of CPAP treatment	Prevalence of OSA in patients with hypertension, coronary artery disease, atrial fibrillation, stroke, and heart failure.	OSA is highly prevalent in the general population and those with cardiovascular disease. Screening and treatment are needed to decrease cardiovascular risk.
Gottlieb et al. <sup>640</sup>	2010	2b	Prospective Cohort Study	Cohort of 4422 men and women who are $\geq 40$ years old and free of coronary heart disease and heart failure followed for incident CHD and HF from the Sleep Heart Health Study	Incident CHD (myocardial infarction, CHD death, or coronary revascularization procedure) and incident heart failure	OSA is associated with increased risk of CV outcomes in community-dwelling middle-aged and older men.
Hla et al. <sup>644</sup>	2015	2b	Prospective Cohort Study	1280 men and women from the Wisconsin Sleep Cohort who were free of CHD or HF at baseline and followed for 24 years	Incident CHD or heart failure	Untreated severe OSA was associated with incident coronary heart disease or heart failure.
Javaheri et al. <sup>633</sup>	2016	2b	Prospective Cohort Study	Cohort of 2865 older men from Osteoporotic Fractures in Men Study	Incidence of heart failure	Older men with elevated central sleep apnea index or Cheyne-Stokes breathing had an increased risk for incident HF. However, OSA was not significantly associated with incident HF.

Kasai et al. <sup>648</sup>	2010	2b	Review	Review of association between OSA and heart failure	Cardiovascular function and autonomic function	OSA has adverse cardiovascular effects and is associated with reduced survival in patients with HF.
Loke et al. <sup>649</sup>	2012	2a	Systematic Review	Association between OSA and incident cardiovascular events	Stroke incidence and cardiovascular mortality	OSA is an independent risk factor for stroke and cardiovascular mortality.
Martinez-Garcia et al. <sup>650</sup>	2012	2b	Prospective Cohort Study	Cohort of 943 elderly patients (≥65 years) with mild/mod OSA or severe OSA between 1998 and 2007 categorized into 4 groups  1) control group (AHI<15) 2) untreated mild/mod OSA without CPAP 3) untreated severe OSA 4) OSA treated with CPAP	Cardiovascular mortality defined as death from stroke, heart failure, or myocardial infarction.	Untreated severe OSA is significantly associated with cardiovascular mortality in the elderly.
Nakashima et al. <sup>643</sup>	2015	2b	Prospective Cohort Study	Cohort of 272 patients with acute myocardial infarction who underwent primary percutaneous coronary intervention within 12h of onset.	MACE (cardiovascular mortality, acute coronary syndrome recurrence, and readmission for heart failure)	Pt with untreated moderate-severe OSA had an increased the risk of acute coronary syndrome recurrence. Moderate-severe OSA also increased risk for MI related percutaneous coronary intervention progressive lesions.



Punjabi et al. <sup>641</sup>	2009	2b	Prospective Cohort Study	Cohort of 6441 men and women from the Sleep Heart Health Study	All-cause and cardiovascular mortality.	OSA is independently and significantly associated with all-cause and cardiovascular mortality with a stronger association in men 40-70 years old with severe OSA.
Rosen et al. <sup>636</sup>	2014	2b	Review	Review of the pathophysiology of OSA and heart failure and review of treatment options for OSA in patients with heart failure	Incident heart failure and mortality	Untreated OSA is an independent risk factor for increased mortality in heart failure patients.
Shah et al. <sup>651</sup>	2010	2b	Prospective Cohort Study	Cohort of 1436 patients ≥50 years of age who were referred during 1997-2001 to the Yale Center for Sleep Medicine for suspected sleep disordered breathing	Cardiovascular outcomes myocardial infarction, coronary artery revascularization procedures, or cardiovascular mortality.	OSA increases the risk of coronary events or cardiovascular mortality.
Shahar et al. <sup>637</sup>	2001	2c	Cross-sectional study	Cohort of 6424 participants from the Sleep Heart Health Study	Self-reported cardiovascular disease outcomes defined as MI, angina, coronary revascularization procedure, heart failure or stroke	OSA is associated CVD outcomes, but more strongly associated with self-reported heart failure and stroke than coronary heart disease.
Wang et al. <sup>634</sup>	2018	2a	Systematic Review and meta-analysis	Review of 9 studies (2 RCTs and 7 observational studies) for a total of 1430 patients with CAD and CVD	Adverse CVD event (MACE) -all-cause or cardiovascular death, myocardial infarction, stroke, repeat revascularization, or hospitalization for heart failure.	CPAP may prevent incident cardiovascular events in patients with CAD and OSA. However, this was only shown in observational studies, not in RCTs.

Yeboah et al. <sup>652</sup>	2011	3b	Nested Case Control Study	5338 men and women from MESA Study cohort	Incident cardiovascular events as defined by myocardial infarction, angina, resuscitated cardiac arrest, stroke, stroke mortality, CHD mortality or other CVD death as defined by the MESA protocol.	OSA, but not habitual snoring, was associated with incident CV events and all-cause mortality in adults without CVD.
Yu et al. <sup>653</sup>	2017	1b	Systematic Review and meta-analysis	Review of 10 RCTs with a total of 7266 patients to determine association of CPAP compared with standard care or sham PAP among adults with OSA or central sleep apnea	Acute coronary syndrome events, stroke, or vascular events or death, major adverse cardiovascular events	CPAP use was not significantly associated with reduced risk of cardiovascular outcomes or mortality for OSA patients.

### VII.A.3 Myocardial Ischemia

OSA has been associated with numerous cardiovascular conditions, including coronary artery disease and myocardial ischemia. A number of possible pathophysiologic mechanisms have been implicated including sympathetic nervous system hyperactivity, hypertension, endothelial dysfunction, metabolic dysregulation, insulin resistance and hypercoagulable state.<sup>640,654-662</sup> In addition, OSA results in repetitive hypoxia and re-oxygenation and this has been associated with increased oxidative stress and systemic inflammation. These mechanisms may contribute to the increased risk of atherosclerosis and myocardial ischemia in patients with OSA.

OSA has been associated with coronary artery calcification<sup>663</sup>, plaque instability<sup>664</sup> and vulnerability<sup>643</sup>. During obstructive apneas, increased adrenergic tone and hypoxemia may increase the risk of myocardial ischemia.<sup>665,666</sup> Interestingly, a temporal relationship between hypoxia and the development of ST changes and chest pain has been reported by Franklin et al.<sup>667</sup>. The severity of hypoxemia also appears to be a determinant of ST depression during sleep<sup>668</sup>.

Shah et al.<sup>651</sup> have reported that in an observational cohort of over 1,400 patients, OSA was associated with a two-fold increased risk of cardiovascular events or death even after adjustment for traditional risk factors. This suggests that OSA might independently increase the risk of coronary events. In patients with ST-segment elevation myocardial infarction (STEMI), the prevalence of undiagnosed OSA is almost

40%<sup>669</sup>. In addition, the onset of MI is more likely to be during the nighttime<sup>665</sup>. Patients who have had prior STEMI are more likely than the general population to have OSA, and have worse event free survival compared to STEMI patients without OSA.<sup>665,669</sup>

Major adverse cardiovascular events (defined as a composite of cardiovascular mortality, non-fatal MI, non-fatal stroke, and unplanned revascularization) after percutaneous coronary intervention also appear to be worse in patients with OSA<sup>670,671</sup>. It is controversial however whether treatment of OSA with CPAP may reduce the risk of repeat revascularization after PCI<sup>672,673</sup>. It has been reported that CPAP use of > 4 hours versus < 4 hours per night may be associated with a significant reduction of cardiovascular risk<sup>672</sup>.

#### Evaluation of OSA in Patients with Coronary Artery Disease

**Aggregate Quality of Evidence:** B (level 1a: 3 studies; level 1b: 4 studies; level 2b: 10 studies; level 3a: 3 studies; level 3b: 3 studies)

**Benefit:** OSA is very likely associated with coronary artery disease and myocardial ischemia and outcomes in these patients.

**Harm:** Inconvenience associated with evaluation and testing for OSA.

**Cost:** Low cost of evaluating and testing patients for OSA.

**Benefits-Harm Assessment:** Benefit of identifying OSA in patients with CAD outweigh the low harms and cost of testing.

**Value Judgments:** Patients of CAD are at high risk for OSA.

**Recommendation Level:** Recommendation.

**Intervention:** Patients with CAD and/or a history of MI should be evaluated for OSA.

**Table VII.A.3: Association between Myocardial Ischemia and OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Sorajia et al. <sup>663</sup>	2008	2b	cross-sectional	202 consecutive patients with no history of coronary disease who underwent electron-beam CT within 3 years of polysomnography between March 1991 and December 2003 were included. OSA was defined by an apnea-hypopnea index (AHI) > or = 5 events per hour, and patients were grouped by quartiles of AHI severity	evaluated the association between OSA and the presence of subclinical coronary disease assessed by coronary artery calcification (CAC)	In patients without clinical coronary disease, the presence and severity of OSA is independently associated with the presence and extent of CAC.

Franklin et al. <sup>667</sup>	1995	2b	prospective cohort	10 consecutive men with severely disabling angina pectoris and nocturnal angina on at least 2 nights per week for at least 1 month	overnight recordings of nasal and oral airflow, abdominal and chest movements, oxygen saturation, body position, electrocardiogram, electro-oculograms, electroencephalograms, and submental electromyogram were registered	Results show a relation between nocturnal angina pectoris and sleep apnea.
Moore et al. <sup>668</sup>	2000	3b	observational study	One hundred thirty-two men and 94 women	overnight sleep study and Holter recording to examine disordered breathing (oxyhemoglobin desaturations > or = 4% and apnea-hypopneas), heart rates, and ST-segment depressions (> or = 1 mm, > or = 1 min).	Episodes of nocturnal myocardial ischemia are common in patients with angina pectoris. However, a temporal relationship between sleep-disordered breathing and myocardial ischemia is present only in a minority of the patients, but occurs more frequently in men and in more severely disordered breathing.
Kuniyoshi et al. <sup>665</sup>	2008	2b	prospective cohort	92 patients with MI for which the time of onset of chest pain was clearly identified. The presence	evaluate the day-night variation of acute myocardial infarction in	The diurnal variation in the onset of MI in OSA patients is

				of OSA was determined by overnight polysomnography.	patients with obstructive sleep	strikingly different from the diurnal variation in non-OSA patients. Patients with nocturnal onset of MI have a high likelihood of having OSA. These findings suggest that OSA may be a trigger for MI.
Xie et al. <sup>674</sup>	2016	2b	prospective study	112 patients without a prior diagnosis of sleep apnea underwent comprehensive polysomnography within a median of 7 days after MI. Patients were followed up at 6-monthly intervals ( $\pm 2$ weeks) for a total of 48 months.	investigate the effects of OSA on prognosis after MI, and to determine which specific measures of OSA severity best predicted outcomes.	Nocturnal hypoxemia in OSA is an important predictor of poor prognosis for patients after MI
Nakashima et al. <sup>643</sup>	2015	2b	prospective cohort	patients with acute MI and followed over time	The main study outcome measures were cardiac death, recurrence of ACS, and re-admission for heart failure. Major adverse cardiac events (MACEs) were defined as composite end points of individual clinical outcomes.	Moderate-to-severe OSA increased the risk of ACS and the incidence of PCI for progressive lesions. Increased plaque vulnerability might be related to these clinical manifestations.
Shah et al. <sup>651</sup>	2010	3b	observational cohort study	1,436 enrolled patients, 1,024 (71%) had an apnea-hypopnea index $\geq 5$	study aimed to determine whether obstructive sleep apnea independently	Obstructive sleep apnea increases the risk of coronary events or death from

					increases the risk of coronary events, including death from cardiovascular causes	cardiovascular causes
Lee et al. <sup>669</sup>	2011	2b	prospective cohort	120 patients underwent an overnight sleep study during index admission for STEMI	determine the effect of severe obstructive sleep apnea (OSA) on long-term outcomes after myocardial infarction	42% of the patients admitted with STEMI have undiagnosed severe OSA. Severe OSA carries a negative prognostic impact for this group of patients. It is associated with a lower event-free survival rate at 18-month follow-up.
Lee et al. <sup>670</sup>	2016	2b	prospective study	Between December 2011 and April 2014, 1748 eligible patients were prospectively enrolled. The 1311 patients who completed a sleep study within 7 days of percutaneous coronary intervention formed the cohort for this analysis. Median follow-up of 1.9 years.	hypothesized that OSA predicts subsequent major adverse cardiac and cerebrovascular events (MACCEs) in patients undergoing percutaneous coronary intervention	OSA is independently associated with subsequent MACCEs in patients undergoing percutaneous coronary intervention
Qu et al. <sup>671</sup>	2018	1a	meta-analysis of prospective cohort studies	seven studies including 2465 patients	followed up with patients after PCI, and evaluated their overnight sleep patterns within 1 month for major adverse cardiac	In patients after PCI, OSA appears to increase the risk of cardiac death, non-fatal MI, and coronary revascularization

					events (MACEs) as primary outcomes including cardiac death, non-fatal myocardial infarction (MI), and coronary revascularization and secondary outcomes including re-admission for heart failure and stroke.	
Xie et al. <sup>675</sup>	2018	2b	prospective study	112 post-myocardial infarction patients	investigate whether excessive daytime sleepiness (EDS) would be an independent prognostic factor after myocardial infarction	EDS may be an independent prognostic factor of adverse outcome in post-myocardial infarction patients with moderate to severe sleep-disordered breathing.
Gottlieb et al. <sup>640</sup>	2010	1b	prospective longitudinal epidemiological study	A total of 1927 men and 2495 women > or =40 years of age and free of coronary heart disease and heart failure at the time of baseline polysomnography were followed up for a median of 8.7 years.	Objective of this study was to assess the relation of obstructive sleep apnea to incident coronary heart disease and heart failure in a general community sample of adult men and women.	Obstructive sleep apnea is associated with an increased risk of incident heart failure in community-dwelling middle-aged and older men; its association with incident coronary heart disease in this sample is equivocal.
Schwarz et al. <sup>662</sup>	2015	1b	systematic review	systematic review and meta-analysis evaluating	assess the effect CPAP therapy on	In patients with OSA, CPAP

			and meta-analysis	RCTs on the effect of CPAP on endothelial function in OSA, assessed by flow-mediated dilatation (FMD) and other validated techniques. Eight RCTs comparing the effects of therapeutic CPAP versus subtherapeutic CPAP (or no intervention) on endothelial function involving 245 OSA patients were included in the systematic review.	endothelial function in patients with OSA	therapy improves endothelial function significantly and to a clinically important extent.
Phillips et al. <sup>660</sup>	2012	2b	randomized crossover trial	28 patients received therapeutic or placebo CPAP, each for 2 months with a 1 month washout between treatments. After each treatment period, a 24 h coagulation study was conducted.	plasminogen activator inhibitor-1 (PAI-1), D-dimer, fibrinogen, von Willebrand Factor (vWF), factor VIII (FVIII), factor VII (FVII) and factor V (FV) were determined at seven time points over the day and night	CPAP may reduce cardiovascular risk in OSA, in part through reducing risk of thrombosis.
Milleron et al. <sup>657</sup>	2004	1a	long-term prospective study	studied 54 patients (mean age 57.3 +/- 10.1 years) with both CAD (> or = 70% coronary artery stenosis) and OSA (apnea-hypopnoea index > or = 15). In 25 patients, OSA was treated with continuous positive airway pressure (n=21) or upper airway surgery (n=4); the remaining 29 patients declined treatment for their OSA.	a composite of cardiovascular death, acute coronary syndrome, hospitalization for heart failure, or need for coronary revascularization	Treatment of OSA in CAD patients is associated with a decrease in the occurrence of new cardiovascular events, and an increase in the time to such events.



Wu et al. <sup>673</sup>	2015	2b	prospective study	390 patients with OSA who had undergone PCI	impact of OSA treatment with CPAP on percutaneous coronary intervention (PCI) outcomes	Untreated moderate-severe OSA was independently associated with a significant increased risk of repeat revascularization after PCI. CPAP treatment reduced this risk.
Peker et al. <sup>672</sup>	2016	1b	Randomized controlled trial	Consecutive patients with newly revascularized CAD and OSA (apnea-hypopnea index $\geq 15/h$ ) without daytime sleepiness (Epworth Sleepiness Scale score $< 10$ ) were randomized to auto-titrating CPAP (n = 122) or no positive airway pressure (n = 122).	determine the effects of CPAP on long-term adverse cardiovascular outcome risk in patients with CAD with nonsleepy OSA	Routine prescription of CPAP to patients with CAD with nonsleepy OSA did not significantly reduce long-term adverse cardiovascular outcomes in the intention-to-treat population. There was a significant reduction after adjustment for baseline comorbidities and compliance with the treatment.

#### VII.A.4 Hypertension

OSA and hypertension (HTN) are highly prevalent conditions in the general population.<sup>95,97,676</sup> Both conditions are highly comorbid, with 50% of subjects with OSA noted to have HTN<sup>677</sup> and 50% of those with HTN found to have OSA.<sup>678</sup> While OSA has been associated with several adverse cardiovascular (CV) consequences, the evidence linking OSA and HTN is the most robust.<sup>679,680</sup> OSA and HTN have shared risk factors such as obesity<sup>681</sup>, but the presence of OSA has been found to be an independent risk factor for prevalent as well as incident pre-HTN and HTN.<sup>115,659,682,683</sup> More recent evidence suggests

that untreated rapid eye movement (REM)-related OSA, a subtype of OSA where sleep disordered breathing (SDB) events are predominantly confined to REM sleep, is significantly associated with the development of HTN.<sup>684</sup>

There is a dose-response relationship between OSA and HTN, in that greater severity of OSA appears to confer a higher risk of HTN.<sup>115,659,683</sup> Furthermore, the effects of OSA on blood pressure (BP) seem to be more pronounced in subjects with subjective and objective daytime sleepiness<sup>685,686</sup>; these individuals may have a greater degree of desaturation and higher diastolic BP following SDB events.<sup>687</sup> Finally, the temporal distribution, night-to-night variability, and degree of desaturation and/or autonomic response associated with SDB events may ultimately affect an individual's risk of developing HTN.<sup>680</sup>

The prevalence of nocturnal non-dipping BP at night, an adverse cardiovascular prognostic risk factor, is high in subjects with OSA, in the range of 50-80%.<sup>688,689</sup> While the severity of respiratory abnormalities appears to be associated with a nocturnal non-dipping BP pattern in younger individuals, in older subjects, the severity of sleep disruption seems to correlate with nocturnal non-dipping status.<sup>690</sup>

Resistant HTN is defined by the use of 3 or more antihypertensive medications; refractory HTN refers to treatment with 5 or more medications.<sup>691,692</sup> OSA is a secondary cause of HTN<sup>693</sup>, and is particularly common in cases of resistant and refractory HTN.<sup>694-696</sup> Over 50% of subjects with resistant HTN have underlying OSA.<sup>697-699</sup> Furthermore, those with severe untreated OSA appear to have a significantly higher risk of having resistant HTN when compared to subjects with moderate OSA.<sup>700</sup> A recent study demonstrated a two-fold increase in risk of resistant HTN in African-Americans with severe OSA, and it is notable that the burden of undiagnosed OSA is high in this population.<sup>701</sup>

#### Evaluation of OSA in Patients with Hypertension

Aggregate Quality of Evidence: C (Level 3b: 6 studies; see Table VII.B).

Benefit: OSA is a treatable secondary cause of refractory hypertension.

Harm: There is minimal harm associated with evaluation and testing for OSA, other than inconvenience to the patient.

Cost: Low to moderate cost of evaluation and testing.

Benefits-Harm Assessment: The benefits of identifying OSA in patients with refractory hypertension may outweigh the inconvenience and cost of testing.

Value Judgments: In patients with resistant or refractory hypertension, identification of co-morbid OSA is indicated because OSA treatment may aid in blood pressure management.

Recommendation Level: Recommendation

Intervention: Patients should be screened for OSA if they have persistent resistant or refractory hypertension after antihypertensive medication treatment has been optimized.

**Table VII.A.4 Association between OSA and Refractory Hypertension**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Pratt-Ubunama et al <sup>698</sup>	2007	3b	Prospective, single-center, case-control study; all	1) RHTN (n=17) 2) Controls with	1)AHI 2) PAC, renin	OSA was common in subjects with RHTN (85%) and was more common and severe in men vs. women. PAC (but not renin

			subjects underwent PSG (n=46)	suspected OSA (n=29).	concentration	concentration) correlated with AHI.
Pedrosa et al <sup>678</sup>	2011	3b	Prospective cohort, study conducted at two outpatient HTN units (n=125)	Consecutive patients with RHTN.	Evaluation for secondary causes of HTN	Moderate-severe OSA was the most common condition associated with RHTN, seen in 64% of subjects.
Walia et al <sup>702</sup>	2014	3b	Secondary analysis of baseline data from the Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT) RCT (n=284)	Subjects with HTN; 64% had OSA, 10% had RHTN.	Association between RHTN and OSA	RHTN was more prevalent in subjects with severe vs moderate OSA (58.3% vs 28.6%, $P=0.01$ ) who were prescribed antihypertensives; those with severe OSA had 4-fold higher adjusted odds of RHTN (OR 4.1, 95% CI: 1.7-10.2).
Johnson et al <sup>701</sup>	2018	3b	Analysis of data from the the Jackson Heart Study, community cohort (n=913)	Subjects with HTN (n=664); 25.7% with OSA (untreated in the vast majority), 14% with RHTN; majority female	Association between OSA and RHTN in blacks	Subjects with moderate-severe OSA had a 2-fold higher odds of RHTN (OR 2.0; 95% CI: 1.14-3.67) after accounting for confounders. OSA and oxyhemoglobin saturation <90% were not associated with uncontrolled BP.
Martinez-Garcia et al <sup>695</sup>	2018	3b	Cross-sectional study (n=229)	Consecutive subjects with RHTN, 18% met criteria for refractory HTN	Association between refractory HTN and presence/severity of OSA.	Subjects with refractory HTN had a 2-fold higher risk of OSA (prevalence of moderate OSA was 95% and severe OSA was 64%) and greater OSA severity (AHI 41.8 vs 33.8; $P=0.026$ ) compared to those with RHTN.
Sapina-Beltran et al <sup>699</sup>	2019	3b	Multicenter cohort study (n=284)	Consecutive subjects with RHTN	Prevalence of OSA in subjects with RHTN and	83.5% had OSA, 25.7% moderate and 26.1% severe OSA. Those with severe OSA had higher BP than those with mild/no OSA, with a greater effect noted on nighttime

					association of OSA with BP control.	BP vs those with no OSA. The prevalence of severe OSA was higher in those with uncontrolled BP (not statistically significant).
--	--	--	--	--	-------------------------------------	---

AHI=apnea hypopnea index, events/hour; BP=blood pressure; CI=confidence intervals; DBP=diastolic blood pressure; OSA=obstructive sleep apnea, PAC=plasma aldosterone concentration; PSG=polysomnography; RCT=randomized controlled trial; RHTN=resistant hypertension; SBP=systolic blood pressure

### VII.A.5 Atrial Fibrillation

Patients with atrial fibrillation (AF) have a high prevalence of obstructive sleep apnea (OSA). Direct comparison of studies regarding the concurrence of OSA and AF is complicated by varying respiratory event definitions and by inclusion in some studies of both OSA and central sleep apnea (CSA). Despite these limitations, studies that systematically evaluated AF patients using home or laboratory sleep testing report a prevalence of OSA (apnea-hypopnea index [AHI]  $\geq 5$ ) of 43-85%, with prevalence  $>75\%$  in most studies.<sup>703-709</sup> Moderate or severe OSA (AHI  $\geq 15$ ) is reported in 20-62%.<sup>329,703,705,709-714</sup> When a comparison group of patients without atrial fibrillation was included, the prevalence of OSA was higher in those with AF than in controls in most<sup>706,714,715</sup> but not all<sup>716</sup> studies.

Community-based cohort studies support an independent association of OSA with the development of AF. In the Multi-Ethnic Study of Atherosclerosis, the prevalence of AF increased from 4.0% in those without OSA to 7.5% in those with severe OSA.<sup>717</sup> In two cohorts, the presence of AF was identified from the polysomnographic recording. In the Sleep Heart Health Study, compared to those with AHI  $<5$ , participants with AHI  $\geq 30$  had an age-, sex-, BMI-, and prevalent cardiovascular disease-adjusted odds ratio (aOR) of 4.0 (95% CI 1.0 to 15.7) for the presence of AF,<sup>718</sup> while in the Outcomes of Sleep Disorders in Older Men Study there was a dose-dependent association of OSA with prevalent atrial fibrillation.<sup>719</sup>

Longitudinal studies have yielded equivocal results regarding the association of OSA with incident atrial fibrillation. While studies using administrative claims data<sup>720</sup> or patient-reported diagnosis of OSA<sup>721</sup> suggest an association of OSA with incident atrial fibrillation, these studies have a high risk of bias. Three large retrospective studies of incident AF in cohorts of patients referred for diagnostic polysomnography have been reported. In one, patients with AHI  $\geq 5$  were twice as likely to develop AF as those with AHI  $<5$ , an effect that was limited to those under age 65; however, adjusting for age, sex, BMI and prevalent cardiovascular disease, mean nocturnal oxygen saturation but not AHI was an independent predictor of incident AF.<sup>413</sup> In another, the incidence of hospitalized AF increased progressively with increasing severity of OSA, although after multivariate adjustment that included BMI, neither AHI nor time at saturation  $<90\%$  was a significant predictor of incident AF, except in those with  $>30\%$  of sleep time at saturation  $<90\%$ .<sup>722</sup> It is unclear whether these measures of oxygen saturation reflect OSA or other conditions, such as reduced pulmonary or cardiac function, that might cause AF. In the third, AHI  $\geq 5$  was associated with an aOR of 1.55 (95% CI 1.21-2.00) for incident hospitalized AF after extensive covariate adjustment, with AF incidence increasing with greater severity of OSA.<sup>723</sup> In contrast, two community-based cohort studies, each of which had shown a cross-sectional association of OSA with prevalent AF, found that CSA but not OSA was independently associated with increased incidence of AF.<sup>724,725</sup>

Data are more consistent regarding the association of OSA with recurrent AF. In six studies that systematically assessed the presence of OSA prior to treatment of AF, OSA was associated with an approximately two- to three-fold increased risk of recurrent AF following electrical cardioversion<sup>713</sup> or pulmonary vein isolation (catheter ablation) procedures.<sup>707,708,710,712,726</sup> A similar increased risk of AF recurrence was reported in several studies that did not systematically screen for OSA, but compared the risk of AF recurrence following ablation procedures in patients with a documented prior diagnosis of OSA to those without known OSA.<sup>727-729</sup> The presence of severe OSA also predicts failure of antiarrhythmic drugs to suppress atrial fibrillation.<sup>730</sup> These studies generally included a mix of patients with paroxysmal and persistent AF, and the finding of increased risk of recurrence in those with OSA does not appear to be limited to either group.

Putative pathophysiological mechanisms linking OSA to atrial fibrillation include both chronic cardiac structural changes and acute arrhythmogenic effects of obstructive events, and has been recently reviewed.<sup>731</sup> Chronic changes include increased atrial dimension and slowed atrial conduction, while acute triggers to atrial fibrillation likely include atrial distension due to intrathoracic pressure swings along with hypoxemia, hypercapnia and the associated acute elevation of sympathetic nervous system activity. In the Sleep Heart Health Study, paroxysmal atrial fibrillation events were markedly more likely to occur during the 90 seconds following an obstructive apnea or hypopnea than during periods without obstructive events (odds ratio 17.9, 95% CI 2.2 to 144.2).<sup>732</sup> Similarly, in patients with paroxysmal atrial fibrillation, night-to-night variation in OSA severity predicts changes in atrial fibrillation burden.<sup>733</sup>

#### Evaluation of OSA in Patients with Atrial Fibrillation

**Aggregate Quality of Evidence:** C (level 1b: 5 studies; level 2b: 5 studies; level 3b: 6 studies; level 4: 5 studies).

**Benefit:** Evaluation for OSA prior to treatment of AF may permit timely OSA treatment and may reduce the risk of AF recurrence.

**Harm:** Inconvenience of OSA evaluation and testing.

**Cost:** Low cost associated with screening and testing AF patients for OSA.

**Benefits-Harm Assessment:** Weakly favors screening for OSA in patients undergoing treatment of paroxysmal or persistent AF with cardioversion or catheter ablation procedures.

**Value Judgments:** The overall quality of evidence favoring diagnosis of OSA solely for prevention of recurrent atrial fibrillation is generally weak, with no adequately powered randomized clinical trials.

**Recommendation Level:** Recommendation.

**Intervention:** Patients who are undergoing cardioversion or catheter ablation for atrial fibrillation may benefit from screening for OSA.

**Table VII.A.5: Association between Atrial Fibrillation and OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Gami et al. <sup>715</sup>	2004	3b	Case-control study	1) 151 consecutive patients undergoing	Presence of OSA identified based on a Berlin Questionnaire	Adjusted OR of 2.19 (95% CI 1.40-3.42) for the association of AF and OSA

				electrocardioversion for AF 2) 312 consecutive patients without AF referred to a general cardiology practice	score of 2-3	
Porthan et al. <sup>716</sup>	2004	4	Case-control study	1) 59 patients with AF identified from hospital records, free of known causes of AF 2) 56 age- and sex-matched controls from general population registry, free of AF or known causes of AF	Presence of "sleep apnea syndrome" based on AHI from in-lab cardiorespiratory polygraphy and sleep apnea symptoms	No significant difference between groups in prevalence of sleep apnea syndrome (32% in AF versus 29% in control)
Mehra et al. <sup>718</sup>	2006	3b	Nested case-control study within a community-based cohort study	Participants in the Sleep Heart Health Study 1) 228 subjects with AHI $\geq 30$ on home polysomnography 2) 338 subjects with AHI $< 5$ , frequency-matched on age, sex, race/ethnicity, BMI	Presence of arrhythmias on bipolar lead I ECG recorded on home polysomnography	Atrial fibrillation was present in 4.8% of severe OSA group and 0.9% of controls, with adjusted OR 4.02 (95% CI 1.03-15.74) for the association of AF and severe OSA
Stevenson et al. <sup>714</sup>	2008	3b	Case-control study	1) 90 patients with paroxysmal	AHI $> 15$ on home polysomnography	Mean AHI was higher in the AF

				or persistent AF 2) 45 patients referred to the same tertiary care center without AF, frequency match for age and sex		group than the control group (23.2 [SD 19.3 vs. 14.7 [SD 12.4]), with adjusted OR 3.04 (95% CI 1.24-7.46) for the association of AF and OSA
Braga et al. <sup>706</sup>	2009	3b	Case-control study	1) 57 consecutive patients with chronic persistent AF in Sao Paulo, Brazil 2) 32 age-, sex- and BMI-similar subjects from the Sao Paulo general population participating in the Epidemiologic Sleep Study (EPISONO)	From in-lab polysomnography: 1) AHI 2) sleep time with SaO <sub>2</sub> <90%	No significant difference between groups in mean AHI (24.3 [SD 16.5 vs. 19.1 [SD 15.3]), but higher prevalence of AHI ≥10 (81.6% vs. 60%, p=0.03) and longer time with SaO <sub>2</sub> <90% in the AF group
Bitter et al. <sup>705</sup>	2009	4	Case series	150 patients with persistent AF and normal left ventricular ejection fraction	AHI from cardiorespiratory polygraphy, classified as central or obstructive based on the predominant event type	OSA was present in 42.7% (18% mild, 12% moderate, 12.7% severe); an additional 31.3% had central sleep apnea
Mehra et al. <sup>719</sup>	2009	3b	Community-based cross-sectional cohort study	2911 participants in the Outcomes of Sleep Disorders in Older Men Study	Association of nocturnal arrhythmias present on home polysomnography with total AHI, obstructive AHI (obstructive	There was a progressive increase in prevalence of AF with increasing quartile of total AHI, from 3.2% to 7.3%. The adjusted OR in the highest AHI

					apneas plus all hypopneas), and central apnea index	quartile was 2.15 (95% CI 1.19-3.89). This effect was stronger for the central apnea index, and was non-significant for the obstructive AHI in adjusted analyses.
Pathak et al. <sup>329</sup>	2014	4	Case series	149 patients referred for pulmonary vein isolation procedure for AF	Presence of severe OSA (AHI $\geq 30$ ) on in-lab polysomnography	86 of 149 patients (57.7%) had severe OSA
Kwon et al. <sup>717</sup>	2015	3b	Community-based cross-sectional cohort study	2048 participants in the Multi-Ethnic Study of Atherosclerosis Sleep Study	Association of AHI from in-home polysomnography at MESA exam 5 with AF based on International Classification of Disease codes or ECG recordings over the preceding approximately 10 years (n=92) or present on the polysomnogram ECG (an additional n=8)	There was an increase in AF prevalence from 4.0% in those with none to mild OSA, 6.0% in those with moderate OSA, and 7.5% in those with severe OSA. The adjusted OR was 1.22 (95% CI 0.99-1.49) for each 1 SD increase in AHI.
Abuammar et al. <sup>703</sup>	2018	4	Case series	100 consecutive patients with AF without prior diagnosis of OSA recruited from arrhythmia clinics	Presence and severity of OSA from mean of 2 nights of home polysomnography	OSA was present in 85% of subjects (38% mild, 23% moderate, 24% severe)
Traaen et al. <sup>709</sup>	2019	4	Case series	579 patients with paroxysmal AF admitted for pulmonary vein isolation	Presence and severity of sleep apnea from mean of 2 nights of cardiorespiratory	Sleep apnea was present in 83% of subjects (41% mild, 30% moderate, 12% severe); this was



				procedure, without known OSA	polygraphy	OSA in 97.5% of those with sleep apnea, central sleep apnea in 2.5%
Gami et al. <sup>413</sup>	2007	2b	Retrospective cohort study	3542 adults without history of AF referred for diagnostic polysomnography  1) OSA defined as AHI $\geq 5$ (n=2626), with group mean AHI 36 (SD 32)  2) No OSA	Incidence of AF based on electronic medical record review, with mean follow-up of 4.7 years	AF occurred in 2.1% of those without OSA, 4.3% of those with OSA, with unadjusted HR 2.18 (95% CI 1.34-3.54). This effect was restricted to those under age 65. In multivariate analysis, the difference between awake and asleep oxygen saturation was a strong predictor of incident AF. It is not clear in this study whether measures of OSA per se are independently associated with incident AF.
Cadby et al. <sup>723</sup>	2015	2b	Retrospective cohort study	6841 adults without history of AF referred for diagnostic polysomnography  1) OSA defined as AHI $\geq 5$ (n=4352)  2) No OSA	Incidence of hospitalization for AF based on review of Western Australia Hospital Morbidity and Mortality Data, with median follow-up of 11.9 years	AF occurred in 8.6% of those with OSA and 3.3% of those without OSA, with adjusted HR 1.55 (95% CI 1.21-2.00) for the association of OSA with incident AF. There was a modest dose-response relationship, with adjusted HR increasing from 1.48 in those with mild OSA to 1.73 in those

						with severe OSA. Both AHI and time at SaO <sub>2</sub> <90% were associated with incident AF.
May et al. <sup>724</sup>	2016	2b	Community-based cohort study	Of 2316 participants in the Outcomes of Sleep Disorders in Older Men Study who were free of AF at baseline, 852 had a follow-up sleep study after approximately 6 years and 843 of these had outcome data and were analyzed	Association of AHI from baseline in-home polysomnography with incident adjudicated or self-reported AF (the proportion of adjudicated versus self-report AF is not stated)	AF occurred in 10.0% of those with AHI <15 and 14.2% of those with AHI ≥15 (adjusted OR 1.15 [95% CI 0.72-1.84]). There was no association of AF with obstructive AHI; however, a central apnea index ≥5 was present in 48 participants at baseline and the incidence of AF in this group was 22.9% (adjusted OR 2.34 [95% CI 1.14-4.77]).
Tung et al. <sup>725</sup>	2017	2b	Community-based cohort study	Of 6441 participants in the Sleep Heart Health Study, 3346 had repeat polysomnography after approximately 5 years. Of these 388 were excluded due to restrictions on data use and 46 due to prevalent AF at baseline, yielding an analytic sample of 2912	Association of OSA and central sleep apnea with incident AF based on parent cohort adjudication or 12-lead ECG at the time of the second polysomnogram; median follow-up was 5.3 years; OSA was classified based on the obstructive AHI (OAHI, obstructive apneas plus all hypopneas per	AF incidence increased with OSA severity from 9.6% of those with OAHI <5 to 16.4% with AHI ≥30; however, adjusting for age, sex, race and BMI there was no positive association of OSA with AF. Central apnea index ≥5 was present in 74 participants at baseline, and the incidence of AF in this group was 25.7% (adjusted OR 1.71, 95% CI 0.89-

				participants.	hour of sleep)	3.30, increasing to 3.00, 95% CI 1.40-6.44, with further adjustment for hypertension, diabetes, and cardiovascular disease.
Kendzierska et al. <sup>722</sup>	2018	2b	Retrospective cohort study	8256 patients without prior history of arrhythmia referred for diagnostic polysomnography 1) 2263 with AHI < 5 2) 2260 with 5 ≤ AHI < 15 3) 1823 with 15 ≤ AHI ≤ 30 4) 2263 with AHI > 30	Time to first hospitalization with a diagnosis of AF or atrial flutter, using Ontario Provincial Health Administrative Data, with median follow-up of 10 years	In unadjusted analyses, incident hospitalized AF increased with increasing severity of OSA based on either AHI or percent time at SaO <sub>2</sub> < 90%; however, in multivariate models that included BMI these associations were not significant, with hazard ratios < 1.0 for each OSA severity compared to AHI < 5. Only when comparing those with more than 30% of sleep time at SaO <sub>2</sub> < 90% (n=463) to those with less severe hypoxemia, was the adjusted HR significant (1.77, 95% CI 1.15-2.74).
Mazza et al. <sup>713</sup>	2009	1b	Clinic-based cohort study	158 consecutive patients admitted for electrocardioversion for AF; all had polysomnography the night prior	Recurrence of AF over 1-year follow-up	AF recurred in 69% of patients with AHI ≥ 15 and in 43% of those with AHI < 15 (adjusted OR 3.04, 95% CI 1.45-6.36)

				to cardioversion 1) AHI $\geq 15$ (n=49) 2) AHI <15 (n=109)		
Matiello et al. <sup>726</sup>	2010	1b	Clinic-based cohort study	174 consecutive patients undergoing pulmonary vein isolation procedure for AF; all screened with Berlin Questionnaire, and the 51 with score of 2-3 underwent home cardiorespiratory polygraphy  1) Low risk Berlin Questionnaire or AHI <10 on polygraphy (n=132) 2) AHI 10-<30 (n=17) 3) AHI $\geq 30$ (n=25)	Recurrence of AF over mean follow-up of 17 (SD 11.5) months	Estimated 1-year recurrence free survival was 48.5% in the low-risk group, 30.4% in those with AHI 10-<30, and 14.3% in those with AHI $\geq 30$ . Adjusted OR for recurrence was 1.57 (95% CI 0.83-3.00) for AHI 10-<30 and 1.87 (95% CI 1.11-3.16) for AHI $\geq 30$ .
Bitter et al. <sup>710</sup>	2012	1b	Clinic-based cohort study	82 consecutive patients undergoing pulmonary vein isolation procedure for AF, 75 evaluable; all underwent in-hospital cardiorespiratory polygraphy  1) AHI <15 (n=53) 2) AHI $\geq 15$ (n=22,	Recurrence of AF over a median follow-up of 12 months	AF recurred in 45.5% of those with AHI $\geq 15$ and 24.5% of those with AHI <15. The adjusted HR for AF recurrence in those with AHI $\geq 15$ was 3.20 (95% CI 1.14-8.95) compared to those with AHI <15. Not analyzed separately by obstructive versus

				of which 15 were predominantly obstructive and 7 were predominantly central)		central pattern.
Szymanski et al. <sup>708</sup>	2015	1b	Clinic-based cohort study	290 consecutive patients admitted for pulmonary vein isolation procedure for AF; in-hospital cardiorespiratory polygraphy the night prior to the procedure; polygraphy was inadequate in 22 patients and ablation was not performed in 14; 3 patients with central sleep apnea excluded 1) AHI <5 (n=136) 2) AHI ≥5 (n=115)	Recurrence of AF over a mean follow-up of 30 months	AF recurred in 65.2% of those with AHI ≥5 and 45.6% of those with AHI <5. AF recurrence increased progressively with more severe OSA, to 81.8% in those with AHI ≥30. The adjusted OR for AF recurrence in those with AHI ≥5 was 2.58 (95% CI 1.91-4.10).
Kawakami et al. <sup>712</sup>	2016	1b	Clinic-based cohort study	133 consecutive patients admitted for pulmonary vein isolation procedure for AF; in-hospital cardiorespiratory polygraphy the night prior to the procedure 1) AHI <15 (n=69) 2) AHI 15-<30	Recurrence of AF over a mean follow-up of 13 (SD 7) months	AF recurred in 25% of those with AHI <15, 49% of those with AHI 15-<30, and 69% of those with AHI ≥30. However, in multivariate analysis, the association of AHI with recurrent AF was significant only in the subgroup with paroxysmal AF (adjusted HR 1.04,

				(n=39)		95% CI 1.002-1.065)
				3) AHI $\geq$ 30 (n=16)		

### VII.A.6 Congestive Heart Failure

Heart failure (HF) is highly prevalent in the United States with 6.5 million adults affected.<sup>734</sup> HF is associated with significant mortality and is identified as the cause of 1 in every 8 deaths in the US.<sup>735</sup> Failure of the left ventricle is the most common subtype and can manifest as impairment of either systolic (HF with reduced ejection fraction--HFrEF) or diastolic (HF with preserved ejection fraction--HFpEF) function.<sup>736</sup> OSA is more common in the HFrEF population, with prevalence estimates varying between 12% and 53%.<sup>737</sup> A study of 700 patients with chronic stable HFrEF with ejection fraction (EF)  $\leq$  40% found a 36% prevalence of OSA, including 19% with severe OSA.<sup>738</sup>

In addition to shared risk factors like age and obesity, another proposed mechanism to explain the high prevalence of OSA in heart failure relates to nocturnal fluid shifting throughout the body. Excess interstitial fluid from the lower extremities redistributes during sleep when in the supine position. This rostral fluid shift correlates with an increase in neck circumference, decrease in diameter of the lumen of the pharynx and increased propensity for obstruction as demonstrated by increase in AHI<sup>739</sup>.

Identification of OSA may be especially important in the setting of HFrEF, where it is an independent risk factor for mortality.<sup>740,741</sup> Although large confirmatory studies are lacking, there is interest in how OSA may adversely affect outcomes in patients with HF and a number of mechanisms have been proposed. HF is a state of sympathetic over-activity, so the autonomic imbalances associated with OSA in response to hypoxemia and repetitive arousals from sleep may generate concomitant physiologic stress. Additionally, large swings in intrathoracic pressure due to inspiratory effort against a closed upper airway exert transmural pressures across the heart and great vessels, leading to increasing afterload, reduced stroke volume and increased myocardial oxygen consumption<sup>679</sup>.

Considering these underlying pathophysiologic mechanisms, PAP therapy would be expected to have beneficial clinical outcomes in patients with HF. In addition to relieving obstruction of the upper airway in OSA and reducing work of breathing, PAP decreases venous return (preload), and may blunt sympathetic activity. These physiologic benefits, however have not yet translated to improvements in clinical outcomes in patients with OSA and HF, which are limited to small, short-term randomized controlled trials (RCT). Some have shown improvements in physiologic parameters that are surrogates for cardiovascular outcomes, but results have not been consistent and it is uncertain if these improvements translate into a meaningful clinical benefit.

In small and select groups of patients with OSA and HFrEF, continuous positive airway pressure (CPAP) has been associated with reduced systolic blood pressure<sup>742,743</sup> and heart rate<sup>742</sup>, small but inconsistent changes in left ventricular EF (LVEF)<sup>742-746</sup>, decreased overnight urinary norepinephrine excretion<sup>745</sup>, improved quality of life<sup>742,745</sup>, improved mean sleep-related oxygen saturation<sup>744</sup>, and decreased pulmonary artery systolic pressure<sup>746</sup>. There are a number of studies that have reported echocardiographic measurements of LVEF before and after CPAP. However, LVEF is but one assessment in the clinical diagnosis of HFrEF, and some would argue a minor determinant. Patil and colleagues performed a meta-analysis of five RCTs measuring LVEF by echocardiography or radionuclide

ventriculography to compare the efficacy of CPAP against control conditions in patients with HFrEF. While some studies showed modest improvements in the absolute value of LVEF associated with CPAP, most reported changes (typically less than 5%) that would not be considered *clinically significant*<sup>39</sup>.

Although most available studies focus on HFrEF, OSA appears to also be prevalent in HFpEF. Presence of OSA in HFpEF has been associated with increased brain natriuretic peptide (BNP) levels, which may serve as a marker for reduced cardiac function<sup>747</sup>. Severity of OSA has also been associated with increasing severity of diastolic dysfunction<sup>748</sup>. One small RCT reported improvement in diastolic function in HFpEF with nasal CPAP but there was no difference in heart rate, systolic function, ventricular structure, blood pressure, or urinary catecholamines after 12 weeks of CPAP use.<sup>749</sup>

In terms of other treatment modalities, a recent randomized study of patients with HFrEF and OSA demonstrated benefits of exercise (three months of aerobic and strength training) as a stand-alone intervention and as an adjunctive therapy to CPAP. AHI decreased significantly in the exercise alone group (28±17 to 18±12, p<.007) and the exercise + CPAP group (25±15 to 10±16, p<.007) compared to controls. Both exercise and CPAP improved NYHA functional class and daytime sleepiness as measured by the Epworth Sleepiness Scale. Quality of life improvements were maximal in the exercise groups.<sup>750</sup>

Prospective data analyzing the association between OSA and HF and high quality data regarding benefits of treatment in this population are lacking (Table VII.A.6a).<sup>653,751</sup> Several societies have made recommendations regarding the testing and treatment of those with HFrEF and OSA but these recommendations are largely based on low-quality evidence (Table VII.A.6b). Current evidence does not support the routine treatment of non-symptomatic OSA with CPAP in patients with HFrEF as a means to improve cardiovascular outcomes. Those with symptoms of OSA, such as excessive daytime sleepiness, should be offered treatment, in accordance with joint guidelines from national heart failure societies and the American Academy of Sleep Medicine.<sup>752</sup>

#### Evaluation of OSA in Patients with Heart Failure

**Aggregate Quality of Evidence:** C (Level 1b: 1 study; Level 2b: 4 studies.)

**Benefit:** Earlier diagnosis and treatment of OSA in patients with heart failure may improve cardiac function and potential impact outcomes.

**Harm:** The potential inconvenience of screening and diagnosing OSA with sleep studies. Inconvenience and noncompliance of potential therapy.

**Cost:** Low to moderate cost associated with screening and testing for OSA in patients with HF.

**Benefits-Harm Assessment:** Benefits of earlier diagnosis and management of OSA in those with HF outweighs the harms of screening and testing for OSA.

**Value Judgments:** Diagnosis and subsequent treatment of OSA in patients with HF improve OSA symptoms and may improve cardiac function. The potential benefits of diagnosis outweigh the low risks of harm.

**Recommendation Level:** Recommendation.

**Intervention:** Patients with heart failure should be screened and evaluated for OSA.

**Table VII.A.6a Association between OSA and Heart Failure.**

Study	Year	LOE	Study Design	Study Group	Relevant Clinical Endpoint	Conclusion
Gottlieb et al <sup>640</sup>	2010	2b	- Prospective cohort - 4422 subjects - Followed for a median of 8.7 years	- Participants had OSA on PSG and no coronary heart disease or heart failure at baseline	- Incident CHF - CHF-free survival	- Incidence of CHF increased with increasing severity of OSA - After adjustment for age, race, smoking, and BMI, AHI was associated with CHF in men but not women
Hla et al <sup>644</sup>	2015	2b	- Prospective cohort of people in South-Central Wisconsin - 1,546 participants	- Participants had OSA on PSG and no documented CHD or CHF at baseline - CHD and CHF was self-reported	- Composite outcome of incident CHD or heart failure	- After adjustment for age, sex, smoking, and BMI OSA was associated with increased incidence of CHD or heart failure - Association of OSA with incident CHD or CHF was attenuated when participants who reported using CPAP were included in the analysis
Kasai et al <sup>753</sup>	2008	2b	-Prospective cohort of patient in Tokyo, Japan -88 patients followed for mean of 25.3±15.3 months	-moderate to severe OSA with AHI≥15 -LVEF<50% and NYHA class II or greater symptoms -65 were treated with CPAP and 23 were untreated	-Event-free survival	-Cumulative event-free survival was higher in patients w/OSA on CPAP vs patients w/OSA not on CPAP. -Cumulative event-free survival was significantly lower in patients with poor compliance than in those with good compliance.
Wang et al <sup>741</sup>	2007	2b	-Prospective, single-center, observational cohort -Patients referred to Mount Sinai Hospital in Toronto - 218 subjects	-Heart failure for at least 6 months - LVEF≤45% at rest - NYHA class II-IV dyspnea - All underwent PSG and were	- Cumulative rate of death	-Mortality was higher in those with untreated OSA compared to treated OSA after adjusting for LVEF, NYHA class, and age.



			were followed for a mean of 2.9±2.2 years - 164 had complete data	divided into categories: AHI<15 and AHI≥15 - Those with central sleep apnea were excluded - Patients with OSA were divided into “treated” and “untreated” groups		
Kaneko et al <sup>742</sup>	2003	1b	- RCT - 24 patients	-Heart failure for at least 6 months - LVEF≤45% at rest - NYHA class II-IV dyspnea - No exacerbations within 3 months - Optimal medical therapy - OSA with AHI of ≥20 with >50% obstructive events - Half of the patients were treated with CPAP, the other half were treated only with medical therapy	-Cardiovascular physiologic parameters as measured by trans-thoracic echocardiography: LVEF, LVEDV, LVESV	- Nocturnal CPAP improves daytime left ventricular systolic function in patients with heart failure and OSA

CHD – coronary heart disease; CHF – congestive heart failure; OSA – obstructive sleep apnea; PSG – polysomnogram; LVEF – left ventricular ejection fraction; LVEDV – left ventricular end diastolic volume; LVESV – left ventricular end systolic volume

Table VII.A.6b Guidelines for Testing and Treatment of OSA in HFrEF

Author	Question	Statement	Class	Level of Evidence
AHA/ACC/HFSA Guidelines on Management of Heart Failure <sup>752</sup>	Should people with HFrEF be tested for OSA?	A formal sleep assessment is reasonable for people with suspicion of SDB or EDS	IIa (moderate recommendation)	C-LD (Limited data, randomized or non-randomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, physiological or mechanistic studies in human subjects)
	Should Patients with HFrEF and OSA be treated with CPAP?	In patients with CVD and OSA, CPAP may be reasonable to improve sleep quality and daytime sleepiness	IIb (Weak recommendation)	B-R (moderate quality evidence from 1 or more RCTs/meta-analysis of moderate quality RCTs)
AASM Guidelines for Evaluation and management of OSA <sup>512</sup> ; AASM Clinical Practice Guideline for Diagnostic Testing of OSA <sup>571</sup> ; AASM guidelines for treatment of adult OSA with PAP <sup>39</sup>	Who should be evaluated for OSA?	Patients with comorbidities considered “high risk” for OSA including HF	N/A	N/A
	Where should patients with suspected OSA and significant comorbidities (including HF) be tested?	Consider initiating PAP using an in-lab strategy	Strong Recommendation	N/A
	Should PAP be recommended or withheld in non-sleepy OSA patients to reduce cardiovascular events or mortality?	Insufficient evidence	No recommendation	N/A

	Initiation of PAP therapy	In patients with significant comorbidities, PAP initiation using an in-lab strategy should be considered	N/A	N/A
--	---------------------------	--	-----	-----

AHA - American Heart Association; ACC - American College of Cardiology; HFSA – Heart Failure Society of America; AASM – American Academy of Sleep Medicine; SDB – Sleep-disordered breathing; EDS – Excessive daytime sleepiness; CVD – cardiovascular disease; NYHA – New York Heart Association; CSA – Central Sleep Apnea; ASV – Adaptive Servoventilation; PAP – Positive Airway Pressure

### VII.A.7 Cerebrovascular Disease

Cerebrovascular accident (CVA) or stroke is one of the leading causes of death and disability globally.<sup>754,755</sup> Obstructive sleep apnea (OSA) is highly prevalent (55%) among the stroke population and significantly increases the risk for incident ischemic stroke.<sup>755</sup>

Johnson and Johnson conducted a meta-analysis of 29 studies consisting of 2,343 patients with ischemic or hemorrhagic stroke and transient ischemic attack (TIA) patients. They found OSA was present in 65% of ischemic/hemorrhagic stroke and TIA patients, with greater prevalence in male patients, patients with recurrent strokes and patients with strokes of unknown etiology.<sup>612</sup>

Most strokes result from a reduction in cerebral blood flow to a specific region of the brain. The subsequent brain injury from blood-brain barrier dysfunction starts a series of inflammation, oxidative stress, excitotoxicity, and apoptosis.<sup>754</sup>

OSA increases the risk for stroke through a variety of factors leading to vascular damage in the brain. The repeated hypoxia can lead to endothelium damage and release of pro-inflammatory factors, such as plasma cytokines, tumor necrosis factor-alpha, and interleukin-6. This may ultimately cause vascular dysfunction by increasing endothelin, neurovascular oxidative stress, and increasing susceptibility to injury. Moreover, the associated large negative intrathoracic pressure swings could result in mechanical stress on the heart and valves. This can result in nocturnal apneic-related right to left shunting through patent foramen ovale and consequently increase risk of embolism and stroke.<sup>33</sup>

A cohort of 5,422 participants without a history of stroke and untreated OSA were followed for a median of 8.7 years for incident stroke. Men with moderately severe OSA were at increased risk for incident ischemic stroke (hazard ratio (HR) 2.86; 95% CI 1.10-7.39) after adjusting for demographic variables (age, race) and cardiovascular risk factors (body mass index, smoking, systolic blood pressure, use of antihypertensive medications, diabetes). Furthermore, there seemed to be a dose response relationship in which the risk of stroke increased 6% with every one-unit increase in apnea-hypopnea index, suggesting as severity of OSA increased, risk of stroke also increased. In women, stroke risk was not significantly associated with obstructive apnea-hypopnea index (OAH) quartiles or desaturation levels, but increased risk was seen at OAH levels greater than 25. After a minimum threshold of 25 obstructive events/hour is met, with unit increase, there is a 2% increase in stroke hazard ratios. Interestingly,

arousal index was a significant negative predictor of incident stroke in women. Women with arousal index >12 was associated with decreased hazard rate of ischemic stroke compared to women with lower arousal index.<sup>33</sup> Future studies should further explore the protective role arousal index may play in incident stroke in women.

A meta-analysis was conducted of 12 prospective cohort studies that followed a total of 25,760 participants for major cardiovascular events, fatal and nonfatal stroke, coronary heart disease, and all-cause mortality. It was found that severe OSA is independently associated with an increased risk of stroke, cardiovascular disease, and all-cause mortality. Three of the 12 studies examined the relationship between severe OSA and risk of stroke. Patients with severe OSA had an increased risk for stroke (combined relative risk (RR)=2.15, 95% CI: 1.42, 3.24).<sup>756</sup>

Another meta-analysis assessed the risk of cerebrovascular events among OSA patients in 15 prospective studies and 43 non-prospective cohort studies (includes cross-sectional studies, case-control studies, and prospective observational studies) to ascertain the prevalence of OSA among patients with cerebrovascular (CV) disease. OSA was found to significantly increase the risk of fatal and non-fatal cerebrovascular disease (pooled HR=1.94, 95% CI: 1.31-2.89) after adjusting for confounders. Furthermore, OSA was shown to be highly prevalent (58.8%) among patients with cerebrovascular disease and there was greater prevalence with increasing age.<sup>757</sup>

It has been reported that CVA patients with OSA experience longer hospitalization and rehabilitation admissions and higher mortality rates compared to CVA patients without OSA. A prospective cohort study examined the relationship and prevalence of OSA in patients with acute ischemic stroke. Of the 174 patients with acute ischemic stroke, only 7 had a past medical history of OSA. Those patients diagnosed with OSA prior to acute ischemic stroke experienced significantly worse functional outcome as measured by lower modified Rankin scale (mRS) scores at hospital discharge after adjusting for age and stroke severity.<sup>758</sup> Untreated OSA can cause impaired cognitive function, decreased concentration, and excessive daytime sleepiness, which ultimately prolongs the hospitalization stay and compromises rehabilitation participation.<sup>759,760</sup>

Therefore, it is recommended to screen for OSA in all patients presenting with TIA or ischemic or hemorrhagic stroke regardless of whether they are symptomatic or asymptomatic. Earlier diagnosis of OSA and early treatment could improve overall health and cognitive status and reduce the risk of recurrent stroke and stroke mortality.

#### Evaluation of OSA in Patients with Cerebrovascular Disease

**Aggregate Quality of Evidence:** C (Level 2a: 10 studies, Level 2b: 1 study, Level 3b: 1 study)

**Benefit:** Earlier diagnosis of OSA may improve overall health and cognitive status and reduce the risk of incident and recurrent stroke and stroke mortality. Patients with stroke have a high pre-test probability of OSA.

**Harm:** Inconvenience of evaluation and sleep testing for OSA diagnosis.

**Cost:** Low cost associated with evaluation and testing patients for OSA.

**Benefits-Harm Assessment:** Moderately favors screening for OSA to reduce incidence of stroke and recurrence of stroke in patients presenting with stroke.

**Value Judgments:** The overall quality of evidence favoring diagnosis of OSA to prevent incident and recurrent stroke and stroke mortality is modest.

**Recommendation Level:** Recommendation

**Intervention:** Recommend patients presenting with TIA, ischemic or hemorrhagic stroke undergo clinical evaluation for OSA.

**Table VII.A.7 Association between OSA and Cerebrovascular Disease**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Birkbak et al. <sup>761</sup>	2014	2a	Systematic Review	10 studies with a total of 1,203 stroke and TIA patients were reviewed to examine relationship between sleep disordered breathing and recurrent stroke and mortality.	All-cause mortality, recurrent vascular events, and case fatality in stroke/TIA patients	Obstructive sleep disordered breathing is a risk factor for recurrent vascular events and all-cause mortality in stroke/TIA patients.
Culebras and Anwar <sup>762</sup>	2018	2a	Systematic Review	Review of cerebrovascular complications of OSA	Factors contributing to CVD	OSA is highly prevalent in the stroke population. OSA increases the risk of hypertension, stroke, myocardial infarction, and afib and is closely linked to vascular dementia. OSA may have worse neurological outcomes in acute stroke patients and have worse recovery in stroke rehab.
Dong et al. <sup>763</sup>	2018	2a	Systematic Review	37 studies with 3242 patients were reviewed to determine prevalence of OSA.	Prevalence of OSA in patients with CVD	OSA is highly prevalent in patients with CVD. Prevalence of AHI>5 was 70.4% and prevalence of AHI>10 was 61.9%.
Johnson and	2010	2a	Meta-analysis	29 studies with a total of 2,343	Prevalence of sleep disordered	SDB is very common in stroke patients

Johnson 612				ischemic or hemorrhagic stroke and TIA patients were reviewed.	breathing (SDB) in ischemic and hemorrhagic stroke and TIA patients	regardless of type of stroke or timing after stroke and is usually obstructive in nature
Li et al. <sup>764</sup>	2014	2a	Meta-analysis	10 cohort studies investigating the effect of OSA on incident ischemic and hemorrhagic stroke.	Incident ischemic and hemorrhagic stroke	There was a significant association between OSA and the risk of fatal or non-fatal stroke after adjustment of established cardiovascular risk factors.
Mansukhani et al. <sup>758</sup>	2011	2b	Prospective cohort study	174 consecutive patients presenting with acute ischemic stroke in Saint Mary's Hospital ED between June 2007 and March 2008	Functional outcomes measured using modified Rankin Scale at discharge.	Previous diagnosis of OSA was an independent predictor of worse functional outcome. Patients with definitive diagnosis of OSA before stroke are at increased risk of death within the first month after an acute ischemic stroke.
McDerrott and Brown <sup>765</sup>	2020	2a	Systematic Review	Assessing the directional relationship between the association between OSA and stroke	Prevalence of OSA in the poststroke patient population	Sleep apnea is an independent risk factor for stroke. OSA is highly prevalent poststroke and is associated with worse outcomes after stroke.
Mohamad et al. <sup>755</sup>	2019	3a	Case-control study	107 patients admitted with acute ischemic stroke who were categorized into 2 groups: those who	Risk for OSA assessed using the Berlin Questionnaire.	Risk for OSA is high among the stroke population, with a greater prevalence among the WUS group. OSA is an

				woke up with stroke symptoms (WUS) and those whose stroke occurred while awake (NWUS)		important risk factor for ischemic stroke during sleep.
Redline et al. <sup>33</sup>	2010	2a	Prospective cohort study	Community-based sample of 5,422 male and female participants in the Sleep Heart Health study without a history of stroke and untreated for OSA were followed for a median of 8.7 years.	Incidence of ischemic stroke	There is a strong association between ischemic stroke and obstructive AHI in community-dwelling men with mild to moderate OSA. In women, stroke was not significantly associated with obstructive apnea-hypopnea index (OAHl) quartiles or desaturation levels, but an increased risk of stroke was observed in women with OAHl levels greater than 25.
Seiler et al. <sup>766</sup>	2019	2a	Systematic Review and Meta-analysis	89 studies with a total of 7,096 patients with ischemic/hemorrhagic stroke or TIA were reviewed to determine prevalence of sleep disordered breathing	Severity and prevalence of SDB	Sleep disordered breathing is highly prevalent in patients after stroke and TIA. 70% of patients have an AHI>5/h and 33% of patients have AHI>30/h.
Wang et al. <sup>756</sup>	2013	2a	Meta-analysis	12 prospective cohort studies with a total of 25,760 participants were reviewed	Incident fatal and non-fatal coronary heart disease, incident fatal and non-fatal stroke, and all-cause mortality.	Severe OSA significantly increases CVD risk, stroke, and all-cause mortality. A positive association with CVD was observed for moderate OSA but not for mild OSA.

Wu et al. <sup>757</sup>	2017	2a	Meta-analysis	58 studies to determine prevalence of OSA among CV patients and risk for cerebrovascular events.	Prevalence of OSA	OSA is prevalent (58%) in patients with CV disease. As age increases, the prevalence of OSA increases. OSA is significantly increases risk for fatal or non-fatal CV disease.
--------------------------	------	----	---------------	--	-------------------	---

## VII.B Comorbidities Associated with OSA: Pulmonary Disorders

### VII.B.1 Primary Pulmonary Hypertension

Pulmonary hypertension (PH), defined as a mean pulmonary artery pressure (mPAP) >20 mmHg<sup>767</sup>, is a pathophysiological disorder<sup>768</sup> that may be of primary origin or a sequelae of clinical conditions most notably cardiovascular and respiratory diseases.

The relationship between Obstructive Sleep Apnea (OSA) and PH was first noted in 1976 by Tilkian et al.<sup>769</sup> Few studies have detailed the link between WHO Group 1 pulmonary arterial hypertension (PAH) and OSA, or the effects of treatment of OSA on hemodynamic variables in adult patients.<sup>746,770-776</sup> (Table VIII.7.a) Although the mechanism behind PH associated with OSA is not entirely understood, it is postulated to be due to a combination of factors including pulmonary arteriolar remodeling, susceptibility to hypoxia and underlying left heart disease.<sup>772</sup> A study of WHO group I PAH patients showed there was no significant difference in mortality in patients with and without OSA, however mortality was significantly higher in patients with nocturnal hypoxemia, defined as an average SpO<sub>2</sub><90%, suggesting that duration and severity of nocturnal oxygen desaturation, well known to occur in OSA patients, is an important risk factor for development of PAH.<sup>775</sup>

The prevalence of OSA in PAH and vice versa is not well elucidated. A study by Minic et al showed that sleep-disordered breathing (OSA, central sleep apnea, hypoventilation) was present in the majority of patients with PAH, with more than half of patients having significant nocturnal hypoxemia.<sup>774</sup> Other reported risk factors including female gender, younger age, obesity, and nocturnal desaturations are thought to increase the risk of developing PAH in OSA patients.<sup>773</sup>

Although data on the effects of continuous positive airway pressure (CPAP), the preferred treatment of OSA, on hemodynamic variables have been inconsistent, two systematic reviews reported that CPAP therapy is associated with a reduction in mPAP in patients with OSA and PH.<sup>771,776</sup> Another study showed that CPAP induced significant improvements in echocardiographic parameters, most notably pulmonary artery systolic pressure (PASP), further highlighting CPAP use and its positive effects on hemodynamic variables.<sup>770</sup> Lastly, it was found that in patients with PH admitted for acute decompensated heart failure, the addition of 48 hours of CPAP to standard care improved left ventricular ejection fraction and significantly reduced PASP.<sup>746</sup>

In summary, there is some indication that survival for OSA patients with PH may be lower than that for OSA patients without PH.<sup>773</sup> Based on limited studies, CPAP appears to improve hemodynamic variables



including mPAP and PASP in patients with combined OSA and PAH, however how these positive effects translate to meaningful clinical outcomes are still unclear.

**Association between OSA and Pulmonary Hypertension.**

Aggregate Grade of Evidence: C (Level 2a: 2 studies; Level 2b: 4 studies)

**Table VII.B.1 Association between OSA and Pulmonary Hypertension.**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Minic et al <sup>774</sup>	2014	2b	Retrospective cross-sectional	Patients with Group 1 PAH (n=52)	Prevalence and clinical predictors of SDB and impact on outcomes	SDB present in 71% of PAH patients; 60% had significant hypoxemia (>10% of total sleep time at < 90% oxyhemoglobin saturation).
Minai et al <sup>773</sup>	2009	2b	Prospective cohort	OSA patients undergoing right heart catheterization for suspected PH	1) Predictors of PAH in OSA patients 2) Survival in patients with OSA and PAH	Female gender, younger age, obesity, and nocturnal desaturation were associated with development of PH and OSA patients.  PH increases mortality in patients with OSA.
Imran et al <sup>771</sup>	2016	2a	Systematic Review	Patients with PH and OSA on CPAP (n=222)	Mean pulmonary artery pressure	CPAP therapy is associated with a significantly lower PA pressure in patients with isolated OSA and PH (13.3 mmHg; 95% CI 12.7–14.0).
Sun et al <sup>776</sup>	2016	2a	Systematic Review	Patients with OSA on CPAP (n=181)	Mean pulmonary artery pressure	CPAP therapy was associated with a statistically significant reduction in pulmonary artery

						pressure in patients with OSA (standardized mean difference -1.34, 95% CI: -2.33 to -0.34, P=0.009).
Arias et al <sup>770</sup>	2006	2b	RCT (cross over)	1) Severe OSA (n=23) 2) Healthy controls (n=10)	Pulmonary artery systolic pressure	CPAP therapy was associated with a decrease in PASP in patients with PAH and OSA (28.9+8.6 mmHg to 24.0+5.8 mmHg; P<0.0001).
Sharma et al <sup>746</sup>	2019	2b	RCT	1) Patients with OSA and heart failure (n=11) 2) Patients with OSA and heart failure on CPAP (n=10)	Pulmonary artery systolic pressure	CPAP therapy was associated with a decrease in PASP in patients with PAH and OSA (58.6±2.5 mmHg to 42.8±2.7 mmHg; p=0.025).

AHI= apnea hypopnea index; CPAP=continuous positive airway pressure; OSA=obstructive sleep apnea; PA= pulmonary artery; PAH= pulmonary arterial hypertension; PASP= pulmonary artery systolic pressure; PH=pulmonary hypertension; PSG= polysomnography; RCT = randomized controlled trial; RHC=right heart catheterization; SDB= sleep disordered breathing

### VII.B.2 Chronic Obstructive Pulmonary Disease (COPD)

The concurrent diagnosis of obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) in an individual is known as overlap syndrome (OS).<sup>777</sup> OS is associated with a more severe clinical course compared to either disease alone.<sup>778-781</sup> Shawon et al. conducted a systematic review to determine the prevalence and clinical outcomes of OS and reported a significantly higher prevalence of OS in patients with either OSA or COPD compared to the general population.<sup>782</sup> OS patients experienced greater degree of nocturnal oxygen desaturation (SpO<sub>2</sub><90%) and lower sleep efficiency compared to OSA patients. OS was also associated with increased cardiovascular complications (pulmonary hypertension, atrial fibrillation, right ventricular dysfunction), COPD exacerbations, hospitalizations, and poorer quality of life compared to either disease alone.

#### Evaluation of OSA in Patients with COPD

**Aggregate Quality of Evidence:** B (Level 2A: 1 study; Level 2b: 7 studies, Level 4: 2 studies)

**Benefit:** Patients with comorbid OSA and COPD are at risk for increased morbidity and mortality compared with either disease alone.

**Harm:** There is minimal harm to screening for OSA other than the inconvenience of testing.

**Cost:** There are low to moderate costs to testing for OSA.

**Benefits-Harm Assessment:** The benefits of OSA evaluation of patients with comorbid COPD outweigh the harm.

**Value Judgments:** There is overwhelming evidence about the worsened clinical outcomes in patients with both COPD and OSA compared to either COPD or OSA alone.

**Recommendation Level:** Recommendation

**Intervention:** Recommend evaluation for OSA in patients with COPD.

**Table VII.B.2a Prevalence and Outcomes in OSA with coexisting COPD (Overlap Syndrome)**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Shawon et al <sup>782</sup>	2016	2a	Systematic Review	1) General and hospital populations  1) COPD 2) OSA  (n=29,341; age 40-90)	1) Prevalence of Overlap Syndrome  2) Clinical endpoints of Overlap: cardiovascular disease, pulmonary hypertension, resistant hypertension, exacerbation of COPD, mortality, quality of life, hospitalization rate	Overlap Syndrome:  --High prevalence of Overlap in either OSA (7.6-55.7%) or COPD (2.9-65.9%) population compared to general population (1.0-3.6%).  Overlap syndrome has greater nocturnal oxygen desaturations, reduced mean peripheral capillary oxygen saturation (SpO <sub>2</sub> ) and increased sleep time spent with SpO <sub>2</sub> <90% (T90) and worse sleep quality than patients with only OSA.  Overlap Syndrome is associated with more frequent cardiovascular morbidity, poorer

						quality of life, more frequent COPD exacerbations and increased medical costs.
Donovan et al <sup>778</sup>	2019	2b	Prospective cohort study	Participants from LOTT study (Long-term Oxygen Treatment Trial) with COPD assessed for OSA risk by STOP-BANG questionnaire  1) Intermediate-to-high risk (score $\geq 3$ ) 2) Low risk (score $< 3$ )	1) Composite of death  2) First hospitalization  3) Overall incidence of COPD exacerbations	High percentage of COPD patients were at intermediate to high risk of undiagnosed OSA based on modified STOP-BANG criteria and were associated with greater risk of poor outcomes.
Sanders et al <sup>780</sup>	2003	2b	Prospective cohort study	Participants from Sleep Heart Health Study (community based), using polysomnography and spirometry results	1) Determine association between OAD and SAH  2) Identify predictors of nocturnal oxyhemoglobin desaturation in OAD with and without SAH	1) No association between mild OAD and SAH.  2) Independent of SAH, FEV <sub>1</sub> /FVC $<65\%$ is associated with more severe nocturnal oxygen desaturation.  3) Nocturnal oxygen desaturation is greater in combined OAD and SAH compared with either disease alone.  4) Mild OAD patients without OSA have minimally disturbed sleep.
Du et al <sup>779</sup>	2018	2b	Cross sectional	NHANES database (2005-2008)	Evaluate factors associated with	Overlap Syndrome and COPD were

			study	1) No COPD or OSA 2) OSA 3) COPD 4) Overlap Syndrome	all-cause mortality	associated with higher all-cause mortality compared to neither disease and OSA alone.
Starr P et al <sup>781</sup>	2019	4	Retrospective cohort study	Enrollment and claims data 2004-2013 from a 5% national sample of Medicare beneficiaries with COPD and Overlap Syndrome	Examine the diagnosed prevalence, trend, and patient characteristics of Overlap Syndrome	Prevalence: 11.0% of the COPD cohort had coexisting OSA compared with patients with COPD alone.  Trend: younger age and male gender have a higher number of comorbid conditions and have more complex COPD.  Over the 10-year study period, overlap syndrome increased from 4.04% in 2004 to 17.80% in 2013 based on visit for OSA.

OSA=obstructive sleep apnea, COPD=chronic obstructive pulmonary disease, OAD=obstructive airway disease, SAH=sleep apnea hypopnea

### VII.C Comorbidities Associated with OSA: Obesity

Obesity is the most common risk factor for Obstructive Sleep Apnea (OSA), diagnosed in more than 70% of OSA patients.<sup>783</sup> Weight gain has been associated with greater sleep disordered breathing (SDB) severity in both observational and intervention studies.<sup>188,190,784</sup> The literature linking obesity with OSA is challenged by the sheer number of confounders among patients with metabolic disease, including behavioral variables (activity level, dietary indiscretion, medication compliance), access to care and socioeconomic status.

The relationship between excess weight and OSA is likely reciprocal. OSA fragments sleep, leading to chronic insufficient sleep and excessive daytime sleepiness. These factors lead to reduced activity levels as well as increased appetite, with resultant weight gain.<sup>785</sup> Patients with OSA appear to be more susceptible to weight gain compared to similarly matched obese counterparts with significant weight gain reported in the year leading up to a diagnosis of OSA.<sup>786,787</sup> Dysregulation of leptin, with adverse implications for weight loss, body fat storage and distribution is well documented in obese patients with OSA.<sup>787,788</sup> Among a cohort of subjects with morbid obesity and OSA who underwent bariatric surgery, long term weight loss outcomes were worse among those that did not continue to use CPAP postoperatively.<sup>789</sup>

Although untreated OSA is associated with weight gain, CPAP adherence has not been associated with weight loss and may even lead to weight gain.<sup>790-793</sup> A number of theories have been put forth to explain the phenomena of weight gain following initiation of CPAP. Tachikawa and colleagues proposed that CPAP leads to a small reduction in basal metabolic rate, likely by eliminating additional energy expenditure due to breathing against an obstructive airway.<sup>794</sup> Stenlof and colleagues have also found a reduction in energy expenditure with CPAP therapy.<sup>795</sup> It is unclear if, and how, these reductions in energy expenditure translate to weight gain or inability to lose weight. Some studies have shown that those who gained weight with CPAP failed to record an increase in daytime activity and had more disordered eating behaviors.<sup>796,797</sup> Others postulate that a resurgence of slow wave sleep following treatment of OSA may lead to increases in growth hormone and subsequent weight gain.<sup>794,798,799</sup> These explanations are all speculative, and the best use of the information at present is tempering messages to patients that treatment of OSA will lead to a reduction in weight. While there are a number of meaningful outcomes from CPAP, including improvements in mood and quality of life, a linear relationship with weight is unclear.

#### Impact of obesity on the management of OSA

Obesity exhibits both a mechanical and neurophysiologic effect on upper airway patency. Adipose deposition in the upper airway leads to a smaller lumen and increased collapsibility, both of which predispose to apnea.<sup>800</sup> In addition, fat deposits around the thorax and abdomen reduce chest wall compliance and diminish functional residual capacity, which both increases oxygen demand and contributes to greater nocturnal hypoxia, especially among apneic patients.<sup>801</sup>

The critical closing pressure,  $P_{crit}$ , is determined by mechanical and neural factors that regulate pharyngeal collapsibility. In obese patients an elevated  $P_{crit}$  is due to upper airway adipose deposition.<sup>802</sup> Obesity can also lead to reduced lung volumes, further compromised during supine sleep. These factors make OSA more common in obese individuals, contributing to increased severity of disease, longer apneic episodes, and more hypoxemia. These factors also reduce the efficacy of OSA-specific therapies.

Positive airway pressure (PAP) therapy remains the most commonly prescribed treatment for OSA. While efficacious, the treatment response may be reduced in obese patients, who tend to have greater residual AHI compared with their non-obese counterparts. In addition, therapeutic pressures required to maintain upper airway patency are generally higher in obese patients.<sup>803</sup> Not surprisingly, weight loss can lead to a reduction in required PAP pressures.<sup>804</sup>

Intuitively, the increased pressure requirements and diminished treatment response seen in obese patients may be expected to contribute to poor adherence. Interestingly, adherence rates are not lower among those with obesity, with some studies even demonstrating superior adherence in this population.<sup>792,805</sup>

Oral appliances (OAs) can provide both efficacious and effective treatment for patients with OSA, including those who are obese.<sup>806-809</sup> However, similar to PAP, the therapeutic effect and likelihood of achieving successful therapy are decreased in obesity. The efficacy of OAs, as measured by the reduction in AHI, decreases with increasing weight in a non-linear relationship. Evidence shows that OAs are more efficacious and have a greater responder rate among those with lower BMIs.<sup>807,809,810</sup> Likewise, the odds of having a high residual AHI are greater in those with increased weight, particularly among those with morbid obesity. As such, many consider morbid obesity to be a relative contraindication for OA therapy, although use of OA as adjunct therapy requires further evaluation.

Surgical procedures specifically intended to reduce or eliminate sleep disordered breathing can present a treatment option for patients with OSA, particularly those unresponsive or intolerant to PAP therapy. The increased deposition of adipose tissue and greater collapsibility of the upper airways commonly seen in obese patients may decrease the probability of a successful surgical outcome. Both the treatment effect and probability of successful therapy with uvulopalatopharyngoplasty (UPPP) decreases with increasing BMI.<sup>811</sup> In addition, higher BMI is associated with greater risk for postoperative complications.<sup>812</sup> Increased BMI may be accompanied by increased adiposity in the tongue base, leading to multi-level collapse of the upper airway necessitating multiple or staged surgical interventions. While this decreased probability for successful treatment does not necessarily negate surgery as a treatment option for obese patients, it does need to be weighed against the increased associated perioperative risks and higher chance for eventual recurrence of OSA. Upper airway staging systems have been developed to help develop individualized approaches.<sup>813</sup> Like other upper airway surgical procedures for OSA, hypoglossal nerve stimulation can provide a treatment option for those intolerant of PAP therapy. However, this therapy is only approved for a limited BMI range.<sup>814</sup>

A determination of whether untreated OSA leads to obesity is complicated by factors which are difficult to study in a controlled fashion, notably patient behaviors and adherence to interventions. The current level of evidence precludes a determination of whether OSA causes obesity and whether OSA therapies improve obesity.

#### VII.D Comorbidities Associated with OSA: Insulin Resistance

Understanding the relationship between obstructive sleep apnea (OSA) and metabolic disorders is of paramount importance for global health. OSA and metabolic disease are common bedfellows with obesity and associated comorbidities. The global impact is striking as 400-700 million individuals have diabetes or metabolic risk factors for the future development of diabetes, with healthcare costs in the tens of billions of dollars. These rates are arguably on track to double in the next 20 years.<sup>815,816</sup>

Sleep disordered breathing is highly prevalent among individuals with impaired insulin sensitivity and diabetes, although underlying mechanisms are nebulous. Many studies control for variables such as age, gender, body mass index (BMI), waist circumference and race.<sup>656,817,818</sup> Unfortunately, other relevant factors are generally ignored (activity level, exercise, diet, socioeconomic status, access to healthcare and adherence with medical treatment). Potential pathophysiological mechanisms for a relationship between OSA and metabolic disease tend to be based on animal studies or uncontrolled cohorts. As a result, although a role for OSA in diabetes is compelling, the rigor of available evidence is not available for developing evidence-based conclusions or recommendations.

Among patients with OSA the available literature has shown a broad prevalence of prediabetes (20-67%), based on impaired fasting glucose and impaired glucose tolerance testing.<sup>819</sup> A linear correlation between OSA severity and insulin resistance has been documented with greater severity at diagnosis predicting the risk of incident diabetes<sup>820,821</sup> In a historical cohort of over 8,000 patients, Kendzerska et

al found that those with an apnea hypopnea index (AHI) of greater than or equal to 30 events per hour had a 30% higher hazard of developing diabetes compared to those with AHI < 5 events per hour.<sup>821</sup> Aside from overall severity, severity in REM and time with an oxygen saturation less than 90% also increased risk of diabetes.

The mechanisms by which OSA may increase insulin resistance and impair glucose tolerance remain unclear. Both animal and human studies have linked intermittent hypoxia to insulin resistance.<sup>822,823</sup> A meta-analysis by Iftikhar et al evaluated 16 case-controlled studies to evaluate the association between OSA and insulin resistance. This study found a significant relationship for increasing HOMA-IR with baseline BMI, but not with age, AHI, or gender.<sup>655</sup> Other studies have shown independent correlations between hypoxemia (increased oxygen desaturation index (ODI), increased time spent with SpO<sub>2</sub> < 90%) and sleep fragmentation to higher glucose and insulin concentrations and insulin sensitivity.<sup>815,824</sup>

Ongoing research continues to evaluate the role of hypoxia and a pro-inflammatory state, focusing on intermittent hypoxia and increased adipose tissue lipolysis. Murphy et al<sup>825</sup> provided evidence in mice that intermittent hypoxia led to a pro-inflammatory phenotype of adipose tissue. In humans, OSA was associated with increased spontaneous lipolysis that correlated with the severity of OSA as well as insulin resistance and impaired insulin secretion in patients with type 2 diabetes mellitus.<sup>816</sup> In a large-scale cross-sectional study, a significant positive interaction was observed between the severity of OSA and decreased lipoprotein(a) concentration.<sup>826</sup> Several authors have outlined a role for episodic hypoxia during apneic events promoting increased adipose lipolysis and levels of free fatty acids systemically which have a pro-inflammatory effects leading to dysregulated glucose homeostasis and reduced insulin sensitivity.<sup>816</sup> Building a link between underlying pathophysiologic mechanisms between OSA and metabolic disease may be confounded by heterogeneity in how metabolic disorders present clinically and deciphering the impact of OSA as opposed to the role of sleepiness, age, gender and obesity.<sup>827</sup> At this time, potential mechanisms for a causative relationship between OSA and metabolic disease are only hypothesis generating. There is not a degree of published evidence to date that firmly establishes a role for untreated OSA as a contributor to diabetes.

## VII.E Comorbidities Associated with OSA: Cognitive Impairment and Dementia

### OSA and Cognitive Performance

Several quantitative reviews evaluating clinical studies have found that OSA is associated with deficits in cognitive performance. Two meta-reviews have examined the quantitative reviews, and both identified associations between OSA and cognitive deficits across many domains<sup>828,829</sup>. Cognitive domains commonly found to be negatively impacted by OSA include attention, vigilance, executive function, processing speed, and subdomains of memory. Although the majority of meta-analyses have demonstrated cognitive deficits in patients with OSA compared to healthy controls, these results have been variable and somewhat inconsistent.(Table VII.E)

### OSA and Mild Cognitive Impairment (MCI)/Dementia

The association between OSA and MCI/dementia is a growing area of research. A large meta-analysis of 19,940 patients has shown that sleep-disordered breathing (SDB) at baseline is associated with risk of cognitive decline<sup>830</sup>. A recent systematic review of 68 studies found that OSA is often associated with the development of mild cognitive impairment and Alzheimer's disease (AD) in older adults<sup>831</sup>, and that OSA is often associated with cognitive impairment in young and middle-aged adults. A meta-analysis showed that patients with AD had a 5x higher chance of presenting with OSA than healthy age-matched



individuals<sup>832</sup>. In MCI patients, the association is less clear, with a highly variable prevalence of OSA (11-71%) based on OSA diagnostic methods and patient recruitment locations<sup>833</sup>.(Table VII.E)

Several cross-sectional, cohort, and case-control studies examined the relationship between OSA and dementia. Cross-sectional studies showed high rates of OSA among dementia patients<sup>834,835</sup>. One recent study found a very high prevalence of OSA in patients with mild to moderate AD (116 of 128 patients, or 90.6%)<sup>834</sup>. In a retrospective cohort study, patients with SDB were 1.58 times more likely to develop AD than those without SDB<sup>836</sup>. Large cohort studies focusing on OSA and dementia appear inconsistent. A prospective cohort study from the Sleep Heart Health Study found that elderly cognitively-normal (mean age = 76.9 y, n = 208) individuals with OSA were found to have increased risk of dementia compared to those without OSA, independent of age, gender, and ApoE4 allele status<sup>837</sup>. In contrast, the Atherosclerosis Risk in Communities Study, a 15-year prospective cohort study, found that sleep apnea severity and nocturnal hypoxemia were not associated with cognitive decline<sup>838</sup>. In another analysis of the same cohort, OSA was not associated with risk of incident dementia; however, when adjudicated outcomes were used, severe OSA was associated with risk of dementia in later life<sup>839</sup>.

Overall, most evidence suggests that OSA may represent a modifiable risk factor for dementia, but conflicting and inconsistent data exist.

#### Evaluation of OSA in Patients with Cognitive Impairment

Aggregate Quality of Evidence: C (level 2a: 9 studies, level 3a: 7 studies)

Benefit: Evaluation and treatment of OSA has the potential to improve select domains of cognitive function and may slow the incidence of cognitive decline.

Harm: The potential harms of OSA screening and testing are low.

Cost: There are low to moderate costs associated with sleep study testing.

Benefits-Harm Assessment: The benefits of diagnosis and treatment for OSA outweigh the potential harm.

Value Judgments: Evidence suggests that OSA is associated with neurocognitive impairment and decline. Most evidence suggests that OSA may represent a modifiable risk factor for dementia, but conflicting and inconsistent data exist.

Recommendation Level: Recommendation.

Intervention: Recommend evaluation and testing for OSA in those at high risk for cognitive decline or impairment.

**Table VII.E Association between OSA and Cognitive Impairment**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
-------	------	-----	--------------	--------------	-------------------	------------

Olaithe et al. <sup>829</sup>	2018	2a	Meta-review	7 OSA meta-analyses (2003-2016): Individuals with OSA and healthy controls. Also included were 5 COPD studies, 2 insomnia studies, 4 sleep deprivation studies.	Cognitive deficits in OSA, COPD, insomnia, or sleep deprivation.	Cognitive deficits in OSA include attention, memory, executive function, psychomotor function, visuospatial and language abilities. Small to large effects were found in most studies across most domains.
Bucks et al. <sup>828</sup>	2013	2a	Meta-review	5 quantitative reviews (2001-2012): older adults (≥50 y) with OSA vs controls/norms	Domains of cognitive function in OSA	OSA is associated with deficits in attention/vigilance, delayed verbal and visual long-term memory, visuospatial/constructional abilities, and executive function, but does not appear to affect language ability or psychomotor function. The data are equivocal for working memory, short-term memory and global cognitive functioning. Treatment with CPAP appears to improve executive dysfunction, delayed long-term verbal and visual memory, attention/vigilance, and global cognitive functioning.

Bubu et al. <sup>831</sup>	2020	2a	Systematic review	68 studies (cross-sectional, longitudinal, and RCTs, 1985-2019). Studies were stratified based on age: young/middle-aged (30-60 y) or older (>60 y) adults.	1) OSA and cognitive performance/impairment 2) OSA and subsequent development of mild cognitive impairment/dementia 3) OSA and biomarkers of Alzheimer Disease	1) OSA and cognition: In young and middle-aged adults, OSA is often associated with cognitive impairment, although unclear whether OSA precedes cognitive decline. CPAP treatment improves certain cognitive domains. In older adults, the OSA-cognition associations are variable and depend on study type and setting. 2) OSA and MCI/dementia: Lack of longitudinal studies for young/middle-aged adults and more research is needed. In older adults, OSA is often associated with the development of MCI/AD. CPAP treatment improved sleep quality and cognitive function in AD patients with OSA. 3) OSA and biomarkers of AD: In middle-aged and older adults, there is an association between OSA and biomarkers of AD pathology in cross-sectional studies. Limited prospective studies show contrasting associations.
----------------------------	------	----	-------------------	---	--	---

Wang et al. <sup>840</sup>	2020	2a	Systematic review/review	40 studies (cohort, case study, RCT)	1) Cognitive impairments associated with OSA 2) OSA and Alzheimer Disease pathological markers 3) Cognitive performance with CPAP treatment	1) Individuals with OSA had worse cognitive performance than controls in domains of attention, executive function, intelligence, memory, psychomotor speed, and alertness. 2) AD pathological markers appear to be increased in OSA. 3) CPAP therapy could improve cognitive impairments in OSA, particularly if duration of therapy is > 4 weeks.
Mubashir et al. <sup>833</sup>	2019	3a	Systematic review	5 studies (4 cross-sectional, 1 retrospective cohort, 2011-2015) reporting the prevalence of OSA among adult patients (>18y) with mild cognitive impairment (MCI)	1) Prevalence of OSA in MCI 2) Risk of OSA in MCI	1) There is a highly variable prevalence of OSA in MCI population (11-71%), compared to 4-70% in included control groups. 2) One study recruiting from memory clinics showed >3-fold risk of OSA in patients with MCI compared to control group. There were no differences in risk of OSA between MCI and control groups in the other included studies with control populations.
Zhu and Zhao <sup>830</sup>	2018	2a	Meta-analysis	6 cohort studies (2011-2016): 19,940 adults $\geq 18$ y, with and without sleep-disordered breathing	Association between sleep-disordered breathing and the incidence of cognitive decline	Baseline SDB is independently associated with risk of cognitive decline (higher risk of mild cognitive impairment compared with dementia). Stratified analyses suggest gender difference (higher risk for incidence of cognitive decline in females, not males).

Cross et al. <sup>841</sup>	2017	3a	Systematic review and meta-analysis	13 studies (cross-sectional, case-control, 1985-2016): 5104 adults, $\geq 50$ y, with or without OSA	Effect of OSA on neuropsychological performance	There was a small negative association between OSA and all combined neuropsychological outcomes, but this association may be due to publication bias (calculations accounting for bias resulted in a null association). Association between OSA and cognition in older age is highly variable and depends on type/setting of study.
Stranks et al. <sup>842</sup>	2016	3a	Meta-analysis	19 studies (1987-2012) of adult OSA patients vs healthy controls	Cognitive function of OSA patients	For OSA patients, statistically significant negative effect sizes were found in the domains of non-verbal memory, concept formation, psychomotor speed, construction, executive functioning, perception, motor control and performance, attention, speed of processing, working and verbal memory, verbal functioning and verbal reasoning. The domain of perception was not impaired. Non-verbal memory, concept formation, and psychomotor speed were most impaired.
Emamian et al. <sup>832</sup>	2016	3a	Meta-analysis	5 cross-sectional studies (1983-1989) of Alzheimer Disease patients vs healthy controls	Odds ratio for OSA in Alzheimer Disease vs. healthy control	Patients with AD had a 5x higher chance of presenting with OSA than healthy age-matched individuals (aggregate odds ratio was 5.05 and homogeneous).

Vaessen et al. <sup>843</sup>	2015	3a	Systematic review	12 studies (9 case-control, 1 longitudinal uncontrolled, 1 descriptive uncontrolled, 1 cross-sectional) with adult patients with OSA vs controls or non-OSA population	Cognitive complaints in untreated OSA	Concentration complaints were increased in untreated OSA patients compared to primary snorers and healthy controls. Memory and executive function may be similarly increased, however insufficient data precluded firm conclusions. Cognitive complaints may be related to higher levels of subjective sleepiness. The authors stress the importance of the difference between subjective cognitive complaints and objective cognitive impairment.
Kilpinen et al. <sup>844</sup>	2014	3a	Systematic review	44 studies: comparison of OSA patients to healthy controls	Information processing speed	Information processing speed was reduced in OSA patients in half of the studies. Reduced information processing speed was seen 75% of the time when compared to norm-referenced data. CPAP treatment improved processing speed marginally when compared to placebo/conservative treatment.

Wallace and Bucks <sup>845</sup>	2013	2a	Meta-analysis	42 studies: 2294 adults with untreated OSA, and 1364 healthy controls	Tasks associated with episodic memory (immediate recall, delayed recall, learning, and/or recognition memory)	Compared to healthy controls, adults with OSA had significant impairment in verbal episodic memory (immediate recall, delayed recall, learning, and recognition) and visuo-spatial episodic memory (immediate and delayed recall), but not visual immediate recall or visuo-spatial learning. Compared to norms, adults with OSA had significant impairment only in verbal immediate and delayed recall.
Saunamäki and Jehkonen <sup>846</sup>	2007	2a	Systematic review	40 studies assessing executive function in OSA	Domains of executive function	Executive function domains that were most adversely affected in OSA include working memory, phonological fluency, cognitive flexibility, and planning. CPAP improved performance times, cognitive flexibility, and planning, but did not significantly improve deficits in working memory and phonological fluency.
Aloia et al. <sup>847</sup>	2004	2a	Systematic review	37 studies (1985-2002):	Pattern of cognitive deficits in OSA, cognitive domains improved by treatment, possible mechanisms of cognitive dysfunction	Findings were equivocal for most cognitive domains. Attention/vigilance, executive function, and memory were impaired in the majority of reviewed studies (6/8, 6/9, and 7/11 studies, respectively). Treatment improved attention/vigilance in most studies and did not improve constructional abilities or psychomotor function.

Beebe et al. <sup>848</sup>	2003	2a	Meta-analysis	25 studies: 1092 patients with OSA and 899 healthy controls	Neuropsychological outcome domains in untreated OSA	Untreated OSA had significant impact on vigilance and executive functioning, and negligible impact on intellectual and verbal functioning. Data were mixed for visual and motor functioning, and memory functioning.
Fulda and Schulz <sup>849</sup>	2003	3a	Meta-analysis	54 studies (1985-2000): 1635 SRBD patients compared with 1737 controls	Cognitive dysfunction in SRBD	Compared with controls, SRBD patients demonstrated: <ul style="list-style-type: none"> <li>- Moderate to large reductions in mental flexibility, visual delayed-memory retrieval, and driving simulation performance</li> <li>- Small to moderate reductions in focused and sustained attention, verbal delayed-memory retrieval, verbal fluency and composite measures of general intellectual functioning</li> <li>- No difference in divided attention, concept formation and reasoning, and verbal or visual immediate-memory performance</li> </ul> Other domains not assessed due to insufficient data or between-study heterogeneity.

### VII.F Comorbidities Associated with OSA: Cancer

The epidemiological association between OSA and cancer was first published in 2012, and since then, a total of 21 studies have been published [Pubmed]. The consensus is that higher OSA severity (e.g. more hypoxic burden) is associated with an increase in cancer risk.



Two *population-based* epidemiological studies with long term (> 20 years) follow up reported a significant association between OSA severity and *all* cancers.<sup>850,851</sup> Five epidemiologic studies with a shorter (<20 years) follow up also reported a significant correlation between OSA severity and *all* cancers. These include increased cancer incidence<sup>852</sup> and increased cancer mortality in patients <65yo with severe OSA<sup>853</sup>; an increased cancer incidence in patients <45yo with severe OSA<sup>854</sup>; an increased cancer prevalence in women with OSA, but not in men<sup>855</sup>; and a higher overall incidence of cancer in a veteran population with OSA.<sup>856</sup> Two shorter follow up studies reported no association between OSA and all cancers<sup>857,858</sup>. However, when epidemiological studies assessed an association of OSA and *specific* cancers, results were heterogeneous but support a higher incidence of breast cancer,<sup>857</sup> primary central nervous system cancers,<sup>859</sup> nasal and prostate cancer,<sup>860</sup> colorectal cancer<sup>861</sup> and melanoma, kidney, breast, uterine cancer.<sup>862</sup>

## Risk factors

### *Changes in upper airway anatomy*

There is a strong increased incidence of OSA in patients with head and neck cancer - both on presentation<sup>863</sup> and after radiation therapy<sup>864</sup>, likely related to changes in craniofacial anatomy.

### *Increased hypoxic burden*

Increased hypoxic burden, specifically, cyclical intermittent hypoxia (CIH) is hypothesized as the primary mechanism on OSA and increased cancer risk. Higher OSA severity as measured by polysomnography, specifically those related to an increased hypoxic burden (e.g. Tsat<90%) have been associated with melanoma aggressiveness,<sup>865</sup> pancreatic cancer progression,<sup>866</sup> lung cancer prevalence<sup>867</sup> and cancer mortality.<sup>868</sup> In addition, potential mechanisms that associate hypoxic burden with increased cancer risk include: significantly reduced levels of circulating invariant natural killer T cells and function (in OSA patients without cancer),<sup>869</sup> alterations of molecules related to HIF1 (in OSA patients with lung cancer),<sup>867</sup> increased microRNAs involved with some cancer types (miR-1254 and miR-320e in OSA patients without cancer),<sup>870</sup> and up-regulation of circulating TGF- $\beta$ 1, VEGF and Foxp3+Tregs (in OSA patients with lung cancer).<sup>871</sup> To date, there have not been studies specifically assessing the effect of CPAP modifying cancer risk.

## Potential Mechanisms

In vitro models have provided two main findings: (1) CIH results in changes that are distinct from sustained hypoxia; (2) CIH results in molecular changes that promote cancer progression or metastases. Most CIH mechanisms that have been explored center around stabilizing HIF1<sup>872</sup> and measuring downstream effects. Examples of these downstream effects are conversion to cancer stem cell properties,<sup>873</sup> increased NOX1 subunit of NADPH oxidase,<sup>874</sup> increased monocyte polarization toward a tumor-promoting phenotype,<sup>875</sup> glycolysis<sup>872</sup> and extracellular matrix remodeling.<sup>876</sup> Other studies focused on why cancer cells exposed to CIH may be more resistant to therapy. These mechanisms including a decrease in topo alpha mRNA and protein,<sup>877</sup> changes in proteasome function,<sup>878</sup> and small interfering RNA.<sup>879</sup> Lastly, CIH may increase expression of genes associated with metastases,<sup>880</sup> and cancer cell migration.<sup>881</sup>

### *Animal models*

Animal models have demonstrated that CIH increases cancer progression.<sup>882</sup> Although most mouse models placed the cancer in the flank (considered to be inherently more hypoxic<sup>883</sup> than typical primary

sites such as the lung) important findings have emerged: CIH accelerates tumor growth,<sup>884</sup> increases tumor angiogenesis,<sup>885</sup> increases metastases,<sup>886</sup> reduces immunosurveillance,<sup>887</sup> increases spontaneous tumorigenesis<sup>888</sup> and increases molecular markers of tumor aggression including PD-L1.<sup>889</sup>

These exciting areas of clinical, *in vitro* and animal studies demonstrate an association of CIH, one of the common features of OSA, to cancer risk. This association could lead to an OSA subtype that would benefit from aggressive screening and treatment, and may identify novel cancer targets.

## VII.G Comorbidities Associated with OSA: Nasal Disorders

Nasal obstruction or congestion can be caused by both inflammatory and structural factors. Common inflammatory diseases causing nasal obstruction include rhinitis, sinusitis, and nasal polyps. Structurally, obstruction may occur at the level of the external or internal nasal valves, septum, and inferior turbinates. Nasal obstruction, allergic rhinitis, and chronic sinusitis have repeatedly been demonstrated as significant risk factors for habitual snoring, chronic excessive daytime sleepiness, and sleep-disordered breathing<sup>69,890-892</sup>.

### VII.G.1 Allergic Rhinitis

Several studies have specifically investigated the relationship between allergic rhinitis and sleep-disordered breathing and have demonstrated that AR negatively impacts sleep quality and successful treatment with nasal corticosteroids and/or montelukast improves sleep disturbance. In a population-based study of individuals enrolled in the Wisconsin Sleep Cohort Study, chronic severe nasal congestion was identified as an independent risk factor for habitual snoring and participants with nasal congestion due to allergy were 1.8 times more likely to suffer from moderate to severe sleep-disordered breathing<sup>69,892</sup>. In a cohort study of allergic rhinitis and non-allergic rhinitis patients, seasonal allergic rhinitis was associated with increased daytime sleepiness and quality of life impairment<sup>891</sup>. While data on the effects of AR on polysomnogram (PSG) parameters remains mixed, medical management of AR has been demonstrated to improve PSG parameters such as improved O<sub>2</sub> nadir, and supine AHI levels<sup>893</sup>. Intranasal corticosteroids have been shown to improve congestion and daytime somnolence in patients with perennial rhinitis. Pooled data from 3 double-blind crossover randomized control trials of budesonide, flunisolide, and fluticasone demonstrated significantly decreased nasal congestion and sleepiness in treated patients<sup>890</sup>. Kiely et al performed a double-blind crossover randomized control trial on the effect of intranasal steroid on sleep-disordered breathing, assessed with polysomnography and nasal resistance at baseline and after 4-week treatment, and found a significant but small reduction in average AHI in patients with OSA using fluticasone<sup>894</sup>.

#### Association between Allergic Rhinitis and OSA

Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 2b: 1 study)

Table VII.G.1 Allergic Rhinitis and OSA

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Young et	1997	1b	Prospective population-based	Population-based sample of individuals	Relationship between nasal obstruction and	Participants with nighttime symptoms of

al. <sup>892</sup>			cohort study	(n=911, response rate 50%) enrolled in Wisconsin Sleep Cohort Study	sleep-disordered breathing assessed via polysomnography, rhinometry, and questionnaires	rhinitis (5+ nights/month) were significantly more likely to report habitual snoring (3-7 nights/wk), chronic excessive daytime sleepiness, or nonrestorative sleep than those who rarely had symptoms(p<0.0001). Those with nasal congestion due to allergy were 1.8x more likely to have moderate to severe sleep-disordered breathing.
Craig et al. <sup>890</sup>	2005	1a	Pooled data from 3 double-blind crossover RCT	69 patients with allergic rhinitis without OSA	Effect of intranasal corticosteroids in patients with perennial rhinitis on reduction of congestion and daytime somnolence	Pooled data of budesonide, flunisolide, and fluticasone demonstrated significantly decreased nasal congestion and sleepiness in treated patients. A correlation between reduction in nasal congestion and an improvement in sleep (p<0.01) and daytime somnolence (p=0.01) was demonstrated.
Stuck et al. <sup>891</sup>	2004	1b	Prospective, cohort study	25 patients with seasonal allergic rhinitis and 25 healthy volunteers assessed with questionnaires (ESS, SF-36) and polysomnography performed before and during pollen season	Effect of seasonal allergic rhinitis on subjective and objective sleep patterns	Seasonal allergic rhinitis leads to increased daytime sleepiness(p=0.006) and quality of life impairment(p<.0001).
Santos et al. <sup>895</sup>	2008	1b	Double blind crossover RCT	31 patients with persistent allergic rhinitis and sleep disturbances treated	Effect of rhinitis therapy on patient-reported sleep quality and symptoms of	Montelukast treatment demonstrated significant improvement in reported daytime

				with montelukast or placebo	daytime sleepiness	somnolence(p=0.0089) and daytime fatigue(p=0.0087).
Golden et al <sup>896</sup>	2010	1b	Double blind crossover RCT	24 patients with perennial AR received azelastine vs saline	Effect of topical nasal antihistamines on symptoms of rhinitis, sleep, and daytime somnolence	Azelastine reduced rhinorrhea(p=0.03) and improved subjective sleep quality(p=0.04) but did not reduce daytime somnolence.
Lavigne et al <sup>893</sup>	2013	2b	Prospective cohort study	21 patients with OSA and allergic rhinitis and 34 patients with OSA without allergic rhinitis	Effect of corticosteroid treatment on disease severity with sleep studies and biopsies obtained from the inferior turbinate, nasopharynx, and uvula	Improved O <sub>2</sub> nadir, supine AHI, and daytime somnolence in AR group(p=0.05).
Kiely JL et al. <sup>894</sup>	2004	1b	RCT	OSA with AHI > 10 (n=13) vs. patients without OSA. Intervention: Fluticasone spray for 4 weeks.	AHI, ESS, Snoring	Reduction in AHI in patients with OSA and AR compared to placebo (23.3 vs. 30.3). Most patients continued to have significant OSA.

### VII.G.2 Nasal Obstruction

Nasal obstruction is a significant risk factor for sleep-disordered breathing. While data remains limited regarding objective measures of sleep-disordered breathing following treatment for nasal obstruction, literature has shown that sleep quality is compromised in patients with chronic nasal obstruction, with significant improvement in subjective sleep quality after medical and surgical treatment. Anatomic nasal obstruction, including septal deviation, internal/external valve collapse, and inferior turbinate hypertrophy, have been repeatedly identified as common findings in patients with sleep-disordered breathing<sup>6,897</sup>.

The effect of medical management of nasal obstruction on sleep-disordered breathing has been studied extensively. Topical nasal decongestion and/or external dilator strip for chronic nasal obstruction has been shown to decrease snoring, but has not demonstrated a significant, persistent change in AHI or improvement in sleep quality<sup>894-896,898-903</sup>. In a double-blind crossover randomized control trial investigating the effects of topical nasal decongestant on nasal conductance, symptom scores, and polysomnography findings, there was a significant decrease in AHI at time of maximal decongestion but

no significant change in overall AHI or sleep quality<sup>899</sup>. Djupesland et al conducted a double-blind crossover randomized control trial on the effects of external nasal dilation on sleep-disordered breathing, assessed by polysomnography, acoustic rhinometry, and questionnaire. While nasal dimensions increased significantly with external dilator compared to placebo, there was no significant decrease in AHI. Kerr et al studied the effect of nasal resistance reduction by application of topical vasoconstrictor and insertion of vestibular stents in patients with OSA. On posterior rhinomanometry and polysomnogram, it was found that while reduction of nasal resistance resulted in no significant change in AHI, significant improvement in subjective sleep quality were reported<sup>901</sup>. Sinonasal surgery continues to play a key role in management of OSA given demonstrated improvement in CPAP tolerance. Further study of the effect of treatment of nasal obstruction on objective polysomnographic parameters is reviewed elsewhere.

### Association between Nasal Obstruction and OSA

Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 2b: 1 study)

Table VII.G.2 Association between Nasal Obstruction and OSA

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Young et al. <sup>69</sup>	2001	1b	Prospective population-based cohort study	Population-based sample of individuals enrolled in ongoing Wisconsin Sleep Cohort Study. In-laboratory polysomnography was performed on subset(n=1032).	Relationship between nasal congestion and snoring	Chronic severe nasal congestion is an independent risk factor for habitual snoring at baseline and 5-year follow-up (OR 4.9; 95% confidence interval, 2.8-8.8).
An et al <sup>898</sup>	2019	1b	Double blind crossover RCT	15 patients with OSA and chronic nasal obstruction without obvious pharyngeal narrowing completed 2 overnight polysomnograms (randomly applying oxymetazoline or placebo)	Effects of nasal patency on sleep architecture in nasal obstruction-predominant obstructive sleep apnea patients by applying nasal decongestant.	Oxymetazoline resulted in significant increase in REM sleep(p=0.027) and reduction of stage 1 sleep(p=0.004). AHI in supine position was significantly reduced(p=0.001).
Kerr et al <sup>901</sup>	1992	1b	Single-blind crossover study	10 patients with OSA receiving oxymetazoline and nasal dilator vs placebo	Effect of nasal resistance reduction on OSA and nasal airflow assessed via posterior rhinomanometry	Reduction of nasal resistance resulted in no change in AHI but improved subjective sleep quality(p<0.001).

					and PSG	
Stradling et al. <sup>532</sup>	1991	2b	Cross sectional study	1001 men surveyed regarding sleep quality and underwent polysomnography	Independent predictors of snoring and obstructive sleep apnea	Multiple linear regression identified nasal stuffiness as a significant independent predictor of snoring but not OSA.
Vidigal et al. <sup>904</sup>	2012	2c	Case control study	47 with moderate/severe OSAS and 20 matched controls	To evaluate nasal obstruction in patients with OSA compared to controls via questionnaires, physical exam, rhinoscopy, nasal inspiratory peak flow(NIPF), and acoustic rhinometry(AR)	OSA group had a significantly higher score on the nasal symptoms scale( $p < 0.01$ ) and higher frequency of nasal alterations including presence of septal deviation( $p = 0.01$ ) and inferior nasal turbinate hypertrophy( $p < 0.01$ ]. NIPF and AR parameters were not significantly different.
McLean et al. <sup>902</sup>	2005	1b	Single blind crossover RCT	10 patients with nasal obstruction and OSA	Effect of topical decongestant and external dilator strip on nasal resistance, mouth breathing during sleep, and OSA severity	While AHI reduced by mean 12 (range 3-22) with treatment, no correlation identified between nasal resistance change and AHI change ( $r^2 = 0.001$ ; $p = 0.92$ ).
Clarenbach et al. <sup>899</sup>	2008	1b	Double blind crossover RCT	12 patients with chronic nasal congestion and OSA treated with nasal xylometazoline or placebo for 1 week	Effects of topical nasal decongestant on nasal conductance, symptom scores, polysomnography	While there was a significant decrease in AHI at time of maximal decongestion( $P < 0.05$ ), there was no significant change in overall AHI or sleep quality.
Djupestrand et al. <sup>900</sup>	2001	1b	Double blind crossover RCT	18 heavy snorers without severe OSA(mean AHI 9.3) reporting nocturnal nasal obstruction	Effects of external nasal dilation (Breathe Right) assessed by polysomnography, acoustic rhinometry, and	Nasal dimensions increased significantly( $p < 0.001$ ) with active dilator compared to placebo. In habitual snorers(AHI<10) with severe morning obstruction, no significant reduction in AHI

					questionnaire	(p=0.06).
Ishii et al. <sup>544</sup>	2015	2a	Meta-analysis	10 studies meeting criteria with 320 patients: 2 RCTs, 7 prospective studies, and 1 retrospective study	Effect of isolated nasal surgery on OSA	Isolated nasal surgery for patients with nasal obstruction and OSA improved ESS by 3.53(95% CI[0.64, 6.23]) and RDI by 11.06(95% CI [5.92, 16.19]), but had no significant AHI improvement(95% CI [-1.6, 11.62]).
Li et al <sup>905</sup>	2011	2a	Meta-analysis	11 prospective noncontrolled clinical trials on outcomes of nasal surgery for OSA	Effect of nasal surgery on daytime sleepiness, snoring and polysomnogram	Mean AHI decreased from 35.2±22.6 to 33.5±23.8 after nasal surgery(p= 0.69). ESS scores decreased from 10.6±3.9 to 7.1±3.7(p <0.001). Significant improvement in snoring assessed by questionnaires and visual analog scale(p<0.05).
Yamasaki et al. <sup>906</sup>	2020	2b	Prospective cohort study	Patients undergoing nasal surgery surveyed through 24 months postoperatively	Longitudinal snoring symptoms and nasal obstruction after functional nasal surgery for patients with SDB	OSA patients achieved clinically significant improvement on Snoring Outcome Survey through 24 months (p>0.05).
Bosco et al <sup>907</sup>	2020	2b	Prospective cohort study	34 patients with AHI>15 and septal deviation treated with nasal surgery	Effects of nasal surgery on upper airway collapse, assessed using drug induced sleep endoscopy	Before nasal surgery, 74% of the patients demonstrated multilevel obstruction. After nasal surgery, 50% patients showed multilevel collapse (P < 0.05) with significant improvement shown in hypopharyngeal collapse
Li et al <sup>908</sup>	2009	2b	Prospective, controlled non-randomized study	66 patients with OSA(AHI>5, BMI<33) and chronic nasal obstruction (surgical, n=44; control,n=22)	Effect of septoplasty with inferior turbinate reduction versus medical therapy	Significantly improved nasal resistance found in the surgical group(p < 0.001). Both groups revealed insignificant changes in

					(steroid or decongestant spray, saline lavage, or oral antihistamine) on snoring, daytime sleepiness, and respiratory adverse events assessed via questionnaire, rhinomanometry, and polysomnogram at baseline and 3 months	polysomnographic parameters. In subgroup analysis, a significant effect of nasal surgery on AHI was found when patients were divided by Friedman Tongue Position (FTP) into “low” (FTP 1 or 2) and “high” (FTP 3 or 4) ( $p=0.007$ ).
Nakata et al <sup>909</sup>	2008	2b	Prospective cohort study	49 OSA patients with symptomatic nasal obstruction	Effect of nasal surgery on nasal resistance, sleep apnea, and sleep quality in patients with OSA assessed via polysomnography before and after surgery	While there was no significant change in AHI, nasal surgery decreased nasal resistance ( $p < 0.001$ ), ameliorated sleep-disordered breathing (increased nadir oxygen saturation, $p < 0.01$ ; shortened apnea–hypopnea duration, $p < 0.05$ ) and improving sleep quality and daytime sleepiness in OSAS (ESS scores, $p < 0.001$ ).
Shuaib et al <sup>910</sup>	2015	2c	Retrospective cohort study	26 patients with chief complaint of nasal obstruction, found to have septal and nasal valve obstruction on examination, who subsequently underwent functional rhinoplasty	Effect of nasal surgery on nasal resistance, sleep apnea, and sleep quality in patients with OSA assessed via polysomnography before and after functional septorhinoplasty.	Mean AHI preoperatively was 24.7, which dropped to mean postoperative AHI 16, a reduction of 35% ( $p=0.013$ ). Among patients with BMI < 30, resulted in 57% mean AHI reduction, from 22.5 to 9.6 ( $p < 0.01$ ).
Hisamatsu et	2015	2c	Retrospective	45 patients with moderate or severe	Effects of nasal surgery on OSA	Postoperative improvement was demonstrated in at least



a <sup>911</sup>			cohort study	OSA and high nasal resistance assessed by rhinomanometry underwent compound nasal surgery (septoplasty, turbinate reduction, and submucosal resection of the posterior nasal nerve)	assessed using polysomnography at 3 months, daytime sleepiness, nasal allergy symptoms, and health-related QOL	1 polysomnography parameter in 57% and 75% patients with moderate or severe OSA respectively. Quality of life measures were also significantly improved.
Silvoniemi et al <sup>897</sup>	1997	2c	Cross-sectional study	46 patients with severe nasal obstruction due to septal deviation	Sleep-disordered breathing as assessed by rhinomanometry and whole night sleep recording	Thirty-one patients (67%) had also heavy disturbing snoring, and apnea periods during sleep were reported by 10 cases.
Lenders et al <sup>912</sup>	1991	2c	Case-control study	45 habitual snorers and 22 patients with OSA examined by PSG, rhinomanometry, and acoustic rhinometry.	Association between anatomic nasal obstruction and sleep-disordered breathing	In 97% of these patients, inferior turbinate hypertrophy was found by acoustic rhinometry, while increased nasal resistance of various degrees was measured in 93% of all patients by active anterior rhinomanometry.

### VII.G.3 Chronic Rhinosinusitis

Sleep quality is compromised in patients with chronic sinusitis (CRS), with significant improvement in subjective sleep quality after medical and surgical treatment<sup>913-915</sup>. Among World Trade Center responders, chronic rhinosinusitis was an independent risk factor for OSA<sup>916</sup>. Data is limited regarding objective measures of sleep following treatment for CRS. In a prospective cohort study of 405 patients undergoing endoscopic sinus surgery for medically refractory chronic rhinosinusitis 15% of CRS patients were found to have a history of comorbid obstructive sleep apnea (OSA) based on chart review prior to treatment<sup>913</sup>. PSG-confirmed OSA was identified in approximately 65% of CRS patients undergoing surgery in another prospective cohort study<sup>917</sup>. Preliminary research has suggested that immune mediators associated with CRS may contribute to sleep-disordered breathing<sup>917</sup>.

#### Association between Chronic Rhinosinusitis and OSA

Aggregate Grade of Evidence: C (Level 2a: 8 studies; Level 2b: 5 studies; Level 2c: 1 study)

Table VII.G.3 Association of Chronic Rhinosinusitis and OSA

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusions
Quinn et al <sup>915</sup>	2017	2a	Meta-analysis	6 prospective cohort studies; 2 retrospective case series	Relationship between sleep-disordered breathing and CRS	Sleep quality is compromised in CRS patients with significant improvement in subjective sleep quality after medical and surgical treatment. Data is limited regarding objective measures of sleep following treatment for CRS.
Alt et al <sup>914</sup>	2019	2b	Case-control study	52 patients with CRS and 56 controls	Objective sleep measures in CRS patients assessed by home polysomnogram	Patients with CRS were found to have an increased number of awakenings (p = 0.004), lower average overnight oxygen saturation (p = 0.042), increased REM latency (p = 0.016), and increased snoring at >40 dB (p = 0.034)
Alt et al <sup>913</sup>	2015	2b	Prospective cohort study	405 patients undergoing endoscopic sinus surgery for medically refractory chronic rhinosinusitis without nasal polyposis	Impact of comorbid OSA on sleep dysfunction in patients with CRS following functional endoscopic sinus surgery as assessed by Pittsburgh Sleep Quality Index (PSQI).	15% of CRS patients had comorbid OSA and had substantial disease-specific QOL improvements following endoscopic sinus surgery (p<0.05).
Rotenberg et al <sup>918</sup>	2015	2b	Prospective cohort study	53 patients undergoing endoscopic sinus surgery for medically refractory chronic rhinosinusitis without nasal polyposis	Sleep quality following sinus surgery recorded at baseline and 6 months after surgery assessed with Epworth Sleepiness Scale (ESS) and the Pittsburgh Sleep Quality Index (PSQI).	Sinus surgery for CRS is associated with improved patient-reported sleep quality (p<0.01).
Tosun et al <sup>919</sup>	2009	2b	Prospective	27 patients with nasal polyposis	Effect of endoscopic sinus surgery on sleep quality in	While endoscopic sinus surgery with polypectomy

			cohort study	underwent endoscopic sinus surgery with polypectomy	patients with chronic nasal obstruction resulting from nasal polyposis evaluated by questionnaire and polysomnography before and 3 months after the surgery	significantly improved snoring and daytime sleepiness in patients with chronic nasal obstruction due to nasal polyposis( $p<0.01$ ), it did not demonstrate a significant change in AHI ( $p=0.55$ )
Yalamanchali et al <sup>920</sup>	2014	2c	Retrospective cohort study	56 patients with OSA and chronic rhinosinusitis who underwent septoplasty with bilateral submucosal inferior turbinate reduction and concurrent endoscopic sinus surgery	Impact of combined nasal surgery and endoscopic sinus surgery on OSA assessed by polysomnography before and 3 months after the surgery	AHI improved significantly after combined nasal surgery and endoscopic sinus surgery in patients with moderate OSA ( $p=0.023$ ) and severe OSA ( $p=0.034$ ), while patients with mild OSA did not have significant changes in AHI.
Sunderram et al <sup>916</sup>	2019	2b	Cross sectional study	601 subjects enrolled in the WTC Health Program underwent two nights of home sleep testing	Association between CRS and OSA	CRS is an independent risk factor for OSA (odds ratio of 1.80; $P = .006$ ), even after adjusting for age, BMI, sex, GERD, and EtOH use.
Jiang et al <sup>917</sup>	2016	2b	Cross sectional study	139 CRS patients who underwent functional endoscopic sinus surgery	Impact of CRS on sleep-disordered breathing as assessed by PSG and ESS	OSA was diagnosed in 64.7% of patients with CRS, but there was no correlation with the severity of rhinosinusitis. The study did not assess for change in PSG or ESS outcomes after treatment.
Alt et al <sup>921</sup>	2014	2b	Cross sectional study	20 CRS subjects completed disease-specific QOL and olfactory instruments	Association between immune mediators that have been associated with CRS and sleep-disordered breathing as assessed by Pittsburgh Sleep Quality	Increased expression of TGF- $\beta$ ( $r = -0.443$ ; $P = .050$ ) and IL-4 ( $r = -0.548$ ; $P = .012$ ) correlated with sleep dysfunction, whereas IL-13 expression was linearly

					Index (PSQI)	associated with worse sleep quality (PSQI scores $r = -0.417$ ; $P = .075$ ).
--	--	--	--	--	--------------	---

### VII.H Comorbidities Associated with OSA: Gastroesophageal Reflux Disease

The relationship between obstructive sleep apnea (OSA) and gastroesophageal reflux disease (GERD) is complex and our understanding of a causative relationship and effects of treatment continues to evolve. Numerous studies have established a high incidence of GERD among patients with sleep-disordered breathing<sup>922-935</sup>. Population-based studies have demonstrated that greater than 75% of patients with obstructive sleep apnea (OSA) report nocturnal reflux symptoms, which have been associated with sleep fragmentation and overall poor sleep quality<sup>926,929,935</sup>. Laryngopharyngeal reflux (LPR), which occurs when gastric contents breach both the lower esophageal sphincter (LES) and upper esophageal sphincter (UES), presents with symptoms such as chronic cough, hoarseness, and throat clearing, and has also been associated with sleep-disordered breathing<sup>922,923,925-929,931,932,935,936</sup>. While the causal relationship between obstructive events and nocturnal reflux has yet to be established, a cycle of increases in respiratory effort with negative intrathoracic pressure leading to reflux of gastric contents at the level of the LES during sleep has been suggested. However, in a prospective cohort study of 27 adults with reflux confirmed by two validated instruments (Reflux Symptom Index (RSI)  $\geq 13$  and reflux finding score (RFS)  $\geq 7$ ) and OSA, no temporal association between reflux and obstructive respiratory events was identified on polysomnography with concomitant multichannel intraluminal impedance-pH esophageal monitoring<sup>935</sup>.

While the high incidence of nocturnal reflux among patients with OSA has been repeatedly demonstrated, the correlation between severity of OSA and GERD remains controversial with studies demonstrating variable findings. Though the gold standard for identifying reflux events consists of pH-monitoring studies and outpatient multichannel intraluminal impedance (MCI), these tests are costly and most retrospective cohort studies rely on clinical diagnoses based on endoscopic findings and validated patient questionnaires such as the RSI and the Reflux Finding Score (RFS). Caparroz et al found that patients with LPR based on endoscopic findings and elevated RSI were more likely to have a higher mean AHI and higher percentage of sleep time with oxyhemoglobin saturation below 90%<sup>923</sup>. Elhennawi et al studied the relationship between OSA and LPR using 24-h pH monitoring and found that while the number of nocturnal reflux episodes and total duration of reflux during sleep were significantly correlated to the degree of OSA, daytime reflux was not related to the degree of OSA<sup>925</sup>. Ultimately, the severity of OSA has not been shown to consistently correlate with gastroesophageal reflux<sup>925,931,932</sup>.

While patients with OSA and gastroesophageal reflux have been shown to have a higher BMI than patients with OSA alone, the exact relationship between OSA, obesity, and gastroesophageal reflux has yet to be elucidated<sup>923,932,937-940</sup>. Obesity is a known risk factor for both OSA and GERD and weight loss has been shown to improve both OSA and nocturnal reflux symptoms in obese patients<sup>929,936,938,939</sup>. In a recent prospective cohort study on the influence of OSA on GERD in obesity, obese patients without OSA, nonobese patients with OSA, and obese patients with OSA underwent simultaneous polysomnography and esophageal manometry and pH monitoring. There was no significant difference in the total number of objective reflux events among obese patients with and without OSA. However, obese patients with OSA had a significantly greater number of reflux events compared to the non-obese

group with OSA. In multivariate analysis, BMI was a significant predictor of the number of objective reflux events, but AHI showed no significant association with GERD severity.<sup>940</sup>

Treatment of GERD has demonstrated significant reduction in snoring and patient-reported daytime sleepiness and improved sleep quality.<sup>926,939</sup> However, treatment of gastroesophageal reflux has not been shown to improve OSA severity based on objective polysomnographic parameters.<sup>939</sup> Treatment for OSA with CPAP therapy and/or multilevel surgery has been shown to significantly improve subjective parameters of reflux.<sup>927,928</sup> In a study of 73 patients who underwent multilevel surgery for OSA, mean RSI score decreased significantly after surgery.<sup>927</sup> In a study of 44 patients with symptoms of sleep-disordered breathing and reflux, subjects underwent 24 hr pH monitoring simultaneously with polysomnography at 0 months and 3 months after CPAP treatment and showed significant improvement of subjective parameters of reflux, such as RSI and RFS<sup>926</sup>. Improvement in objective parameters of gastroesophageal reflux with treatment for OSA has yet to be demonstrated.

Ultimately, the relationship between OSA and GERD is multifactorial and closely tied to obesity. Treatment for both OSA and reflux results in subjective improvement in reflux and sleep quality, but objective improvement demonstrated through polysomnogram and/or pH monitoring is lacking. Further study of the causal relationship between reflux and sleep-disordered breathing using objective parameters are needed.

#### Association between GERD and OSA

Aggregate Grade of Evidence: B (Level 1b: 2 studies; level 2b: 7 studies; level 2c: 1 study)

#### GERD Treatment with PPI Improves Snoring and Sleep Symptoms, Not OSA Severity

Aggregate Grade of Evidence: C (Level 1b: 1 study; level 2a: 1 study)

#### OSA Treatment Improves GERD Symptoms

Aggregate Grade of Evidence: C (Level 1b: 1 study; Level 2b: 1 study)

Table VII.H: Association between OSA and GERD

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Teklu et al. <sup>934</sup>	2020	2c	Cross-sectional study	101 adult patients who underwent polysomnogram	Relationship between reported reflux symptoms and OSA	Patients with OSA have worse symptoms of laryngopharyngeal reflux based on RSI (p=0.003).
Morse et al. <sup>930</sup>	2004	2b	Cross sectional	136 patients referred for	Relationship between OSA and	Subjective reports of sleep quality were

			study	polysomnogram	GERD in a large group of patients with OSA	affected by GERD severity, but no significant correlation between OSA and GERD.
Sundar et al. <sup>933</sup>	2010	2b	Cross sectional study	75 patients with isolated chronic cough	Rates of OSA among patients with chronic cough	37% of patients with chronic cough had a diagnosis of GERD. 44% were found to have OSA. 93% of the patients that had interventions to optimize their sleep-disordered breathing reported improvement in cough.
Chan et al. <sup>924</sup>	2010	2b	Cross sectional study	108 consecutive patients referred for evaluation of SDB	Prevalence and severity of chronic cough in patients with sleep-disordered breathing	33% of patients with SDB reported a chronic cough. Patients with SDB and chronic cough were predominantly females ( $p < 0.001$ ), reported nocturnal heartburn ( $p = 0.03$ ), and rhinitis ( $p = 0.02$ ) compared to those without SDB.
Caparroz et al. <sup>936</sup>	2019	2b	Cross sectional study	56 patients with moderate or severe OSA	Prevalence of laryngopharyngeal reflux in patients with moderate and severe OSA by reflux symptom questionnaire and indirect videolaryngoscopy	64.3% of patients with moderate or severe OSA had laryngopharyngeal reflux (positive RSI and/or positive endolaryngeal reflux finding score). BMI was a predictor of reflux presence. In patients with positive score for endoscopic findings and reflux symptom index, there was a trend toward significance for a higher mean AHI and a percentage of sleep time with oxyhemoglobin saturation below

						90%(p=0.05).
Lee et al <sup>928</sup>	2018	3b	Case control study	19 OSA patients with unilevel complete obstruction and 69 OSA patients with multilevel complete obstruction on drug induced sleep endoscopy(DISE)	Relationship between level of obstruction determined by DISE, and laryngopharyngeal reflux (LPR)-related clinical parameters	No significant correlation between OSA severity and LPR-related symptoms. Multilevel complete obstruction on DISE did not affect the LPR-related clinical parameters (p>0.05).
Kim et al <sup>927</sup>	2017	2b	Cross sectional study	73 patients who underwent multilevel surgery for OSA	Effect of multilevel surgery for OSA on symptoms of laryngopharyngeal reflux (LPR) and polysomnogram	Treatment for OSA using multilevel surgery reduced symptoms of LPR; mean RSI score decreased from 11.48±7.95 to 4.95±6.19 after surgery(p<0.001).
Altintas e al <sup>922</sup>	2017	2b	Cross sectional study	62 patients with AHI>5	Relationship between presence of LPR and level of depression and anxiety in patients with OSA assessed via questionnaire and laryngeal examination	There were significantly higher levels of depression and anxiety in patients with LPR and OSA(p=0.016). A positive correlation was found between RSI and AHI scores (r=0.338; p=0.007).
Elhennawi et al <sup>925</sup>	2016	2b	Cross sectional study	62 patients with OSA	Relationship between OSA and LPR assessed with ambulatory 24-h pH monitoring	LPR is common in patients with OSA (66%). Patients with severe OSA have significantly higher nocturnal LPR(p<0.05). Number of reflux episodes and total duration of reflux during sleep are significantly correlated to degree of OSA (p<0.05). Daytime reflux was not related to degree of OSA(p>0.05).

Qu et al <sup>931</sup>	2015	2b	Case control study	36 OSA patients and 10 healthy controls underwent 24-h double-probed combined esophageal multichannel intraluminal impedance and pH monitoring simultaneously with polysomnography	Esophageal functional changes observed in OSA	63.9% of patients had both OSA and LPR by pH monitoring and polysomnogram. Significant differences were found in the onset velocity of liquid swallows( $p=0.029$ ) and percent relaxation of the lower esophageal sphincter(LES) during viscous swallows( $p=0.049$ ) between patients with OSA versus healthy controls.
Rodrigues et al <sup>932</sup>	2014	2b	Cross sectional study	105 OSA patients divided into obese group ( $n=39$ ) and non-obese patients ( $n=66$ )	Relationship between obesity on LPR and OSA	In the obese group, mean RSI was 6.7 in patients with mild OSA and 11.53 in patients with moderate to severe OSA( $p<0.05$ ). No correlation between OSA severity and RSI in non-obese group.
Xavier et al <sup>935</sup>	2019	1b	Cross sectional study	27 adults with LPR confirmed by two validated instruments ( $RSI\geq 13$ and reflux finding score $\geq 7$ ) and OSA underwent full polysomnography with concomitant multichannel intraluminal impedance-pH esophageal monitoring	Temporal correlation between reflux episodes and respiratory events in patients with LPR and OSA	Among patients with well-established laryngopharyngeal reflux and OSA, there is no temporal association between reflux and obstructive respiratory events.
Eryilmaz et al <sup>926</sup>	2012	1b	Prospective cohort study	44 patients underwent double probed 24 h pH monitoring	Effect of OSA therapy on LPR parameters	OSA and LPR coexist frequently. LPR treatment did not improve the polysomnographic



				simultaneously with polysomnography due to the complaints of SDB and reflux, at 0 months and 3 months		parameters, but significantly reduced ESS( $p=0.02$ ) and snoring( $p=0.007$ ). Although CPAP treatment significantly improved subjective parameters of reflux, such as RSI and RFS ( $p = 0.016$ for both), there was no significant improvement in objective parameters of 24-h pH monitoring.
Magliulo et al <sup>929</sup>	2018	2a	Meta-analysis	10 papers studying LPR in OSA were included with 870 identified OSA patients	Incidence of LPR in OSA patients	There is a high incidence of LPR (45.2%) among OSA patients. AHI severity did not correlate with presence of laryngopharyngeal reflux( $p=0.3$ ). OSA patients with LPR had higher BMI compared with LPR-patients( $p=0.001$ )
Caparroz et al <sup>923</sup>	2019	2b	Cross sectional study	70 patients with moderate or severe OSA underwent validated questionnaires, laryngoscopy to calculate the Reflux Finding Score (RFS), and fiber-optic endoscopic evaluation of swallowing (FEES)	Association between presence of dysphagia with signs and symptoms suggestive of LPR in patients with moderate and severe OSA	Although 17.9% of patients presented with findings suggestive of concomitant LPR and dysphagia, there was no statistically significant association between these two conditions.
Kim et al <sup>938</sup>	2018	1b	Cross sectional study	216 patients underwent both PSG and EGD	Relationship between OSA and GERD	Endoscopically proven GERD was associated with more severe OSA( $p=0.01$ ). GERD

						symptoms were also associated with worse sleep quality(p = 0.03).
Rassameehiran et al <sup>939</sup>	2016	2a	Meta-analysis	2 randomized trials and 4 prospective cohort studies on the effect of treatment for GERD on OSA	Association between PPI treatment for GERD and improvement in OSA	No differences in AHI before and after treatment with PPIs (SMD 0.21; 95% CI[-0.11,0.54]).
Gilani et al <sup>937</sup>	2016	2b	Retrospective study	Adults with OSA and GERD and potentially confounding conditions were identified in the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey	Association between GERD and OSA controlling for concurrent confounders in a national database	Significant positive association between GERD and OSA was observed, which persisted after adjustment for age, sex, race/ethnicity, sino-nasal obstruction, inflammatory disorders, obesity, asthma, and lung disorders (OR 1.94, 95% CI [1.07-3.54], p=0.030).
Shepherd et al <sup>940</sup>	2016	1b	Prospective cohort study	20 obese individuals (BMI>30), 9 non-obese individuals (BMI<30) with moderate-to-severe OSA, and 17 obese control subjects (BMI>30) underwent high-resolution esophageal manometry, 24-h esophageal pH-impedance monitoring, and in-laboratory	Effect of OSA on GERD independent of obesity	The two obese groups did not show any significant differences in the total number of acidic reflux events (41±20 vs 28±16); however, the obese OSA group had a greater number of acidic reflux events compared to the non-obese OSA group (22±12 events, p< 0.05). In multivariate analysis, BMI significantly predicted number of acidic reflux events (r(2)=0.16, p=0.01). However, AHI showed no significant association

				polysomnography.		with GERD severity.
Xavier et al <sup>941</sup>	2013	2c	Cross-sectional study	74 patients with OSA	Prevalence of symptoms of reflux in OSA patients assessed with questionnaire	98% of the subjects with suspected OSA had symptoms suggestive of LPR; prevalence was significantly higher among obese individuals(p=0.002).

## VII.I Comorbidities Associated with OSA: Other Sleep Disorders

### VII.I.1 Insomnia

The available literature addressing the prevalence of insomnia in patients with OSA (Table VII.I.1)<sup>587,942-955</sup> suffers from several significant shortcomings. Variable definitions are used for OSA and insomnia and different studies focus on “insomnia symptoms” vs “insomnia disorder”. The former is likely to be more common in OSA patients as it requires the presence of less significant symptoms. Additionally, very few studies examined cohorts that are representative of the general population. Only 3 studies were available with representative population samples<sup>945,947,950</sup> while ten studies were convenience samples. Thus, the estimates of prevalence may not generalize to the broader population.

Insomnia symptoms and insomnia disorder are quite common in OSA patients; however, the above-noted limitations are reflected in the wide-range of prevalence estimates found. The reported rates of an insomnia disorder diagnosis in patients with OSA ranged from 6.4% to 74%. Notably, the majority of studies found rates that were clustered in the range of 29-50%. For insomnia symptoms, the prevalence varied from 7-68% with most estimates being in the range of 36-58%. Notably, the studies with the lowest prevalence rates tended to be the general population studies.

Despite significant limitations in the literature, it is clear that insomnia symptoms and insomnia disorder are seen commonly in OSA patients. Co-morbid insomnia and sleep apnea (COMISA) is associated with greater impairment of sleep quality, reduced quality of life, complex diagnostic decisions, and reduced acceptance and response rates to treatments that require adherence (ie. PAP, MAD, and HNS therapy).<sup>954,956</sup> Effective management of patients with both insomnia and OSA requires targeted therapies for both disorders.<sup>957</sup> Treatment reviewed in Sections VIII.A.5.i and VIII.B.9.

#### Association between OSA and Insomnia

Aggregate Grade of Evidence: C (Level 2: 3 studies; Level 4: 12 studies)

**Table VII.I.1** Prevalence of Insomnia in Patients with OSA

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
-------	------	-----	--------------	--------------	-------------------	------------

Zhang et al. <sup>955</sup>	2019	4	Systematic review and meta-analysis	31 Studies assessing the prevalence of insomnia symptoms in OSA; 4 studies assessing the prevalence of OSA in patients with insomnia; 2 studies assessing prevalence of both insomnia in OSA and OSA in insomnia	Presence of insomnia symptoms or diagnosis, PSG	38% of patients with OSA had comorbid insomnia; In patients with insomnia, the pooled prevalence rates of OSA were 35% for AHI $\geq$ 5 events/hr and 29% for AHI $\geq$ 15 events/hr.
Luyster et al. <sup>587</sup> .	2010	4	Systematic review	4 studies assessing the prevalence of insomnia symptoms in OSA; 3 studies assessing the prevalence of OSA in patients with insomnia.	Presence of insomnia symptoms or diagnosis, PSG.	39-58% of patients with OSA had comorbid insomnia symptoms; 29-67% of patients with insomnia had an AHI of >5 events/hr.
Gupta and Knapp <sup>945</sup>	2014	2c	Retrospective, cross-sectional, case-control study of epidemiologic databases	62,253,910 $\pm$ 5,274,747 (unweighted count = 7234) patient visits with diagnosis of OSA from 1995–2010.	ICD-9 coded diagnosis of sleep apnea or insomnia	6.4% $\pm$ 0.9% of patient visits for OSA also contained a diagnosis of insomnia. Visits with both OSA and insomnia were significantly more likely to also list essential hypertension (OR = 1.83, 95% CI 1.27–2.65).

Sivertsen et al. <sup>950</sup>	2013	2c	Historical cohort case-control design	6892 participants aged 40-45 years.	Karolinska Sleep Questionnaire, Norwegian official registry data, Health information from the Hordaland Health Study in western Norway (1997-99)	8.4% of the population had OSA and 0.6% had comorbid insomnia.
Lang et al. <sup>947</sup>	2017	2b	Prospective, general population, cohort study	837 randomly selected men without prior diagnosis of OSA	At-home unattended PSG; 36-item short form (SF-36) vitality scale, Beck Depression Inventory	46% of the population had OSA; Of these, 14.5% had comorbid insomnia.
Stelzer et al. <sup>952</sup>	2020	4	Prospective, cross-sectional case series	238 patients with OSA	ICSD-3, PSG-3, Beck Depression and Anxiety Inventories	29% of patients diagnosed with OSA had comorbid insomnia. Depression and anxiety were higher in the group with insomnia.
Wallace and Wohlgemuth <sup>954</sup>	2019	4	Prospective, cross-sectional, case series	630 veterans with a new diagnosis of OSA	Insomnia Severity Index (ISI), PSG	74% of patients with OSA had moderate or severe insomnia

Cho et al. <sup>944</sup>	2018	4	Prospective, cross-sectional case series	476 patients with OSA seen at two tertiary hospital sleep centers.	ISI, PSG, SF-36, PSQI, Beck Depression Inventory	29.2% of patients with OSA had significant insomnia. Patients with both OSA and insomnia had higher rates of heart disease, lower quality of life, and worse depression than those with OSA only. No significant differences in CPAP adherence between those with vs. without insomnia.
Taskaban et al. <sup>953</sup>	2018	4	Prospective, cross-sectional case series	197 consecutive patients with OSA seen in a sleep laboratory	PSG, WHO Quality of Life form.	18.8% of patients with OSA had comorbid insomnia. Patients with both OSA and insomnia had lower physical and social scores than those with OSA only.
Bjorvatn et al. <sup>943</sup>	2014	4	Prospective, cross-sectional, general population sample case series	1502 randomly selected participants from the general population	Bergen Insomnia Scale. Self- or spouse-reported OSA symptoms	6.2% of participants were diagnosed with OSA; Of these, 57.6% reported comorbid insomnia.
Mysliwiec et al. <sup>948</sup>	2013	4	Prospective cross-sectional case series	110 military personnel who returned from combat with sleep disturbances	ICSD-2, PSG	24.5% diagnosed with OSA alone and 38.2% with comorbid OSA and insomnia. Patients with both OSA and insomnia were significantly more likely to meet criteria for depression.

Bjornsdottir et al. <sup>942</sup>	2013	4	Prospective cross-sectional case series	705 adults with OSA	Basic Nordic Sleep Questionnaire, HSAT	68.3% had comorbid insomnia; 15.5% exhibited symptoms of initial insomnia, 59.3% had symptoms of middle insomnia, and 27.7% exhibited symptoms of late insomnia, with overlap between groups.
Nguyen et al. <sup>949</sup>	2010	4	Prospective, cross-sectional, case series	148 consecutive patients with OSA treated in a sleep clinic	ISI, PSG	50% of patients had moderate to severe comorbid insomnia. Presence of insomnia did not significantly affect CPAP adherence.
Smith et al. <sup>951</sup>	2004	4	Prospective, cross-sectional, case series	105 patients with OSA	ISI, PSG, sleep diary, reported daytime consequences of insomnia, Depression Anxiety Scale-21	35% of patients had comorbid insomnia. Patients with both OSA and insomnia had increased levels of depression, anxiety and stress.
Krakov et al. <sup>946</sup>	2001	4	Retrospective cross-sectional case series	231 patients with OSA	Reported insomnia symptoms, sleep Diary; reported psychiatric disorders; reported use of sedative and psychotropic medications	50% reported insomnia complaints. OSA+insomnia had significantly more psychiatric disorders and physical/mental symptoms that disrupted sleep. OSA+insomnia also reported greater use of sedative and psychotropic medications.

## VII.I.2 Sleep Movement Disorders

In patients with OSA, specific considerations are warranted in the presence of comorbid restless legs syndrome (RLS), periodic limb movements (PLMs), REM sleep behavior disorder (RBD), and sleep-related movement disorders. While the evidence supporting specific recommendations is limited, the available data provide indications regarding clinically-important aspects of OSA management in these patient populations.

RBD is a REM-related parasomnia marked by dream-enactment behavior and absence of atonia during REM sleep.<sup>81</sup> RBD may be idiopathic, i.e. occurring in the absence of clear etiology, or may be secondary to underlying neurodegenerative synuclein-mediated disorders,<sup>958</sup> structural lesions, or narcolepsy.<sup>959</sup> Screening for OSA is indicated in patients with history of dream-enactment behavior, as untreated sleep-disordered breathing can mimic RBD.<sup>960</sup> The presence of OSA may be associated with reduced response to RBD treatments such as clonazepam.<sup>961</sup> On the other hand, treatment of OSA in patients with RBD may improve RBD manifestations.<sup>962</sup> Individuals with a neurodegenerative disorder who are diagnosed with RBD may be particularly at risk for OSA.<sup>963</sup>

RLS is marked by sensory symptoms, often in the limbs, combined with urge to move the limbs that temporarily improves with limb movement and exhibits diurnal variation.<sup>81</sup> OSA may be comorbid with RLS, and treatment of OSA is indicated in patients with RLS and can improve RLS severity.<sup>964,965</sup>

Periodic limb movements (PLMs) may emerge after initiation of CPAP for treatment of OSA, with risk factors including older age<sup>966</sup> and female sex.<sup>967</sup> PLMs comorbid with OSA may be associated with increased REM latency and reduced stage 3 sleep.<sup>968</sup> There may not be a significant impact of treatment-emergent PLMs on daytime sleepiness.<sup>969,970</sup> Nevertheless, presence of PLMs has important clinical implications as they may indicate greater risk of atrial fibrillation and other cardiovascular diseases,<sup>971-974</sup> perhaps related to increased sympathetic activation.<sup>973</sup> Patients with OSA and treatment-emergent PLMs thus warrant age- and comorbidity-appropriate monitoring for cardiac disease.<sup>971-974</sup>

As for other sleep-related movement disorders, screening for OSA may be indicated in select patients with bruxism though a clear relationship between sleep bruxism and OSA has not been established.<sup>975,976</sup> Finally, limited data indicate that in select adults with rhythmic movement disorder it may be appropriate to perform PSG to identify OSA.<sup>977</sup>

### Association between REM Sleep Behavior Disorder and OSA

Aggregate Grade of Evidence: C (level 3b: 4 studies; level 4: 2 studies)

### Association between RLS and OSA

Aggregate Grade of Evidence: C (level 3b: 1 study; level 4: 2 studies)

### Association between PLMS/PLMD and OSA

Aggregate Grade of Evidence: C (level 2b: 1 study; level 3b: 8 studies; level 4: 2 studies)



Table VII.I.2 Association between Sleep Movement Disorders and OSA

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
<b>REM Behavior Disorder</b>						
Li et al. <sup>961</sup>	2016	4	Case series	39 iRBD patients assessed pre- and post-treatment with clonazepam	Modified RBD questionnaire, ESS, PSG measures	Clonazepam reduced subjective measures of sleep related injury, nightmares, limb movements, and objective measures of REM sleep tonic mentalis surface EMG activity. Residual symptoms were common. Presence of OSA was associated with reduced response to clonazepam.
Iranzo et al. <sup>960</sup>	2005	3b	Case-control study	16 patients with dream enactment behavior and witnessed apneas were compared, via VPSG, with 20 healthy controls	Describe VPSG features of patients with OSA that mimic behaviors of RBD.	Severe OSA may mimic the symptoms of RBD. A clinical history of dream enactment behavior but normal atonia during REM sleep should suggest this RBD mimic VPSG is mandatory to establish the diagnosis of RBD, and identify or exclude other causes of dream- enacting behaviors.
Gabryelska et al. <sup>962</sup>	2017	4	Cross-Sectional survey study	72 out of 120 patients previously diagnosed with RBD and OSA responded to a mailed questionnaire: 27 patients reported use of CPAP. 45 patients	Determine the prevalence of obstructive sleep apnea (OSA) in RBD patients and determine whether continuous positive airway pressure (CPAP) therapy improved RBD	OSA is a common comorbidity of RBD, being self-reported in 89% of patients with diagnosed RBD. CPAP therapy might improve self-reported RBD symptoms

				reported noncompliance with CPAP	symptoms	
Bugalho et al. <sup>978</sup>	2017	3b	Case-control study	10 patients with RBD and AHI>14 were compared to 22 with RBD with AHI ≤14	To understand the influence of OSA on symptoms in RBD	RBD patients with OSA had less O <sub>2</sub> desaturation compared to those without OSA
Koo et al. <sup>963</sup>	2018	3b	Case control study	35 patients with idiopathic RBD compared to 42 patients with RBD plus a neurodegenerative Parkinsonian syndrome (25 with PD and 17 with MSA).	Compare sleep parameters in RBD patients with vs without neurodegenerative Parkinsonian syndromes	RBD patients with diagnosed neurodegenerative Parkinsonian syndromes may be more prone to OSA than patients with idiopathic RBD
<b>Restless Leg Syndrome</b>						
Rodrigues et al. <sup>964</sup>	2006	4	Case series	17 patients with OSA and RLS or PLMs underwent CPAP titration and follow-up assessment 3 months later	Determine if CPAP therapy improves RLS, as measured by the IRLS, in patients with OSA	IRLS severity decreased significantly post-CPAP compared to pre-CPAP levels.
Silva et al. <sup>965</sup>	2017	4	Case series	28 patients with RLS and OSA were reviewed for evolution of RLS symptoms	Determine if CPAP therapy for OSA is associated with improved RLS symptoms	RLS symptoms improved following CPAP initiation and allowed for reductions in medications for RLS.

				following CPAP therapy		
Lakshmanan et al. <sup>979</sup>	2019	3b	Case-control study	IRLS scores were compared in 325 individuals with OSA who received PAP therapy vs 109 controls, and participants were screened for RLS using a single question	Determine if CPAP therapy for OSA is associated with improved RLS symptoms, as measured with IRLS	OSA patients with RLS who reported adherence to PAP had significant improvements in RLS symptoms compared to those who reported non-adherence.
<b>PLMS/PLMD</b>						
Wu et al. <sup>973</sup>	2018	3b	Case-Control	30 patients with OSA and treatment-emergent PLMs vs 30 patients with OSA without treatment-emergent PLMs	HRV spectral analysis (FFT) applied to investigate basal autonomic regulation reflecting cardiovascular risk in patients with OSA with treatment-emergent PLMs. Parameters examined included RMSSD, LF, HF, and LF/HF ratio.	PLMS emerging after CPAP therapy was associated with a decreased HRV during leg movement-free intervals and a shift toward sympathetic predominance in basal autonomic regulation.
Ren et al. <sup>967</sup>	2016	3b	Case-	(1) 182	Differences in	In age groups of 55 or less,

			Control	females with OSA matched for severity and age  (2) 182 males with OSA matched for severity and age	PLMS in males vs females with OSA	females with OSA are significantly more likely to have PLMS (PLMI $\geq$ 15) than males with OSA of similar severity (OR 2.48; 95% CI 1.06–5.79)
Haba-Rubio et al <sup>970</sup>	2005	4	Case series	In 57 patients diagnosed with OSA on CPAP:  (1) 22 patient with PLMS (PLM index $\geq$ 5/h)  (2) 35 patients without PLMS	Examine the role of PLMS on objective and subjective parameters of sleepiness before and after CPAP use in OSA patients.	The presence of PLMS showed no correlation with increased sleepiness as measured by MSLT or by ESS after a 1 year follow up on CPAP.
Al-Alawi et al <sup>969</sup>	2006	3b	Case Series	In data of 795 patients who underwent polysomnography:  (1) 729 patients had OSA (AHI $\geq$ 5/h)  (2) 377 patients had PLMS (PLM arousal Index $\geq$ 5/h)  (3) 351 patients had PLMS and	Examine the prevalence of PLM arousals in OSA patients  Examine relationship of PLM arousal index with risk factors	There was a higher PLMI in OSA subjects (44% had both).  Patient with PLM arousal index $\geq$ 5/h had higher relationships with predisposing conditions (Depression, Fibromyalgia and DM), older age, more predisposing medications, obesity, and more likely to have OSA. There was no difference in the relationship with ESS or Hypertension between patient with OSA only or OSA and PLM with arousals.

				OSA (4) 26 patients had PLMS without OSA		
Xie et al. <sup>974</sup>	2017	2b	Cross-sectional study	In 15,414 patients who attended a PSG, 50.8% had PLMI>15/h, 36.1% had PLM>30/h, and 13.1% had PLMI between 15 to 30/h. The prevalence of Atrial Fibrillation was 15.3%.	Examine whether PLMS is associated with the prevalence of Atrial Fibrillation in a group of patients with Sleep Disordered Breathing (SDB)	In a multivariate adjustment model, only mild SDB patients with PLMI>30/h had 1.21 times higher odds for Atrial Fibrillation compared with patients with PLMI<15/h (OR 1.21, 95% CI 1.00-1.47, p-value = 0.048). Similarly, PLMAI >5/h had higher odds compared to PLMAI<1 for Atrial Fibrillation in mild SDB patients (OR 1.27, 95% CI 1.03-1.56, p-value = 0.024).
Iriarte et al. <sup>968</sup>	2009	4	Cross-sectional study	In a referral sleep center for sleep symptoms, patients were recruited and grouped:  (1) 35 patients with no diagnosis for OSA and PLMS  (2) 94 patients with OSA only  (3) 37	Examine the importance of PLMS on sleep quality in patient referred for sleep symptoms in patients with our without OSA.	In a multivariate analysis, adjusting for age, sex, and AHI, PLMS was associated significantly with an increase in REM latency of 38 minutes (CI 95% CI 4.4-71.6; p-value = 0.03) and a decrease stage NREM 3 and 4 of 3.7% (CI 95% CI 0.2-7.2; p-value = 0.04), when comparing all 4 groups. The effects of PLMS on sleep architecture parameters were worse in th PLMS only group as compared to OSA only or combined OSA and PLMS group.

				patients with PLMS only  (4) 64 patients with PLMS and OSA		
Loewen et al. <sup>980</sup>	2009	3b	Case-Control	(1) 12 patients with OSA and end-stage renal disease  (2) 18 patients with OSA and normal renal function	Differences in effect of PLMS on subjective and objective measures of sleep quality.	There were significant differences in objective measurements of sleep quality ( $\downarrow$ TST, $\downarrow$ SE, $\uparrow$ duration of stage 1 NREM sleep) in ESRD group with OSA compared to normal renal function with OSA attributed to difference in PLMS. No differences in association of PLMS with subjective measurements of sleep quality were noted.
Aritake-Okada et al. <sup>966</sup>	2012	3b	Case control	997 patients diagnosed with OSA: 67 in persistent group (PLMI $\geq$ 15/h in both diagnostic and CPAP titration study), 80 in CPAP-emergent group (PLMI <15/h in diagnostic, PLMI $\geq$ 15/h in CPAP titration study), 40 CPAP-disappeared group (PLMI $\geq$ 15/h	Examine the change in prevalence of PLMS in diagnostic and CPAP titration study in OSA patients (AHI >20 events per hour). Examine the associated factors on PLMS groups.	PLMS were significantly increased from diagnostic to CPAP titration study in the persistent group, CPAP-emergent group, and non-PLMS group and decreased in the CPAP-disappeared group (all p-value <0.001).  In a multivariate regression analysis, CPAP-emergent PLMS group was associated with older age (age >47 years: OR: 1.69, 95% CI 1.05-2.71, p-value = 0.03) and higher AHI (diagnostic AHI >30/h: OR: 2.19, CI: 1.16-4.11, p-value: 0.015).

				in diagnostic study, PLMI<15/h in CPAP titration study), non PLMS group (PLMI<15/h in diagnostic and CPAP titration study).		
Drakatos et al <sup>971</sup>	2016	3b	Case control	49 males without comorbid cardiovascular disease: 8 controls, 13 with PLMs (defined as PLMI>15/hr), 17 OSA (defined as AHI>10/h) and 11 OSA+PLMs.	Compare stiffness index derived from the digital volume pulse (SI-DVP) among the groups.	Patients with PLMS had higher arterial stiffness measures compared to controls. The OSA/PLMS group had the highest SI-DVP.
Xie et al <sup>981</sup>	2019	3b	Case control	14,444 PSGs conducted over a 4-year period were examined. 314 patients with CSA completed the study with CPAP titration and in cases of persistent	To examine changes in PLMS in response to ASV for CSA	In the age group >68, presence of heart failure was associated with increases in PLMI and PLMAI, even after adjustment for age and severity of HF.

				CSA, ASV titration.		
Murase et al. <sup>972</sup>	2014	3b	Case control study	46 patients with OSA and PLMs were compared to 208 patients with OSA without PLMS	Compare inflammatory markers in OSA patients with vs without PLMs	The OSA and PLMS group had higher CRP and fibrinogen levels compared to the OSA group without PLMS.
<b>SRRMD; Aggregate Level of Evidence: D; (level 4: 1 study)</b>						
Chiaro et al. <sup>977</sup>	2017	4	Case Series	5 patients with diagnosed SRRMD with RMEs seen following OSA events.	Investigate the role of sleep apnea as a trigger for rhythmic motor events as a respiratory related arousal mechanism.	SRRMD in adult patients may imply sleep-disordered breathing, possibly associated with longer respiratory events.
<b>Bruxism; Aggregate Level of Evidence: B; (level 2a: 2 studies)</b>						
Lopes <sup>976</sup>	2019	2a	Systematic review	Systematic review; 200 articles identified after initial search and 7 included in the qualitative synthesis.	Examine the association between sleep bruxism and OSA	Well-designed studies are lacking but based on available evidence, OSA patients do not experience sleep bruxism significantly more than controls. A subtype of patients with OSA may have sleep bruxism. Occurrence of sleep bruxism has been proposed as a protective mechanism for respiratory events.
Jokubauskas <sup>975</sup>	2017	2a	Systematic review	Systematic review; 691 articles	Examine the association between sleep	There are insufficient data to establish an association between OSA and sleep



				identified after initial search and 3 included in the synthesis.	bruxism and OSA	bruxism. Sleep bruxism events occur during microarousal events resulting from apneas/hypopneas and most often are temporally related to the termination of an apnea/hypopnea.
--	--	--	--	--	-----------------	---

### VII.1.3 Narcolepsy

Narcolepsy is a chronic neurologic disorder characterized by excessive daytime sleepiness and abnormal regulation of REM sleep. Narcolepsy type 1 (NT1) refers to narcolepsy with cataplexy and narcolepsy type 2 (NT2) to narcolepsy without cataplexy. NT1 occurs with a prevalence of 25 to 50 per 100,000 people.<sup>982</sup> It is associated with a deficiency of hypocretin, also called orexin, which is a neuropeptide hormone secreted by a small group of cells located in the lateral hypothalamus. NT1 is thought to be autoimmune in nature; though no antibody has been detected, there is a strong HLA association to HLA-DQB1\*06:02.<sup>983</sup> The primary diagnostic test for NT1 and NT2 is the multiple sleep latency test (MSLT), consisting of overnight polysomnography followed by a series of five daytime naps at two hour intervals and assessing average sleep latency across the naps and the number of sleep-onset REM periods (SOREMPs), i.e. REM during the naps.

Patients with narcolepsy have an increased risk of multiple comorbidities compared to age matched controls including obesity, diabetes, depression, thyroid disease, and hypertension; however, obstructive sleep apnea is the most common comorbidity, both at time of diagnosis and follow up.<sup>984</sup> The incidence of OSA is approximately 25% in those with narcolepsy and nearly half of these patients have moderate to severe OSA.<sup>985,986</sup> At the time of the initial diagnosis of narcolepsy, the odds of having a diagnosis of OSA compared to matched controls is markedly increased, ranging from 18-69.<sup>984,987,988</sup>

There is on average a 6-10 year delay to diagnosis for those with narcolepsy,<sup>985,989</sup> which underscores the need to be alert to the frequency with which OSA and narcolepsy can co-occur. If treatment of OSA results in no or minimal improvement in excessive daytime sleepiness, the provider should consider the possibility of another sleep disorder, such as narcolepsy or other central disorder of hypersomnolence.<sup>986</sup> The presence of cataplexy, unique to NT1, can also assist in this differentiation. If pursuing polysomnography and MSLT to quantify sleepiness in a patient with treated OSA and persistent excessive daytime sleepiness, the test result validity is maximized when OSA treatment is used during the polysomnogram and during MSLT naps.

It is also possible for a patient to be misdiagnosed with narcolepsy when the etiology of sleepiness is OSA alone, as polysomnographic findings similar to narcolepsy can result from untreated or undertreated OSA.<sup>990</sup> Five percent of those with sleep related breathing disorders can have two or more SOREMPs on an MSLT, suggesting REM periods during naps are less specific to narcolepsy than initially believed.<sup>990</sup> Male sex, sleepiness, short REM latency on nocturnal polysomnogram and minimal oxygen saturation are risk factors for two or more SOREMPs in a patient with OSA.

Among the treatments for narcolepsy are daytime stimulant medications and sodium oxybate. While sodium oxybate can improve excessive daytime sleepiness and cataplexy, it is also known to be a respiratory depressant at higher doses, raising concern that it could worsen sleep apnea. Though current data is mixed regarding this possibility,<sup>991-994</sup> use of sodium oxybate in a patient with narcolepsy could potentially contribute to the development or worsening of OSA and repeat screening for this may be pursued in certain clinical contexts.

In summary, OSA is a common comorbidity in patients with narcolepsy. OSA is a more common explanation for excessive daytime sleepiness than narcolepsy based on population prevalence. However, in patients with excessive daytime sleepiness, it is imperative to confirm efficacy of OSA treatment before ruling out narcolepsy.

#### Association between OSA and Narcolepsy

Aggregate Grade of Evidence: B (Level 2b: 1 study; Level 2c: 3 studies; Level 3b: 4 studies)

**Table VII.I.3 Narcolepsy and prevalence of comorbid sleep apnea**

STUDY	Year	LOE	Study Design	N/Age/Cohort	Sample Population	Conclusion
Sansa et al, 2010 <sup>986</sup>	2010	2c	Cross-sectional	N=133; Ages 11-80	Single university hospital sleep clinic	AHI>10 events/hour in 24.8% of those with narcolepsy, 30% of these led to a delay in diagnosis of 6.1 ± 7.8 years. Excessive daytime sleepiness improved in 21% of those treated with CPAP.
Frauscher et al, 2013 <sup>985</sup>	2013	2c	Cross-sectional	N=100, ages 16-78; Innsbruck narcolepsy cohort	Single center, academic facility, tertiary referral center	24% of those with narcolepsy had sleep-related breathing disorders: 14 had mild sleep apnea, 8 moderate sleep apnea, and 2 had severe sleep apnea. The majority had obstructive sleep apnea syndrome (21/24); 2/24 had mixed sleep apnea syndrome; and 1/24 central sleep apnea syndrome.

Jennum et al, 2013 <sup>995</sup>	2013	3b	Case-control	N=757; age <20 to >80; Danish National patient registry	Patients diagnosed with narcolepsy in Denmark	Prior to narcolepsy diagnosis OR for sleep apnea diagnosis 44.5, 95% CI 13.1-151.3; after the narcolepsy diagnosis OR for sleep apnea 19.2, 95% CI 7.7-48.3.
Pizza et al, 2013 <sup>996</sup>	2013	2c	Cross-sectional	N=35; mean age 40 ± 16	Narcolepsy with cataplexy patients seen at a university hospital	31% of patient had sleep-disordered breathing; Mild SDB was diagnosed in 4 (11%) subjects, moderate SDB in 4 (11%), and severe SDB in 3 (9%). In 5 out of 11 (46%) patients with SDB, apneas were mostly obstructive, in one it was central. The remaining 5 patients (46%) showed mixed, obstructive and central apneas.
Black et al, 2017 <sup>987</sup>	2017	3b	Case-control	N=9321; mean age 46.1 ± 13.3	US medical claims data (private insurance and Medicare)	Sleep apnea was present in 51.4% of those with narcolepsy and 5.8% of matched controls, 45.6% excess prevalence, p<0.0001, OR 18.7, 95% CI (17.5-20.0).
Jennum et al, 2017 <sup>988</sup>	2017	3b	Case-control	N=339; 20-50 years old; Danish National Patient Registry	Patients diagnosed with narcolepsy in Denmark	Prior to narcolepsy diagnosis OR for sleep apnea 34.6, 95% CI 18-66.5; after narcolepsy diagnosis OR 35.2 for sleep apnea, 95% CI 19.4-63.9.
Cohen et al, 2018 <sup>984</sup>	2018	2b	Prospective cohort	N=68; ages 5-74; Rochester Epidemiology Project	Population-based in Olmsted Count, MN	At time of narcolepsy diagnosis OR of having OSA 69.25, 95% CI 9.26-517.99;. OR of having OSA after observation period 13.55, 95% CI 5.08-36.14.

Filardi et al, 2020 <sup>997</sup>	2020	3b	Case-control	N=38; ages 2-18	Children and adolescents with narcolepsy with cataplexy at academic medical center	No difference in prevalence of sleep-disordered breathing between narcolepsy and controls.
------------------------------------	------	----	--------------	-----------------	--	--

### VII.J Conditions Associated with OSA: Pregnancy

Due to a number of physiologic and hormonal changes, pregnancy is a time of unique vulnerability among women for sleep-disordered breathing (SDB). High estrogen levels can lead to nasal congestion (i.e. rhinitis of pregnancy)<sup>998</sup> and may contribute to upper airway narrowing<sup>999</sup>. While high progesterone levels increase ventilatory drive, whether this effect promotes or protects against respiratory instability and SDB during sleep is uncertain.<sup>1000</sup> Diaphragmatic elevation leads to decreased functional residual capacity, which in turn contributes to reduced oxygen reserve; these changes become more pronounced in the supine position and during late pregnancy.<sup>1000</sup>

Both subjective and objective measures of SDB increase with advancing pregnancy.<sup>1001-1003</sup> By the end of the second trimester, women report increases in the frequency of snoring, gasping or snorting, and witnessed apneas compared to the first trimester;<sup>1001</sup> these symptoms generally further increase until delivery. Recently, when more than 3,300 women underwent home sleep testing in the prospective, multicenter Sleep-Disordered Breathing substudy of the Nulliparous Pregnancy Outcomes Study (nuMoM2b), the prevalence of SDB (AHI $\geq$ 5 events/hour) increased from 3.6% in early pregnancy to 8.3% in mid-pregnancy.<sup>1002</sup> The vast majority of SDB cases in the nuMOM2b cohort were mild,<sup>1002</sup> a similar finding to other studies.<sup>1000</sup> Older age, higher BMI, larger neck circumference, non-Hispanic black race, smoking and chronic hypertension were all associated with increased AHI.<sup>1002</sup> Other studies have identified similar risk factors for gestational OSA.<sup>1004,1005</sup>

An accumulating body of data demonstrates an increased risk of cardiometabolic complications among women with gestational SDB.<sup>1000</sup> Women in the nuMOM2b study with SDB in early or mid-pregnancy were nearly twice as likely to develop preeclampsia compared to women without SDB. The odds for hypertensive disorders of pregnancy (gestational hypertension or preeclampsia) were increased only among women with mid-pregnancy SDB, and not among women with early pregnancy SDB. The nuMoM2b study also observed an approximately threefold increase in the odds for gestational diabetes mellitus among women with early and mid-pregnancy SDB, compared to women without SDB.

A recent meta-analysis examined associations between subjectively and objectively measured SDB and multiple maternal and fetal outcomes, with preeclampsia, gestational hypertension and GDM having the largest numbers of studies available for inclusion (i.e. 15-20 individual studies).<sup>1006</sup> In these analyses, the risks for gestational hypertension, preeclampsia and GDM were all increased among women reporting SDB symptoms.<sup>1006</sup> Among women with objectively diagnosed OSA, the risk for preeclampsia more than doubled, whereas risks for gestational hypertension and GDM nearly doubled.<sup>1006</sup> The risk for cesarean section also increased significantly among women with either subjective or objective SDB.<sup>1006</sup> Other

studies have found increased risks for severe maternal morbidity including eclampsia, cardiomyopathy, pulmonary embolism and in-hospital mortality.<sup>1007,1008</sup>

Studies examining fetal outcomes have largely focused on preterm birth and growth-related outcomes, especially small for gestational age (SGA) births.<sup>1006</sup> A recent meta-analysis found that the risk for preterm birth increased approximately 50% among women who reported subjective SDB symptoms or had been diagnosed with OSA.<sup>1006</sup> While some individual studies have observed increased risks for SGA infants among women with SDB, 2 meta-analyses did not find an increased risk for SGA births among women with SDB symptoms or objectively documented OSA.<sup>1006,1009</sup>

Case reports and case series suggest that treatment of SDB during pregnancy improves maternal-fetal outcomes.<sup>1010,1011</sup> However, there is a paucity of controlled trial data. Several trials examining the effect of CPAP therapy on outcomes including blood pressure, glycemic control and cardiovascular risk are in progress.<sup>1000,1012</sup> The current approach to treatment is extrapolated from recommendations and data in the general population, as there are no pregnancy-specific guidelines. CPAP therapy is generally considered first line treatment for gestational OSA, as it is widely effective and can be initiated quickly. Furthermore, auto-adjusting CPAP can accommodate changes in SDB severity during and after pregnancy. Women with preexisting OSA may also benefit from switching at least temporarily from fixed CPAP or oral appliances to auto-adjusting CPAP therapy during pregnancy to accommodate fluctuations in OSA severity. For women with positional (i.e. supine) SDB, the left lateral sleep position may be sufficient to avoid apneic events and maximize venous return via the inferior vena cava.<sup>1013</sup>

While pregnancies in women with OSA are widely considered high risk,<sup>1014</sup> clinical practice guidelines specifically for management of pregnant women with OSA have not been offered. Use of continuous pulse oximetry during labor and the postpartum period can identify hypoxic episodes and guide management.<sup>1014</sup> Early consultation with the anesthesia service can help to avoid the use of general anesthesia, which poses increased risks to individuals with OSA,<sup>1015</sup> should delivery by cesarean section be indicated.

Postpartum, women receiving treatment for OSA should resume therapy as soon as is feasible. Use of opioids should be carefully considered, given increased risks for morbidity and mortality among OSA patients taking opioids.<sup>1014,1016</sup> In a group of women in the immediate postpartum period (within 48 hours after delivery), elevating the upper body to 45 degrees during sleep reduced the AHI significantly compared to sleeping in a non-elevated position.<sup>1017</sup> This low technology intervention was well tolerated and can be easily recommended to patients.

While the severity of gestational OSA generally improves after delivery,<sup>1018-1020</sup> women diagnosed with or suspected of having OSA during pregnancy should be followed postpartum to determine whether OSA has resolved or requires further treatment.<sup>1014,1016</sup> Little is known about how frequently SDB during pregnancy persists or recurs afterwards, or about the effect of gestational SDB on risk later in life for adverse cardiometabolic outcomes such as hypertension and diabetes mellitus.

## VIII. Medical Treatment for OSA

### VIII.A Medical Management of OSA: Positive Airway Pressure (PAP) Therapy

#### VIII.A.1 Types of PAP for OSA

### VIII.A.1.a Types of PAP: Continuous Positive Airway Pressure (CPAP)

Continuous positive airway pressure (CPAP), the gold standard OSA treatment, acts as a pneumatic splint to maintain upper airway patency. Typically, after OSA diagnosis, CPAP is initiated with in-lab titration polysomnogram. A systematic review by Patil et al<sup>39</sup> demonstrated a clinically significant reduction in disease severity as evidenced by complete resolution or near resolution of the apnea-hypopnea index; improvement in subjective sleepiness (reduction in Epworth Sleepiness Scale score of 2.4 points based on metaanalysis of 38 RCTs, and ability to maintain wakefulness based on the maintenance of wakefulness test); sleep related quality of life, and blood pressure. Two additional systematic reviews<sup>1021,1022</sup> that studied the effect CPAP therapy had on quality of life showed similar results. The randomized clinical trial by Ponce et al<sup>1021</sup> compared the use of CPAP to no CPAP in 154 patients and demonstrated that the use of CPAP decreased subjective sleepiness based on a reduction in the Epworth Sleepiness Scale (ESS) by 2.6 points. A positive correlation between duration of CPAP use and reduction in ESS score was also seen. The Zhao study<sup>1022</sup> was a systematic review and demonstrated that the use of CPAP therapy in non-sleepy individuals with obstructive sleep apnea improved health-related quality of life (HRQOL) by using the SF-36 questionnaire. Improvements were specifically seen in vitality, general health, bodily pain, and physical health. Given the extent of conflicting data about effect of CPAP use on cardiovascular outcomes, the systematic review by Patil et al<sup>39</sup> noted that there is “insufficient and inconclusive evidence to either recommend or withhold PAP to treat non-sleepy adults with OSA as a means to reduce cardiovascular events or mortality.”

A systematic review of empirical studies with observational or experimental designs with monetized health economic outcomes of obstructive sleep apnea (OSA) treatments based on comparisons showed that, compared with no treatment, positive airway pressure (PAP) was associated with favorable economic outcomes; these outcomes were greater with adherence to PAP therapy.<sup>1023</sup> In 2015, the average cost of CPAP inclusive of testing, appointments, treatment devices, and surgery, if necessary, was estimated at \$2,105 per patient per year<sup>132</sup>.

#### CPAP for OSA

Aggregate Quality of Evidence: A (Level 1a: 7 studies, 1b: 5 studies, 2a: 3 studies).

Benefit: CPAP reduces disease severity and sleepiness and likely has beneficial effects on blood pressure, quality of life, and cognitive impairment.

Harm: Inconvenience and minor discomforts associated with PAP therapy. Variable adherence levels.

Cost: Low cost associated with CPAP device, replacement supplies and follow-up visits. Direct cost to patients depends on insurance coverage.

Benefits-Harm Assessment: CPAP therapy for the treatment of OSA is associated with greater benefit than harm.

Value Judgments: CPAP therapy is effective for the treatment for obstructive sleep apnea and improves multiple factors related to sleep and daytime functioning.

Recommendation Level: Strong recommendation

Intervention: CPAP therapy should be employed for treatment of OSA.

**Table VIII.A.1.a Evidence for the Use of CPAP to Treat OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
-------	------	-----	--------------	--------------	--------------------	------------

Wang et al <sup>840</sup>	2019	2a	SR	1. CPAP 2. No therapy	Cognitive decline	CPAP likely improves memory impairment in patients with OSA and cognitive decline
Ponce et al <sup>1021</sup>	2019	1b	RCT	145 patients 1. CPAP 2. no CPAP	ESS, QSQ, sleep related symptoms, anxiety and depression.	CPAP therapy improved HRQOL measures in patients over the age of 70.
Patil et al <sup>39</sup>	2019	1a	SR	336 studies that met inclusion criteria; 184 studies provided data suitable for meta-analyses.	Multiple outcomes of sleep apnea	CPAP reduces disease severity, sleepiness, blood pressure, and motor vehicle accidents.
Zheng et al <sup>1024</sup>	2019	1a	SR	17 studies comparing 1. CPAP 2. Control/Placebo/Sham CPAP in treatment of anxiety and depression in patients with OSA.	Various measurements of anxiety and depression.	CPAP reduced symptoms of depression.
Ning et al <sup>1025</sup>	2019	1a	SR	15 RCTs evaluating effect of CPAP therapy on various cardiac biomarkers	Cardiac Biomarkers	CPAP therapy improves levels of inflammatory biomarkers.
Khan et al <sup>1026</sup>	2018	1a	SR	7 RCTs studying the use of CPAP in reducing MACE in patients with moderate to severe sleep apnea.	MACE: MI, CV mortality	CPAP therapy of greater than 4 hours a night significantly reduced MACE.
Wang et al <sup>634</sup>	2018	2a	SR	9 studies (7 observational and 2 RCTs) studying cardiovascular outcomes in patients with coronary artery disease and OSA.	MACE: cardiovascular death, stroke, hospitalization for heart failure.	CPAP may decrease cardiovascular events in patients with CAD and OSA.
Labarca et al <sup>1027</sup>	2018	1a	SR	6 RCTs studying effects of CPAP therapy in OSA and type II diabetes	HbA1c, fasting glucose	CPAP therapy does not significantly reduce HbA1c or fasting glucose

						levels.
Gupta et al. <sup>1028</sup>	2019	1b	RCT	70 patients with OSA and recent stroke randomized to 1. CPAP 2. Non-CPAP	New vascular events	CPAP therapy reduces the presence of new vascular events in patients with a stroke.
Congrete et al <sup>1029</sup>	2018	2a	SR	7 studies reviewing the risk of recurrent atrial fibrillation after catheter ablation in patients with obstructive sleep apnea.	Recurrent episodes of atrial fibrillation	Treatment of OSA with CPAP decreased the incidence of recurrent atrial fibrillation.
Joyerux-Faure et al <sup>1030</sup>	2018	1b	RCT	37 patients with obstructive sleep apnea and resistant hypertension randomized to 1. CPAP 2. Sham CPAP	Blood pressure	Treatment with CPAP lowered nocturnal systolic blood pressure.
Zhao et al <sup>1022</sup>	2017	1b	RCT	169 Patients with moderate to severe OSA and CVD randomized to 1. Medical therapy 2. Medical therapy + sham CPAP. 3. Medical therapy + CPAP 4. Medical therapy + CPAP + motivational enhancement.	Health related quality of life.	CPAP improves health related QOL metrics.
Abuzaid et al <sup>1031</sup>	2017	1a	SR	4 RCTs studying cardiovascular outcomes in patients with moderate to severe OSA treated with CPAP.	MACE	CPAP therapy did not reduce the number of cardiovascular events.
Campos-Rodriguez et al <sup>1032</sup>	2017	1b	RCT	307 women with moderate to severe OSA randomized to 1. CPAP 2. Conservative therapy	Blood pressure	CPAP therapy significantly decreases diastolic blood pressure.
Wickwire et al <sup>1023</sup>	2019	1a	SR	Empirical studies with observational or experimental designs	Health economic outcomes	Relative to no treatment, PAP was associated



				with monetized health economic outcomes of OSA treatments based on comparisons.		with favorable economic outcomes.  PAP adherence was positively associated with greater economic outcomes.
Hoyos et al <sup>1033</sup>	2015	1a	SR	7 RCTs studying the effect of CPAP therapy on blood pressure	Blood pressure	CPAP therapy reduces nocturnal systolic and diastolic blood pressures.

APAP = auto-titrating CPAP; BPAP = bi-level PAP; CAD = coronary artery disease; CPAP = continuous PAP; CV = cardiovascular; ESS = Epworth Sleepiness Scale; HbA1c = glycated hemoglobin; HRQOL = health-related quality of life; MACE = major adverse cardiovascular events; MI = myocardial infarction; OSA = obstructive sleep apnea; PAP = positive airway pressure; QOL = quality of life; QSQ = Quebec Sleep Questionnaire; RCT = randomized control trial.

#### VIII.A.1.b Types of PAP: Auto-titrating Positive Airway Pressure (APAP)

Two systematic reviews<sup>39,1034</sup> evaluated the differences between auto-titrating positive airway pressure (APAP) and continuous positive airway pressure (CPAP) devices. Both modalities resulted in a clinically significant reduction of the apnea-hypopnea index (AHI), sleepiness as measured by the Epworth Sleepiness Scale (ESS), and quality of life. There was no significant difference between the two treatment modalities. The randomized equivalence trial of 208 sleepy patients (mean ESS 13.1) by Bloch et al<sup>1035</sup> comparing APAP to CPAP demonstrated reductions of ESS scores of 6.3 and 6.2, respectively. The systemic review by Ip et al<sup>1034</sup> demonstrated that APAP reduced ESS score by 0.5 points when compared to CPAP, though this increased benefit is likely not clinically relevant. One of the presumed benefits of APAP therapy is that it will lead to increased compliance due to its ability to automatically adjust pressures based on patient need. The systematic review by Patil et al<sup>39</sup> did not demonstrate any difference in PAP adherence as measured by hours used, nights used, or nights used with greater than 4 hours of usage per night. While the systematic review by Ip et al<sup>1034</sup> did show an 11-minute increase in PAP usage per day with APAP therapy, this is likely to be clinically insignificant. These studies did not evaluate peak or mean pressures achieved during APAP use. In addition, a RCT demonstrated that APAP was not found to lower mask leak rates when compared to CPAP.<sup>1036</sup> Additional RCTs<sup>1035,1037</sup> demonstrated similar findings in the reduction of sleepiness<sup>1035</sup> and improvement in quality of life measures.<sup>1038</sup>

APAP was shown to have no added benefit in blood pressure reduction when compared to CPAP. The large meta review performed by Ip<sup>1034</sup> included three RCTs that evaluated the effect of APAP and CPAP on blood pressure and found that there was no significant difference between the two modalities. The RCT by Pepin et al<sup>1037</sup> was a double-blind RCT, which randomized 322 patients with OSA to receive either APAP or CPAP, found reductions in diastolic BP with CPAP but not APAP in the intention to treat analysis.

Patil et al.<sup>39</sup> examined the comparison between in-lab titration of CPAP and home APAP (without lab titration) for initiation of PAP therapy. Analysis showed similar effects on OSA severity, sleepiness, and adherence with APAP initiated at home. Patients value preferences and resource utilization are considerations when choosing in-home APAP initiation versus CPAP titration. CPAP or APAP for treatment of OSA is recommended.

#### APAP for OSA

Aggregate Quality of Evidence: B (Level 1a: 2 studies, 1b: 4 studies).

Benefit: Reduction of sleep apnea severity, sleepiness, and improvement in measures of quality of life.

Harm: Inconvenience and minor discomforts associated with PAP therapy. Similar to CPAP.

Cost: Low cost associated with APAP device, replacement supplies and follow-up visits. Direct cost to patients depends on insurance coverage.

Benefits-Harm Assessment: APAP therapy for the treatment of OSA is associated with greater benefit than harm.

Value Judgments: APAP therapy is effective for the treatment for obstructive sleep apnea and improves multiple factors related to sleep and daytime functioning. For appropriately selected patients newly diagnosed with OSA, APAP can be initiated in lieu of in-lab titration of PAP therapy with consideration for patient value preferences and resource utilization.

Recommendation Level: Recommendation

Intervention: APAP may be employed for treatment of OSA.

**Table VIII.A.1.b: Evidence for APAP for OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Wimms et al <sup>1037</sup>	2019	1b	RCT	301 patients with mild OSA randomized to 1. APAP + standard care 2. Standard care	QOL from SF-36	APAP usage improved QOL in patients with mild obstructive sleep apnea.
Patil et al <sup>39</sup>	2019	1a	SR	26 RCTs comparing APAP to CPAP	OSA severity, adherence, sleepiness, QOL, neurocognitive function	No difference between APAP and CPAP.
Lebret et al <sup>1036</sup>	2019	1b	RCT	276 patients with OSA randomized to 1. CPAP 2. APAP	Mask leak	PAP modality did not affect level of mask leak.
Bloch et al <sup>1035</sup>	2018	1b	RCT	208 patients randomized to 1. CPAP 2. APAP (5-15 cmH2O)	Subjective and objective sleepiness	APAP is effective in treating EDS
Pepin et al <sup>1038</sup>	2016	1b	RCT	322 patients with OSA randomized to	Difference in office based	APAP can lower office

				1. CPAP 2. APAP	systolic blood pressure after 4 months of therapy	based systolic blood pressure.
Ip et al <sup>1034</sup>	2012	1a	SR	24 RCTs comparing CPAP to APAP	Adherence	11-minute increase in PAP adherence with APAP.

APAP = auto-titrating CPAP; BPAP = bi-level PAP; CPAP = continuous PAP; OSA = obstructive sleep apnea; PAP = positive airway pressure; QOL = quality of life; RCT = randomized control trial.

### VIII.A.1.c Types of PAP: Bilevel PAP

Few studies included in the systematic review studied bi-level PAP (BPAP). A systematic review of PAP treatments for OSA found no benefit for BPAP over CPAP.<sup>39</sup> Review of studies showed no significant difference between BPAP, CPAP and APAP for improvement in OSA severity, sleepiness and quality of life. BPAP also confers no significant advantage over CPAP or APAP in improved adherence, except as a potential therapy option for patients nonadherent to CPAP.<sup>39</sup> Patients who require high PAP levels greater than what CPAP devices can deliver may benefit from use of BPAP. For patients with routine OSA, BPAP devices may cost more and may not provide sufficient reduction in the AHI if the expiratory pressure setting is too low, thus BPAP should not be considered in these patients.

A single center randomized control trial that studied an enhanced education support program for patients with OSA reported no difference in PAP adherence, nightly duration of PAP use or reduction in subjective daytime sleepiness between use of BPAP, CPAP or APAP.<sup>1039</sup>

BPAP may be indicated when CPAP is not tolerated. Ballard et al.<sup>1040</sup> examined 100 patients who were persistently noncompliant with CPAP after mask optimization, humidification and education measures and performed a double-blind randomized trial of standard CPAP vs. BPAP use and showed more participants in the BPAP group achieved compliance of PAP use more than 4 hours per night.

#### Use of Bilevel PAP for OSA

**Aggregate Quality of Evidence:** B (Level 1a: 1 study; Level 1b: 2 studies)

**Benefit:** BPAP may be beneficial for patients who require high treatment pressure and those who are unable to tolerate CPAP at high pressure settings.

**Harm:** Studies show no difference in PAP adherence with BPAP compared with CPAP. Side effects are similar to CPAP.

**Cost:** BPAP devices are associated with higher costs compared with CPAP devices.

**Benefits-Harm Assessment:** Balance of benefit and harm.

**Value Judgments:** Studies show no significant difference between BPAP, CPAP and APAP for improvement in OSA severity, sleepiness and quality of life. BPAP also confers no significant advantage over CPAP or APAP in improved adherence, except as a potential therapy option for patients nonadherent to CPAP.

**Recommendation Level:** Option

**Intervention:** BPAP should not be used over CPAP for initial treatment of routine OSA. BPAP is an option when the treatment pressure requirements are greater than can be delivered via CPAP or when a patient is unable to tolerate CPAP at high pressure settings.

**Table VIII.A.1.c: Evidence for Use of BPAP for OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Patil et al. <sup>39</sup>	2019	1a	SR	5 RCTs comparing BPAP or auto-BPAP to CPAP.	OSA severity, treatment adherence, sleepiness, QOL	No difference between BPAP or auto-BPAP and CPAP for OSA severity, sleepiness, QOL.
Sarac et al. <sup>1039</sup>	2016	1b	RCT	115 patients with OSA randomized to standard care or enhanced educational support.	PAP adherence rates, PAP hours/night, reduction in Epworth Sleepiness Scale Score	No stated difference between BPAP, CPAP and APAP.
Ballard et al. <sup>1040</sup>	2007	1b	RCT	104 OSA patients persistently noncompliant with CPAP: double blind randomized CPAP vs. flexible BPAP	Compliance with PAP	More on BPAP 25/51 (49%) achieved compliance vs. 15/53 (28%) randomized to CPAP.

APAP = auto-titrating CPAP; BPAP = bi-level PAP; CPAP = continuous PAP; OSA = obstructive sleep apnea; PAP = positive airway pressure; RCT = randomized control trial; QOL = quality of life;

#### VIII.A.1.d Types of PAP: Adaptive Servo Ventilation

Adaptive servo-ventilation (ASV) is a form of auto-adjustable bilevel positive pressure support with a backup rate which is used to treat central sleep apnea syndromes (CSAS). ASV devices provide expiratory positive airway pressure (EPAP) to achieve and maintain upper airway (UA) patency during sleep as well as variable inspiratory pressure support (IPS) and auto-backup rate (BUR) in order to stabilize the respiratory control circuit and alleviate cyclical episodes of hyper- and hypoventilation. The EPAP supplied by ASV devices is either titrated to the critical airway opening pressure needed to achieve upper airway patency during an attended PSG or auto-adjusted by the device (if equipped with auto-EPAP capabilities).<sup>1041,1042</sup> IPS and the BUR are dynamically auto-adjusted, in relation to the patient's native respiratory efforts and device-specific minute-ventilation-associated targets, with the goal of preventing episodes of respiratory instability.<sup>1043,1044</sup> Importantly, the proprietary algorithms used for dynamic IPS and BUR adjustment have been shown to vary by device<sup>1044,1045</sup> which could potentially lead to difficulties achieving therapeutic targets.<sup>1044</sup>

ASV therapy is not recommended for uncomplicated OSA.<sup>39</sup> However, there is a limited body of literature to support its use in cases of persistent treatment-emergent central sleep apnea (TECSA).<sup>1046-1054</sup> TECSA is defined by the initial presence of OSA (obstructive AHI  $\geq 5$  events/hr in at least 2 hours of recorded sleep) followed by resolution of obstructive events with CPAP titration, and the subsequent appearance of central respiratory events with ongoing CPAP therapy (residual central AHI [CAHI]  $\geq 5$ /hr in at least 2 hours of recorded sleep time).<sup>81,1041</sup> TECSA does not include patients with CHF-associated CSAS. ASV can be used in CSAS with concurrent heart failure and opioid-associated CSAS.<sup>1055</sup> Updated guidelines examined the increased risk for cardiac mortality in patients with an LVEF less than 45% and moderate to severe CSA predominant sleep disordered breathing. Guidelines recommend against the use of ASV in patients with LVEF  $\leq 45\%$ .<sup>1056</sup>

### VIII.A.2 PAP Use: Mask Interfaces

Continuous positive airway pressure (CPAP) therapy was originally designed for use with a nasal interface that would deliver positive pressure through the nares and act as a pneumatic splint, pushing the soft palate and tongue forward and away from the posterior oropharyngeal wall to prevent upper airway occlusion<sup>3</sup>. Over time, numerous nasal masks, oronasal masks, nasal pillow interfaces and even oral masks have been developed for use with CPAP, with the goal of maximizing mask tolerability, a major determinant of CPAP adherence<sup>1057</sup>. Nevertheless, questions about which types of CPAP interfaces are associated with the best adherence and about the effectiveness of oronasal and oral interfaces persist.

A 2006 Cochrane review of CPAP delivery interfaces for OSA identified only 4 randomized, controlled studies that met the stringent criteria for inclusion and concluded that the optimal form of CPAP delivery interface remained unclear<sup>1058</sup>. The authors indicated that nasal pillows or the Oracle oral mask could be useful alternatives for patients unable to tolerate conventional nasal masks. Similarly, they suggested that oronasal masks should not be recommended for initial use but could be considered among individuals whose nasal symptoms limited nasal mask use.

Subsequently, a meta-analysis that included 5 randomized and 8 non-randomized trials found that oronasal masks were associated with a significantly higher CPAP level, higher residual AHI and poorer adherence compared to nasal masks<sup>1059</sup>. While data from a total of 4563 individuals with OSA was included, the majority of the data came from a single study<sup>1060</sup>. Limitations including moderate to high heterogeneity between studies with regards to CPAP level and adherence were noted.

Most recently, as part of a systematic review focused on the use of positive airway pressure for treatment of OSA in adults, the American Academy of Sleep Medicine published a series of meta-analyses evaluating the effects of different PAP interfaces on outcomes including reducing AHI, improving adherence to PAP therapy and sleepiness<sup>39</sup>. These analyses utilized data from 8 RCTs and 3 observational studies. Residual AHI was higher using oronasal masks compared to nasal interfaces, though the difference was not clinically significant. Adherence to CPAP was similar when intranasal (nasal pillows) and nasal interfaces were compared; however, adherence was significantly higher with nasal interfaces compared to oronasal interfaces. No significant differences in sleepiness were observed in comparisons of oronasal and nasal masks, nor in comparisons between nasal pillows and nasal masks. Data were insufficient to perform analyses examining differences in quality of life or interface-associated side effects.

The current review identified eleven small ( $n = 14$  to  $85$ ) randomized trials of different mask interfaces that examined outcomes including optimal CPAP pressure, residual AHI on CPAP, CPAP adherence

(duration or frequency of use), Epworth Sleepiness Scale score, side effects and patient preference<sup>1061-1071</sup>. Most were crossover trials in which participants were assigned to use CPAP with nasal masks and oronasal masks in random order<sup>1062,1064,1067,1068,1070</sup>; two trials included a third arm using nasal pillows<sup>1063,1064</sup>.

In one trial, oronasal mask use required significantly higher final CPAP pressures to treat OSA compared to use of nasal masks or nasal pillows<sup>1063</sup>. Another found no difference between oronasal and nasal masks in optimal CPAP pressures<sup>1070</sup>. Four trials found significantly higher residual AHIs using oronasal masks compared to nasal masks, despite delivery of the same or similar CPAP pressures during both study arms<sup>1062,1064,1068,1070</sup>, but differences were not clinically meaningful.

While some studies have observed significantly longer durations of CPAP use with nasal masks compared to oronasal masks<sup>1064,1067</sup>, others have found no significant differences<sup>1062,1068</sup>. Comparisons of objective and subjective sleep quality and daytime sleepiness have demonstrated more slow wave and total sleep time during CPAP titration using nasal masks compared to oronasal masks<sup>1070</sup>, better sleep quality using CPAP with nasal masks compared to oronasal masks<sup>1068</sup>, and less sleepiness (i.e. lower Epworth Sleepiness Scale scores) using nasal masks compared to oronasal masks<sup>1067</sup>. Patients also expressed an overall preference for nasal masks compared to oronasal masks<sup>1067,1068,1070</sup>.

When nasal masks and nasal pillows were compared, no significant differences were observed in 95<sup>th</sup> percentile auto-titrating pressures<sup>1071</sup>. Three randomized crossover trials observed no significant differences in mean nightly duration of CPAP use or residual AHI when comparing nasal masks to nasal pillows<sup>1066,1069,1071</sup>. Patients reported similar or fewer adverse effects with nasal pillow use compared to nasal mask use<sup>1066,1069</sup>. Sleep quality<sup>1071</sup>, Epworth Sleepiness Scale scores and quality of life<sup>1066,1069</sup> generally did not differ during nasal pillow use compared to nasal mask use. Patients did not express a clear preference for nasal pillows or nasal masks in these studies<sup>1069,1071</sup>.

Oral masks have been compared to nasal masks in two randomized crossover studies<sup>1061,1065</sup>. Significant differences between the interfaces were not observed when effective CPAP pressure<sup>1061</sup>, average duration of CPAP use<sup>1061,1065</sup> residual AHI during PAP titration<sup>1061</sup>, and sleepiness<sup>1061</sup> were compared. The side effect profiles differed: while oral mask use was associated with more dry mouth and throat, gum discomfort and excessive salivation, nasal mask use was associated with more complaints of nasal congestion and mask leak<sup>1061,1065</sup>.

Four observational studies comparing CPAP mask interfaces were identified<sup>1060,1072-1074</sup>. The largest was a prospective cohort study of 2311 newly diagnosed OSA patients who were given a choice of nasal masks, oronasal masks or nasal pillows<sup>1060</sup>. Users of oronasal masks and nasal pillows were more likely to be non-adherent to CPAP (mean use <4 hours/night) at follow up compared to nasal mask users. Oronasal mask users were more likely than the other groups to report side effects and to find CPAP inconvenient. Two other studies have observed that effective CPAP pressure and residual AHI were higher with oronasal mask use compared to nasal masks<sup>1073</sup> and/or nasal pillows<sup>1074</sup>.

In general, the data suggest that nasal interfaces should be utilized initially in patients starting CPAP therapy. Use of oronasal masks is associated with the need for higher levels of CPAP pressure, and with higher residual AHI. Compared to nasal masks, adherence in several studies was lower with oronasal mask use. Mostly, outcomes including CPAP adherence and residual AHI were similar when nasal pillows and nasal masks were compared. Data on use of oral masks was particularly sparse. Oronasal and oral

masks may be appropriate for a select group of patients who are predominantly mouth breathers, or who have large air leaks during sleep due to mouth opening, but these studies have not been performed.

### Nasal Mask Interfaces for PAP Therapy

**Aggregate Quality of Evidence:** B (Level 1a: 2 studies; Level 1b: 1 study; Level 2b: 12 studies; Level 4: 3 studies)

**Benefit:** Better control of OSA, better adherence to CPAP therapy, less sleepiness associated with use of nasal mask and nasal pillow interfaces compared to oronasal masks.

**Harm:** Lower rates of CPAP adherence among oronasal mask users may be associated with greater likelihood of OSA treatment abandonment. Not all users can tolerate nasal masks.

**Cost:** Low<sup>1075</sup> cost differences. Cost of different types of masks are not substantively different.

**Benefits-Harm Assessment:** Preponderance of benefit of nasal interfaces over harm, given consistent evidence from small RCTs and observational studies.

**Value Judgments:** The preponderance of evidence favors the initial use of nasal interfaces (nasal masks or nasal pillows) over oronasal masks. Oronasal and oral masks may be appropriate for a select group of patients who are intolerant to nasal masks, or who have large air leaks during sleep due to mouth opening, but these studies have not been performed.

**Recommendation Level:** Recommendation.

**Intervention:** In general, nasal interfaces should be utilized initially in patients naïve to CPAP therapy.

**Table. Summary of the evidence for PAP Mask Interfaces.**

Study	Year	LoE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Patil et al <sup>39</sup>	2019	1a	Meta-analyses	8 RCTs, 3 observational studies	Residual AHI, CPAP adherence, sleepiness, QOL, side effects	No significant differences between NP and NM in residual AHI or adherence. Higher residual AHI and lower CPAP adherence using ONM compared to NM. No differences in sleepiness between NM and NP, or between NM and ONM.
Goh et al <sup>1064</sup>	2019	2b	Randomized unblinded crossover	Newly diagnosed moderate-severe OSA (n=85) 1. Nasal masks 2. Oronasal	CPAP adherence, residual AHI	Significantly better adherence with NM compared to ONM and NP. Significantly higher residual AHI with ONM compared to NM and NP.

				masks 3. Nasal pillows		
Rowland et al <sup>1068</sup>	2018	2b	Randomized unblinded crossover	Moderate-severe OSA (n=48) 1. Nasal masks 2. Nasal masks plus chinstrap 3. Oronasal masks	CPAP adherence, residual AHI, sleepiness, patient satisfaction, sleep quality, side effects, patient preference	No significant difference in CPAP adherence. Significantly higher residual AHI with ONM compared to NM or NM plus chin strap. No significant differences in sleepiness. Greater comfort, better sleep quality and overall preference for NM compared to ONM.
Andrade et al <sup>1059</sup>	2018	1b	Meta-analysis	5 randomized, 8 nonrandomized trials (n=4563)	CPAP level, residual AHI, CPAP adherence	ONM associated with higher CPAP level, higher residual AHI, lower adherence than nasal masks.
Deshpande et al <sup>1074</sup>	2016	4	Retrospective observational	OSA patients having CPAP titration studies (n=358) 1. Nasal masks (34.6%) 2. Oronasal masks (46.1%) 3. Nasal pillows (19.3%)	CPAP therapeutic level, residual AHI	CPAP level higher for ONM compared with NP and NM. Residual AHI higher for ONM than NM and NP.
Bettinzoli et al <sup>1073</sup>	2014	4	Retrospective observational	OSA patients with AHI $\geq$ 15 (n=109) 1. Nasal masks (61.5%) 2. Oronasal masks (38.5%)	CPAP therapeutic level, residual AHI, mask preference	Patients using ONM had significantly higher therapeutic level and higher residual AHI.
Ebben et al <sup>1062</sup>	2014	2b	Randomized unblinded crossover	Moderate-severe OSA naïve to CPAP (n=14) 1. Nasal masks	Residual AHI, CPAP adherence	Residual AHI was significantly higher using ONM compared to NM. No significant



				2. Oronasal mask		difference in CPAP adherence.
Borel et al <sup>1060</sup>	2013	2b	Prospective observational cohort	OSA newly prescribed CPAP (n=2311) 1. Nasal masks (62.4%) 2. Oronasal masks (26.2%) 3. Nasal pillows (11.4%)	CPAP adherence, CPAP level, CPAP-related side effects	Both ONM and NP associated with higher risk of non-adherence than NM. ONM associated with higher pressures than NM or NP. Proportion reporting side effects significantly higher with ONM than NM.
Zhu et al <sup>1071</sup>	2013	2b	Randomized unblinded crossover	OSA using CPAP with NM for $\geq 6$ mos (n=20) 1. Nasal masks 2. Nasal pillows	CPAP daily usage, residual AHI, CPAP level, mask leak, mask performance/preference	No significant differences in average daily usage, pressure levels, mask leak or residual AHI. Minor differences in side effects, no differences in patient preference.
Ebben et al <sup>1063</sup>	2012	2b	Randomized unblinded trial	OSA with AHI $> 5$ /hr (n=55) 1. Nasal masks 2. Oronasal masks 3. Nasal pillows	Final pressure levels, AHI on CPAP, final mask leak from CPAP titration study	Patients titrated using ONM required significantly higher final pressure levels compared to NM or NP. Final pressures not significantly different between NM and NP. Final AHIs not significantly different. Mask leak greater using ONM compared to NP but not NM.
Ryan et al <sup>1069</sup>	2011	2b	Randomized unblinded crossover	OSA (AHI $\geq 10$ /hr) naïve to CPAP (n=21) 1. Nasal masks 2. Nasal pillows	CPAP adherence, residual AHI, sleepiness, side effects, QOL, preference	No significant differences between NM and NP in adherence, residual AHI, sleepiness, side effects, QOL or interface preference.

Teo et al <sup>1070</sup>	2011	2b	Randomized single-blind crossover	OSA (RDI > 15/hr) naïve to CPAP (n=24) 1. Nasal masks 2. Oronasal mask	PSG titration study CPAP level, residual RDI, mask leak, SWS, TST	CPAP levels not significantly different between NM and ONM. Residual AHI, arousals, mask leak all significantly greater with ONM than NM. Significantly less SWS and TST with ONM. Greater satisfaction with NM than ONM.
Chai-Coetzer et al <sup>1058</sup>	2006	1a	Systematic review	4 RCTs 1. 2 studies comparing NM v. OM 2. 1 study comparing NM v. NP 3. 1 study comparing NM v. ONM	CPAP compliance, sleep physiological parameters, ESS, OSA symptoms, adverse effects, interface satisfaction	Optimum CPAP delivery interface remains unclear given the limited number of available studies
Anderson et al <sup>1061</sup>	2003	2b	Randomized single-blind crossover, intention to treat analysis	OSA (AHI > 20/hr) naïve to CPAP (n=21) 1. Nasal masks 2. Oral masks	PSG variables, questionnaires, compliance	No significant differences in PSG variables during CPAP titration between OM and NM. No differences in residual AHI, CPAP compliance, CPAP pressure, sleepiness, overall side effects or mask preference.
Beecroft et al <sup>1072</sup>	2003	4	Prospective observational	OSA (AHI > 5/hr) naïve to CPAP (n=98) 1. Nasal masks (66%) 2. Oronasal mask (7%) 3. Oral masks (23%)	Optimal CPAP level, residual AHI, self-reported adherence, mask comfort, side effects	No significant difference in optimal CPAP levels, residual AHI, self-reported usage or satisfaction between NM, ONM and OM users
Khanna et al <sup>1065</sup>	2003	2b	Randomized unblinded trial	Patients with OSA (RDI > 15/hr, n=38) 1. Nasal masks	CPAP compliance, overall satisfaction, side effects	No significant differences in CPAP compliance between NM and OM users.

				2. Oral masks		Overall satisfaction similar between groups, types of side effects differed by mask type. Dropout rates similar between groups.
Massie et al <sup>1066</sup>	2003	2b	Randomized unblinded crossover	Patients with OSA (n=39) 1. Nasal masks 2. Nasal pillows	CPAP compliance, residual AHI, sleepiness, QOL, side effects, overall satisfaction	Higher percentage of days using CPAP for NP compared to NM but no differences in overall adherence. No significant differences in residual AHI or QOL. Better sleep quality and overall satisfaction with nasal pillows.
Mortimore et al <sup>1067</sup>	1998	2b	Randomized unblinded crossover	New OSA patients naive to CPAP (n=20) 1. Nasal masks 2. Oronasal mask	Compliance, symptoms on CPAP, side effects	Higher CPAP compliance and less sleepiness using NM compared to ONM. Significantly fewer side effects with NM compared to ONM.

OSA = obstructive sleep apnea; CPAP = continuous positive airway pressure; RCT = randomized controlled trial; NM = nasal masks; ONM = oronasal masks; NP = nasal pillows; OM = oral masks; AHI = apnea-hypopnea index; RDI = respiratory disturbance index; PSG = polysomnogram; ESS = Epworth Sleepiness Scale; SWS = slow wave sleep; TST = total sleep time; QOL = quality of life

### VIII.A.3 PAP Titration Paradigms

The immediate goal of an efficacious PAP titration is to determine the pressure required to eliminate apneas, hypopneas and inspiratory flow limitation (IFL)<sup>39,1076,1077</sup> whilst preventing arousal and central apnea events. The midterm and longer-term goals are for patient acceptance of PAP therapy, continued effectiveness in eliminating respiratory events during sleep, ongoing patient adherence to therapy, and improvement in symptoms and outcomes related to sleep disordered breathing. PAP titration paradigms can be viewed along 3 dimensions: method of pressure changes (manual versus automatic), PAP titration setting (in-lab versus at-home) and time spent titrating pressure (partial or full night, or multiple nights).

The AASM has published several guidelines detailing practice parameters and guidelines for PAP titration<sup>39,1078,1079</sup> with the goal being to identify a pressure that reduces AHI to <5 events/hour in all sleep positions and sleep stages. The gold standard PAP titration is an in-laboratory technician-guided, manual titration with continuous monitoring of airflow, leak, sleep and oxygen saturation.<sup>1078</sup> This approach assumes a single positive airway pressure can be determined that maintains airway patency

despite changes in sleep stage, sleep position and other factors that change upper airway collapsibility such as weight change, seasonal allergies, use of medication and alcohol. With the introduction of auto-titrating positive airway pressure (APAP) devices this provided an alternative approach to identifying a therapeutic pressure where 90% or 95% of all titration pressures fall.<sup>1079</sup> The effective pressure values identified by manual titration versus auto algorithms have not demonstrated systematic differences. Titration of Bilevel PAP (BPAP) is not addressed here as BPAP is not recommended over CPAP or APAP for routine treatment of OSA in the absence of sleep-related breathing disorders associated with hypercapnia.<sup>39</sup>

A systematic review and meta-analysis of 10 RCTs comparing APAP at-home and in-lab PAP titration for *initiation of PAP* demonstrates high grade evidence that both approaches are effective in reducing OSA severity (AHI), daytime sleepiness, and for PAP adherence and quality of life measures.<sup>39</sup> However, study participants were predominately those with moderate to high OSA severity and excluded patients with significant comorbidities. Of importance, these comparisons assume equivalent levels of patient CPAP education and mask fitting prior to titration plus equal opportunity for therapy support post initiation.

Split-night titration, where the first couple of hours of the polysomnography are for diagnostic purposes and the remainder of the study involves PAP titration, compared to a full-night titration, is not significantly different in terms of outcomes such as subjective sleepiness or adherence over time.<sup>1080-1082</sup> However, certain criteria must be met to initiate a split-night PSG, i.e. moderate-severe OSA and least 3 hours available for CPAP titration.<sup>571</sup> This results in the exclusion of those with mild OSA from the research comparing full night and split titration paradigms and contributes to the weak recommendation regarding the appropriateness of split night PSGs for all patients.<sup>571</sup> Additionally, there is recent evidence that the prevalence of treatment-emergent central sleep apnea tends to be higher for split-night compared to full night titration studies.<sup>1041,1083</sup> Nevertheless, there is no evidence that treatment-emergence central sleep apnea poses any harm to the patient.<sup>39</sup>

Determination of effective pressures using equations that combine anthropomorphic and OSA severity variables have been suggested as alternatives to manual titration.<sup>1084</sup> While these equations may provide a starting pressure for titration their use as the sole determinant of a patient's therapeutic pressure has not been accepted as they differ from manually determined pressures by up to 5cmH<sub>2</sub>O.<sup>1074,1085,1086</sup>

From the perspective of the treating physician, avoidance of delays to therapy initiation is a pertinent driver for the chosen PAP titration paradigm. The only RCT assessing patient preference demonstrated a preference for home management<sup>601</sup> compared to an in-lab titration. As the necessity for increased telehealth technology grows, we will likely see a concomitant increase in telemonitoring approaches to PAP titration, perhaps including patient-directed titration paradigms.<sup>1087-1089</sup> Based on the above considerations that all show no clinically significant differences in outcomes between titration paradigms, the choice of strategy should be based on patient preferences and abilities, judgment of the sleep clinician, and availability of resources.

#### **VIII.A.4 PAP Adherence**

##### **VIII.A.4.a Measurement of PAP Adherence**

The use of PAP is objectively measured by the device and defined as the number of hours PAP is used at the prescribed pressure. This is most often reported as a single summary measure of the amount of time PAP was used across the 24-hour day. While the term “use” is the most concise descriptor, treatment compliance and adherence are terms that are often utilized for prescribed medical interventions. Treatment adherence, implying a partnership between provider and patient, is the more commonly used term and is more consistent with the broader chronic illness medical literature.

CPAP adherence is in large part a behavioral measurement because the act of putting on a mask at night prior to sleep requires voluntary action. PAP adherence is therefore a measure of the extent to which an individual uses their prescribed medical device and can be categorized into 0 hours of use; >0 hours of use; or missing data. Missing data represents problems with data measurement (*e.g.*, internal CPAP device problems) or transmission (*e.g.*, poor cellular coverage). In these cases, the only way to know if PAP was used is to ask the patient directly. Some studies include a CPAP use questionnaire to determine if the patient had a medical reason to not use CPAP for some amount of time. In this case, a true 0 may be reclassified as missing data.

The quantity of PAP use as a marker of adherence requires some clarification. Measurement of the amount of CPAP use does not take into account the amount of sleep during a defined 24-hour period. Because the CPAP device does not measure sleep, it is not known whether CPAP is used during wake or sleep periods. CPAP is often used during times of attempted sleep. To increase accuracy of measurement, one should consider combining CPAP with a reliable and valid measure of sleep duration to determine the percentage of the actual sleep period that CPAP is used to account for individual differences in sleep and wake. CPAP devices also do not measure respiratory effort, and unless equipped with an oxygen probe, do not monitor oxygenation.

The medical prescription for PAP includes a pressure mode and pressure level(s). Pressure modes include fixed and auto-adjusting continuous single and bi-level pressure modes. The amount of PAP use and the efficacy of PAP in controlling sleep-disordered breathing can be affected by pressure mode, pressure level and/or mask type and fit. In addition, it should be stated that the CPAP device provides measures of treatment efficacy, including residual apnea-hypopnea index (AHI) and mask leak.

Given the single measure of time a PAP device is used in a given 24h period is the foundation of defining adherence, it is important to understand additional limitations that exist when objective device-reported measurements are not available. In this case, estimated CPAP use provided by patients (or their bedpartners) is the next best surrogate. The mean difference between subjectively and objectively measured CPAP adherence is 0.96 hours (See Table VIII.A.4a), meaning that patients tend to overestimate their PAP use by approximately one hour per night.

While PAP adherence is measured as a continuous variable (*i.e.*, number of hours per night), it is often reported as a categorical variable (adherent/not adherent) to foster understanding and discussion. The threshold most often used for “adherent” is use > 4 hours per night on >70% of nights over a rolling 30-day period over a defined period of time. This threshold was based on a very early study of 35 CPAP users that showed a bimodal distribution,<sup>1090</sup> which was then subsequently adopted as policy for coverage determinations.<sup>1091-1093</sup> Since that time, very few studies have examined this relationship, though increasing data suggests disparities exist with PAP adherence across socioeconomic and racial groups<sup>1094-1096</sup> and use of the 4-hour, 70% threshold may be contributing to reduced access to treatment by rendering users below this threshold ineligible for coverage. One study found that more CPAP use

was associated with better outcomes, finding a linear dose-response relationship up through 7 hours of use.<sup>1097</sup> This suggests current threshold definitions should be reexamined and that more research is needed to identify clinically meaningful adherence thresholds.

#### Use of Objective Measures of PAP Adherence

**Aggregate Quality of Evidence:** B (Level 2b: 7 studies)

**Benefit:** Objective PAP adherence provides a direct measure of PAP usage times in order to understand and improve PAP adherence with interventions.

**Harm:** Harm associated with PAP use and monitoring is low. In some, adherence data has implications for PAP payment and coverage.

**Cost:** Minimal additional financial cost – objective measures are incorporated into most PAP machines.

**Benefits-Harm Assessment:** Benefit outweighs harm.

**Value Judgments:** PAP adherence levels are important to measure and follow. The current definitions of adherence may not be optimally matched to outcomes.

**Recommendation Level:** Recommendation

**Intervention:** Recommend objective measurement of PAP use over subjective queries.

**Table VIII.A.4a Subjective vs Objective measures of CPAP adherence**

Study	Year	n	LOE	Study Design	Clinical End-Point*	Conclusion
Kribbs <sup>1090</sup>	1993	35	2b	Prospective cohort	SR: 6.3 ± 1.47; Obj: 5.1 ± 1.87	Subjective was 1.2 hrs more than objective
Rauscher <sup>1098</sup>	1993	63	2b	Prospective cohort	SR: 6.3 ± 0.2 SEM*; Obj: 4.9 ± 0.3 SEM*	Subjective was 1.4 hrs more than objective
Meurice <sup>1099</sup>	1994	44	2b	Prospective cohort	SR: 7.0 ± 1.65; Obj: 6.02 ± 2.48	Subjective was 1.0 hrs more than objective
Pepin <sup>1100</sup>	1995	193	2b	Prospective cohort	SR: 7.4 ± 2.0; Obj: 6.5 ± 3.0	Subjective was 0.9 hrs more than objective
Engleman <sup>1101</sup>	1996	204	2b	Prospective cohort	SR: 6.0 ± 1.9; Obj: 5.1 ± 2.5	Subjective was 0.9 hrs more than objective
Drake <sup>1102</sup>	2003	71	2b	Prospective cohort	SR: 5.86 ± 2.02; Obj: 5.04 ± 2.59	Subjective was 0.8 hrs more than objective
Means <sup>1103</sup>	2003	39	2b	Prospective cohort	SR: 4.82 ± 2.49; Obj: 4.31 ± 2.31	Subjective was 0.5 hrs more than objective

\*Note: Data all in mean ± SD except for row with mean ± SEM (standard error of measurement); Abbreviations: Level of evidence (LOE); sample size (n).

#### VIII.A.4.b Predictors of PAP Adherence

Predictors of positive airway pressure (PAP) adherence are factors that have been found to be independently associated with treatment use. While the term “predictor” implies causation, most if not all studies in this literature are based on finding an association between a given factor and PAP adherence. PAP adherence predictors are most often categorized into the following groups: sociodemographic (*e.g.*, age, sex), disease-related (*e.g.*, apnea-hypopnea index (AHI), treatment-related (*e.g.*, pressure mode, pressure level), and psychological (*e.g.*, mood) factors. For the purposes of this review, we are separating out behavioral predictors into their own category (*e.g.*, self-efficacy, readiness to change). Predictors are most often measured before starting CPAP therapy but are sometimes measured after some CPAP usage. In addition, predictors may be measured as change variables, such that a difference score is calculated between a defined follow-up period and baseline.

Table VIII.A.4b provides the list of primary PAP adherence studies and predictor categories studied. Although some studies included early adherence as a predictor for comparison purposes, this analysis does not include early adherence level as a predictor since the goal is to identify independent factors associated with future PAP adherence, and it is well known that past behavior predicts future behavior.<sup>1104</sup> For example, Aloia *et al* found that adherence measured at 1 week and 3 months accounted for 52% and 79% of the variance in 6-month adherence, respectively, and further did not find other measured predictors that could independently account for any additional variance.<sup>1105</sup> Understanding factors that influence PAP adherence behavior will inform the creation of effective interventions to promote PAP use.<sup>1106</sup>

There are several important findings by predictor category:

*Sociodemographic (Dem).* While sociodemographic variables were the most studied predictor category, only increasing age (n=2 studies), increasing BMI (n=2), and female sex (n=1) were found to be significantly associated with higher CPAP adherence across 22 studies. CPAP adherence is also influenced by race, with reduced adherence reported in Black, Hispanic, and Asian Pacific Islander users compared to white users.<sup>1107-1111</sup> Variables such as overall sleep duration, presence of comorbid insomnia, latency to sleep onset, socioeconomic status, and education levels contribute in part to reduced use of PAP.

*CPAP-related (CPAP).* One study found the presence of reporting problems on the first night of CPAP use was associated with reduced adherence.<sup>1112</sup>

*OSA-related (OSA).* The most common OSA-related predictors were baseline disease severity (*e.g.*, AHI and oxygen desaturation index (ODI)) and symptom severity (*e.g.*, daytime sleepiness as measured by the Epworth sleepiness scale (ESS)), with worse disease and symptoms at baseline being related to higher subsequent CPAP adherence. Three other notable findings from this category were: (1) change in ESS (*i.e.*, reduction in sleepiness) was predictive of higher CPAP use, which represented the only change score across the included studies; (2) higher baseline insomnia symptoms were associated with higher subsequent CPAP use; and (3) REM-related OSA was found in one study.

*Psychological (Psych).* A wide variety of predictors were found in this category, but each only once: ways of coping, health locus of control, health value, anxiety, and perceived partner autonomy.

*Behavioral (Beh)*. This class of predictors was primarily driven by self-efficacy (in 7/22 studies). The decisional-balance index, which is a relative weighting of the pros and cons of sleep apnea was identified in 2 studies. This class of predictors has the advantage of being modifiable (*i.e.*, amenable to change), and therefore can provide the basis for an intervention.

*Other*: The other category included a variety of predictors including presence of cardiovascular disease, smoking history, and change in sleeping location.

Attempting to identify predictors of PAP adherence is an important area of investigation. Much progress has been made in recent years, with multivariate models explaining ~40-50% of the variance in PAP adherence scores. Predictors of adherence have been identified. It seems clear that patients with more severe disease and sleepiness symptoms at baseline and those who experience a relief of those symptoms (*i.e.*, perceive a benefit) tend to use CPAP more. Behavioral predictors, including self-efficacy and readiness for change, represent factors that significantly increase PAP adherence and have the additional benefit of being modifiable and a basis for interventions. The primary goal of identifying PAP adherence predictors is to help design interventional protocols and to inform the sleep care team about important factors to help provide care. While predictors could potentially identify patients who would not benefit from PAP, none of the PAP adherence studies specifically addressed this issue.

Despite PAP being considered a complex treatment regimen, there are very few studies of predictors derived from a systems perspective, *e.g.*, factors related to the provision of health services (quality of care provided, type of care provided, organization that provides the care [DME vs Clinic]); cost (whether to patient or reimbursement levels to care team that likely affects amount and/or quality of care); or disparities (socioeconomic status or race/ethnicity).

#### Predictors of PAP Adherence

Aggregate Grade of Evidence: C (Level 2b: 12 studies; Level 4: 10 studies)

Table VIII.A.4b Predictor of PAP Adherence

Study	Year	LOE	n	Predictor Categories	Effect Size/Outcomes	Conclusion
McArdle <sup>1113</sup>	1999	4	1,211	Dem, OSA	Snoring history, AHI $\geq 15$ and ESS $> 10$ were independent predictors of CPAP adherence. Early adherence was the strongest predictor of subsequent adherence.	This was one of the first studies to systematically examine predictors of CPAP adherence, finding the <b>higher AHI and sleepiness levels</b> were associated with CPAP adherence.
Pelletier-Fleury <sup>1114</sup>	2001	2b	163	Dem, OSA, Other	Female sex, a BMI of $> 30$ kg/m <sup>2</sup> , an ESS score of $> 15$ , an AHI of $> 30/h$ , and a level of nCPAP of $< 12$ cmH <sub>2</sub> O were independent predictors of poor CPAP adherence.	This study largely replicated the findings of McArdle et al by finding that <b>higher AHI and sleepiness levels</b> were independently associated with CPAP adherence, as were <b>BMI, female sex and CPAP pressure</b> .



					Age was not associated.	
Sin <sup>1115</sup>	2002	2b	296	Dem, OSA, CPAP	Higher age, greater reduction in ESS score and female sex were all associated with higher CPAP adherence.	This was first study to show the <b>change in ESS</b> score was associated with CPAP adherence, such that the larger the decrease in sleepiness level, the higher the CPAP adherence.
Stepnowsk y <sup>1116</sup>	2002	2b	23	Dem, OSA, CPAP, Psych, Beh	Ways of coping independently accounted for 20% of the variance, beyond that by AHI and ESS (total model = 35%). Active (but not passive) coping was the primary driver (15% variance).	Two components of <b>active coping</b> (confrontive coping and planful problem solving) were identified through post hoc analyses as being the most important predictors of CPAP adherence.
Stepnowsk y <sup>1117</sup>	2002	2b	51	Dem, OSA, CPAP, Beh	Social Cognitive Theory (SCT) variables accounted for an adjusted 40% and Transtheoretical Model variables 33% of the variance in CPAP adherence.	<b>Self-efficacy</b> was the driving factor of the SCT variables and <b>decisional-balance index</b> was the driving factor for the TM variables.
Lewis <sup>1112</sup>	2004	2b	80	Dem, OSA, CPAP, Psych, Other	Stepwise regression identified 2 (out of 21) predictors: Recent Life Events and Initial Problems on the first night of CPAP. Though not included in the regression, change scores (for ESS, anxiety & depression) were all significant.	Having a <b>major recent life event</b> over the last 6 months and reporting <b>problems with CPAP on the first night</b> of use were both associated with lower CPAP adherence. The study also identified change scores as being potentially important predictors.
Lloberes <sup>1118</sup>	2004	2b	133	Dem, OSA, CPAP,	No predictors were identified for 3-mo CPAP use at 3 months, Higher AHI and impaired QoL before treatment were found to be independent predictors of 1-year CPAP adherence.	<b>Higher AHI and impaired QoL</b> at baseline were predictive of CPAP adherence.
Wild <sup>1119</sup>	2004	2b	119	Dem, OSA, CPAP, Psych, Beh	24% of the variance in CPAP adherence was explained by ESS, AHI, BMI, pressure, and psych	The 3 psychological variables explained 6% of the variance in CPAP adherence, which is relatively low compared to some measured

					variables (health value, internal locus of control and powerful others).	behavioral variables.
Aloia <sup>1105</sup>	2005	2b	98	Dem, OSA, CPAP, Beh	Dem, OSA, & CPAP predictors non-significant; Beh predictors measured at 1 wk and 3 mos accounted for 23% and 42% of variance, respectively.	<b>Self-efficacy, readiness to change, and decisional balance</b> were all significant predictors of 6-mo CPAP adherence.
Stepnowsk y <sup>1120</sup>	2006	4	58	Dem, OSA, CPAP, Beh	Social Cognitive Theory (SCT) variables accounted for 12% and Transtheoretical Model variables 16% of the variance in CPAP adherence. Note that CPAP pressure and side effects accounted for 31% of the variance.	<b>Self-efficacy</b> was the driving factor of the SCT variables and decisional-balance index was the driving factor for the TM variables. Of note, CPAP pressure and side effects were important predictors in this study of experienced CPAP users.
Kohler <sup>1121</sup>	2010	4	639	Dem, OSA, CPAP	Multivariate analysis (including gender, age, neck circumference, ESS, ODI and participation in a research study) indicated that ODI event rate was significantly associated with long-term compliance with CPAP (ODI: HR 0.97, SE 0.01, p<0.001, 95% CI 0.96 to 0.98).	Higher baseline <b>Oxygen Desaturation Index</b> values were associated with higher CPAP adherence.
Wallace <sup>1122</sup>	2013	4	248	Dem, OSA, CPAP, Beh, Other	The following predictors were found to be independently associated with CPAP adherence: fewer insomnia symptoms and higher self-efficacy. Being Black was associated with lower adherence.	Key feature of this study was the study of 3 races (Black, White and Hispanic). White and Hispanics had higher adherence rates. <b>Fewer insomnia symptoms and higher self-efficacy</b> were the only predictors identified.
Wallace <sup>1123</sup>	2013	2b	124	Dem, OSA, CPAP, Psych, Beh, Other	<i>7-day CPAP adherence:</i> Lower ISI scores were associated with higher 7-day adherence (6% variance). <i>30-day CPAP</i>	While ISI was an important predictor for 7-day adherence, it was not significant for 30-day adherence. <b>Lower ESS and higher self-efficacy and outcome</b>

					<i>adherence</i> : The model with baseline ISI, ESS<10, outcome expectations and self-efficacy accounted for 50% of the variance in CPAP adherence; a second model that added week 1 adherence then accounted for an additional 30% of the variance.	<b>expectations</b> were associated with higher 30-day adherence in this sample of Hispanic Veterans. Early adherence again was a predictor of subsequent adherence.
Schoch <sup>1124</sup>	2014	4	1,756	Dem, OSA	Cox regression found that only ESS, ODI and AHI were significantly associated with long-term adherence (while age, gender, BMI and ESS were not significantly associated).	Higher baseline <b>sleepiness, oxygen desaturation</b> and <b>AHI</b> scores were associated with higher 3-year CPAP adherence rates.
Budhirja <sup>1125</sup>	2016	2b	1,105	Dem, OSA	<i>2-month CPAP adherence</i> : age, presence of CVD and decrease in ESS score. <i>6-month CPAP adherence</i> : age, AHI, lower anxiety, decrease in ESS score.	Consistent predictors across both time points include <b>age</b> and <b>decrease in ESS score</b> ; other potentially important predictors include <b>AHI, presence of CVD, and lower anxiety</b> . One additional interesting predictor found in this RCT was belief that one is in the active treatment group.
Dzierzewski <sup>1126</sup>	2016	4	191	Dem, OSA, CPAP, Psych, Beh	<b>Age, self-efficacy and self-efficacy by pressure interaction</b> accounted for 29% variance in CPAP adherence.	First study to find that <b>self-efficacy</b> has a moderating effect on adherence such that higher self-efficacy scores related to adherence only for those with higher pressure levels.
Jacobsen <sup>1127</sup>	2017	4	695	Dem, OSA	Using Cox regression, <b>higher AHI</b> and <b>ESS</b> scores and lower <b>smoking</b> levels were related to higher adherence.	This was one of the larger studies of CPAP users with a median duration of use of 3 years.
Hoshino <sup>1128</sup>	2018	4	161	Dem, OSA	REM-related OSA was the strongest independent predictor to distinguish good adherence (OR=64; p<0.001) and poor	Based on this study, further research is warranted on the predictive value of the of <b>REM-related OSA</b> on CPAP adherence.

					adherence (OR=3.2; p=0.014) from those who stopped using CPAP over a 6-month time period. 0/43 patients in the good adherence group had REM-related OSA.	
Liou <sup>1129</sup>	2018	4	119	Dem, OSA, CPAP	After adjusting for demographics, comorbidities and sleep apnea severity, changing sleeping location = 1x/mo was associated with 77% lower odds of reaching CMS adherence compared to rarely changed sleeping location.	This was the first known study to rigorously evaluate “ <b>changing sleeping location = 1x/mo</b> ” as a predictor of CPAP adherence and emphasizes some of the logistical challenges patients face in using a complex medical device on a nightly basis.
Philip <sup>1130</sup>	2018	4	404	Dem, OSA, CPAP, Beh	The model containing 6 variables (age, BMI, AHI, number of years with CPAP, ISI total score, and self-efficacy) explained 19% of the variance in CPAP adherence.	Individual independent predictors in this study included <b>age, BMI, ISI total score, and self-efficacy.</b>
Wallace <sup>1123</sup>	2018	2b	53	Dem, OSA, CPAP, Psych, Beh	In adjusted analyses, pre-treatment insomnia symptoms (early, late, and aggregated nocturnal symptoms) and sleep dissatisfaction were predictive of lower CPAP use at 6 months.	<b>Insomnia symptoms</b> , measured at multiple time points, were negatively associated with CPAP adherence.
Baron <sup>1131</sup>	2020	2b	92	Dem, OSA, Psych, Beh, Other	Perceived partner autonomy was significantly associated with CPAP adherence, beyond the covariates (age, gender, ODI, sleep-related impairment, OSA risk perception, self-efficacy), which were all significant.	<b>Perceived partner autonomy</b> (defined as a sense of choice or volition regarding behavior) was found to be significantly related to 2-mo CPAP adherence.

Predictor Categories: Dem = Demographic; OSA = OSA-related; CPAP = CPAP-related; Psych = psychological; Beh = Behavioral. LOE = levels of evidence; n = sample size.

\*Studies were selected for inclusion based on these three criteria: (1) primary objective was to study the predictors of CPAP adherence, (2) examination of groups of predictors from 2 or more categories; and (3) utilization of multivariate analysis.

### VIII.A.5 Optimization of PAP Therapy

#### VIII.A.5.a Educational Interventions for PAP Adherence

Educational interventions focus on improving the understanding of OSA, its consequences, and benefits of treatment. The underlying premise is that imparting knowledge can affect personal beliefs and preconceptions that may ultimately lead to changes in behavior.

The type and method of educational therapies varied among different studies, which included printed documents, video clips, web-based education, telephone calls, face-to-face individual counseling sessions, personalized feedback, and review of individual PSGs. These interventions were largely passive and did not require patients' active participation. While some studies included additional study arms, every study included a separate educational arm. The study by Richards et al. was included in this section despite having an intervention arm called "Cognitive Behavioral Therapy (CBT)" group. This was due to the fact that despite the name of the study arm, the intervention only entailed reading or observing prepared materials and did not involve active engagement from the participants.<sup>1132</sup>

The effects of educational interventions on CPAP adherence are mixed, with 3 studies showing no significant effect on adherence and the other 4 showing increased compliance with therapy to various degrees. The 2014 Cochrane review showed moderate-quality evidence that short-term educational interventions lead to a small increase in average PAP use of about 35 minutes per night.<sup>1133</sup> Additionally, the systematic review by Patil et al showed moderate quality evidence that PAP adherence increased by 0.6 hours/night with an educational intervention and is the basis for the AASM guidelines that strongly recommends the use of education with PAP therapy.<sup>39</sup>

#### Educational Interventions to Improve PAP Adherence

**Aggregate Quality of Evidence:** A (Level 1a: 2, Level 1b: 7).

**Benefit:** Increased CPAP adherence in analysis of systematic reviews.

**Harm:** Minimal, time required for education.

**Cost:** Low to moderate; variable costs of different educational interventions.

**Benefits-Harm Assessment:** Preponderance of benefit over harm.

**Value Judgments:** Educational therapies are overall low-cost, time-limited interventions that can be used to potentially increase adherence in certain CPAP users, however variation in educational therapies across trials limits specific recommendations for optimal type of education.

**Recommendation Level:** Recommendation

**Intervention:** Recommend patient education to increase PAP adherence.

Table VIII.A.5.a Educational Interventions and PAP Adherence

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion

Patil et al. <sup>39</sup>	2019	1a	Systematic review  7 RCTs	RCTs examining the impact of a pure educational intervention as an adjunct to PAP therapy to improve adherence with PAP.	PAP usage	Moderate quality evidence that showed significant improvement in PAP adherence by 0.6 hours/night in adults with OSA with an educational intervention compared to usual care.  Based on this systematic review, AASM guidelines strongly recommends that educational interventions be given with initiation of PAP therapy in adults with OSA.
Wozniak <sup>113</sup> <sub>3</sub>	2014	1a	Systematic review  30 RCTs	RCTs examining the effectiveness of educational, supportive, or behavioral strategies in encouraging CPAP usage	CPAP usage	Low- to moderate-quality evidence that all 3 types of interventions led to increasing machine use. Supportive interventions increased machine usage by 50 minutes per night, educational interventions increased machine usage by 35 minutes per night, behavior therapy increased machine usage by 1.44 hours per night
Chervin <sup>1134</sup>	1997	1b	RCT  N=33  Duration: 8 weeks	1. Intervention 1: telephone call each week during trial; N=12 2. Intervention 2: two printed documents; N=14 3. Control: no additional support; N=7	Machine usage at 1 to 2 months; dropouts/lost-to-follow-up	No significant differences in CPAP adherence between intervention groups and control
Falcone <sup>1135</sup>	2014	1b	RCT	1. Standard support: sleep medicine physician gave a full	CPAP usage at 1, 3, 12 months;	The educational support group had higher retention rates at 1, 3,

			N=206  Duration: 12 months	<p>explanation of the need for and benefits of CPAP</p> <p>2. Educational support: standard support and viewing of the rapid-eye-movement phase of diagnostic and CPAP-titration PSG, with explanations and attention to flow and oxyhemoglobin saturation curve</p>	sleepiness; retention rate	and 12 months. CPAP use at 1, 3, and 12 months was higher in the educational support group but did not reach significance.
Hwang <sup>1136</sup>	2017	1b	<p>Four-arm, randomized, factorial-design clinical trial</p> <p>N=1455</p> <p>Duration: 90 days</p>	<p>1:1:1:1 to one of 4 arms:</p> <p>1. Web-based OSA education (Tel-ed); N=380</p> <p>2. Telemonitoring and automated feedback (Tel-TM); N=375</p> <p>3. Tel-ed + tel-TM (Tel-both); N=346</p> <p>4. Usual care; N=354</p>	CPAP usage at 90 days	Tel-TM and Tel-both groups showed significant increase in average usage at 90 days. Tel-ed had no significant effect on CPAP usage at 90 days.
Pengo <sup>1137</sup>	2018	1b	<p>RCT</p> <p>N=112</p> <p>Duration: 6 weeks</p>	<p>1. Negative: negatively framed messages in addition to CPAP read out to patients during CPAP collection appointment and during weekly phone calls; N=36</p> <p>2. Positive: positively framed messages in addition to CPAP read out to patients during CPAP collection</p>	APAP usage, % days used >4 hours, sleepiness, withdrawals at 2 and 6 weeks	Patients in the positive group had higher APAP use compared to the negative and control groups at 2 weeks. There was no difference in compliance between groups at 6 weeks, 2 months, and 6 months. The positive group had a reduction in the dropout rate at 6 weeks.

				<p>appointment and during weekly phone calls; N=37</p> <p>3. Standard care: explanation of importance of treating OSA, APAP introduction and instruction for use, compliance assessment at 2 weeks; N=39</p>		
Richards <sup>113</sup> <sub>2</sub>	2007	1b	<p>RCT</p> <p>N=100</p> <p>Duration: 28 days</p>	<p>1. Treatment as usual: standardized group education session, explanation of CPAP titration and equipment, explanation of side effects; N=50</p> <p>2. Cognitive behavioral therapy (CBT): 2 one-hour CBT interventions that included a standardized educational slide presentation, 15-min video of real-life CPAP users, an additional booklet on sleep, OSA/CPAP, and general health</p>	Machine usage, withdrawal	The CBT group had increased mean nightly usage at 28 days.
Roeklein <sup>11</sup> <sub>38</sub>	2010	1b	<p>RCT</p> <p>N=30</p> <p>Duration: 3 months</p>	<p>1. Standard education: written information from American Academy of Sleep Medicine on OSA, snoring and PAP therapy for OSA; N=16</p> <p>2. Personalized feedback: written</p>	Objective CPAP usage, self-reported CPAP usage	There was no significant difference in CPAP usage.



				personalized feedback report with severity of disease, self-reported daytime sleepiness, individually estimated risk of adverse health outcome and risk of MVA; feedback addressed barriers using CPAP, ambivalence about treatment and difficulties of behavior changed and promoted self-efficacy and personal responsibility; N=14		
Sarac <sup>1039</sup>	2017	1b	RCT  N=115  Duration: 6 months	1. Standard support: general explanation of OSA and CPAP; N=63  2. Educational support: additional 20 min education by sleep MD including viewing own PSG, comparing PSG from diagnostic and CPAP titration studies that emphasized obstructive events and O2 desaturations; N=52	CPAP usage, N of adherent participants, sleepiness, withdrawal	Average PAP usage was increased in the educational support group compared to the standard support group at long-term follow up.

#### VIII.A.5.b Supportive Interventions for PAP Adherence

Supportive interventions include telemonitoring under various formats, including telephone calls, texting, personalized support platforms, and peer buddy systems. These interventions engage patients, increase support, and reinforce strategies to increase CPAP adherence.

One RCT by Fox et al. had a telemedicine intervention arm which provided a modem enabled PAP device, which sent information regarding adherence, interface leak, and residual AHI directly to a web-based database. A coordinator reviewed the transmitted information and contacted the patient if there was a significant reduction in PAP usage or increase in pressure or residual AHI. At 3 months, PAP

adherence was significantly greater in the modem PAP group compared to the standard group. The telemedicine group utilized an additional 65 minutes of technician time.<sup>1139</sup> A different type of supportive intervention was used by Hoy et al. in which the intensive support arm received standard support in addition to education at home with the partner, two additional nights in the hospital, and home visits by sleep nurses. This group had higher CPAP usage than those in the usual care group at 6 months.<sup>1140</sup> Parthasarathy et al. used a peer buddy system, in which trained peers with OSA and good CPAP adherence were paired with newly diagnosed participants and engaged in face-to-face sessions as well as telephone conversations. CPAP adherence was greater in the peer buddy system group after 3 months.<sup>1141</sup>

Out of the 13 RCTs, 7 showed that supportive interventions had a positive impact on CPAP adherence, while 6 showed no difference between the groups. The 2014 Cochrane review showed low-quality evidence that supportive interventions increased CPAP usage by 50 minutes per night compared to control.<sup>1133</sup>

#### Supportive Interventions to Improve PAP Adherence

**Aggregate Quality of Evidence:** A (Level 1a: 1, Level 1b: 13).

**Benefit:** Increased CPAP adherence.

**Harm:** Minimal.

**Cost:** Moderate to potentially high depending on type of supportive intervention and resources required.

**Benefits-Harm Assessment:** Benefit outweighs the harm.

**Value Judgments:** Supportive interventions provide additional encouragement and reinforcement through various strategies that may increase CPAP usage by a modest amount. Supportive mechanisms are variable between studies and consideration of costs and resources required for support platforms should be assessed.

**Recommendation Level:** Recommendation

**Intervention:** Supportive interventions may be used to increase CPAP adherence if resources are available.

**Table VIII.A.5.b Supportive Interventions for PAP Adherence**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Wozniak <sup>1133</sup>	2014	1a	Systematic review  30 RCTs	RCTs examining the effectiveness of educational, supportive, or behavioral strategies in encouraging CPAP usage	CPAP usage	Low- to moderate-quality evidence that all 3 types of interventions led to increasing machine use. Supportive interventions increased machine usage by 50 minutes per night. Educational interventions increased machine usage by 35 minutes per night. Behavior therapy

						increased machine usage by 1.44 hours per night.
Chervin <sup>1134</sup>	1997	1b	RCT  N=33  Duration: 8 weeks	1. Intervention 1: telephone call each week during trial; N=12  2. Intervention 2: two printed documents; N=14  3. Control: no additional support; N=7	Machine usage at 1 to 2 months; dropouts/lost-to-follow-up	There were no significant differences in CPAP adherence between intervention groups and control.
DeMolles <sup>1142</sup>	2004	1b	RCT  N=30  Duration: 8 weeks	1. Usual Care (UC): usual medical care, patient education, and demonstration of equipment use; N=15  2. Telephone-linked communication technology (TLC): UC + computerized digitized human speech program. TLC asks questions designed to elicit information from participant regarding adherence, education, and reinforcement; N=15	CPAP usage at 2 months; sleep-related symptoms	There was no difference in average nightly CPAP use between the groups, but the TLC group had fewer sleep-related symptoms.
Fox <sup>1139</sup>	2012	1b	RCT  N=75  Duration: 12 weeks	1. Telemedicine intervention: physiologic information (adherence, air leak, residual AHI) was transmitted daily to a website that could be reviewed. If problems were identified, the patient was advised over the phone or visited the PAP	Machine usage, adherence after 3 months, subjective sleep quality, any side effects	PAP adherence was significantly greater in the telemedicine group compared with the standard group. An additional 65 min of technician time was spent on patients in the telemedicine group.

				<p>coordinator; N=39</p> <p>2. Standard care</p>		
Hoet <sup>1143</sup>	2017	1b	<p>RCT</p> <p>N=46</p>	<p>1. Usual care: group education session 1 month after CPAP initiation, and medical visit at 1.5 and 3 months; N=23</p> <p>2. Telemonitoring: telemonitoring device attached to CPAP, through which participant data was analyzed and patients were contacted in the case of air leak, residual AHI&gt;10/hour, or CPAP use less than 3 hours in 3 consecutive days); N=23</p>	<p>CPAP usage at 3 months; time to delay to first technical intervention after CPAP initiation</p>	<p>Compliance at 3 months was significantly better in the telemonitoring group. Telemedicine reduces delay to first technical intervention in CPAP-treated patients.</p>
Hoy <sup>1140</sup>	1999	1b	<p>RCT</p> <p>N=80</p> <p>Duration: 6 months</p>	<p>1. Standard support: video education, titration of CPAP pressure overnight, nurses telephoned on days 2, 21, reviewed in hospital at 1, 3, 6 months; N=40</p> <p>2. Intensive support: standard support + initial education at home with partner, 2 extra nights in hospital, sleep nurses' home visits to participant and partner at 7, 14, 28 days, and 4 months after starting CPAP;</p>	<p>Machine usage at 6 months</p>	<p>Intensive support group had higher CPAP usage than those in the usual care group.</p>

				N=40		
Hwang <sup>1136</sup>	2017	1b	Four-arm, randomized, factorial-design clinical trial  N=1455  Duration: 90 days	1:1:1:1 to one of 4 arms:  1. Web-based OSA education (Tel-Ed); N=380  2. Telemonitoring and automated feedback (Tel-TM); N=375  3. Tel-ed + tel-TM (Tel-both); N=346  4. Usual care; N=354	CPAP usage at 90 days	Tel-TM and Tel-both groups showed significant increase in average usage at 90 days. Tel-ed had no significant effect on CPAP usage at 90 days.
Mendelson <sup>1144</sup>	2014	1b	RCT  N=107	1. Standard care: baseline evaluation, patients were contacted at day 2 to ask about adherence and to troubleshoot, met with sleep specialist at 4 weeks and at 4 months; N=53  2. Telemedicine: standard care + smart phone for uploading BP measurements, CPAP adherence, sleepiness, and QoL data; participants received daily pictograms containing health-related messages; N=54	Home self-measured BP, CPAP usage, cardiovascular risk evolution, sleepiness, QoL, fatigue, dyspnea, withdrawals	CPAP adherence did not differ between the groups.  Self-measured BP did not improve in either group.
Munafo <sup>1145</sup>	2016	1b	RCT	1. Standard of care  2. SOC + telehealth messaging program:	CPAP usage, sleepiness, residual AHI,	Adherence rates were similar in both groups. There was a significant reduction in the mean aggregate time required

			N=122  Duration: 3 months	patients and providers were messaged based on CPAP device data	resource use	to coach a patient in the telehealth group versus standard of care group.
Parthasarathy <sup>1141</sup>	2013	1b	RCT  N=39  Duration: 90 days	1. Usual care: educational brochures regarding OSA and CPAP therapy; N=17  2. Peer buddy system: trained peers with OSA and good CPAP adherence record were paired with newly diagnosed participants and participated in 2 face to face sessions and 8 telephone conversations; N=22	Participant ratings of acceptability of peer-buddy system; CPAP adherence	Weekly CPAP adherence was greater in the intervention group.
Pepin <sup>1146</sup>	2019	1b	RCT  N=306  Duration: 6 months	1. Usual care; N=149  2. Multimodal telemonitoring: CPAP related factors, BP, physical activity recorded by connected devices. Symptoms and QoL recorded via electronic questionnaires. Patients received demonstration home telemonitoring use and explanation of why monitoring these physiological variables was relevant; N=157	SBP, CPAP usage at 6 months, sleepiness, QoL, physical activity	Self-measured BP did not differ significantly between groups. There was a significant increase in CPAP adherence and an improvement in daytime sleepiness and QoL in favor of the multimodal telemonitoring.
Stepnowsk	2007	1b	RCT	1. Usual care: telephone call from	CPAP usage, % nights	There were no statistically significant differences in CPAP

y <sup>1147</sup>			N=45  Duration: 2 months	staff at 1 week, office visit at 1 month; N=21  2. Telemonitoring: Compliance and efficacy data garnered as objective compliance data and subjective reports of usage. Follow up tailored to how CPAP used by participants; N=24	with CPAP use >4 hours	compliance.
Stepnowsk y <sup>1148</sup>	2013	1b	RCT  N=241  Duration: 4 months	1. Telemonitoring: allow both the patient and provider access to telemonitored adherence and efficacy data on a daily basis and act on the data collaboratively to guide CPAP management and troubleshoot problems, emphasize ways for patient to express their preferences and needs; N=126  2. Usual care: CPAP instruction and setup by a healthcare provider, follow up at 1 week and 1 month; N=115	CPAP usage at 2 and 4 months	There was higher CPAP adherence at 2- and 4-months in the telemonitoring group compared to control.
Turino <sup>1149</sup>	2017	1b	RCT  N=100	1. Standard management: a short instruction session on CPAP device use and 1-month visit; N=48  2. Telemonitoring program: daily information on CPAP	Machine usage at 1, 3 months; cost-effectiveness	No significant difference in CPAP compliance between the groups. Telemedicine was less expensive than standard management and was cost-effective.

				adherence, pressures, mask leak, and respiratory events were sent to the database; automatic alarms for the provider were generated if mask leak >30L/min for >30% of the night or usage <4 hours/night on 2 consecutive nights. Provider contacted the patient, providing case by case problem solving; N=52		
--	--	--	--	---	--	--

#### VIII.A.5.c Behavioral Interventions and PAP Adherence

Behavioral interventions focus on modifying behavioral constructs to improve adherence to CPAP. These interventions require participant engagement and aim to enhance behavioral action, motivation for change, self-efficacy, and outcome expectations.

All 6 RCTs show increased compliance with behavioral interventions, which include motivational enhancement therapy, cognitive behavioral therapy, and progressive muscle relaxation training. The 2014 Cochrane review showed low-quality evidence that behavioral interventions increased CPAP usage by 1.44 hours per night compared to control.<sup>1133</sup>

Most of these interventions are not time intensive. Aloia et al. study included 2 45-minute cognitive behavioral sessions with a therapist that increased compliance at 12 weeks.<sup>1150</sup> A study by Bakker et al. utilized motivational enhancement via 2 1-hour in-person sessions, in addition to phone calls and an educational video. This intervention resulted in a significantly improved average nightly adherence (99 min/night) within the treatment group at 12 months.<sup>1151</sup> An additional study by Lai et al. utilized motivational enhancement via a 20-minute patient-centered interview, a 25-minute video, and 10-minute telephone follow up. Within this study the intervention group had higher CPAP use, a 4-fold increase in the number using CPAP for  $\geq 70\%$  of days with  $\geq 4$  h per night, and greater improvements in daytime sleepiness as well as treatment self-efficacy at 3 months.<sup>1152</sup>

In summary, behavioral therapies are effective, time-limited interventions that can positively influence CPAP adherence. More studies are needed to determine whether these interventions have long-term effects and which group of patients will benefit most.

#### Behavioral Interventions to Improve PAP Adherence

Aggregate Quality of Evidence: A (Level 1a: 2, Level 1b: 6).



**Benefit:** Behavioral interventions lead to increased CPAP adherence.

**Harm:** Minimal, time required for intervention.

**Cost:** Moderate to high; variable costs of different behavioral interventions including time, resources, and healthcare personnel. Interventions may require development of infrastructure.

**Benefits-Harm Assessment:** Balance of benefit and harm

**Value Judgments:** Behavioral interventions utilize different psychotherapeutic techniques derived from various models of health behavior change which have a positive impact on CPAP adherence. Populations that benefit most from behavioral interventions is not well understood and interventions may be burdensome for patients and resource intensive.

**Recommendation Level:** Option.

**Intervention:** Consideration should be given to using behavioral therapies to increase adherence in CPAP users, however, it is unclear which group of OSA patients will most benefit from behavioral therapies.

**Table VIII.A.5.c Behavioral Interventions and PAP Adherence**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Patil et al. <sup>39</sup>	2019	1a	Systematic review  6 RCTs	RCTs examining the efficacy of a behavioral intervention as an adjunct to PAP therapy to improve adherence with PAP.	PAP usage	There was moderate to high quality level evidence that significant improvement in PAP adherence by 1.2 hours/night in adults with OSA with an educational intervention compared to usual care.  Based on this systematic review, AASM guidelines conditionally recommends that behavioral interventions be given during the initial period of PAP therapy in adults with OSA.
Wozniak <sup>133</sup>	2014	1a	Systematic review  30 RCTs	RCTs examining the effectiveness of educational, supportive, or behavioral strategies in encouraging CPAP usage	CPAP usage	There was low- to moderate-quality evidence that all 3 types of interventions led to increasing machine use. Supportive interventions increased machine usage by 50 minutes per night. Educational interventions increased machine usage by 35 minutes per night.

						Behavior therapy increased machine usage by 1.44 hours per night.
Aloia <sup>1150</sup>	2001	1b	RCT  N=12  Duration: 12 weeks	1. Cognitive behavior intervention (two 45-min sessions with a therapist designed to educate subjects on the consequences of OSA and efficacy of CPAP); N=6  2. Control (same therapist contact, but no information on OSA or CPAP); N=6	Machine usage at 1 week, 4 weeks, 12 weeks; N of adherent participants (>= 6 hours per night); vigilance testing	The intervention increased compliance at 12 weeks. A modest cognitive-behavioral intervention may substantially increase CPAP use and vigilance in older adults.
Bakker <sup>1151</sup>	2016	1b	RCT  N=83  Duration: 12 months	1. Active CPAP; N=42  2. Active CPAP + ME (motivational enhancement; 1-hour in-person sessions at baseline and week 1, educational video, phone calls with psychologist); N=41	CPAP usage at 6, 12 months	Average nightly adherence for 6 months was significantly higher (99 min/night) with CPAP+ME compared with CPAP alone.
Dantas <sup>1153</sup>	2015	1b	RCT  N=41  Duration: 2 months	1. Intervention group (motivation strategies applied according to patient's motivation, assessed by the degree of confidence and conviction); N=20  2. Control 1 (only standard information about APAP)  3. Control 2 (routine procedures)	APAP usage at 1 and 2 months; % of days of APAP use (>4 hours/night on 60% of the nights); sleepiness; AHI	There was higher adherence to APAP and lower AHI at 2 months in the intervention group compared to control groups.
Lai <sup>1152</sup>	2014	1b	RCT	1. Control group (usual advice on importance of CPAP therapy and its	CPAP usage at 1 and 3 months; N of	The intervention group had better CPAP use, a 4-fold increase in the number using

			N=100  Duration: 3 months	care); N=51  2. Usual care + brief motivation enhancements program directed at enhancing the subjects' knowledge, motivation, and self-efficacy to use CPAP through a 25-min video, a 20-min patient-centered interview, and a 10-min telephone follow-up; N=49	adherent participants; intention to use; sleepiness; self-efficacy; QoL	CPAP for >=70% of days with >=4 h/d, greater improvements in daytime sleepiness, and treatment self-efficacy compared with the control group.
Olsen <sup>1154</sup>	2012	1b	RCT  N=106  Duration: 52 weeks	1. Motivational interviewing intervention (3 sessions of CPAP-specific nurse led motivational interview therapy one month apart); N=53  2. Control (standard 1 on 1 45-min education session, follow up at 2 to 4 weeks by MD and 2 months by RN); N=53	CPAP acceptance and adherence, FOSQ, self-efficacy measure for sleep apnea, ESS	The intervention group had improved CPAP acceptance and overall adherence rates compared to standard care alone.
Wang <sup>1155</sup>	2012	1b	RCT  N=152  Duration: 12 weeks	1. PMR (progressive muscle relaxation training): one night of CPAP titration in the hospital, 12 x 40 min group PMR practice sessions over 12 weeks, 1 per week. Self-practice of PMR before each CPAP treatment; N=38  2. EDU (education): 3 nights of CPAP titration in, 4 hour group education session on OSA and CPAP, brochure on benefits of	CPAP usage at 4, 8, 12 weeks; N of adherent participants (>=4 hours/night, 9/14 nights); sleepiness, sleep quality, anxiety, depression	EDU+PMR showed significant improvement in CPAP adherence, sleepiness, and sleep quality compared to control at 4, 8, and 12 weeks of intervention. EDU only showed significant improvement in CPAP adherence, sleepiness, and sleep quality at 4 weeks of intervention. The PMR group showed no significant improvement over time.

				<p>CPAP and 20 min video on how to optimize CPAP treatment, 24 hour consultation telephone line to sleep nurse; N=38</p> <p>3. EDU+PMR: 3 nights of CPAP titration in the hospital; N=38</p> <p>4. Control: one night of CPAP titration in the hospital; N=38</p>		
--	--	--	--	---	--	--

#### VIII.A.5.d Aerophagia Management and PAP Adherence

Aerophagia—excessive and repetitive air swallowing that can result in abdominal pain and bloating—is a reported side effect of positive airway pressure (PAP). Aerophagia is reported in 16% of CPAP users<sup>1100</sup> and is associated with gastroesophageal reflux disease.<sup>1156</sup> The interventions that help reduce aerophagia are largely anecdotal and are targeted towards reducing therapeutic pressure. While many studies report decreased average pressures with use of APAP versus CPAP in addition to increased compliance, there has only been one trial that prospectively studied whether APAP reduces aerophagia symptoms. In this double-blinded, randomized crossover study by Shirlaw et al., APAP reduced symptoms of aerophagia.<sup>1157</sup>

#### Management of Aerophagia for PAP Adherence

Aggregate Grade of Evidence: B (Level 1b: 1)

**Table VIII.A.5.d: Evidence for Aerophagia Management and PAP Adherence**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Shirlaw et al. <sup>1157</sup>	2017	1b	Double-blinded randomized crossover trial  (n = 56)	Two weeks on each therapy mode in random order  1. APAP 6-20cm H2O  2. CPAP	Usage hours and visual analog scale to measure symptoms of aerophagia	APAP reduces the symptoms of aerophagia while not affecting compliance compared with CPAP.

#### VIII.A.5.e Claustrophobia Management and PAP Adherence

Claustrophobia can negatively affect adherence in PAP users. One review shows that almost half the participants stated that they would not use CPAP if it made them feel claustrophobic, caused nasal

symptoms, or disturbed their bed partner<sup>1158</sup>. In a secondary analysis of a prospective, longitudinal study of 97 OSA patients, 63% had claustrophobic tendencies which were associated with non-adherence<sup>1159</sup>. To date, only a few studies have looked at behavioral interventions that target claustrophobia to increase compliance. Two case reports have shown success with in vivo desensitization or exposure therapy to treat claustrophobia to improve CPAP usage<sup>1160,1161</sup>. One retrospective case series of 13 patients showed that after exposure therapy, patients used CPAP for significantly longer compared to pre-treatment<sup>1162</sup>. Larger-scale, randomized control studies are required to validate the effects of behavioral therapy to treat claustrophobic reactions to optimize CPAP adherence.

### Claustrophobia Management to Improve PAP Adherence

Aggregate Quality of Evidence: D (Level 4: 3 studies)

Benefit: Unclear. Reducing claustrophobic tendencies may lead to a potential increase in CPAP use.

Harm: Time and resources needed to attend therapy sessions.

Cost: Cost of therapy sessions may have out of pocket fees.

Benefits-Harm Assessment: Balance of benefit and harm.

Value Judgments: Exposure or desensitization therapy could be used to reduce claustrophobic symptoms associated with PAP, but further studies are needed.

Recommendation Level: No Recommendation.

Intervention: No specific recommendation can be made about the use of exposure or desensitization therapy to treat claustrophobic tendencies to optimize PAP use.

**Table VIII.A.5.e: Evidence for Claustrophobia Management and PAP Adherence**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Means & Edinger <sup>1162</sup>	2007	4	Case series	One or more sessions of exposure therapy with a behavioral sleep psychologist	CPAP adherence data	Patients used CPAP significantly longer after exposure therapy compared to pre-treatment.
Edinger <sup>1160</sup>	1993	4	Case report	Male apnea patient, who initially failed CPAP due to claustrophobia, underwent in vivo desensitization	CPAP tolerance	The patient had increased tolerance to CPAP and continued to use CPAP after desensitization.
McCrae <sup>1161</sup> 1	2006	4	Case report	Patient with trauma-related claustrophobic response to CPAP underwent graduated in vivo	CPAP compliance	The patient reported increased CPAP compliance without anxiety and decreased symptoms of OSA.

				exposure over a 3 month period		
--	--	--	--	--------------------------------	--	--

### VIII.A.5.f Humidification and PAP Adherence

Upper airway symptoms-nasal congestion, dry nose and mouth, and sore throat-are common undesirable effects of positive airway pressure (PAP) and are associated with decreased adherence to therapy. Koutsourelakis et al.<sup>1163</sup> showed that CPAP with heated humidification reduced pre-existing nasal airway inflammation and decreased the level of pro-inflammatory cytokines. By reducing nasal symptomatology, heated humidification is an intervention aimed to improve comfort and compliance.

Humidification systems are built into current PAP devices and are widely available for use. However, the clinical significance of reduced nasal inflammation on PAP adherence, subjective daytime sleepiness, and PAP-related side effects remain unclear.

There have been several systematic reviews evaluating the effect of heated humidification on compliance. The first, published in 2018, reviewed 9 RCTs, and found no improvement in compliance or ESS scores with heated humidification.<sup>1164</sup> Even in the subgroup analysis of subjects with nasal symptoms prior to PAP therapy, a group expected to benefit most from humidification, there was no statistical difference in PAP usage time. Another systematic review by Patil et al. in 2019 reviewed 9 RCTs, also showed no clinically significant difference in adherence with or without humidification. However, it did show a significant reduction in incidence of side effects based on 3 RCTs, 2 of which were included in the 2018 review.<sup>39</sup> In a recent Cochrane review, humidification was found to increase average night use by 0.37 hours per person per night based on 6 RCTs, but it was low-certainty evidence.<sup>1165</sup>

#### Humidification to Improve PAP Adherence

**Aggregate Quality of Evidence:** B (Level 1a: 3, Level 2b: 2, Level 3b: 1)

**Benefit:** Potential benefit in reduction of PAP-related side effects. 3 systematic reviews showed no clinical improvement in adherence or symptom scores, while 1 cohort study showed greater adherence with humidification.

**Harm:** Possibility for excess condensation of water into the PAP circuit or into the user's face, nose, or mouth. Inconvenience of purchasing additional supplies and cleaning the humidification system.

**Cost:** Low cost of humidification system and supplies.

**Benefits-Harm Assessment:** Balance of benefit and harm.

**Value Judgments:** Although the evidence was inconclusive, humidification could be appropriate for some patients to consider based on their preference and symptoms.

**Recommendation Level:** Option.

**Intervention:** Heated humidification may be considered in select OSA patients that report nasal congestion, dry nose or mouth, and sore throat.

**Table VIII.A.5.f Humidification and PAP Use**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Zhu et al. <sup>1164</sup>	2018	1a	Systematic review and meta-analysis	1. Heated humidification 2. No heated humidification	PAP compliance and subjective daytime sleepiness	There was no improvement in compliance or ESS scores.
Patil et al. <sup>39</sup>	2019	1a	Systematic review	1. Heated humidification 2. No heated humidification	Adherence, sleepiness, QOL, PAP-related side effects	There was no clinically significant differences in adherence, sleepiness, or QOL. The heated humidification group had significant reduction in PAP-related side effects.
Kennedy et al. Cochrane Review <sup>1165</sup>	2019	1a	Systematic review	1. Heated humidification + fixed CPAP 2. Fixed CPAP alone	1. Primary outcome: machine usage 2. Secondary outcomes: symptom scores (ESS), quality of life scores (SF-36), sleep disruption (AHI), adverse events, patient preference	There was low-certainty evidence that humidification increased average night usage and improved ESS. There was insufficient evidence on QOL, sleep disruption, and adverse events. There was no significant difference in patient preference.
Palm et al. <sup>1166</sup>	2018	2b	Cohort study	Patients with OSA on CPAP	Adherence	Use of humidifier is associated with greater adherence to CPAP.
Jacobsen et al. <sup>1127</sup>	2017	2b	Retrospective cohort study	Patients with OSA on CPAP	Adherence	The frequency of patients offered humidification was higher in persistent CPAP users.
Wiest et al. <sup>1167</sup>	2002	3b	Case control study	1. Heated humidification 2. No heated humidification	Patient comfort and acceptance	The use of heated humidification was not associated with improvement in comfort or treatment

						acceptance.
--	--	--	--	--	--	-------------

### VIII.A.5.g Nasal Obstruction and PAP Adherence

Patients initiating PAP therapy may have pre-existing nasal obstruction due to a variety of inflammatory or structural etiologies. These may limit PAP adherence because nasal PAP interfaces require nasal airway patency.

Multiple observational studies found that increased objective nasal resistance on anterior rhinomanometry was predictive of nasal PAP intolerance<sup>543,1168</sup>. Additional observational studies have found that smaller nasal cavities on acoustic rhinometry at the time of PAP initiation led to lower PAP adherence at 3 months<sup>1169</sup> and 2 years<sup>1170</sup>. Subjective baseline nasal obstruction alone did not affect PAP adherence at 2 years follow-up<sup>1170</sup>. Objective nasal function testing is not standard clinical practice and not routinely used to identify patients at the highest risk of non-adherence.

New subjective nasal symptoms can arise as a result of PAP use and can cause PAP non-adherence. As many as 65% of patients using PAP report nasal congestion, dry nose or throat, and discomfort likely due to mucosal swelling and the drying effects of positive pressure<sup>1171</sup>. In an international randomized-control trial, adults who developed PAP-related nasal side effects were associated with lower PAP adherence at 12 months post-initiation but not at 24 months<sup>1172</sup>. The long-term adherence in this study may have improved due to symptom management with intranasal corticosteroid and heated humidified air during the study. Advances in PAP technology to limit nasal congestion may contribute to more promising recent evidence. Värendh et al's recent prospective cohort study found decreased subjective and objective nasal obstruction after 2 years of PAP therapy<sup>1170</sup>.

No studies have directly examined how the presence of rhinitis affects CPAP adherence.

There is mixed evidence on CPAP use in patients with OSA and allergic rhinitis alters nasal symptomatology. One cohort study found that CPAP users with baseline allergic rhinitis have less improvement in nasal obstruction than those without allergic rhinitis<sup>1173</sup>. A smaller cohort study found increased cytological inflammation in both allergic rhinitis and non-allergic rhinitis patients, but worse nasal dryness in non-allergic rhinitis patients<sup>1174</sup>.

There is insufficient evidence on the effect of chronic sinusitis alone on CPAP adherence. One small experimental study applied 2 hours of CPAP on 20cmH<sub>2</sub>O to patients with chronic rhinosinusitis with polyps but without OSA and found a reduction in nasal polyp size but no change in subjective nasal obstructive symptoms or objective acoustic rhinometry<sup>1175</sup>.

#### Nasal Obstruction Reduces Limits PAP Adherence

Aggregate Grade of Evidence: C (Level 2b: 4 studies)

**Table VIII.A.5.g: Effects of Nasal Obstruction on PAP adherence**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion



Varendh et al <sup>1170</sup>	2019	2b	Prospective cohort	728 CPAP users evaluated with acoustic rhinometry	CPAP adherence, subjective and objective nasal obstruction	Small nasal volumes at baseline associated with lower adherence, subjective and objective nasal obstruction decreased after 2 years of PAP use.
Van Ryswyk et al <sup>1172</sup>	2019	2b	Cohort study (secondary analysis of SAVE RCT)	CPAP users in SAVE trial.	PAP adherence at 12 and 24 months.	Nasal symptoms found to be predictive at 12-months but NOT found to be predictive of adherence at 24-months.
Sugiura et al <sup>543</sup>	2006	2b	Prospective cohort	77 OSA patients evaluated with anterior rhinomanometry	Initial CPAP acceptance vs. non-acceptance	Higher objective nasal resistance was a predictor of initial CPAP non-acceptance via nasal interface.
Li et al. <sup>1169</sup>	2005	2b	Prospective cohort	60 OSA patients with small and large minimal nasal cross sectional area based on acoustic rhinometry.	CPAP use hrs/night after 3 months	Smaller nasal cavities associated with lower adherence but subjective nasal stuffiness did not correlate with objective nasal dimensions.

#### VIII.A.5.g.1 Management of Nasal Obstruction for PAP Adherence

Nasal obstruction management strategies that may affect PAP adherence include conservative, medical, and surgical options. When patients cannot tolerate a conventional nasal mask, they can trial nasal pillows or oronasal/full face masks as second-line interfaces, though adherence with nasal masks is known to be superior to oronasal masks<sup>1058</sup>. For nasal obstruction and dryness, the addition of sodium hyaluronate nasal spray or saline nasal spray is associated with significant improvement in PAP adherence in a randomized trial.<sup>1176</sup> The effect of heated humidification on nasal symptoms and PAP adherence has mixed evidence<sup>1165,1177</sup>.

Intranasal corticosteroid sprays are widely used and effective for patients with established allergic and non-allergic rhinitis, and are commonly prescribed for OSA patients with presumed nasal congestion to increase CPAP adherence. A systematic review and meta-analysis of two randomized control trials studying unselected OSA patients found only a small 24-minute increase in CPAP use in favor of nasal steroid use at 4 weeks<sup>1178</sup>. Notably, the efficacy of the treatment may be diluted as both studies included unselected OSA patients with no subgroup analyses for the presence of clinical rhinitis or severity of nasal obstruction. Although clinically logical, there is insufficient published evidence on the efficacy of intranasal corticosteroids for improving CPAP adherence specifically in patients with allergic rhinitis.

Nasal surgery has shown benefit for improving PAP adherence. A systematic review and meta-analysis performed by Camacho et al. demonstrated that isolated nasal surgery converted 89% (57 of 64 patients) of non-PAP users to PAP-tolerant users, and improved objective CPAP use hours from  $3.0 \pm 3.1$  hours per night to  $5.5 \pm 2.0$  hours per night in short-term follow-up for 33 patients in whom objective data was available.<sup>1179</sup> The studies included had high heterogeneity in patient population and selection. Clinicians should use this evidence in combination with best judgment for appropriate patient selection to ensure that nasal obstruction is the primary contributor to CPAP non-adherence, and whether the degree of obstruction on examination is significant enough to warrant surgical correction. The use of surgery for decreasing PAP pressures will be discussed in another section, though improvement in adherence as a result of lower pressures should be acknowledged. Kempfle et al. used financial modeling to determine cost-effective ways to improve CPAP adherence. Compared to medical management of nasal obstruction, inferior turbinate reduction was found to be more cost-effective in the short-term while septoplasty was more cost-effective in the long-term<sup>1180</sup>.

#### Treatment of Nasal Obstruction to Improve PAP Adherence

**Aggregate Quality of Evidence:** C (level 1a: 1 study, level 1b: 2 studies, level 2b: 4 studies, level 2c: 1 study, level 3a: 1 study).

**Benefit:** Objective and subjective nasal obstruction is associated with lower PAP adherence. Treating nasal obstruction either medically or surgically may improve PAP adherence.

**Harm:** Complications of individual management options (i.e. oronasal mask discomfort, nasal sprays side effects/inconvenience of use, turbino-plasty or septoplasty surgery risks and complications).

**Cost:** Ranges from low cost (humidification, nasal spray) to high cost (surgery).

**Benefits-Harm Assessment:** In patients with symptomatic nasal obstruction, there is a preponderance of benefit over harm for medical nasal therapy; balance of benefit and harm for surgical nasal therapy for improving PAP adherence.

**Value Judgments:** Treating nasal obstruction can promote PAP adherence and optimize OSA therapy outcomes

**Recommendation Level:**

Recommendation to treat nasal obstruction with topical medical therapies to improve PAP adherence.

Option to treat nasal obstruction with surgery to improve PAP adherence.

**Intervention:** Consider medical or surgical management of symptomatic nasal obstruction in OSA patients who cannot tolerate PAP therapy.

**Table VIII.A.5.g.1 Evidence for the Nasal Obstruction Treatment to Improve PAP Adherence**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Charakorn et al. <sup>1178</sup>	2017	1a	Systematic review and meta-analysis of 2 RCT (144 patients)	1) CPAP with nasal steroids 2) CPAP only	PAP adherence, subjective nasal symptoms.	Nasal steroids provided small but non-significant increase in average nightly PAP use (0.4 h); subjective nasal symptoms were not significantly affected.

Camacho et al <sup>1179</sup>	2015	3a	Systematic review and meta-analysis; 11 studies looked at adherence (153 patients)	CPAP users who underwent isolated nasal surgery	Pressure reduction, self-reported adherence, objective adherence.	Isolated nasal surgery reduced CPAP pressures and may increase CPAP use (self-reported and objective measures).
La Mantla et al <sup>1176</sup>	2017	1b	RCT (102 patients)	1) Sodium hyaluronate + CPAP 2) Saline + CPAP 3) CPAP only	Mini-Rhinoconj QOL score, CPAP adherence, sleepiness, nasal resistance.	Sodium hyaluronate and saline groups showed improved CPAP adherence at 4 weeks.
Ryan et al <sup>1177</sup>	2009	1b	RCT (125 patients)	1) Dry CPAP 2) Humidified CPAP 3) CPAP with INCS	Objective adherence, self-reported surveys	Humidifier decreased nasal symptoms; no difference in adherence or QOL between groups at 4 weeks.
Kempfle et al <sup>1180</sup>	2016	2c	Economic analysis	1) IT reduction 2) Septoplasty 3) Medical treatment	Total cost of untreated OSA, surgery, complications, post-op compliance, QOL.	Surgical options are cost-effective over multiple model assumptions.

#### VIII.A.5.h Treatment Emergent Central Sleep Apnea (TECSA)

Treatment emergent central sleep apnea (TECSA), previously known as complex sleep apnea before its definition in the International Classification of Sleep Disorders, 3<sup>rd</sup> edition (ICSD-3), is the emergence or persistence of central apneas with the treatment of OSA in the absence of another cause of central sleep apnea (CSA).

The prevalence of TECSA ranges from 3.5-19.8% at the time of titration, but can also emerge later with 0.7-4.2% having a new finding of TECSA after a month or more of CPAP therapy).<sup>1181</sup>

The most common treatment is continued use of CPAP at the lowest pressure setting which limits the obstructive apnea index to less than 5 events per hour. A systematic review of the natural history of TECSA<sup>1181</sup> found that majority of cases resolved with CPAP use when reassessed 4-28 weeks after starting CPAP therapy. In this group, persistence of TECSA was found in 31.1% (range 14.3%-46.2%) of TECSA patients across 5 studies.<sup>1181</sup>

In an EBRR of therapies for the treatment of TECSA, three randomized controlled studies (RCT) involved adaptive servo ventilation (ASV). Morgenthaler, et al showed that ASV decreased AHI compared to CPAP

both at the time of titration and at 90-day follow up.<sup>1051</sup> Dellweg et al showed that in patients with TECSA after 6 weeks of CPAP use, both ASV with auto-adjusting EPAP and Bilevel PAP with backup rate similarly reduce AHI at the time of titration but the ASV arm maintained a lower AHI after 6 weeks of use.<sup>1048</sup> Javaheri et al compared two ASV devices available in 2011 (BiPAP-AutoSV advanced and BiPAP-AutoSV) in a mixed population of TECSA patients and found greater improvement in the AHI with the BiPAP-Auto advanced device.<sup>1182</sup> The remaining lower quality studies all supported the use of ASV in various ways. ASV improved sleep efficiency in those with TECSA and heart disease with preserved EF > 50%,<sup>1183</sup> ASV improved adherence when switching from CPAP in patients with presumed TECSA,<sup>1052</sup> and ASV improves AHI compared to CPAP, BPAP-S, or BPAP-ST. Kuzniar et al compared two ASV devices available in 2011 (VPAP-AdaptSV and BiPAP-AutoSV) and found them to be comparable; however the populations varied as the study was not randomized.<sup>1045</sup> Javaheri et al found that default ASV settings reduced the overall apnea hypopnea index, central apnea index, obstructive apnea index, and hypopnea index AHI, CAI, OAI and HI over 90 days with sustained adherence and improvement in Epworth Sleepiness Scale and subjective sleep quality.<sup>1184</sup>

Insufficient evidence was found for treating TECSA with modalities used for other forms of CSA including phrenic nerve stimulation, supplemental O<sub>2</sub> or CO<sub>2</sub>, and medications such as acetazolamide, theophylline, or hypnotic agents.

At the time of diagnosis both CPAP and ASV are treatment options as most TECSA resolves with CPAP use; however when TECSA is severe, ASV can be used. The evidence suggests that ASV is more effective than CPAP for persistent TECSA (Recommendation, grade B). However, more studies are needed to predict those who will develop persistent TECSA due to the excess cost of ASV.

#### Treatment of TECSA

Aggregate Quality of Evidence: B (Level 1b: 1 study; Level 1c: 2 studies; Level 3b: 5 studies; Level 4; 2 studies).

Benefit: ASV improves AHI more than CPAP in patients with TECSA.

Harm: ASV is currently contraindicated for those with central sleep apnea related to HFREF (LVEF < 45%).

Cost: Higher costs associated with ASV compared to CPAP.

Benefits-Harm Assessment: Benefits exceed harm in patients without HFREF.

Value Judgments: In the majority of cases, TECSA resolves spontaneously with CPAP use. The evidence compares ASV to CPAP at time to of diagnosis in most studies, including patients with persistent-TECSA and those likely to improve on CPAP alone.

Recommendation Level: Recommendation

Intervention: ASV or CPAP can be considered at diagnosis of TECSA. If found to have persistent TECSA despite CPAP use or if TECSA is severe at diagnosis, ASV can be used.

Table VIII.A.5.h: Evidence for Treatment of TECSA

Study	Year	LOE	Study Design	Study Group	Clinical End-point	Conclusion
-------	------	-----	--------------	-------------	--------------------	------------

Morgenthaler, Timothy et al. <sup>1051</sup>	2014	1b	RCT	1) ASV; 2) CPAP	Primary endpoint: AHI < 10 at 90 days; Secondary endpoints: compliance, ESS, and SAQLI.	1) ASV reduces AHI more than CPAP.
Dellweg, Dominic et al. <sup>1048</sup>	2013	1c	RCT	1) ASV; 2) NPPV (Bilevel PAP with backup rate)	Primary endpoint: AHI after 6 weeks. Secondary endpoint: AHI on ASV titration	1) ASV showing sustained significant improvement at 6 weeks; 2) ASV and NPPV similarly treated TECSA on the titration
Javaheri, Shahrokh et al. <sup>1182</sup>	2011	1c	RCT	1) ASV (BiPAP autoSV Advanced); 2) ASV (BiPAP autoSV)	Primary endpoint: AHI on ASV titration	1) BiPAP autoSV Advanced lowered AHI more than BiPAP autoSV.
Pépin, Jean-Louis D. et al. <sup>1052</sup>	2018	3b	Case Control	1) CPAP switched to ASV; 2) ASV; 3) CPAP	Primary endpoint: Adherence data; Secondary endpoint: Average AHI	1) Increased adherence in patients switching from CPAP to ASV 2) Lower AHI in patients switching from CPAP to ASV
Heider, Katharina et al. <sup>1183</sup>	2018	3b	Case Control	1) HFpEF with TECSA; 2) HFpEF with CSA	Primary endpoint: Sleep fragmentation and quality at ASV titration and after 27 months of ASV use	1) AHI and arousal index improve with ASV 2) Increased sleep efficiency only in TECSA group with ASV 3) ESS improves with ASV
Neu, Daniel et al. <sup>1185</sup>	2017	3b	Case control	1) AutoCPAP with TECSA; 2) AutoCPAP without TECSA	Primary endpoint: AHI; Secondary endpoints: Quality of life, sleep fragmentation	1) Auto-titrating CPAP has relative treatment failure for TECSA compared to those without TECSA.
Kuzniar, Tomasz, et al. <sup>1045</sup>	2011	3b	Retrospective Cohort	1) ASV (VPAP AdaptSV); 2) ASV (BiPAP autoSV)	Primary endpoint: AHI; Secondary endpoints: adherence data, sleepiness using ESS	1) Both ASV devices were comparable. 2) Baseline populations were significantly different.
Allam, Joanne et al. <sup>1046</sup>	2007	3b	Case Control	1) ASV; 2) CPAP; 3) BPAP-S; 4) BPAP-ST; CPAP + O <sub>2</sub>	Primary endpoint: AHI on titration	1) ASV reduced AHI more than other modalities
Javaheri, Shahrokh et al. <sup>1184</sup>	2015	4	Case series	1) ASV using default settings	Primary endpoint: AHI; Secondary endpoints: subjective sleep quality using	1) Default ASV settings improve AHI. 2) Adherence, sleep disordered breathing,

					Likert scale and adherence and therapy data at 90 days.	ESS and subjective sleep quality are improved at 90 days
Brown, Stephen et al. <sup>1047</sup>	2011	4	Case Series	1) ASV	Primary endpoint: AHI on titration	ASV can be effective in reducing AHI

### VIII.A.5.i Insomnia Treatment and PAP Adherence

Patients with insomnia and OSA show reduced acceptance and lower average nightly use of CPAP therapy compared to patients with OSA alone.<sup>957</sup> Published studies on the effects of insomnia therapies for patients with OSA and comorbid insomnia are limited to studies evaluating non-medication therapies (See Table 10.c.2.b).<sup>956,1186-1190</sup> The systematic review concluded that these trials demonstrate the beneficial effects of therapist-administered cognitive behavioral therapy for insomnia (CBTi) on improving insomnia symptoms and increasing CPAP therapy usage.<sup>1188</sup> Two of these randomized controlled trials have demonstrated an improvement in CPAP adherence by an average of 48 and 61 minutes per night six months after CBTi administration. Two RCTs found no between-group differences in average CPAP use.<sup>1187,1191</sup> There is preliminary evidence that CBTi delivered by trained therapists may be more effective than self-administered CBTi using a self-guided resource.

Studies have also examined the effect of sedative-hypnotic medications on OSA severity, however these medicines are not currently recommended as first-line or long-term treatment for insomnia due to risks for side-effects, dependence and withdrawal.<sup>1192</sup> Further evaluation of the therapeutic potential of medications that do not alter OSA severity is required.

#### Insomnia Treatment to Improve PAP Adherence

**Aggregate Quality of Evidence:** B (Level 1b: 5 studies)

**Benefit:** Treatment of adult patients with insomnia/insomnia symptoms and OSA via CBTi delivered by trained therapists may improve insomnia symptoms and increase use of PAP therapy.

**Harm:** Low harms associated with CBTi including time required for therapy and risk for persistent symptoms.

**Cost:** There are no published data on costs of CBTi in patients with OSA. May depend on insurance policy coverage.

**Benefits-Harm Assessment:** Benefit outweighs harm.

**Value Judgments:** Small number of studies; No studies of pharmacotherapy for insomnia in patients with OSA.

**Recommendation Level:** Recommendation

**Intervention:** Patients with insomnia and OSA should be offered CBTi for improvement in insomnia symptoms and PAP adherence.

**Table VIII.A.5.i** Insomnia Treatment and PAP Adherence

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Sweetman et al. <sup>1188</sup>	2019	1b	Systematic review	4 RCTs considered	CPAP adherence, Insomnia outcomes: Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Bergen Insomnia Scale (BSI)	RCTs provide tentative support for the effect of therapist-administered CBTi in improving insomnia symptoms and increasing CPAP use in OSA patients with comorbid insomnia; CBTi delivered by trained therapists may be more effective than self-administered CBTi.
Ong et al. <sup>1187</sup>	2020	1b	RCT	121 adults with OSA and comorbid insomnia randomized to: 1) CBTi followed by PAP, 2) CBTi concurrent with PAP, or 3) PAP only.	Apnea diagnosed with PSG; Primary Outcome: 90-day PAP adherence; Secondary outcomes: PSQI, ISI	No significant group differences in PAP adherence between groups; Compared to PAP alone, the concomitant treatment arms led to greater improvement in ISI.
Alessia et al. <sup>1186</sup>	2020	1b	RCT	125 with comorbid insomnia and newly-diagnosed OSA by PSG (AHI $\geq$ 15 events/hr) randomized to: 1) 5-weekly sessions integrating CBTi with a PAP adherence program provided by a "sleep coach" or 2) 5-weekly sleep education control sessions.	Apnea diagnosed with PSG (AHI $\geq$ 15 events/hour); PSQI, 7-day sleep diary, 7-day actigraphy; objective PAP use, ISI, Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10).	Six months after CBTi intervention, 90-day PAP use was increased by 0.9 hrs/night. CBTi led to greater improvement in PSQI, ISI, ESS, FOSQ-10, diary sleep onset latency and sleep efficiency; and actigraphic sleep efficiency

Sweetman et al. <sup>1189</sup> Sweetman et al. <sup>1190</sup> Sweetman et al. <sup>956</sup>	2019, 2020	1b	RCT	145 patients with insomnia and untreated OSA randomised to: 1) a four-session CBTi programme followed by CPAP or 2) no treatment followed by CPAP.	Insomnia diagnosed with ICSD-3; Apnea diagnosed with PSG (AHI $\geq$ 15); Sleepiness evaluated with ESS, ISI, Dysfunctional Beliefs and Attitudes about Sleep Questionnaire  Primary outcome: AHI	The CBTi group showed a 7.5 event/hr greater AHI difference compared to control ( $p=0.012$ ), a greater reduction in total number of nocturnal awakenings ( $p=0.031$ ), and higher initial CPAP treatment acceptance (99% vs. 89%; $p = 0.034$ ). By six months after intervention, the CBTi group had 61 min greater average nightly adherence to subsequent CPAP ( $p = 0.023$ ) and greater improvement of global insomnia severity, and dysfunctional sleep-related cognitions ( $p < 0.001$ )
Bjorvatn et al., <sup>1191</sup>	2018	1b	RCT	164 patients with HSAT-based OSA diagnosis randomized along with CPAP to: 1) a self-help book for insomnia or 2) sleep hygiene advice	BIS, ISI Apnea: AHI $\geq$ 5 events/hour	No differences were found between groups; BIS and ISI improved significantly in both groups.

#### VIII.A.5.j Long Term PAP Adherence Assessment

Positive Airway Pressure therapy (PAP) is the mainstay of treatment for obstructive sleep apnea (OSA) and can include auto-adjusting PAP, CPAP and BiPAP, among others. Predictors of PAP adherence include severe OSA (AHI  $\geq$ 30), symptoms of excessive daytime sleepiness (Epworth score  $>10$  or  $\geq 12$ )<sup>1113,1193</sup> and early PAP adherence in the first week or month of treatment<sup>1140,1194</sup>. As OSA is a chronic condition, PAP should be continued as long-term treatment to maintain symptomatic improvements.

The goals of PAP therapy are to improve day and nighttime symptoms and reduce risks of cardiovascular and neurocognitive morbidities. For AHI, the recommended metrics during PAP titration are: optimal AHI $<5$ , good AHI $<10$ , and adequate  $>75\%$  AHI reduction<sup>1078</sup>; these metrics can be reasonably applied to analysis of AHI data from PAP machines with small adjustments as described in the American Thoracic Society (ATS) Statement from 2013.<sup>1195</sup> The ATS statement describes the current standards and issues with CPAP tracking systems for monitoring PAP adherence and outlined a clinical algorithm for PAP adherence management. Currently, with the availability of PAP data, long-term therapy should



optimally include both patient assessment and PAP data analysis, which can be performed on routine basis when patients are doing well and also when new clinical issues arise.

Several trials have assessed PAP adherence and treatment responses for follow up durations from 3 months up to 10 years. Patient education has been shown to improve adherence<sup>1133</sup>. A large database analysis showed an outstanding 87% adherence at 90 days in patients who enrolled in internet-based active patient engagement software.<sup>1196</sup> Applications that allow OSA patients to access and track their own CPAP adherence data on computers and smartphones are also available (e.g., SleepMapper from Resironics) and have been shown to increase hours of usage one hour or more over the initial 3 months of CPAP use.<sup>1197</sup> Additionally, automatic feedback messages via text messaging, emails or phone calls, directly to patients based on predetermined thresholds for CPAP usage have also shown improved 90-day CPAP adherence.<sup>1136</sup> These studies demonstrate the value of methods to improve and maintain adherence.

Despite the importance of long-term PAP therapy for chronic OSA, the current emphasis is on the initial 3 months of PAP<sup>39</sup>, and there are limited data on long-term PAP after 3 months; therefore, long-term guidelines are based on expert opinion. After the initial 3 months of treatment, CMS provides ongoing coverage for patients who are successfully adherent, showing PAP use for  $\geq 4$  hours on  $\geq 70\%$  of nights; coverage includes mask, headgear and tubing every 3 months for patients receiving clinical benefit.

For Protocol guidelines, CMS mandates ongoing annual clinical follow-up, either with PCP or specialist, to assess PAP therapy, or sooner if new clinical issues arise. Assessment should include subjective symptoms, weight changes, new medical issues, changes in medication, and mask fit/comfort. A review of PAP objective data including PAP hours, residual AHI, and leak is highly valuable to confirm subjective reports. If a full face mask shows high leak value, which can occur due to a larger contact area between mask and face, consider switching to a nasal mask or pillows. If nasal masks or pillows show high leak value, consider a chin strap or a full face mask. Patient education regarding the rationale for therapy and also maintaining clean and effective equipment should consistently be emphasized, since it has been shown to improve adherence.

When patients are on APAP, PAP pressure can vary based on weight and sleep position; if AHI data from APAP is in optimal or good ranges ( $<5$  or  $<10$  respectively), then continue APAP therapy and reassure the patient. For higher APAP AHI values, consider interventions to optimize mask or nasal pillows, or higher AHI values persist, consider polysomnogram for all-night titration. When patients using fixed-pressure CPAP experience significant weight change of  $>10\%$ , adjusting PAP pressure may be clinically necessary; therefore, consider polysomnogram for all-night titration to optimize PAP pressure. For adherent patients who are benefitting from PAP, annual follow-up is appropriate. In non-adherent patients, closer follow-up within 3-6 months is warranted. For patients who either can't or won't use PAP, alternative therapies should be pursued.<sup>1195</sup>

Since OSA is a chronic medical condition, long-term adherence to PAP is important for long-term symptom management and reduction of cardiovascular risks. Long-term PAP use is supported by both evidence and expert opinion to maintain symptomatic improvements. Since PAP adherence improves with a range of educational and patient engagement approaches, regular use of one or more of these approaches should also be emphasized. Annual follow-up should include subjective symptom assessment, objective PAP data analysis, and patient education.

## VIII.B Efficacy of PAP for Symptoms and Comorbidities

### VIII.B.1 PAP and Daytime Sleepiness

Obstructive sleep apnea (OSA) commonly presents with daytime sleepiness. Sleepiness can be measured both subjectively and objectively. Additionally, there are methods to measure objective wakefulness.

A systematic review<sup>1198</sup> from 2006 evaluated the effect of CPAP compared to placebo or conservative management on objective/subjective sleepiness and objective wakefulness in subjects with mild to moderate OSA. Meta-analyses showed a reduction in the Epworth Sleepiness Scale (ESS) score of 1.2 points (95% CI: 0.5, 1.9), an increase in the Maintenance of Wakefulness (MWT) sleep latency of 2.1 minutes (95% CI: 0.5, 3.7), and no significant change in the Multiple Sleep Latency Test (MSLT) values. An additional systematic review<sup>1199</sup> that compared subjects receiving CPAP to sham CPAP, oral placebo, usual care, or a dental device demonstrated a reduction in ESS score of 2.7 points, (95% CI: -3.5, -2.0). for all levels of symptom severity, with greatest improvement in the subjects that were sleepest (mean difference -5.0 points, 95% CI: -6.5, -3.5). MWT values improved in CPAP versus control (mean difference 3.3 minutes, 95% CI: 1.3, 5.3), however, MWT values were not significantly different in CPAP versus dental devices (0.7 minutes, 95% CI: 1.6, 2.9). MSLT values were not significantly different in CPAP versus control for all participants (mean difference 0.6 minutes, 95% CI: -0.7, 1.9), however, there was a statistically significant increase in mean sleep latency of 2.3 minutes (95% CI: 9, 3.7,  $I^2$  0%) for subjects with severe disease, as measured by apnea hypopnea index (AHI). A recent systematic review<sup>39</sup> evaluated subjective and objective sleepiness and objective wakefulness in subjects treated with PAP compared to control groups. The control groups primarily used sham PAP or no PAP, with one study using nasal dilator strips, one study using sleep hygiene and counselling, and one study utilizing usual care. The meta-analysis of 38 RCTs demonstrated a clinically significant decrease in ESS score by 2.4 points in subjects using PAP compared with controls (95% CI: -2.8, -1.9). A meta-analysis of 7 RCTs showed a reduction in MWT or Oxford Sleep Resistance Test (OSLER) sleep latency by 0.5 minutes in subjects treated with PAP (95% CI: 0.2, 0.8) compared to control subjects. A meta-analysis of 7 RCTs found no significant difference in mean sleep latency in subjects treated with PAP compared to controls (mean difference 0.25 minutes, 95% CI: -0.89, 1.38).

#### PAP to Improve Daytime Sleepiness

**Aggregate Quality of Evidence:** A (Level 1: 3 studies)

**Benefit:** Treatment with CPAP leads to modest reductions in the Epworth Sleepiness Scale and improved performance on MWT or OSLER.

**Harm:** The potential harms of CPAP are inconvenience and therapy-related side effects (including, but not limited to, sleep disruption, airway dryness, nasal congestion, and aerophagia).

**Cost:** CPAP treatment for OSA is associated with a low-to-moderate cost for CPAP equipment and visits for maintenance.

**Benefits-Harm Assessment:** The benefits of PAP therapy for reducing daytime sleepiness outweigh the harms associated with PAP.

**Value Judgments:** Successful treatment of OSA with CPAP leads to improved daytime alertness, with improvements in subjective sleepiness and objective wakefulness.

**Recommendation Level:** Strong Recommendation

**Intervention:** Patients with OSA and daytime sleepiness should be offered PAP therapy as it can effectively reduce daytime sleepiness related to OSA.

Table VIII.B.1 Evidence for Improvement in Sleepiness with PAP

	Year	LOE	Study Design	Study Groups	Clinical End-Point	Conclusion
Marshal <sup>1198</sup>	2006	1a	SR	7 RCTs comparing CPAP to placebo or conservative management in subjects with mild to moderate OSA	Objective and subjective daytime sleepiness and objective wakefulness	Meta-analyses demonstrated a significant reduction in subjective sleepiness (ESS) by 1.2 points (95% CI: 0.5, 1.9), improved objective daytime wakefulness (MWT) by 2.1 minutes (95% CI 0.5, 3.7), and no significant change in MSLT.
McDaid <sup>1199</sup>	2009	1a	SR	48 studies comparing CPAP vs alternatives (oral placebo, sham CPAP, dental device, and usual care)	Objective and subjective daytime sleepiness and objective wakefulness	CPAP significantly reduced ESS score compared to control by 2.7 points (95% CI: -3.5, -2.0). CPAP improved daytime wakefulness (MWT) by 3.3 minutes (95% CI: 1.3, 5.3). CPAP did not significantly change MSLT values for all participants, but there was a benefit (mean difference 2.3 minutes, 95% CI: 9, 3.7, I <sup>2</sup> 0%) for those with severe disease (as measured by AHI).
Patil <sup>39</sup>	2019	1a	SR	Up to 38 RCTs comparing PAP vs alternatives (predominantly sham PAP or no PAP, but also nasal dilator strips, sleep hygiene and counselling, and usual care)	Objective and subjective daytime sleepiness and objective wakefulness	Meta-analyses of 38 RCTs demonstrated a clinically significant decrease in ESS score by 2.4 points with the use of PAP compared with controls (95% CI: -2.8, -1.9). A meta-analysis of 7 RCTs showed a reduction in MWT or OSLE sleep latency by 0.5 minutes in subjects treated with PAP (95% CI: 0.2, 0.8). A meta-

						analysis of 7 RCTs found no significant difference in mean sleep latency in subjects treated with PAP compared to controls.
--	--	--	--	--	--	---

### VIII.B.2 PAP and OSA Severity

Continuous positive airway pressure (CPAP) therapy has been utilized as a non-invasive treatment for obstructive sleep apnea (OSA) since the 1980's. Multiple systematic reviews have consistently demonstrated that CPAP is effective at reducing the apnea hypopnea index (AHI).<sup>39,1200,1201</sup> CPAP was shown to be superior to placebo, conservative management, or positional therapy during follow-up polysomnography over weeks to months.<sup>1200</sup> A systematic review<sup>1201</sup> of eight randomized controlled trials (RCTs) demonstrated a mean decrease in AHI of 17 events per hour compared to control groups in seven RCTs and a decrease in AHI of 9 events per hour compared to a control group in one RCT crossover study. A recent systematic review<sup>39</sup> using two different meta-analyses evaluated 11 RCTs that compared CPAP to control interventions (sham CPAP, conservative measures, no intervention, sham surgery, a placebo tablet, or nasal dilator strips). One meta-analysis demonstrated a mean decrease in AHI of 23 events/hour with CPAP therapy compared to control interventions. The other meta-analysis showed a mean decrease in AHI of 29 events per hour comparing subjects pre- and post-treatment. The mean difference in AHI was most pronounced in study groups where the mean pre-treatment AHI was greater than 30 events/hour.

#### PAP for OSA Severity

**Aggregate Quality of Evidence:** A (Level 1a: 3 studies).

**Benefit:** Treatment with CPAP improves AHI compared to placebo tablet, no intervention, conservative management, positional therapy, sham CPAP, sham surgery, or nasal dilator strips.

**Harm:** The potential harms of CPAP are inconvenience and therapy-related side effects (including, but not limited to, sleep disruption, airway dryness, nasal congestion, and aerophagia).

**Cost:** CPAP treatment for OSA is associated with a low-to-moderate costs for CPAP equipment and visits for maintenance.

**Benefits-Harm Assessment:** The benefits of PAP therapy on reducing the AHI outweigh the harms associated with CPAP.

**Value Judgments:** There is strong evidence that treatment of OSA with CPAP leads to reductions in AHI.

**Recommendation Level:** Strong Recommendation.

**Intervention:** Patients should be offered PAP therapy to reduce OSA severity. There is greater reductions in AHI in patients with severe OSA.

**Table VIII.B.2: Evidence for PAP to Improve OSA Severity**

	Year	LOE	Study Design	Study Groups	Clinical End-Points	Conclusion
Gay <sup>1200</sup>	2006	1a	SR	11 RCTs comparing	AHI	CPAP was superior to

				CPAP vs. placebo, conservative management, or positional therapy		placebo, conservative management, and positional therapy as demonstrated on PSG several weeks or months after treatment.
Giles <sup>1201</sup>	2006	1a	SR	8 RCTs comparing CPAP to control interventions (sham CPAP, conservative measures, no intervention, or placebo tablet)	AHI	Seven RCTs (parallel and partial crossover studies) showed a significant mean difference in AHI of -17 events/hour with CPAP therapy.  One RCT (crossover study) demonstrated a difference in AHI of -9 events/hour with CPAP therapy.
Patil <sup>39</sup>	2019	1a	SR	11 RCTs comparing CPAP to a control intervention (sham CPAP, conservative measures, no intervention, sham surgery, placebo tablet, or nasal dilator strips)	AHI	Meta-analysis of RCTs showed a significant mean difference in AHI of -23 events/hour with CPAP therapy. Another meta-analysis of these RCTs demonstrated a significant mean difference in AHI of -29 events/hour before and after CPAP therapy.

### VIII.B.3 PAP and Mortality Risk

Obstructive sleep apnea (OSA) is a common disorder that is known to be associated with a variety of poor health outcomes, including increased mortality<sup>95</sup>. Positive airway pressure (PAP) therapy is an effective form of treatment for OSA and is considered to be standard first-line therapy.

A recent multi-center randomized controlled trial (RCT) from Spain<sup>1202</sup> did not demonstrate significant benefit with continuous PAP (CPAP) therapy compared to usual care for either all-cause mortality or

cardiovascular mortality in a group of non-sleepy subjects with acute coronary syndrome. It is important to note that the mean adherence to CPAP therapy in this trial was only 2.78 hours/night. An earlier meta-analysis<sup>39</sup> evaluated both randomized controlled trials and non-randomized trials comparing PAP therapy to no PAP therapy in middle-aged and older subjects with at least moderate OSA. This systematic review performed two meta-analyses and had conflicting conclusions regarding all-cause mortality. The meta-analysis of four RCTs demonstrated that CPAP therapy did not reduce all-cause mortality, however, there was variability in CPAP adherence among the four trials. A meta-analysis of nine non-RCTs did demonstrate a clinically significant reduction in all-cause mortality with CPAP with a risk ratio of 0.4 (95% CI 0.24 to 0.69). An additional RCT from China<sup>1203</sup> evaluated subjects with moderate to severe OSA who had uncontrolled hypertension and coronary heart disease. This study demonstrated a non-significant trend toward lower severe cardiovascular and cerebrovascular events with one death in the control group.

In the face of cohort data showing a significant effect of CPAP therapy on reduction in all-cause mortality and negative findings from multiple RCTs, it is difficult to interpret the overall benefit of PAP. Pack et al. summarized the biases and limitations associated with the negative RCT studies on the effects of PAP therapy and cardiovascular events. Specifically, RCT studies were secondary prevention studies and all trials excluded OSA subjects with excessive sleepiness who are increased risk for cardiovascular events and most likely to benefit from treatment.<sup>1204</sup> RCTs also had inadequate adherence to PAP therapy and on secondary analysis of data in adherent patients, CPAP benefit was found to be consistent with prior epidemiological studies.<sup>1205</sup>

#### CPAP Therapy and Mortality Risk

**Aggregate Quality of Evidence:** B (Level 1a: 1 study; Level 1b: 2 studies; Level 2a: 1 study).

**Benefit:** Treatment with CPAP is not consistently associated with reduction in cardiovascular and all-cause mortality in available studies, although CPAP adherence was variable and severe OSA and excessively sleepy patients were excluded in the RCT studies. Modest reductions in mortality have been demonstrated in non-randomized studies.

**Harm:** The potential harms of CPAP are inconvenience and therapy-related side effects (including, but not limited to, sleep disruption, airway dryness, nasal congestion, and aerophagia).

**Cost:** Low costs for PAP equipment and visits for maintenance.

**Benefits-Harm Assessment:** Based on the best available evidence, benefits are unclear and harms are minimal for PAP therapy in reducing cardiovascular and all-cause mortality.

**Value Judgments:** Successful treatment of OSA with CPAP may lead to reduced cardiovascular and all-cause mortality. Observational cohort studies support the use of PAP to reduce mortality, although the RCT data has not shown this benefit.

**Recommendation Level:** Option.

**Intervention:** PAP therapy may be considered for OSA patients as an option to reduce mortality. There is potential for reduction in cardiovascular and all-cause mortality with PAP therapy in patients with severe OSA, excessive daytime sleepiness, and adherent PAP use.

**Table VIII.B.3 Evidence for PAP Use and Mortality Risk Reduction**

	Year	LOE	Study Design	Study Groups	Clinical	Conclusion
--	------	-----	--------------	--------------	----------	------------

					End-Point	
Sanchez-de-la-Torre <sup>1202</sup>	2020	1b	RCT	<p>1264 patients hospitalized for acute coronary syndrome and AHI &gt; 15 randomized to CPAP treatment plus usual care vs. usual care alone.</p> <p>ISAACC Study: Impact of sleep apnea syndrome in the evolution of acute coronary syndrome – effect of intervention with CPAP.</p>	Cardiovascular mortality and all-cause mortality	No significant benefit with CPAP therapy for cardiovascular mortality (hazard ratio 0.83) or all-cause mortality (hazard ratio 0.82), however, the mean adherence to CPAP therapy was only 2.78 hours/night.
Patil <sup>39</sup>	2019	1a, 2a	SR	<p>4 RCTs comparing CPAP to no CPAP</p> <p>9 non-randomized trials comparing PAP vs. control conditions</p>	All-cause mortality	Meta-analysis of RCTs showed that CPAP therapy did not reduce all-cause mortality (risk ratio 0.96), however, there was variability in CPAP adherence. Meta-analysis of non-randomized trials demonstrated a clinically significant reduction in all-cause mortality (risk ratio 0.4).
Huang <sup>1203</sup>	2015	1b	RCT	83 patients randomized to CPAP vs. no	Severe cardiovascular and cerebrovascular events (includ-	There was a non-significant trend toward lower severe cardiovascu-

				therapy	ing death)	lar and cerebrovascular events with one death in the control group.
--	--	--	--	---------	------------	---

## VIII.B.4 PAP and Cardiovascular Outcomes

### VIII.B.4.a PAP and Control of Hypertension

There are many published randomized controlled trials measuring blood pressure (BP) before and after initiation of continuous positive airway pressure (CPAP) therapy.<sup>39</sup> Although several systematic reviews and meta-analyses have noted reductions in BP with CPAP treatment of OSA, particularly moderate to severe OSA, caution is warranted because of heterogeneity in the pooled studies.<sup>39,653,1206-1210</sup> Examples include variability in severity of OSA, presence of daytime sleepiness, control conditions, blinding, adherence to CPAP treatment, measurement of BP, HTN status at baseline, lack of controlled antihypertensive treatment, and duration of follow-up. A majority of the subjects included in the studies were middle-aged, obese, and male. Meta-analyses with overall low to moderate homogeneity of included studies are shown in Table 2. The recent meta-analysis by Yu et al, comprising patients with both OSA and central sleep apnea was largely driven by the results of the Sleep Apnea Cardiovascular Endpoints (SAVE) trial and did not show a reduction in major adverse CV events.<sup>653,1211</sup> However, a borderline statistically significant ( $p=0.05$ ) reduction of systolic BP with positive airway pressure was noted. It is notable that adherence to CPAP in the SAVE trial was suboptimal at a mean of 3.3 hours per night and REM-related SDB events, most of which tend to occur in the latter part of the night, were likely left untreated.

The magnitude of reduction of 24-hour mean BP with CPAP treatment of OSA is modest, in the range of 2-4 mm Hg, may be related to the severity of OSA<sup>1212</sup> and to the number of hours of nightly usage of the device.<sup>39,1206-1208</sup> Based on a metanalysis of antihypertensive medication RCTs, clinically significant 24-hour systolic BP reduction as low as 1-2 mm Hg is associated with decreased risk of stroke and major cardiovascular events; larger blood pressure reductions are associated with larger reductions in risk for stroke, major CV events and total mortality.<sup>1213</sup> The effect on BP appears to be sustained over time with continued use of CPAP and some evidence suggests that fixed CPAP devices may be better at decreasing BP than auto-titrating devices (APAP), although better tolerated APAP may be used for longer durations.<sup>39</sup> Additionally, some studies have evaluated the synergistic effects of antihypertensive medication with CPAP in decreasing BP in those with HTN<sup>39</sup>, but the evidence on the optimal timing of antihypertensive medication to lower nocturnal BP and eliminate the nocturnal non-dipping pattern of BP is conflicting. While CPAP treatment has been shown to reduce BP in those with existing pre-HTN and HTN, the evidence for the impact of treatment of OSA on incident HTN is mixed.<sup>39</sup>

Meta-analyses have indicated a greater magnitude of BP reduction with CPAP therapy, in the range of 5-7 mm Hg in systolic BP and 3-5 mm Hg in diastolic BP, in those with resistant HTN.<sup>1209,1210</sup> However, not all reports are consistent<sup>39</sup>, likely relating to differences in baseline severity of OSA and adherence to CPAP. These meta-analyses have shown a significant decrease in nighttime BP as well as a long-term (12 weeks) reduction in mean and diastolic BP with CPAP device usage of 4 or more hours a night.<sup>39,1209,1210</sup>

Individuals with OSA who report daytime sleepiness appear to demonstrate greater decline in BP compared to those who are not sleepy.<sup>39,1210</sup> Precision medicine may help identify subgroups of



patients most likely to benefit in terms of BP reduction from optimal CPAP treatment. These factors, amongst others, may help individualize treatment of OSA in the future to help decrease the risk of HTN and other adverse long-term CV consequences.

### PAP for Hypertension Control

**Aggregate Quality of Evidence:** A (Level 1a: meta-analyses including 54 RCTs).

**Benefit:** Successful treatment of OSA with CPAP leads to a modest reduction BP in subjects with HTN, especially in those with severe OSA. Antihypertensive medications will likely still be required. The reduction in BP may be greater in subjects with resistant HTN and those who report daytime sleepiness.

**Harm:** The harms associated with treatment of OSA with CPAP therapy are minimal.

**Cost:** Low cost involved with CPAP equipment and visits for maintenance.

**Benefits-Harm Assessment:** The benefits of treating patients with moderate to severe OSA with PAP to reduce BP outweigh risks of treatment.

**Value Judgments:** Successful treatment of OSA with CPAP leads to reduction in BP. Antihypertensive medications will likely still be required.

**Recommendation Level:** Strong recommendation.

**Intervention:** Patients with OSA, particularly those with moderate to severe OSA and/or resistant hypertension, should be offered CPAP to help decrease BP.

**Table VIII.B.4.a Evidence for PAP therapy and Blood Pressure Control**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Bazza no et al. <sup>1206</sup>	2007	1a	Meta-analysis of 16 RCTs (n=818)- low heterogeneity	1) OSA, treated with CPAP for at least 2 weeks (and up to 24 weeks, with good adherence in most studies). 2) OSA controls (sham-CPAP, pill, or usual care).  OSA was mostly moderate-severe. All but 5 studies used ambulatory BP monitoring.	1) SBP 2) DBP 3) MAP	Mean SBP decreased by 2.46 mm Hg (95% CI:-4.31to -0.62), mean DBP by 1.83 mmHg (95% CI:-3.05 to -0.61) and MAP by 2.22 mmHg (95% CI: -4.38 to -0.05) with CPAP. Decreases in nocturnal and daytime BP were not statistically different.  Dose-response relationship between mean hourly usage of CPAP and reduction in SBP was noted.
Fava et	2014	1a	Meta-analysis of	1) OSA, treated with CPAP (good	1) SBP	Mean SBP decreased by 2.6±0 .6 mmHg and DBP by 2.0±0.4 mmHg; <i>P</i>

al. <sup>1208</sup>			29 RCTs (n=1820)- moderate heterogeneity	adherence in most studies) for 2-52 weeks. 2) OSA controls (sham-CPAP, pill, or usual care).  OSA was mostly moderate-severe. Most studies used ambulatory BP monitoring, some included subjects with HTN.	2) DBP	<0.001) with CPAP. Daytime SBP and DBP fell by 2.2±0.7 and 1.9±0.6 mmHg respectively and nighttime SBP and DBP by 3.8±0.8 and 1.8±0.6 mmHg respectively.  Higher severity of OSA was associated with a greater decline in mean SBP.
Yu et al. <sup>653</sup>	2017	1a	Meta-analysis of 10 RCTs evaluating the primary outcome; 2 of these and 2 others i.e. a total of 4 studies (n=3017) measured BP before and after CPAP)- low to moderate heterogeneity	1) OSA, treated with CPAP (most with suboptimal adherence). 2) OSA, receiving sham-CPAP or usual care.	Major adverse cardiovascular events. BP (SBP, DBP) was an “intermediate” outcome	Pooled mean difference in SBP was 0.20 mmHg (95%CI:-2.29 to -1.89, P=0.05 and DBP was 0.21 mmHg (95%CI:-1.06 to -0.65, P=0.80) in CPAP vs control groups.
Patil et al. <sup>39</sup>	2019	1a	Meta-analysis of 26 RCTs (n=2444 had 24-h BP measured	1) OSA, treated with CPAP (many with suboptimal adherence). 2) OSA, various control conditions	1) Multiple outcomes assessed, one of which was BP (SBP, DBP, and	Mean nighttime SBP and DBP fell by 4.2 mmHg (95%CI:-6.0 to -2.5) and 2.3 mmHg (95%CI:-3.7 to -0.9) respectively with CPAP. Mean daytime SBP and DBP fell by -2.8 mmHg (95%CI:-4.3 to -1.2) and -2.0 mmHg (95%CI:-3.0 to -0.9) respectively; 24-h

			before and after)- moderate heterogeneity	(sham-CPAP, pill, or usual care).  OSA was mostly moderate-severe. Five studies included subjects with HTN, 5 with RHTN.	mean BP)	SBP, DBP and mean BP all decreased significantly.  In those with HTN, nighttime SBP and DBP, daytime SBP and DBP, and 24-h SBP and mean BP all decreased.  In those with RHTN, significant reductions in nighttime SBP and DBP, daytime DBP, 24-h SBP and DBP, but no clinically significant reduction in daytime SBP was noted.
Bratton et al. <sup>1207</sup>	2015	1a	Meta-analysis of 51 studies (n=4888)- moderate heterogeneity	1) OSA, on CPAP. 2) OSA, on OA. 3) OSA, inactive control.  OSA was mild, moderate and severe OSA, follow-up ranged between 4-157 weeks, with variable adherence to CPAP. Many studies had subjects with HTN, including RHTN. Forty-four studies compared CPAP to inactive control, 3 compared OA to inactive control, 1 compared CPAP to OA and 3 compared those on CPAP, OA and inactive control.	1) SBP 2) DBP	CPAP reduced SBP by 2.5mmHg (95%CI:-1.5 to -3.5; $P<0.001$ ) and DBP by 2.0mmHg (95%CI:-1.3 to -2.7; $P<0.001$ ) vs inactive control; a dose-response relationship between hours of usage of CPAP and reduction in SBP/DBP was noted. OA reduced SBP by 2.1mmHg (95%CI:-0.8 to -3.4; $P=0.002$ ) and DBP by 1.9mmHg (95%CI:-0.5 to -3.2; $P=0.008$ ).  There were no significant differences in reduction in SBP/DBP between CPAP and OA in the network meta-analysis.
Iftikhar et al. <sup>1209</sup>	2014	1a	Meta-analysis (2 observational studies,	1) OSA and RHTN, treated with CPAP for 2-6 months.	1) 24-h SBP 2) 24-h DBP	24-h SBP decreased by 7.21 mmHg (95%CI: -9.04 to -5.38; $P <0.001$ ) and DBP by 4.99 mmHg (95%CI: -6.01 to -3.96; $P <0.001$ ) with CPAP. Ambulatory

			n=44; 4 RCTs, n=320)-moderate heterogeneity	2) OSA and RHTN, not treated.  OSA was mostly severe. CPAP adherence was good. All but 1 study used ambulatory BP monitoring.		SBP and DBP from 4 RCTs showed a decrease of 6.74 mmHg (95% CI: -9.98 to -3.49; $P<0.001$ ) and 5.94 mmHg (95% CI: -9.40 to -2.47; $P=0.001$ ) respectively.
Liu et al. <sup>1210</sup>	2016	1a	Meta-analysis of 5 RCTs (n=216), moderate heterogeneity	1) OSA and RHTN, treated with CPAP for 8 weeks to 6 months. 2) OSA and RHTN, not treated or on sham CPAP.  OSA was moderate-severe. CPAP adherence was good and subjects reported no or mild sleepiness at baseline.	1) 24-h SBP and DBP 2) Daytime SBP and DBP 3) Nocturnal SBP and DBP.	24-h SBP fell by 4.78 mmHg (95%CI:-7.95 to -1.61) and 24-h DBP by 2.95 mmHg (95%CI: -5.37 to -0.53) with CPAP. Nocturnal DBP decreased by 1.53 mmHg (95%CI: -3.07 to 0) with CPAP.

BP=blood pressure; CI=confidence intervals; CPAP=continuous positive airway pressure; CSA=central sleep apnea; CV=cardiovascular; DBP=diastolic blood pressure; MAP=mean arterial pressure; OSA=obstructive sleep apnea, OA=oral appliance; RCT=randomized controlled trial; RHTN=resistant hypertension; SBP=systolic blood pressure

#### VIII.B.4.b PAP and Control of Atrial Fibrillation

Several observational studies have evaluated the association of CPAP treatment for OSA with risk of recurrent AF following electrical cardioversion or ablation procedures. These studies have generally found that patients with OSA who are not treated with CPAP are significantly more likely to have recurrent AF than CPAP-treated patients, with two- to six-fold higher adjusted risk of recurrence.<sup>707,728,729,1214,1215</sup> No significant difference in rate of recurrence was seen, however, in two very small studies<sup>711,727</sup> and one large, retrospective cohort study.<sup>1216</sup> A single randomized clinical trial has been published comparing CPAP to usual care for prevention of recurrence following electrical cardioversion of AF. In this study, only 25 of a planned 180 patients were randomized, with no significant difference in outcome between groups.<sup>1217</sup> In a randomized trial evaluating the impact of CPAP versus supportive care in older adults with OSA, cardiovascular outcomes were a secondary endpoint. Incident AF was not separately analyzed but was reported in a supplementary table and

occurred in 16.5% of supportive care patients over 12 months of follow-up, versus 7.6% in the CPAP group, a difference that is not statistically significant.<sup>1218</sup>

A recent randomized clinical trial tested the effect of 5 months of treatment with CPAP plus usual care to usual care alone on AF burden (percentage of time in AF) in 109 patients with paroxysmal atrial fibrillation who were found on screening to have moderate or severe OSA (defined as AHI  $\geq 15$ ). Despite a mean nightly CPAP use of 4.4 hours, the adjusted difference in AF burden between CPAP and usual care was 0.6% (95% CI -2.6 to 1.3; P = 0.52), nor was there a significant difference in the percentage of patients achieving a 25% reduction in AF burden or in the frequency or duration of AF episodes.<sup>709</sup> Limiting the analysis to those using CPAP  $\geq 4$  hours per night did not alter the findings.

#### PAP for Control of Atrial Fibrillation

**Aggregate Quality of Evidence:** C (level 1b: 1 study; level 2b: 6 studies; level 4: 4 studies).

**Benefit:** Treatment of OSA with PAP therapy may reduce the recurrence of atrial fibrillation following restoration of sinus rhythm with electrical cardioversion or catheter ablation procedures. Based on a single RCT, there is no evidence that CPAP reduces AF burden in patients with paroxysmal AF who have not undergone cardioversion or ablation procedures. The impact of OSA treatments other than PAP on risk of recurrent AF has not been reported.

**Harm:** Inconvenience and side effects of CPAP therapy.

**Cost:** Cost of treating patients for OSA.

**Benefits-Harm Assessment:** The harm of OSA diagnosis and treatment in patients with AF are low, however the evidence for treatment to reduce AF recurrence is mixed. Balance of benefit and harm.

**Value Judgments:** The overall quality of evidence favoring diagnosis and treatment of OSA solely for prevention of recurrent atrial fibrillation without cardioversion or ablation is generally weak, with no adequately powered randomized clinical trials. Patients with paroxysmal AF did not demonstrate AF burden reduction with CPAP therapy.

**Recommendation Level:** Option.

**Intervention:** Patients who are undergoing cardioversion or catheter ablation for atrial fibrillation may benefit from adjunctive treatment of OSA with CPAP to prevent AF recurrence. Shared decision making regarding CPAP treatment is suggested to weigh individual patient symptoms, preferences and comorbidities.

**Table VIII.B.4.b Evidence for Use of PAP and Atrial Fibrillation Control**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Kanagala et al. <sup>1215</sup>	2003	4	Clinic-based cohort study	Patients referred for DC cardioversion; OSA diagnosis based on prior documented polysomnography; CPAP use based on self-report 1) 12 patients with treated	Recurrence of AF at 12 months	AF recurred in 82% of untreated OSA patients, which was significantly high than the 42% of treated OSA patients ( $p=0.01$ ) and 53% in the patients without known

				OSA 2) 27 patients with untreated (or inadequately treated) OSA 3) 79 patients without known OSA		OSA (p=0.009).
Jongnara ngsin et al. <sup>727</sup>	2008	4	Clinic- based cohort study	324 patients referred for radiofrequency catheter ablation of AF (pulmonary vein isolation, other atrial regions if needed; OSA diagnosis based on prior documented polysomnography 1) 18 patients with treated OSA 2) 14 patients with untreated OSA 3) 292 patients without known OSA	Recurrence of AF over a mean follow-up of 7 (SD 4) months	AF recurred in 37% of patients without known OSA and 59% of patients with OSA (p=0.02). The recurrence rate was 50% in the CPAP-treated OSA patients and 71% in the untreated OSA patients (p=0.29). In multivariate analysis, the adjusted OR for AF recurrence was 3.04 (95% CI 1.11-8.32) in those with OSA compared to those without known OSA.
Patel et al. <sup>729</sup>	2010	2b	Clinic- based, multi- center cohort study	3000 consecutive patients undergoing pulmonary vein and posterior wall isolation procedure for AF; OSA diagnosis based on prior documented polysomnography with AHI >15 and >80% of events obstructive; CPAP use based on self-report 1) 315 OSA patients with regular CPAP use 2) 325 OSA patients with no or erratic CPAP use 3) 2360 patients without known OSA	Recurrence of AF over a mean follow-up of 32 (SD 14) months	AF recurred in 22% of patients without known OSA and 27% of patients with OSA. The adjusted OR for AF recurrence was 1.59 (95% CI 1.25-2.08) for OSA versus no known OSA. Among those with OSA, AF recurred in 21% of those treated with CPAP and 32% of those not using CPAP (p=0.003). The adjusted OR for AF recurrence was 0.16 (95% CI 0.07-0.35) for CPAP use versus no or erratic CPAP use.
Fein et	2013	4	Clinic-	92 patients undergoing	AF-free survival	The 1-year AF-free

al. <sup>1214</sup>			based cohort study	<p>pulmonary vein isolation for treatment of AF; OSA diagnosis based on prior documented polysomnography with AHI &gt;15 and ≥80% of events obstructive; method of CPAP use determination not stated</p> <p>1) 32 patients with treated OSA</p> <p>2) 30 patients with untreated OSA</p> <p>3) 30 patients without known OSA</p>		<p>survival was 71.9% in those with CPAP-treated OSA, significantly higher than the 33.3% in those with untreated OSA (p=0.02) but not significantly different from the 66.7% in those without OSA. Compared to those without OSA, the adjusted HR for AF recurrence was 2.15 (95% CI 1.10-5.44) in those with OSA not using CPAP and 0.7 (95% CI 0.3-1.59) in those with OSA using CPAP.</p>
Naruse et al. <sup>707</sup>	2013	2b	Clinic-based cohort study	<p>153 patients undergoing pulmonary vein isolation for treatment of AF; all patients underwent polysomnography approximately 1 week after the procedure, with OSA defined as AHI ≥5 and ≥50% of events obstructive; objective CPAP data</p> <p>1) 82 patients with CPAP-treated OSA (60 with use ≥4 hrs/night, 22 with use &lt;4 hrs/night)</p> <p>2) 34 patients with untreated OSA</p> <p>3) 37 patients without OSA</p>	AF recurrence over mean follow-up of 19 (SD 10) months	<p>AF recurred in 53% of those with untreated OSA, 30% in those treated with CPAP, and 22% of those without OSA. The multivariate adjusted HR for AF recurrence was 2.61 (95% CI 1.12-6.09) for presence of OSA and 0.41 (95% CI 0.22-0.76) for CPAP use.</p>
Neilan et al. <sup>728</sup>	2013	2b	Clinic-based cohort study	<p>720 consecutive patients referred for pulmonary vein isolation for AF; OSA diagnosis based on prior documented polysomnography; CPAP</p>	Late AF recurrence (AF occurring >3 months after PVI) over median follow-up of 42	<p>The cumulative incidence of late AF was 68% in patients with untreated OSA, 35% in treated OSA, and 30% in those without OSA. Compared to those</p>

				usage by self-report 1) 71 patients with treated OSA (CPAP use >4 hrs/night) 2) 71 patients with untreated OSA (or CPAP use <4 hours/night) 3) 578 patients without known OSA	months	without OSA, the multivariate adjusted HR for AF recurrence was 2.79 (95% CI 1.97-3.94) in untreated OSA and 1.14 (95% CI 0.74-1.76) in treated OSA.
McMillan et al. <sup>1218</sup>	2014	2b	Randomized multi-center clinical trial	278 patients with 4% oxygen desaturation index >7.5 events/hr plus Epworth Sleepiness Scale score of ≥9 1) CPAP plus “best supportive care” 2) “Best supportive care” alone	Incident AF was reported as part of a secondary composite endpoint and was not itself a pre-specified endpoint	Supplementary table S13b includes baseline prevalence and 12-month incidence of AF. In the Best Supportive Care group, incident AF occurred in 14 of 85 patients free of AF at baseline, versus 7 of 92 in the CPAP group (OR 0.42 for CPAP group, p=0.07).
Caples et al. <sup>1217</sup>	2019	2b	Randomized clinical trial	25 patients with recent successful electrocardioversion for AF screened for enrollment; of 1757 patients screened, 34 were enrolled and underwent in-lab polysomnography; 25 with AHI ≥5 and predominantly obstructive events were randomized to: 1) CPAP plus usual cardiovascular care (n=12) 2) Usual cardiovascular care alone (n=13)  The pre-planned sample size was 90 patients per group with a minimum 1-year follow-up	Recurrence of AF	36% of participants withdrew or were lost to follow-up prior to 1-year follow-up; 3 patients in each group had recurrence of AF (p=0.98). This study was markedly underpowered to observe a treatment effect.



Hojo et al. <sup>711</sup>	2019	4	Clinic-based cohort study	<p>100 patients undergoing pulmonary vein isolation for AF; all had cardiorespiratory polygraphy at baseline, with OSA defined as AHI <math>\geq 15</math> and <math>\geq 50\%</math> of events obstructive; all patients had a second PVI procedure at 6 months, after which CPAP was recommended based on local guidelines</p> <p>1) 11 patients with treated OSA</p> <p>2) 23 patients with untreated OSA</p> <p>3) 66 patients without OSA</p>	Recurrence of AF or other atrial tachyarrhythmia following the second PVI procedure	No significant difference among groups was noted in rate of AF recurrence (12.1% in no OSA group, 9.1% un treated OSA group, 8.7% in untreated OSA group).
Srivali et al. <sup>1216</sup>	2019	2b	Retrospective clinic-based cohort study	<p>429 patients with a diagnosis of sleep apnea by in-lab PSG (351 OSA, 21 CSA, 57 mixed sleep apnea), with a subsequent diagnosis of AF, treated with PVI or with electrical or chemical cardioversion</p> <p>1) 269 PAP-adherent patients, defined as <math>\geq 4</math> hrs/night at least 70% of nights</p> <p>2) 160 PAP non-adherent patients</p>	Recurrence of AF over a median follow-up of 4.6 months; analyzed for all sleep apnea and separately by type of sleep apnea	Time to recurrence of AF did not differ between PAP-adherent and non-adherent patients overall or for any sleep apnea type. In OSA patients, median recurrence-free survival was 9.4 months in the adherent and 9.5 months in the non-adherent group. PVI (vs. cardioversion) was the strongest predictor of recurrence-free survival, and was more common in PAP non-adherent (33%) than PAP adherent (20%) patients; however, the authors state that in multivariate models adjusting for type of intervention, there was no significant difference between PAP adherent

						and non-adherent patients in hazard of AF recurrence
Traaen et al. <sup>709</sup>	2021	1b	Randomized clinical trial	<p>Patients with paroxysmal atrial fibrillation, screened for sleep apnea with 2 nights of home respiratory polygraphy with a mean AHI <math>\geq 15</math>, and use of CPAP <math>\geq 4</math> hours on each night of a 7-night run-in period.</p> <p>1) Usual care alone (n=54, no dropouts), baseline AF burden 5.0%</p> <p>2) Usual care plus CPAP (n=55, one dropout), baseline AF burden 5.6%; mean CPAP use 4.4 (SD 1.9) hours/night</p>	<p>Primary outcome: between-group difference in change in AF burden (percent of time in AF) from the 1-month period prior to treatment to the final 3 months of the 5-month treatment period</p> <p>Secondary outcome: Percent of patients with a <math>\geq 25\%</math> reduction in AF burden</p> <p>Post-hoc analyses: (1) frequency of AF episodes; (2) duration of AF episodes</p>	<p>AF burden decreased from 5.0 to 4.3% in the control group and from 5.6% to 4.1% in the CPAP group (adjusted mean difference -0.6%, 95% CI -2.6 to +1.3%, p=0.52). No significant difference in “per protocol” analysis including only those using CPAP <math>\geq 4</math> hours/night.</p> <p>The percent of patients with a <math>\geq 25\%</math> reduction in AF burden was 41% in the CPAP group and 31% in the usual care group (adjusted mean difference -9.3%, 95% CI -26.4 to +8.7%, p=0.33).</p> <p>No significant difference in frequency or duration of AF events.</p> <p>Serious adverse events occurred in 13% of CPAP and 4% of control patients.</p>

#### VIII.B.4.c PAP after CVA

Despite the high prevalence of OSA in the stroke population and the well-established literature stating OSA is an independent risk factor for cerebrovascular events, it is not common practice to evaluate and treat OSA as a part of post-stroke workup.

A recent small randomized control trial of stroke patients who were admitted for neurorehabilitation was conducted to determine if OSA treatment with CPAP would improve cognitive and functional outcomes post-stroke. Twenty patients were randomly assigned to receive 4 weeks of CPAP treatment and 16 patients were assigned to receive treatment as usual (control). Patients who received and were

compliant with 4 weeks of CPAP showed greater improvement in cognitive status (attention and executive functioning) compared to the control group. However, there was no significant difference in functional status (neurological status and ADL) between the treatment and control groups.<sup>1219</sup>

There have been mixed results about the efficacy of CPAP treatment on stroke outcomes, but currently there is promising evidence suggesting CPAP improves cognitive functioning of stroke patients, which is consistent with the benefits of CPAP in the general OSA population. In a randomized control trial by Gupta et al.<sup>1028</sup> patients with moderate sleep apnea (AHI >15 events per hour) and recent stroke were randomized to receive either standard of care for stroke or standard of care + CPAP. The patients in the CPAP + standard of care group were found to have a non-statistically significant decrease in new vascular events, and a statistically significant improvement in post stroke function based on the Barthel Index.

Therefore, it is recommended to screen for OSA in all patients presenting with TIA or ischemic or hemorrhagic stroke regardless of whether they are symptomatic or asymptomatic. Earlier diagnosis of OSA and early treatment could improve overall health and cognitive status and reduce the risk of recurrent stroke and stroke mortality. The standard of treatment of OSA is CPAP. However, CPAP is poorly tolerated in both the general population and even less so in the stroke patient population. Apart from the general obstacles, such as mask claustrophobia, nasal congestion, and mask leak, there are unique difficulties stroke patients face, including aphasia, facial or oropharyngeal weakness, and limb weakness. Thus, alternative options for treating OSA should also be considered. The effects of alternative OSA treatments on risk of recurrent stroke have not been reported.

#### **PAP Therapy for OSA after a Stroke**

Aggregate Quality of Evidence: B (Level 1b: 9 studies, Level 2a: 2 studies, Level 2b: 2 studies).

Benefit: Treatment of OSA with CPAP may improve overall health and cognitive status and reduce the risk of recurrent stroke and stroke mortality.

Harm: Side effects and inconvenience of CPAP therapy.

Cost: Low cost associated with PAP therapy and maintenance.

Benefits-Harm Assessment: Preponderance of benefit over harm for use of CPAP in stroke patients.

Value Judgments: The overall evidence favors diagnosis and treatment of OSA to improve neurologic recovery and functional status after stroke. Treatment may also prevent recurrent stroke and reduce risk of stroke mortality, although the evidence is mixed.

Recommendation Level: Recommendation

Intervention: Patients may benefit from OSA treatment with CPAP within the acute stroke phase after a TIA, ischemic or hemorrhagic stroke.

**Table VIII.B.4.c PAP after CVA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Aaronson et al. 1219	2016	1b	Randomized Control Trial	36 stroke patients who were admitted to a	Cognitive status measured by neuropsychologic	CPAP treatment significantly improves attention and executive functioning of stroke

				neurorehabilitation unit with OSA were randomly assigned to receive 4 weeks of CPAP therapy (20) or standard of care (16).	al examination, and functional status measured by two neurological scales and a measure of activities of daily living (ADL).  Recovery rate in the two groups of OSA patients.	patients with OSA. CPAP treatment did not significantly improve functional status (neurological and ADL).
Bravata et al. <sup>1220</sup>	2011	1b	Randomized Control Trial	70 acute TIA patients were randomized to control (25) or treatment group (45) who received auto-CPAP for 2 nights and those in treatment group with OSA received auto-CPAP for remaining 90 days.	Prevalence of OSA  CPAP adherence rate among TIA patients  Recurrent vascular events such as recurrent TIA, stroke, hospitalization for CHF, MI, death	OSA is highly prevalent among patients with acute TIA.  Increasing auto-CPAP use was not significantly associated with reduced rate of recurrent vascular events.
Bravata et al. <sup>598</sup>	2017	1b	Randomized Control Trial	225 pts with cerebrovascular disease and HTN from the GoToSleep study at 2 Veteran Health Affairs centers were randomized to control group or treatment group of auto-CPAP for 1 year.	OSA prevalence, OSA treatment as measured by CPAP adherence, and HTN control	There is a high prevalence of OSA among patients with chronic cerebrovascular disease and hypertension. Portable polysomnography and auto-CPAP use improved the diagnosis and the treatment for OSA compared with standard care, but did not lower blood pressure.
Catalan-Serra et al. <sup>646</sup>	2019	2b	Prospective cohort study	Cohort of 1005 consecutive patients referred to Sleep Units at 2 Spanish University hospitals who were ≥65 years. They	Incidence of coronary heart disease and incidence of stroke after adjusting for OSA group, age, BMI,	The incidence of stroke, but not coronary heart disease, is increased in elderly patients with untreated severe OSA.

				<p>were categorized into 4 groups based on AHI values from sleep studies and CPAP adherence:</p> <p>1) control group 2) untreated mild-moderate OSA 3) untreated severe OSA 4) CPAP-treated OSA</p>	HTN, sex, smoking, ESS, and AF	
Gupta et al. <sup>1028</sup>	2018	1b	RCT	70 patients with OSA and recent stroke randomized to 1. CPAP 2. Non-CPAP.	New vascular events. Secondary: clinical stroke outcomes and neuropsychological parameters.	Nonsignificant lower rate of vascular event in CPAP group (3%) vs. non-CPAP group (15%). Significantly improved clinical stroke outcomes (modified Rankin scale) at 12-months in CPAP group.
Khot et al. <sup>760</sup>	2016	1b	Randomized Control Trial	Pilot study: 40 patients in stroke rehabilitation who were randomized to APAP or sham CPAP without testing for OSA.	Change in Functional Independence Measure (FIM) was assessed between rehabilitation admission and discharge.	There were positive trends towards better FIM score improvement with APAP compared to sham CPAP.
Kim et al. <sup>1221</sup>	2016	2a	Systematic Review and meta-analysis	8 studies (1 RCT and 5 cohort and 2 administrative data) to evaluate effects of CPAP on risk of stroke.	Stroke incidence and mortality	Treating with CPAP in patients with OSA might decrease the risk of stroke as seen only in the cohort studies.

King and Cuellar <sup>1222</sup>	2016	2a	Systematic Review	28 studies (14 observational cohort studies, 5 case-control, 4 cross-sectional, and 4 RCTs) of 10,671 subjects were reviewed on the independent risk, mortality, and prevalence relationship between OSA and stroke/TIA including recurrence and recovery outcomes with CPAP therapy.	Prevalence of OSA and stroke/TIA, recurrence and recovery outcomes with CPAP	OSA is highly prevalent in patients with stroke/TIA and is independently associated with increased risk. CPAP studies revealed reduced stroke recurrence and improved recovery with feasible initiation in stroke units.
McEvoy et al. <sup>26</sup>	2016	1b	Randomized Control Trial	2717 adults between 45-75 y/o with moderate to severe OSA and coronary or cerebrovascular disease from SAVE study were randomized to receive standard care or standard care and CPAP.	Cardiovascular mortality, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or TIA.	CPAP with standard care did not prevent cardiovascular events in patients with moderate-to-severe OSA and established cardiovascular disease. However, patients adherent to CPAP had a lower risk of stroke compared to control group, although this was not seen on primary analysis and only in propensity score-matched analysis.
McKee et al. <sup>1223</sup>	2020	2b	Retrospective observational study	527 post-stroke patients at inpatient rehab who underwent overnight oximetry and those at high risk for OSA (3%ODI>10) were on trial of Auto CPAP.	Recovery measured by changes in functional and cognitive outcomes calculated by functional independence measure (FIM) scores	APAP in high-risk patients was poorly tolerated and did not improve FIM.
Parra et al. <sup>1224</sup>	2015	1b	Randomized Control	235 patients <75 years old admitted	Cardiovascular events: cardiac	Ischemic stroke patients treated with early nasal CPAP

			Trial	with ischemic stroke for the first time and with moderate-severe OSA with an AHI $\geq 20$ events randomized to standard care or nasal CPAP during the acute stroke phase.	ischemic events, recurrent stroke, and cardiovascular mortality	improves long-term survival with better neurological recovery compared to the control group.
Parra et al. <sup>1225</sup>	2011	1b	Randomized Control Trial	140 patients admitted with first time ischemic stroke and AHI $\geq 20$ events/hr randomized to early nasal CPAP or standard care during acute stroke phase.	Cardiovascular events: cardiac ischemic events, stroke recurrence and cardiovascular mortality  Neurological parameters measured by Barthel index, Canadian scale, Rankin scale and SF-36	Patients who received nasal CPAP treatment earlier had significantly greater and faster neurological recovery compared to the control group. Stroke patients treated with CPAP experienced less Incident cardiovascular events in the first 24 months compared to control group.
Ryan et al. <sup>1226</sup>	2011	1b	Randomized Control Trial	Patients with ischemic or hemorrhagic stroke patients with moderate to severe OSA were assigned to standard rehabilitation alone (22) or to CPAP (22)	Motor, functional, and neurocognitive recovery as measured by Canadian Neurological scale, the 6-minute walk test distance, sustained attention response test, and the digit or spatial span-backward.	CPAP in stroke patients undergoing rehabilitation improved functional and motor, but not neurocognitive outcomes.
Sánchez-de-la-Torre et al. <sup>1202</sup>	2020	1b	Randomized Control Trial	2551 patients admitted with acute coronary syndrome (ACS) symptoms who had a respiratory polygraphy within	Prevalence of cardiovascular events: cardiovascular death or non-fatal events [acute myocardial	The prevalence of cardiovascular events was not significantly associated with CPAP use in patients with ACS and OSA compared to standard care treatment. Moreover, OSA diagnosis was

				24h-72h of admission. Patients had a sleep study and those with OSA were randomized to either CPAP with standard care or standard care alone. Those ACS patients without OSA were the control group.	infarction, non-fatal stroke, hospital admission for heart failure, and new hospitalizations for unstable angina or transient ischemic attack]	not associated with worse prognosis in ACS patients.
--	--	--	--	--	--	--

#### VIII.B.4.d PAP for Heart Failure

The prevalence of OSA is significantly higher than the general population, ranging from 11-37%, in patients with heart failure<sup>1227,1228</sup>. In the Sleep Heart Health Study, a cross-sectional analysis in 6,424 individuals demonstrated that OSA was associated with increased relative odds ratio of 2.38 (1.22-4.62) of having heart failure<sup>637</sup>. Treatment of OSA in individuals with heart failure has been shown to directly improve cardiac mechanical function in addition to various factors that perpetuate the pathologic abnormalities in heart failure.

Optimization of blood pressure and heart rate are part of core strategies recommended in the clinical guidelines for heart failure management<sup>752</sup>. Untreated OSA in patients with heart failure with reduced ejection fraction (HFrEF) increases systolic blood pressure<sup>1229</sup>, whereas CPAP treatment of OSA in this population improves systolic and diastolic blood pressure<sup>742,1229-1231</sup>, heart rate<sup>742,1231</sup>, heart rate variability<sup>1232</sup>, oxidative metabolism<sup>1233</sup> and sympathetic activity<sup>1231,1234</sup>.

CPAP treatment of OSA in patients with HFrEF is associated with a modest increase in left ventricular ejection fraction (LVEF)<sup>744,1230,1233,1235-1238</sup>, whereas this increase is not observed in OSA individuals without HFrEF<sup>1236</sup>. The impact of CPAP on LVEF was more prominent in individuals with a baseline LVEF > 30% in a study by Egea et al<sup>744</sup>. While another study did not show an improvement in LVEF with CPAP use, adherence to PAP therapy was low and efficacy of treatment on autoCPAP was not reported, limiting the analysis of PAP impact<sup>1238</sup>. Kasai et al showed that use of CPAP in OSA patients with HFrEF improved event-free survival compared to no CPAP use, with even greater improvement in event-free survival in individuals with higher CPAP use<sup>753</sup>.

Obstructive sleep apnea is associated with diastolic dysfunction<sup>1239</sup> and with left ventricular hypertrophy<sup>1240</sup>. CPAP use among patients with heart failure with preserved ejection fraction (HFpEF) and OSA also improves diastolic function<sup>749,1241-1243</sup> and reduces LV thickness<sup>1240,1243</sup>. Adherence to therapy appears to determine impact of CPAP on diastolic function in OSA patients as well. In a study by Glantz and colleagues, no improvement was seen in diastolic function with CPAP in non-sleepy patients with OSA; however, in post hoc analysis, it was noted that use of CPAP for > 4 hours per night resulted in improved diastolic function<sup>1244</sup>.

#### PAP for Improving Clinical Outcomes in Heart Failure with Reduced Ejection Fraction (HFrEF)

Aggregate Quality of Evidence: B (Level 1a: 1 study; Level 1b: 7 studies; Level 2b: 5 studies; Level 3b: 2 studies).



**Benefit:** Treatment of OSA with CPAP in HFrEF results in direct amelioration of systolic function, stroke volume and daytime sleepiness, as well as systolic blood pressure, heart rate, daytime sympathetic nerve activity, and improved heart rate variability.

**Harm:** Inconvenience of use. Evidence for CPAP and reduction in mortality and event free survival is limited.

**Cost:** Low to moderate costs are associated with PAP machine and supplies. There may be additional costs related to provider visits to monitor for treatment efficacy and adherence.

**Benefits-Harm Assessment:** There may be a benefit conferred by use of CPAP to treat patients with moderate-to-severe OSA and HFrEF.

**Value Judgments:** Treatment of OSA with CPAP in HFrEF is successful in improving LVEF, daytime sleepiness and other factors that influence heart failure management. There is little high-quality evidence to support or dispute the treatment of moderate-to-severe OSA in patients with HFrEF to reduce mortality. Balanced with low risk of harm, it may be appropriate to offer patients with moderate-to-severe OSA and concomitant HFrEF treatment with CPAP.

**Recommendation Level:** Option

**Intervention:** CPAP therapy should be strongly considered in patients with HFrEF and symptomatic OSA. CPAP therapy impacts some treatment outcomes.

#### PAP for Improving Clinical Outcomes in Heart Failure with Preserved Ejection Fraction (HFpEF)

**Aggregate Quality of Evidence:** C (Level 1b: 3 studies; Level 2b: 5 studies).

**Benefit:** Treatment of OSA with CPAP in HFpEF resulted in improvement in LV diastolic function and reduced LV and intraventricular septal thickness.

**Harm:** Inconvenience of use associated with CPAP.

**Cost:** Low costs are associated with PAP machine and supplies. There may be additional costs related to provider visits to monitor for treatment efficacy and adherence.

**Benefits-Harm Assessment:** Benefits of PAP therapy outweighs the harms in this population.

**Value Judgments:** Treatment of OSA in HFpEF results in improved diastolic dysfunction and its surrogates such as IV septum and LV thickness. Evidence on impact of CPAP on event-free survival is limited.

**Recommendation Level:** Option.

**Intervention:** CPAP therapy should be considered in patients with HFpEF and OSA. CPAP therapy impacts some treatment outcomes.

#### VIII.B.4.d1 Evidence for PAP and Clinical Outcomes in HFrEF

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Tkacova et al. <sup>1229</sup>	1998	3b	Prospective CS	Pharmacologically treated HF patients with OSA were studied during PSG and recordings were done before, during, and after CPAP application n = 8	BP and esophageal pressures before onset of sleep and during stage 2 NREM sleep before, during, and after application of CPAP	1. OSA was associated with increased systolic BP and systolic LVPTm from wakefulness to stage 2 NREM sleep 2. CPAP alleviated

						OSA, improved SaO <sub>2</sub> , and reduced systolic BP in stage 2 NREM sleep, LVPtm, Pes amplitude, and RR. <sup>1229</sup>
Usui et al. <sup>1231</sup>	2005	1b	RCT	Pharmacologically treated HF patients with LVEF < 45% and OSA (AHI ≥ 20/h) randomized to PAP and usual therapy vs. only usual therapy. n = 17	Recording at baseline and at 1 month the morning after PSG: -ECG -BP -peroneal MSNA With subjects awake, resting quietly supine, and breathing without apnea	1. In OSA patients treated with CPAP, there was significant reductions in daytime MSNA (from 58 +/- 4 bursts/min to 48 +/- 5 bursts/min; 84 +/- 4 bursts/100 heart beats to 72 +/- 5 bursts/100 heart beats; p < 0.001 and p = 0.003, respectively), systolic BP (from 135 +/- 5 mm Hg to 120 +/- 6 mm Hg, p = 0.03), and HR (from 69 +/- 2 min(-1) to 66 +/- 2 min(-1); p = 0.013). 2. In control OSA patients, there were no changes in MSNA, systolic BP, or HR. <sup>1231</sup>
Kaneko et al. <sup>742</sup>	2003	1b	RCT	Pharmacologically treated HF patients with LVEF ≤ 45% and OSA (AHI ≥ 20/h) randomized to PAP and usual therapy vs. only usual therapy. n = 24	Recording at baseline and at 1 month: -AHI -Daytime BP and HR -LV end-diastolic dimensions -LVEF	1. In OSA patients treated with CPAP, there was significant reductions in AHI, daytime systolic BP, HR, LV end-diastolic dimension and improved LVEF (absolute improvement by 8.8%) 2. In control OSA patients, there were no changes in AHI, daytime systolic BP, HR, LV

						end-diastolic dimensions, and LVEF. <sup>742</sup>
Gilman et al. <sup>1232</sup>	2008	1b	RCT	Pharmacologically treated HF patients with LVEF $\leq$ 45% and OSA (AHI $\geq$ 20/h) randomized to PAP and usual therapy vs. only usual therapy. n = 19	Morning HF-HRV at baseline and at 1 month.	1. In OSA patients treated with CPAP, there was HF-HRV increased significantly during wakefulness in the morning. 2. In control OSA patients, there were no changes in HF-HRV during wakefulness in the morning. <sup>1232</sup>
Mansfield et al. <sup>745</sup>	2004	1b	RCT	Pharmacologically treated HF with LVEF $<$ 55% and NYHA II, AHI $\geq$ 5/h, CSA $\leq$ 20%) randomized to PAP and usual therapy vs. only usual therapy. n = 55	Recording at baseline and at 3 months: -LVEF -Overnight urinary norepinephrine -BP -quality of life	1. In OSA patients treated with CPAP, there was increased LVEF (absolute improvement by 5%), reduced urine norepinephrine excretion (42% decrease), ESS, and minimum oxygen saturation. 2. No changes in blood pressure or peak oxygen consumption were noted. 3. In control OSA patients, there were no significant changes in LVEF, urine norepinephrine or ESS. <sup>745</sup>
Smith et al. <sup>1238</sup>	2007	1b	RCT with Crossover Design	Pharmacologically treated symptomatic HF with LVEF $<$ 45% and NYHA class II-VI with OSA (AHI $\geq$ 15/h) randomized to APAP vs. sham CPAP for 6 weeks each in crossover design. n = 23	Recordings at baseline, 6 weeks and 13 weeks (one week washout before crossover): -Clinical assessment -TTE -CPET -6 minute walk distance (MWD) -neurohumoral markers (NT-pro-BNP and NT-pro-ANP)	1. CPAP improved daytime sleepiness, but not LVEF, 6 MWD, Peak VO <sub>2</sub> , VE/VCO <sub>2</sub> , or quality of life. 2. Study limitations were poor adherence (~3 hours) and use of autoCPAP without report of treatment

					- Oxford Sleep Resistance Test -Quality of life	efficacy in AHI reduction. <sup>1238</sup>
Malone et al. <sup>1237</sup>	1991	3b	Prospective CS	Pharmacologically treated, obese patients with idiopathic cardiomyopathy, LVEF < 55%, and severe OSA n = 8	Recording at baseline, 4 weeks after nasal CPAP, and 1 week after withdrawal of nasal CPAP -TTE	1. CPAP results in mean LVEF increase of 37% to 49% from pre-treatment to 4 weeks after therapy. 2. Withdrawal of CPAP resulted in reduction of LVEF from 53% to 45%. <sup>1237</sup>
Egea et al. <sup>744</sup>	2008	1b	RCT	Pharmacologically treated HF with LVEF < 45% and OSA with AHI > 10/h and randomized to PAP vs. sham CPAP. n = 60	Recording and baseline and 3 months of treatment with optimal CPAP or sham-CPAP - LVEF - 6 minutes walking test - ESS - SF-36 - NYHA - Dyspnea	1. LVEF improved by an absolute 2.2% in the treatment group with even greater improvement in patients with LVEF > 30%. 2. ESS with significant improvement in both groups. 3. No change in NYHA, 6 minute walk distance, SF-36 or dyspnea. <sup>744</sup>
Johnson et al. <sup>1236</sup>	2008	2b	Prospective CS	HF patients with NYHA class II or III and LVEF < 40% and AHI > 15/h. Patients with OSA were treated with CPAP and those without were not. n = 12	TTE at baseline (awake, before, and after acute CPAP administration) and after CPAP therapy (7 weeks) in OSA patients. Recording were done at baseline and follow-up for non-OSA patients.	1. In OSA patients, acute CPAP resulted in decreased stroke volume and LVEF by ~5% compared to baseline. 2. In OSA patients, chronic CPAP resulted in increased stroke volume and increased LVEF from 38.4% to 43.4%. 3. There was no change in LVEF, diastolic function or filling pressures in patients without OSA. <sup>1236</sup>
Ferrier et al. <sup>1235</sup>	2008	2b	Prospective CS	Outpatient patients with HF (LVEF < 45%) and OSA (AHI > 15/h) treated with	Recording at baseline and at 6 months - Minnesota HF score	1. In the study group, there was absolute

				CPAP and control group with HF (LVEF < 45%) and AHI < 10/h n = 26	<ul style="list-style-type: none"> <li>- ESS</li> <li>- Shuttle walk distance</li> <li>- BNP</li> <li>- Urine catecholamines</li> <li>- TTE</li> </ul>	improvement in LVEF by 4.7%. 2. In the study group, there was decrease in the LV end-diastolic volume, systolic blood pressure, and ESS. 3. Walk distance, catecholamines, BNP levels, and symptoms remained unchanged in both groups. <sup>1235</sup>
Yoshinaga et al. <sup>1233</sup>	2007	2b	Prospective CS	Outpatients with HF (LVEF < 40%, NYHA II or III, unchanged > 4 weeks) with and without OSA (AHI > 15/h) n = 12	<ul style="list-style-type: none"> <li>- Oxidative metabolism using mono-exponential fit of the of the myocardial [11C] acetate positron emission tomography time-activity curve (correlate for myocardial oxygen consumption).</li> <li>- Myocardial efficiency from work metabolic index and at baseline, short-term CPAP and after 6 +/- 3 weeks of CPAP.</li> </ul>	1.Short-term CPAP reduced oxidative metabolism and stroke volume index, but did not change work metabolic index. 2. Longer-term CPAP improved left ventricular ejection fraction by 5%, reduced oxidative metabolism and improved work metabolic index. <sup>1233</sup>
Kasai T et al. <sup>753</sup>	2008	2b	Prospective CS	Medically optimized heart failure with LVEF ≤ 50%, without hospitalizations in the preceding month and AHI ≥ 15/hour, NYHA Class II or above, CAI < 50% of overall AHI. -Participants grouped into CPAP untreated, “more compliant” and “less compliant” groups. n = 88	<p>Baseline recordings:</p> <ul style="list-style-type: none"> <li>- BMI</li> <li>- heart rate</li> <li>- ESS</li> <li>- LVEF by echo</li> <li>- plasma norepinephrine</li> <li>- NYHA class</li> <li>- etiology of HF (ischemic or nonischemic)</li> <li>- presence of AFIB</li> <li>- administered medications</li> </ul> <p>Primary end point:</p> <ul style="list-style-type: none"> <li>- event-free survival at 25.3 months</li> </ul>	1. Use of CPAP was associated with improved event-free survival compared to no CPAP use. 2. Greater adherence to CPAP therapy (~6.0 hours/night) was associated with greater improvement in event free-survival than less adherence (~3.5 hours/night). <sup>753</sup>
Wang et al. <sup>741</sup>	2007	2b	Prospective CS	Medically optimized heart failure patients with LVEF ≤ 45% and NYHA class II to IV with OSA (AHI ≥ 15) with a CPAP treated	<p>Primary end point:</p> <ul style="list-style-type: none"> <li>- Cumulative rate of death from the date of the diagnostic sleep study until January 1, 2005</li> </ul>	There was trend for reduced mortality in the treated OSA group. <sup>741</sup>

				and untreated group n = 164		
Hall et al. <sup>1234</sup>	2014	1b	RCT	Medically optimized patients with HFrEF (EF < 45%, NYHA ≥ II and OSA (AHI > 10, OA > 80%) randomized to CPAP versus usual care. n = 45	Evaluated at baseline and 6-8 weeks after therapy initiation: - ECG - echocardiography - c-acetate and c-hydroxyephedrine PET imaging.	1. Short-term CPAP increased hydroxyephedrine retention, indicating improved sympathetic nerve function in patients with OSA and HFrEF. 2. No changes in hemodynamic, LV or energetics parameters in the whole study population. <sup>1234</sup>
Aggarwal et al. <sup>1230</sup>	2014	1a	SR	Systemic review and meta-analysis with pooled data from 15 randomized controlled trials in which patients had sleep disordered breathing and heart failure and consisted of a group receiving PAP therapy and another group receiving no PAP therapy or sham PAP therapy.	End points analyzed are: - Left ventricular ejection fraction - Diastolic blood pressure - Systolic blood pressure - Heart rate - Mortality	1. A significant improvement in LVEF was noted with CPAP (mean difference of 5.05%; 95% CI 3.72-6.38), diastolic blood pressure (mean difference of -1.67; 95% CI of -3.09--0.25) and heart rate (mean difference of -5.92; 95% CI of -10.12--1.72).  2. No significant changes in mortality (OR 0.63; 95% CI 0.40-1.00) and systolic blood pressure (mean difference -6.35; 95% CI -16.11-2.41) were noted.

## VIII.B.4.d2 Evidence for PAP and Clinical Outcomes in HFpEF

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Arias et al. <sup>749</sup>	2005	1b	RCT	Patients with OSA (AHI ≥ 10/hr and excessive daytime sleepiness with	Recording at baseline, after effective nasal CPAP therapy for 12 weeks, and	1. Diastolic function improved in the OSA patients after 12 weeks of

				ESS $\geq$ 10) and healthy control subjects. OSA patients were randomized to 12 weeks of sham CPAP vs. effective CPAP and crossed-over to alternate therapy. n = 32	sham CPAP therapy for 12 weeks - TTE - Blood pressures - Urine catecholamines	effective CPAP therapy. 2. There was also significant increase in ratio of peak early filling velocity (E) to peak late filling velocity (A) of diastolic transmitral flow (E/A) and reduction in mitral deceleration time and isovolumic relaxation.
Alchanatis et al. <sup>1242</sup>	2000	2b	Prospective CS	Patients with OSA (AHI > 15/h). n = 15	Blood pressure and TTE at baseline and after 12-14 weeks of nasal CPAP therapy	1. At baseline, there was diastolic dysfunction present in OSA patients and was improved (increased E/A ratio, decreased IVRT) after 12 weeks of CPAP therapy.
Cloward et al. <sup>1240</sup>	2003	2b	Prospective CS	Patient with desaturation index >40/h and $\geq$ 20% cumulative time spent with arterial oxygen saturation (SaO <sub>2</sub> ) < 90% n = 25	TTE at baseline, 1 month and 6 months following initiation of PAP therapy.	1. Severe OSA was associated with left ventricular hypertrophy (LVH), left atrial enlargement (LAE), right atrial enlargement (RAE), and right ventricular hypertrophy (RVH) 2. Those compliant with CPAP therapy, there significant reductions in LVH after 6 months of CPAP therapy as measured by interventricular septal distance. 3. RAE and LAE were unchanged after CPAP therapy.
Dursunoglu et al. <sup>1243</sup>	2007	2b	Prospective CS	Patients with severe OSA (AHI > 33/h) n = 25	TTE and blood pressure in patients with severe OSA at baseline and 6 months of CPAP therapy	1. There was significant reduction in LV wall thickness (interventricular septum and LV posterior wall) in the CPAP treated group. 2. There was significant improvement in LV global dysfunction after 6 months of PAP therapy.
Shivalkar et al. <sup>1245</sup>	2006	2b	Prospective CS	Patients with severe, age- and gender-matched	TTE and blood pressure at baseline and after 6 months of PAP.	1. PAP therapy significantly improved heart rate and blood pressure.

				controls n= 40		2. PAP resulted in improved pulmonary artery pressures, interventricular septum thickness, right ventricle dimensions, mitral annular systolic tissue doppler velocity (Sm), tricuspid annular Sm, and right ventricle free wall Sm.
Akar Bayram et al. <sup>1241</sup>	2009	2b	Prospective CS	Newly diagnosed OSA patients with AHI $\geq$ 15 and control patients without OSA. n = 46	TTE at baseline and after 6 months of PAP therapy in the study group compared to control patients.	1. Patients who were on CPAP therapy had improved systolic and diastolic function after 6 months of CPAP therapy.
Glantz et al. <sup>1244</sup>	2017	1b	RCT	Revascularized CAD patients with non-sleepy OSA (AHI $\geq$ 15, ESS < 10) were assigned to CPAP or no-CPAP group. n = 171	-Echocardiographic measurements were obtained at baseline, 3 months and 12 months.	1. There was no improvement in diastolic dysfunction in non-sleepy CAD patients with OSA on CPAP therapy. 2. CPAP use of >4h/night resulted in improved diastolic dysfunction in post hoc analysis.
Craig et al. <sup>1246</sup>	2015	1b	RCT	Two centers randomized 238 patients to 6 months of CPAP or standard care. n = 238	Echocardiograms were done for 168 patients and cardiac magnetic resonance scans were done for 68 patients. Baseline ODI was 13.5/hour and ESS was 8.4. Baseline LV ejection fraction was well preserved (60.4%).	1. CPAP had no significant effect on ECHO-derived LA area or early to late left ventricular filling velocity (E/A). 2. Small change in echo-derived LV end diastolic volume (EDV) with CPAP was noted (-5.9mL with 95% CI -10.6 - -1.2; p=0.015). 3. No significant changes were detected by CMR or LV mass index or LVEF.

#### VIII.B.4.e PAP and Cardiovascular Events

Obstructive sleep apnea may increase the risk of coronary artery disease three-fold relative to the general population (16.2% CAD in OSA patients versus 5.4% in patients without OSA)<sup>672</sup>. The Sleep Heart Health cohort reported a prevalence of self-reported CAD ranging from 9% to 19% in OSA patients depending on the severity of the sleep-disordered breathing<sup>637</sup>. The risk of CAD is highest in those with severe OSA.



Observational data have shown that CPAP therapy may attenuate this risk of CAD development from 16.2% to 3.9%, when there is adherence to CPAP and efficacy of CPAP in resolving OSA<sup>1247</sup>. Multiple long-term studies evaluating CPAP use in OSA spanning five to 10 years have shown reduction in CAD-related mortality and cardiovascular events with CPAP<sup>118,1248,1249</sup>. Doherty and colleagues showed that death from cardiac events was reduced from 14.8% to 1.9% with PAP therapy compared to untreated OSA, and total cardiac events were also reduced with PAP therapy relative to untreated OSA (18% versus 31% respectively) over an average of 7 years<sup>1249</sup>. An additional retrospective study showed improved CAD mortality with PAP treatment in moderate to severe OSA but did not show reduction in CAD events<sup>1250</sup>.

Prospective randomized controlled trials investigating the impact of CPAP therapy for newly diagnosed OSA after index cardiac or vascular event did not show reduction in secondary cardiac or vascular events, including cardiovascular death<sup>26,672,1202</sup>. These studies may have failed to demonstrate benefits of PAP therapy in cardiovascular risk reduction due to poor adherence (<4 hours per night)<sup>26,1202</sup>. Adherence may play a role in improving cardiovascular outcomes, as demonstrated by Peker et al in which the secondary analysis of the RCT, individuals using CPAP for more than 4 hours per night relative to those nonadherent to therapy had a significant reduction in cardiac events<sup>672</sup>.

#### CPAP for Cardiovascular Event Risk Reduction in Coronary Artery Disease

**Aggregate Quality of Evidence:** B (Level 1a: 2 studies; Level 1b: 4 studies; Level 2a: 2 studies; Level 2b: 5 studies) Mix of positive and negative findings.

**Benefit:** PAP therapy in patients with OSA reduced fatal and non-fatal cardiac events in cohort studies. However, RCT studies did not uniformly show this benefit. CV risk reduction may be related to PAP adherence levels on secondary analyses.

**Harm:** Minor effects associated with discomfort and inconvenience of PAP. Variable adherence rates on PAP.

**Cost:** Low costs are associated with PAP machine and supplies and provider visits to monitor for treatment efficacy and adherence.

**Benefits-Harm Assessment:** Low harm associated with OSA treatment with CPAP. The evidence for benefit is mixed. Balance of benefit and harm.

**Value Judgments:** There is moderate quality evidence that OSA leads to cardiovascular disease, but low quality evidence that treatment with CPAP reduces this risk. RCT trial design may underestimate the effects of CPAP.

**Recommendation Level:** Option.

**Intervention:** CPAP use in patients with CAD does not clearly reduce CV risk in all patients. Further studies are required to identify the best candidates for improved outcomes. Shared decision making regarding CPAP treatment is suggested to weigh individual patient symptoms, preferences and comorbidities.

Table VIII.B.4.e: Evidence for PAP and Cardiovascular Risk Reduction

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Peker Y et al. <sup>1247</sup>	2006	2b	Prospective CS	Patients age 30-69 who underwent in-lab polysomnography and were not known to have heart disease were	Cohort was observed over 7 years for development of CAD and CAD related fatality.	1.16.2% of patients with OSA and 5.4% of patients without OSA developed CAD. 2. Patients on effective therapy for OSA (PAP use > 50% of sleep

				stratified by presence or absence of OSA (AHI $\geq 15$ ), and treatment with PAP therapy if OSA diagnosis present. n = 308		time, use of oral appliance, or effectively treated with surgery) had reduction in incidence of CAD to 3.9%.
Peker Y et al. <sup>672</sup>	2016	1b	RCT	Patients with newly revascularized CAD and OSA (AHI $\geq 15$ /hr) without daytime sleepiness (ESS < 10) randomized to auto-titrating PAP or no PAP. n = 122	Primary endpoint was first event of repeat revascularization, MI, or cardiovascular mortality. Median follow up was 57 months.	1. Incidence of the primary endpoint did not differ significantly in patients who did vs did not receive CPAP (18.1% vs. 22.1%; HR 0.80 with 95% CI 0.46-1.41, p = 0.449). 2. Significant cardiovascular risk reduction in those who used CPAP for $\geq 4$ hrs vs. < 4 hrs per night or did not receive treatment (HR 0.29 with 95% CI 0.10-0.86, p=0.026)
McEvoy et al. <sup>26</sup>	2016	1b	RCT	Adults between 45-75 years of age with moderate to severe OSA and coronary or cerebrovascular disease were randomized to receive CPAP treatment plus usual care or usual care alone. n = 2717	The primary end-point was death from cardiovascular causes, MI, CVA, or hospitalization for unstable angina, heart failure, or TIA.	1. After a mean follow-up of 3.7 years, there was no significant difference in the primary end point in the CPAP vs. usual care group (HR 1.10 with 95% CI 0.91-1.32; p=0.34). 2. No significant effect on any individual or other composite cardiovascular end point was observed. 3. Mean duration of adherence to CPAP therapy was 3.3 hours per night and mean AHI decreased from 20 events/hr to 3.7 events/hr.
Sanchez-de-la-Torre et al. <sup>1202</sup>	2020	1b	RCT	Patients with ACS at 15 hospital in Spain. Non-sleepy, adult patients admitted to hospital for documented symptoms of ACS. Respiratory polygraphy completed in the first 24-72 hours after admission. OSA patients were randomly assigned to CPAP	Cohort was followed for minimum of 1 year. The primary endpoint was the prevalence of composite of cardiovascular event (cardiovascular death or non-fatal events such as MI, CVA, hospital admission for heart failure, and new	1. The prevalence of cardiovascular events was similar between patients in the CPAP and control groups HR 0.89 with 95% CI of 0.68-1.17; p=0.40) during follow up. 2. Mean time of adherence to CPAP was 2.78 hr/night. 3. The prevalence of cardiovascular events seem not

				plus usual care or usual care alone group. n = 1264	hospitalizations for unstable angina or TIA)  Cohort was followed for median of 3.35 years.	to be related to CPAP compliance or OSA severity.
Marin JM et al. <sup>118</sup>	2005	2b	Prospective CS	Men with OSA (AHI $\geq 5$ /hour) and age- and BMI-matched snorers and healthy adults without sleep apnea, stratified further by whether or not sleep apnea was treated. n = 1651	Cohort was observed for up to 10.1 years for development of CAD and CAD-related fatality.	PAP treatment of OSA was associated with lower nonfatal (0.64 per 100 person-years) and fatal cardiovascular events (0.35 per 100 person-years), than untreated severe sleep apnea (1.06 and 2.13, respectively), untreated mild to moderate sleep apnea (0.55 and 0.89, respectively).
Doherty LS et al. <sup>1249</sup>	2005	2b	Prospective CS	Patients with OSA (AHI $\geq 5$ ) receiving CPAP for at least 5 years. n = 168	Cohort was observed for average follow-up of 7.5 years. Prevalence of cardiovascular was evaluated on those intolerant of CPAP versus those actively using CPAP.	1. Death from cardiac events was lower in the CPAP-treated patients than untreated patients (1.9% versus 14.8%, p=0.009). 2. Total cardiac events were also lower in CPAP-treated patients (18% versus 31%, respectively; p<0.05).
Buchner NJ et al. <sup>1248</sup>	2007	2b	CS	Patients that underwent polysomnography and had OSA (AHI $\geq 5$ ) n = 384	Fatal and nonfatal cardiac events and PAP adherence were evaluated over a median follow-up of 6 years.	1. In treated patients, AHI reduced from an average of 30.8 to 5.6/hour. 2. Cardiovascular events were less frequent in treated patients (14.3%) than untreated patients (28.3%). 3. Estimated event-free survival at 10 years was 79.7% in treated versus 51.8% in untreated. 4. Estimated event-free survival at 10 years was 80.3% in treated versus 51.8% in untreated.
Paulitsch FdS et al. <sup>1251</sup>	2019	1a	SR	Randomized controlled trials that compared CPAP with no active treatment in adults with OSA and CVD. n = 3314	Primary outcomes were: - All cause mortality - Cardiovascular mortality	The duration (median) of CPAP treatment varied from 1 – 56.9 months. 1. The pooled RR was 0.58 (95% CI 0.6-1.23) for cardiovascular

					<ul style="list-style-type: none"> <li>- Acute MI</li> <li>- CVA</li> <li>- Any major cardiovascular event</li> </ul>	<p>death.</p> <p>2. The pooled RR was 1.11 (95% CI 0.76-1.62) for MI.</p> <p>3. The pooled RR was 0.93 (95% CI 0.70-1.24) for any major cardiovascular event.</p>
Wang et al. <sup>634</sup>	2018	2a	SR	<p>Observational studies and randomized controlled trials that included patients with OSA and CAD and reported impact of PAP therapy versus no PAP therapy.</p> <p>n = 1430</p>	<p>Primary outcomes was major adverse cardiovascular event (MACE) including:</p> <ul style="list-style-type: none"> <li>- All-cause or cardiovascular death</li> <li>- Myocardial infarction</li> <li>- Stroke</li> <li>- Repeat revascularization</li> <li>- Hospitalization for heart failure</li> </ul>	<p>Median duration of follow up was 36 to 86.5 months.</p> <p>1. Treatment with CPAP was associated with significantly lower risk of MACE in 6 observational studies (RR 0.61; 95% CI 0.39-0.49) but this was not reproduced in 2 RCTs (RR 0.57; 95% CI 0.32-1.02).</p> <p>2. CPAP significantly reduced the risk of all-cause death (4 observational studies) and cardiovascular death (3 observational studies), which were not confirmed in RCTs.</p>
Labarca et al. <sup>751</sup>	2020	2a	SR	<p>Pooled data from 8 RCTs including adults with OSA (AHI<math>\geq</math>5) with average follow-up 6 to 84 months. Three studies included patients in sleep clinics (primary prevention), whereas five studies included patients with known CAD (secondary prevention).</p> <p>n = 5,817</p>	<p>Outcomes observed were relative risk of:</p> <ul style="list-style-type: none"> <li>-major adverse cardiovascular events (MACE)</li> <li>-CV mortality</li> <li>-Myocardial infarction</li> <li>-Unstable angina</li> <li>-AFIB</li> <li>-Heart failure</li> </ul>	<p>CPAP did not improve cardiovascular outcomes. Heterogeneity in studies including study population (primary versus secondary prevention), bias due to lack of blinding, and inclusion of sleepy and nonsleepy patients cited.</p>
Abuzaid et al. <sup>1031</sup>	2017	1a	SR	<p>Randomized controlled trials with adult patients with OSA who were assigned to either PAP therapy or non-PAP therapy (standard therapy).</p> <p>n = 3,780</p>	<p>Primary outcome:</p> <p>Major cardiovascular event</p> <p>Other outcomes:</p> <ul style="list-style-type: none"> <li>- Cardiac mortality</li> <li>- Myocardial infarction</li> <li>- Angina pectoris</li> </ul>	<p>1. Compared with medical therapy alone, CPAP use was not associated with reduced risk of major adverse cardiovascular events (RR 0.94; 95% CI 0.78-1.15) EXCEPT in the subgroup that wore CPAP &gt; 4 hours/night (RR 0.70; 95% CI 0.52-0.94)</p> <p>2. No reduction in the risk of cardiac mortality (RR 1.14; 95%</p>

					<ul style="list-style-type: none"> <li>- Stroke</li> <li>- Transient ischemic attack</li> </ul>	<p>CI 0.66-1.97), myocardial infarction (RR 0.96; 95% CI 0.64-1.44) and angina pectoris (RR 1.16; 95% CI 0.9-1.50) was noted.</p> <p>3. Subgroup analysis of CPAP adherence demonstrated that CPAP use was not associated with decreased risk of heart failure (RR 0.91; 95% CI 0.50-1.66).</p>
Barbé et al. <sup>38</sup>	2012	1b	RCT	Nonsleepy patients with moderate to severe OSA (AHI $\geq 20$ , ESS $\leq 10$ ), randomized to CPAP versus no treatment. n = 725	Incidence of hypertension or cardiovascular events assessed over an average of 4 years.	CPAP use was not associated with a statistically significant reduction in HTN or cardiovascular events. The hypertension or cardiovascular event incidence density rate was 9.20 per 100 person-years (95% CI, 7.36-11.04) in the CPAP group and 11.02 per 100 person-years (95% CI, 8.96-13.08) in the control group.
Cassar et al. <sup>1250</sup>	2007	2b	Retrospective CS	Patients with moderate to severe OSA (AHI $\geq 15$ ) on polysomnography between 1992 and 2004 who underwent PCI, stratified by treated or untreated for OSA. n = 10	Observed for: <ul style="list-style-type: none"> <li>-Cardiac death</li> <li>-General mortality</li> <li>-Major adverse cardiac events</li> <li>-Major adverse cardiac or cerebrovascular events</li> </ul>	<ol style="list-style-type: none"> <li>1. Treatment of OSA reduced number of cardiac deaths from 10% to 3% at 5 years.</li> <li>2. No difference in number of major cardiac events or adverse cerebrovascular events.</li> </ol>

### VIII.B.5 PAP and Cognitive Measures

Sleep apnea treatment could potentially influence the central nervous system (CNS) through amelioration of recurrent nocturnal hypoxia, sympathetic activation, sleep deprivation, and inflammation, amongst others, which may accelerate decline in cognitive function if left untreated<sup>1252-1254</sup>. If the benefits of CPAP are largely due to reduced daytime sleepiness, the related cognitive benefits would cease shortly after stopping CPAP or may attenuate over time. However, it is also possible that CPAP has disease-modifying effects that provide a long-term, sustained benefit that fundamentally alters the trajectory of age-related cognitive decline by reducing neuronal cell death and maintaining neural plasticity<sup>831,1252,1255,1256</sup>.

Several mechanisms could underlie the potential for long-term cognitive benefits. From a vascular perspective, OSA episodes lead to sympathetic vasoconstriction, which can increase the risk of hypertension and subsequent end-organ damage, including neuronal cell death from cerebrovascular

injury<sup>1257</sup>. Imaging studies in sleep apnea patients have shown evidence of multiple changes, including in hippocampal subfields<sup>1255,1258,1259</sup>. OSA may also act on several elements of the staged biomarker model of more severe cognitive impairment, such as in Alzheimer's Disease (AD) where Amyloid- $\beta$  is the first detectable stage, followed by tau pathology, neuronal injury, memory dysfunction and decreased cognitive function<sup>1252,1255,1256</sup>. Specifically, nocturnal hypoxia and oxidative stress can increase the risk of diffuse neuritic plaques<sup>1255,1260</sup>. Sleep fragmentation, can also have multiple negative consequences with long-term sequelae impacting this AD model: 1) reduced glymphatic clearance of A $\beta$ <sup>1261</sup>; and 2) increased cerebrospinal fluid tau levels<sup>1256</sup>. Apolipoprotein E may mediate these effects<sup>1262</sup>. Complicating this process is the growing body of evidence that this relationship can be bi-directional<sup>1256</sup>. For example, tauopathy can lead to neuronal loss in key sleep-wake centers, such as the locus coeruleus<sup>1263</sup>. Cholinergic neurons are important in respiratory control, including upper airway motor neurons, and are often affected in AD<sup>1264</sup>.

A subsection of the 2019 AASM systematic review and meta-analysis evaluated RCTs for the neurocognitive improvements with CPAP therapy for OSA and concluded no significant difference between PAP and control groups.<sup>39</sup> Of note, the studies in the meta-analysis include patients of a wide range of ages, with a wide range of severity of OSA, with variable symptoms (including a group of non-sleepy patients), and a variable treatment duration (1-12 months). No included studies selectively enrolled patients with dementia or MCI. Given the complex relationship between OSA and cognitive function, it is likely that certain subsets of patients (such as MCI/dementia patients, or elderly patients with severe OSA) may derive greater cognitive benefits from CPAP therapy than the general adult OSA population. Additionally, other quantitative reviews of RCTs (see Table 9b) indicate a slight benefit in cognitive function from CPAP use<sup>1254,1265-1268</sup>, but three of these reviews have reported significant benefit in only one cognitive domain each – attention (Kylstra)<sup>1265</sup>, vigilance (Pan)<sup>1267</sup>, or memory (Labarca)<sup>1266</sup>. Of note, two of the reviews focused on elderly patients<sup>1266,1268</sup>, and one focused on AD patients<sup>1254</sup>. Many RCTs evaluating CPAP and neurocognitive function have found modest improvements in certain cognitive domains, while other studies have found no significant effect. Many of the published RCTs are limited by small sample sizes and/or short trial durations (as short as 1 week of treatment), with the majority not exceeding 3 months of CPAP treatment. Based on the available evidence, it is uncertain that treatment of OSA with CPAP therapy improves neurocognitive function. Quantitative reviews of the data demonstrate inconsistent benefits, but this may be due to the variable quality and study populations of the RCTs on which they are based.

Data suggests that treatment of OSA with continuous positive airway pressure (CPAP) therapy may offer benefit with minimal risk<sup>831,1252,1254-1256,1258,1262,1263,1269,1270</sup>. PAP effects on cognitive function in cognitively normal adults may differ from outcomes in cognitively impaired adults.

In cognitively normal adults, several RCTs have been performed examining the effect of PAP on cognitive function. The most notable was the APPLES study, which showed an improvement in sleepiness (both objective and subjective), but no sustained impact on cognitive function aside from a transient improvement at two months in executive and frontal lobe function<sup>1271</sup>. One possible explanation suggests that the study sample from this cohort had sufficient cognitive reserve that there was minimal room for improvement<sup>1272</sup>. A 2015 meta-analysis of 13 studies found a significant but small effect size ( $d=0.12$ ) in improved vigilance measures only. A later 2020 meta-analysis of 14 studies noted that those with more sleepiness or more severe OSA are more likely to benefit, with a significant but small effect size on attention and speed of information processing only ( $SMD=0.17$ )<sup>1273</sup>. Most of the studies are limited by short trial durations ranging from 1 to 24 weeks, whereas prior neuroimaging studies suggest effects may require up to 12 months to be apparent<sup>1273</sup>.

In cognitively impaired populations, there are relatively few RCTs. One RCT in mild-moderate Alzheimer's Disease patients with OSA was performed using sham-CPAP vs CPAP for a 3-week period, then the sham-CPAP group crossed over to CPAP for a subsequent 3 weeks<sup>1274</sup>. They noted statistically significant improvements in a composite endpoint as well as on two individual tests (Hopkins Verbal Learning Test-Revised and Trail Making) when including the 3 week + cross-over data<sup>1274</sup>. An additional long-term follow-up (13.3 months) was done in a subset of five CPAP adherent vs five non-CPAP adherent patients from this cohort. While findings were not statistically significant due to the sample size, the effect size on the composite measure was small to moderate at 0.4.<sup>1275</sup> In mild cognitive impairment patients, Richards and colleagues conducted a quasi-experimental study with one-year follow-up that demonstrated moderate to large effect sizes for psychomotor/cognitive processing and other domains.<sup>1270</sup> A secondary analysis published in 2020 from the same cohort showed that elderly MCI patients with mild OSA also derived cognitive benefit from CPAP adherence<sup>1276</sup>. Only two studies with >1 year follow-up have been conducted on the effect of CPAP in older adults with mild cognitive impairment (MCI) and sleep apnea. One retrospective study (MCI n=62, follow-up 2-3 yrs) suggested a sustained benefit<sup>1277</sup>. However, another recent retrospective study (MCI n=96, mean follow-up n=2.8 yrs) showed no cognitive benefit<sup>1278</sup>. MCI patients are heterogeneous with only a subset having high A $\beta$  burden, tauopathy or neurodegeneration associated with increased risk of progression to AD with dementia. The impact of OSA may vary depending upon MCI subtype.<sup>1260,1279</sup>

Research elucidating which patients might derive the most cognitive benefit from CPAP usage can help focus treatment efforts on certain patient populations (i.e., elderly, MCI/dementia patients). Certain subsets of patients may derive greater cognitive benefits from CPAP therapy. Given the ethical limitations related to long-term placebo treatment in at-risk populations, additional research using large cohort studies is warranted to better understand cognitive effects of PAP over time.

### PAP to Improve Cognitive Measures

#### Aggregate Quality of Evidence:

Cognitively intact patients: B (Level 1a: 2 studies; Level 1b: 2 studies; Level 2a: 1 study; Level 2b: 2 studies)

Cognitively impaired patients: C (Level 1b: 1 study; Level 2a: 1 study; Level 2b: 1 study)

Benefit: In cognitively intact patients PAP treatment offers a small degree of benefit in a limited number of domains. In cognitively impaired patients PAP treatment may offer benefit based on a few short-term and observational studies. Effects of PAP therapy on longitudinal progression of cognitive impairment is unknown.

Harm: Harms associated with PAP use are minimal.

Cost: Low to moderate cost associated with CPAP treatment for OSA.

Benefits-Harm Assessment: Balance of potential for benefits and the low risk of harm.

Value Judgments: Most studies are limited by short treatment periods. Research in cognitively intact patients may have ceiling effects limiting the measurable effect size. While the current evidence is limited for cognitively-impaired patients, there are few other options available that may delay cognitive decline. High-quality longitudinal studies are needed to better understand which patient populations may obtain cognitive benefits from CPAP therapy.

Recommendation Level: Option.

Intervention: CPAP therapy may be considered in OSA patients (including those with dementia/MCI) to potentially improve select domains of cognition and potentially reduce in the incidence of cognitive decline

**Table VIII.B.5 PAP to Improve Cognitive Measures**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
<b>Cognitively Intact (i.e., inclusion criteria did not require mild cognitive impairment or dementia)</b>						
Kushida et al. (APPLES trial) <sup>1271</sup>	2012	1b	Randomized, double-blind, controlled trial comparing CPAP to sham-CPAP (placebo), multicenter trial	1,098 participants enrolled across 5 sites, with assessments at baseline, 2 months and 6 months.	Neurocognitive domains: 1) Executive and frontal lobe function (Sustained Working Memory Test-Overall Mid-Day Score); 2) Attention and psychomotor function (Pathfinder Number Test-Total Time); 3) Learning and memory (Buschke Selective Reminding Test-Sum Recall). Sleepiness: 1) Epworth Sleepiness Scale; 2) Maintenance of Wakefulness Test (MWT)	Neurocognitive domains: Transient improvement in Executive and frontal lobe function only at 2 months, but no sustained benefit.  Sleepiness: CPAP led to improvements in subjective and objective sleepiness, especially in those with an AHI>30 events/hr.
Pan et al. <sup>1269</sup>	2015	1a	Meta-analysis of randomized controlled trials (duration 1-24 weeks)	PubMed, CINAHL, Medline, PsycInfo, EMBASE, Cochrane Library, CNKI, WanFang, VIP, and CBMdisc from June 1971 to July 2014. 13 studies were identified involving 1,744 participants. 1,098 were from APPLES trial. Did not include trials of cognitively impaired	Cognitive domains: 1) Attention; 2) Vigilance; 3) Processing Speed; 4) Working Memory; 5) Memory; 6) Verbal fluency; 7) Visuoconstructive Skills.	CPAP led to a small but statistically significant improvement in Vigilance only.



				patients.		
Dalmases et al. <sup>1280</sup>	2015	2b	Open label randomized pilot study of CPAP vs conservative care for 3 months	33 cognitively intact participants age>65 years with severe OSA enrolled at a single site, parallel arm study.	Cognitive domains: 1) Episodic memory; 2) Short-term memory; 3) Executive function-working memory, speed, visuomotor speed, mental flexibility, verbal fluency. MRI scans at baseline and 3 months also	CPAP led to statistically significant improvements in episodic, short-term memory, speed of mental processing and mental flexibility. MRI scan showed reduced cortical thinning and increased right middle frontal gyrus connectivity in the CPAP group. No change in Epworth Sleepiness Scale.
McMillan et al. <sup>1281</sup>	2015	1b	Open label randomized study of CPAP+best supportive care (BSC) vs BSC alone	278 participants age > 65 years with an oxygen desaturation index >7.5 events/hour + Epworth Sleepiness Scale >=9 for a 12 month period	Cognitive measures included the Mini-Mental Status Exam, Trail Making Test Part B, Digit Symbol Substitution Test and reaction time test.	CPAP did not lead to any cognitive changes. Of note, CPAP objective adherence (defined as >=4 hours of use/night) was 35% and median usage was 2:22 (hours:min)/night at 12 months.

Bubu et al. <sup>831</sup>	2020	2a	Systematic review	PubMed/Medline, Embase, PsychINFO and Cochrane library for clinical trials published prior to May 1st, 2019 related to OSA and cognitive function.	Included research in cognitively intact and cognitively impaired populations.	CPAP treatment may offer cognitive benefits for middle-aged and older adults, including those with Alzheimer's Disease.
Martinez-Garcia et al. <sup>1282</sup>	2015	2b	Open label randomized study of CPAP vs no CPAP for 3 months	224 older adults age $\geq 70$ years, with severe OSA (AHI $\geq 30$ events/hr) enrolled at 12 sites; excluded participants with severe impairment of cognitive performance and ESS $\geq 18$ .	Cognitive domains: Executive function, visual attention, speed of processing/mental flexibility, and working memory. Other domains: Subjective sleepiness, anxiety, depression and sleep quality.	CPAP treatment led to statistically significant improvements in depression, anxiety, and sleepiness (small, moderate and large effect sizes, respectively). Statistically significant improvements for working memory (digit symbol test and Trail Making A) that were small and moderate, respectively. No effect on other domains.
Patil et al. <sup>39</sup>	2019	1a	AASM systematic review and meta-analysis	9 RCTs of variable patient populations with mild-mod OSA; control groups were sham CPAP, oral placebo, or conservative treatment. Duration of RCTs was at least 1 month (1-12 mo)	Neurocognitive function across domains of executive function, processing speed, attention and vigilance, memory, and intelligence	Meta-analyses showed no clinically significant difference between CPAP and control groups in any of the neurocognitive domains.

Wang et al. <sup>1273</sup>	2020	1a	Meta-analysis of randomized controlled trials (duration 1-24 weeks)	PubMed, EMBASE, and Cochrane Library were systematically searched for RCTs from database inception to Oct 24, 2019. 14 studies were identified, involving 1,926 participants; 843 were from APPLES trial. Did not include trials of cognitively impaired patients except for one study of Parkinson's Disease patients and one of stroke patients.	Cognitive domains: 1) Attention and speed of information processing; 2) Executive function; and 3) Memory. Also reviewed individual cognitive scales when available, such as Trail Making A/B and subjective sleepiness.	CPAP led to a small but statistically significant improvement in attention and vigilance only in severe OSA.  No difference in subjective sleepiness. Of note, did not include APPLES trial data and large heterogeneity existed for sleepiness data analyses.
<b>Cognitively Impaired (i.e., Mild Cognitive Impairment or Alzheimer's Disease)</b>						
Ancoli-Israel et al. <sup>1274</sup>	2008	1b	Randomized, controlled trial comparing CPAP to sham-CPAP (placebo).	52 participants with mild to moderate Alzheimer's Disease and OSA. Assessed at baseline and 3 weeks, then the placebo sham-CPAP arm crossed over to receive CPAP.	14 cognitive measures assessing multiple domains including attention, vigilance, psychomotor speed, memory and executive function. Also derived a Composite neurocognitive score from these 14 items.	No significant difference in cognitive measures for a priori analyses, possibly due to sample size. When an additional analysis was conducted including the cross-over data (pre/post paired comparison), statistically significant benefits noted on the composite score, Hopkins Verbal Learning Test-Revised (HVLT-R) and Trail

						Making test.
Richards et al. <sup>1270</sup>	2019	2b	Quasi-experimental pilot study comparing CPAP adherent and non-adherent participants	54 participants with mild cognitive impairment. Assessed at one year follow-up	Memory (Hopkins Verbal Learning Test-Revised), psychomotor/cognitive processing speed (Digit Symbol subtest from the Wechsler Adult Intelligence Scale Substitution Test). Progression measures were the Everyday Cognition, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Scale, and Clinical Dementia Rating Scale	At one-year: statistically significant improvements in psychomotor/cognitive processing speed in the CPAP adherent patients; small to moderate but not statistically significant improvements noted in memory, attention and everyday function.
Perez-Cabezas et al. <sup>1254</sup>	2020	2a	Systematic review of randomized controlled trials and cohort studies for CPAP treatment of OSA in Alzheimer's Disease (AD)	Review of publications in PubMed, PEDro, SCOPUS, SPORTDiscus, CINHALL and Web of Science up to July 2019 using PRISMA framework	Identified 5 studies involving CPAP treatment of patients with AD and OSA: 3 clinical trials and 2 pilot studies. Treatment duration ranged from 3 weeks to 3 months.	Noted some evidence to support attenuation of cognitive decline in AD patients, but there were several methodological limitations and a paucity of studies.

### VIII.B.6 PAP and Insulin Resistance

OSA and obesity are independently linked with insulin resistance. PAP therapy has been associated with reductions in glycemic index and insulin sensitivity among obese patients with OSA and insulin resistance.<sup>1283-1285</sup> Unfortunately, evidence has generally been low quality with unclear clinical significance. While several studies have demonstrated improvements in glycemic control associated with PAP use<sup>1283,1284</sup> others have failed to find benefit.<sup>1285</sup> These observational studies may have been limited by patient heterogeneity and duration of follow up. Relatively few clinical trials have evaluated the impact of PAP on glycemic control, most of which have failed to demonstrate a positive impact of PAP on insulin sensitivity.<sup>1286,1287</sup> These trials had limited duration of follow-up (1-3 months). A more recent randomized clinical trial explored the benefits of PAP among patients with inadequately controlled type II diabetes mellitus and OSA.<sup>1288</sup> Compared with no treatment, PAP therapy produced significant improvement in glycemic control, particularly for patients with more severe hypoxemia and elevated inflammatory markers (IL-1B) at baseline. Subsequent systematic reviews and meta-analyses have failed to show a clinically significant benefit of PAP in reducing glycemic index and insulin sensitivity in OSA.<sup>1027,1289</sup> Evidence for PAP as an adjunctive therapy to improve glycemic control in patients with type 2 diabetes and OSA is evolving and may hold for insulin control and obesity for patients with sleep disordered breathing. Further research delineating the relationship of variables such as OSA severity, sleep quantity, sleep architecture, degree of daytime sleepiness, and PAP adherence metrics are necessary to better quantify benefits. Comprehensive weight loss strategies, including medically supervised very-low calorie diet and bariatric surgery when conservative measures fail, are worthy of consideration in patients with OSA and insulin resistance.

#### PAP to Improve Glycemic Control

**Aggregate Quality of Evidence:** B (level 1a: 2 studies; level 1b: 3 studies; level 2a: 1 study; level 2b: 3).

**Benefit:** Treatment of OSA with PAP therapy may improve insulin resistance, however, systematic reviews have failed to show consistent improvements in glycemic control with PAP therapy.

**Harm:** Inconvenience and side effects of CPAP therapy.

**Cost:** Low cost of PAP therapy for treatment of OSA.

**Benefits-Harm Assessment:** Balance of benefit to harm for PAP treatment in insulin resistant patients to improve glycemic control.

**Value Judgments:** The overall quality of evidence for treatment of OSA with PAP therapy to improve insulin resistance is generally weak, with no adequately powered randomized clinical trials. Only one study showed significant reduction in HgA1c. It is unknown whether greater PAP adherence could lead to better glycemic control.

**Recommendation Level:** Option.

**Intervention:** Patients with OSA and insulin resistance may benefit from adjunctive treatment of OSA with PAP to improve insulin resistance. Further studies are needed to identify the relationship between PAP therapy and glycemic control

**Table VIII.B.6 PAP to Improve Insulin Resistance**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Abud et al <sup>1289</sup>	2019	1A	SR	9 RCTs evaluating CPAP therapy vs. no therapy in non-diabetic adults with OSAHS	HOMA index, fasting glucose	CPAP improves HOMA IR index

Labarca et al <sup>1027</sup>	2018	1A	SR	6 RCTs evaluating effect of HbA1c or glycemic control using CPAP treatment versus no treatment for patients with T2DM	HbA1c, fasting glucose	CPAP does not improve HbA1c or fasting glucose
Martinez-Ceron, Fernandez-Navarro et al <sup>1290</sup>	2016	2A	SR	28 non-randomized studies and 9 RCTs evaluating the effects of CPAP on glucose metabolism in OSA patients	Effect of CPAP on glucose metabolism	CPAP could improve the control of glucose metabolism
Martinez-Ceron, Barquiel et al <sup>1288</sup>	2016	1B	RCT	50 patients with T2DM and OSA 1. CPAP 2. No CPAP	Multiple markers of glycemic control	CPAP resulted in improved glycemic control and insulin resistance
Myhill et al <sup>1285</sup>	2012	2B	Randomized parallel group intervention	59 patients with T2DM and new dx of OSA 1. early CPAP (<1wk) 2. late CPAP (1-2 months)	CVD risk factors	CPAP decreased blood pressure and pulse rate but did not influence metabolic control
Comondore et al <sup>1286</sup>	2009	1B	RCT (randomized crossover trial)	13 patients with OSA 1. CPAP or no therapy for 4 weeks followed by 4 week washout 2. crossover to other intervention	Fasting morning blood and urine, 24-h BP measurements, endothelial function	CPAP showed potential improvements in a variety of cardiovascular biomarkers
West et al <sup>1287</sup>	2007	1B	RCT	42 men with T2DM and new dx of OSA 1. CPAP 2. placebo CPAP	IR, HbA1c	CPAP does not improve HbA1c or IR
Hassaballa et al <sup>1284</sup>	2005	2B	Cohort Study	38 patients with T2DM and OSA	HbA1c	CPAP leads to a significant drop in HbA1c
Babu et al <sup>1283</sup>	2005	2B	Cohort Study	25 patients with T2DM before and after CPAP therapy for OSA	Interstitial glucose levels, HbA1c	CPAP improved glycemic control in obese subjects with T2DM

BP = blood pressure; CPAP = continuous PAP; CVD = cardiovascular disease; HbA1c = glycated hemoglobin; HOMA = homeostasis model assessment of insulin resistance; IR = insulin resistance; OSA = obstructive sleep apnea; OSA = obstructive sleep apnea hypopnea syndrome; RCT = randomized control trial; T2DM = type 2 diabetes mellitus;

### VIII.B.7 PAP and Motor Vehicle Accidents

Obstructive sleep apnea (OSA) has been associated with driving accidents in recent cohort studies,<sup>1291</sup> and meta-analyses<sup>39,1292,1293</sup>. This association may be the result of a number of neurocognitive sequelae of OSA, including daytime sleepiness and impairments in sustained attention.

Meta-analyses that include data from randomized controlled trials which assessed performance in driving simulators have concluded that sufficient evidence supports the role of continuous positive airway pressure (CPAP) in reducing the risk of driving accidents in patients with OSA<sup>1294-1297</sup>.

In our systematic review of the English-language literature to review the evidence of the effects of CPAP on driving accidents, we found 3 meta-analyses<sup>39,1292,1293</sup> and one observational study<sup>1291</sup>. These data support the beneficial effects of CPAP in reducing driving accidents and improving performance on a driving simulator.

In the most recent meta-analysis and systematic review conducted in 2019 by Patil et al, assessed the literature related to the treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) therapy. Four of the included studies were randomized clinical trials<sup>1294-1297</sup> that assessed performance in a driving simulator, and an additional ten were observational studies<sup>1298-1307</sup> in which a motor vehicle crash rate risk ratio was available, comparing PAP pre-treatment versus post-treatment. Crashes were ascertained by self-report or objective reports.

Self-reported sleepiness was present among participants of three of the randomized trials<sup>1295,1296</sup>. One trial recruited patients with mild OSA and self-reported sleepiness<sup>1295</sup>, and another<sup>1294</sup> included those with mild to moderate OSA without sleepiness. Comparison groups included an oral placebo tablet<sup>1295,1296,1308</sup>, sham CPAP<sup>1294</sup>, or advice regarding weight loss and sleep hygiene counseling<sup>1297,1309</sup>. Duration of the trials ranged 1-6 months. The meta-analyses of the four RCTs did not demonstrate a clinically significant reduction in the number of percent of obstacles hit when assessed by driving simulator; however, these results should be interpreted cautiously, since performance on-the-road may not correlate with performance in a simulated, controlled laboratory setting. The observational data, by contrast, demonstrated that PAP compared to no treatment results in a clinically significant reduction in motor vehicle accidents. This effect was independent of whether or not PAP therapy was initiated directly at home versus following an in-laboratory titration; and independent of the type of PAP administered (auto-adjusting, bilevel or standard continuous). Patients receiving pressure-profile PAP had outcomes similar to those receiving fixed PAP. The overall quality of evidence was rated as low to moderate in this meta-analysis due to limitations in study design and ascertainment of outcomes. The data demonstrated that PAP compared to no treatment results in a clinically significant reduction in motor vehicle accidents.

In an earlier meta-analysis, Tregear et al<sup>1293</sup> included 9 observational studies<sup>1101,1298,1299,1301-1303,1306,1307,1310</sup> examining crash risk of drivers with OSA pre- vs. post-CPAP. All of these observational studies except two<sup>1101,1310</sup> were also included in the meta-analysis by Patil et al<sup>39</sup>. They concluded that PAP treatment results in motor vehicle crash risk reduction, with a risk ratio of 0.278, 95% CI: 0.22 to 0.35;  $P < 0.001$ . They also concluded that daytime sleepiness improves significantly after just one night of PAP therapy, and that performance on a driving simulator improves significantly within 2 to 7 days of using PAP therapy.

A third meta-analysis by Antonopoulos et al included 8 of the studies also included in the study by Tregear et al<sup>1293</sup>, as well as an abstract and several others<sup>1311-1316</sup>. The outcomes assessed in response to

CPAP included real accidents (ten studies, N=1221 patients)<sup>1101,1298,1299,1301-1303,1306,1307,1315,1317</sup>; near-miss accidents (five studies, N=769 patients)<sup>1101,1306,1307,1315,1317</sup>; and performance on a driving simulator one abstract<sup>1315</sup>, (five studies, N=110 patients)<sup>1311-1314,1316</sup>. The authors concluded that CPAP was both highly effective and cost-effective in preventing traffic accidents among patients with OSA, and that CPAP reduced not only real accidents, but also near-misses and performance on a driving simulator. They further advised that the number of patients needed to be treated with CPAP to avoid one real road traffic accident was five and to avoid a near-miss, only two. Therefore, they concluded that CPAP constitutes an efficient use of healthcare resources in the treatment of OSA<sup>1292</sup>.

In addition to the studies included in these meta-analyses, an additional retrospective study<sup>1291</sup> evaluated data from a large-scale, employer-mandated program to screen, diagnose, and monitor OSA treatment adherence. Drivers identified as having OSA by polysomnography (n = 1,613) were compared against those (n = 403) without OSA and a control group of drivers (n = 2,016) who were matched based on experience-at-hire and length of job tenure. Auto-adjusting positive airway pressure (APAP) treatment was provided to all drivers with OSA. Treatment adherence was monitored objectively using data retrieved from the APAP devices. The analysis group included (n = 682) who adhered fully, n = 571 who adhered partially, and n = 360 with no adherence. Those with OSA and no adherence to APAP had a Department-of-Transportation reportable crash rate that was fivefold greater (incidence rate ratio = 4.97, 95% CI: 2.09 to 10.63) than matched controls (0.070 versus 0.014 per 100,000 miles). Those who adhered fully to APAP had crash rates that were statistically similar to those of controls (incidence rate ratio = 1.02, 95% CI: 0.48 to 2.04; 0.014 per 100,000 miles). The program also resulted in the removal of non-treatment-adherent drivers through dismissal or voluntary exit from the company, and retention of adherent drivers.

#### **PAP to reduce Motor Vehicle Accidents**

Aggregate Quality of Evidence: B (Level 2a: 3 studies; 2b: 1 study).

Benefit: High potential benefit exists for patients with OSA who adhere to PAP therapy and also for public health and safety, as driving accidents pose a risk to others on the road

Harm: Patients may have difficulty tolerating PAP therapy or experience side effects.

Cost: Lack of insurance coverage may result in moderate financial burden for the patient. The average cost of diagnosis and treatment with CPAP was estimated at \$1190 per patient per year.<sup>132</sup>

Benefits-Harm Assessment: Benefits to the individual and public health clearly outweigh potential harms, which include minor adverse effects of PAP therapy and potential costs

Value Judgments: The choice of whether or not to use PAP therapy to reduce driving related accidents must be weighed against harms to public health and safety. Those in high-risk workplace settings may be mandated by the employer to adhere to PAP therapy. The value of adherence has been shown in clinical trials to benefit both the individual, the employer and to payers who may reap reductions in overall healthcare costs and in costs related to accidents.

Recommendation Level: Recommendation.

Intervention: PAP therapy in OSA patients is recommended to reduce motor vehicle accidents.

**Table VIII.B.7: Summary of Data Evaluating the Efficacy of PAP in Lowering Crash Rates by Subjective or Objective Reports and in Driving Simulator**



Study	Year	LOE (1a – 5)	Study Design	Study groups	Clinical Endpoints	Conclusion
Patil <sup>39</sup>	2019	2A	Systematic review, meta-analysis	10 observational studies of crash rates  2 randomized clinical trials in driving simulators	Crash rate (pre- versus post-treatment) risk ratio.  Proficiency in driving simulator (difference in mean number and percent obstacles hit).	PAP associated with reduction in <u>Crash rates</u> [risk ratio 0.28].  No significant change in <u>Mean number obstacles hit in simulator</u> : PAP treated group; mean difference= -0.08
Tregear <sup>1293</sup>	2010	2A	Systematic review, meta-analysis	9 observational studies	Crash risk ratio pre-versus post-CPAP.	PAP reduced <u>Crash risk</u> : risk ratio 0.278; P < 0.001
Antonopoulos <sup>1292</sup>	2011	2A	Systematic review, meta-analysis	Fifteen studies included: -Real accidents: 10 studies (1,221 participants) -Near-miss accidents: 5 studies (769 participants) -Performance in driving simulator 6 studies (110 participants)	Outcome measures: odds ratios (ORs), incident rate ratios (IRRs), risk differences (RDs) and mean differences.  Incident rate ratio = incidence rate of	PAP associated with significant reduction in real accidents and near-misses: <u>Real Accidents</u> (10 studies): OR 0.21, IRR 0.45 NNT (95CI) =5 <u>Near-miss accidents</u> (5 studies): OR 0.09; IRR 0.23 NNT =2. <u>Driving performance</u> (6 studies): CPAP was associated

				<p>Total:</p> <p>1 RCT with low risk of bias;</p> <p>6 observational studies with low risk of bias;</p> <p>2 observational studies with high risk of bias;</p> <p>6 case reports or series.</p>	<p>accidents after CPAP divided by the incidence rate before CPAP;</p> <p>Number needed to treat (NNT) derived from risk differences.</p>	<p>with a significant reduction in accident-related events in the driving simulator</p>
Burks <sup>1291</sup>	2016	2B	Retrospective, controlled cohort	<p>OSA positive n = 1,613 cases, OSA negative n = 403;</p> <p>Controls n = 2,016 matched on experience-at-hire and length of job tenure, matched on the date of each diagnosed driver's polysomnogram.</p> <p>Cases categorized by adherence to automatically-adjusting PAP:</p> <p>“Full Adherence” (n = 682);</p> <p>“Partial Adherence” (n = 571);</p> <p>“No Adherence” (n = 360).</p>	<p>Preventable Department-of-Transportation-reportable crashes/100,000 miles, based on subgroup.</p>	<p>“No Adherence” cases had a fivefold higher preventable reportable crash rate than matched controls:</p> <p>IRR = 4.97; (0.070 versus 0.014 per 100,000 miles).</p> <p>“Full Adherence” cases had crash rates statistically similar to controls: IRR = 1.02; 0.014 per 100,000 miles.</p>

## VIII.B.8 PAP and Work Productivity

Obstructive sleep apnea (OSA) has been shown in observational studies to reduced work-productivity. However, the effect of continuous positive airway pressure (CPAP) on work productivity has only been studied in a very limited fashion, even though improvements in OSA-related symptoms such as daytime sleepiness, which affect productivity, are well appreciated. A systematic review of the English-language literature was performed to identify studies of CPAP effects on work productivity. Of the five studies identified, four of them were prospective, observational cohort studies, and one cross-sectional with retrospective recall of the outcomes assessed.

Outcome measures between studies varied and included both validated and non-validated work productivity surveys. Validated questionnaires included the Work Role Functioning Questionnaire (WRFQ; impact of health on work performance), Job Content Questionnaire (JCQ; job stress), Maslach Burnout Inventory - General Survey (MBI-GS; a measure of burnout), Shirom-Melamed Burnout Questionnaire (SMBQ; a measure of burnout), Indice de Impactode la Enfermedad en la Productividad Laboral (IMPALA; work productivity), and the Work Limitation Questionnaire (WLQ; work productivity).

Participants were middle-aged, predominantly male, and had moderate-severe OSA. In all studies, outcomes were assessed before and after a period of CPAP use with a follow-up period from 3 months to 2 years (3 studies had 6-month follow-up). One study asked participants to recall symptoms experienced 6 months prior to the time of assessment.<sup>1310</sup> Four of the five studies<sup>1310,1318-1320</sup> indicated a high level of adherence to CPAP, which was an inclusion criterion in only three of the studies.<sup>1318-1320</sup> There was no comparison group in any of the studies. The sample size of the studies included ranged from 33 to 254 participants.

The earliest published evidence,<sup>1310,1320</sup> which used Likert-scale questions, reported improvements in job productivity, concentrating on new tasks, learning tasks, performing monotonous tasks, and work-related absenteeism. More recent studies,<sup>1318,1319,1321</sup> used standardized questionnaires, which differed between the studies, thus preventing direct comparisons. One study,<sup>1318</sup> which only included participants adherent to CPAP, reported improvements in work productivity, mental and social demands and schedule management compared to pre-treatment scores. Another study<sup>1319</sup> which also only assessed participants who adhered to CPAP, demonstrated improvements in job productivity, professional efficacy, and burnout but not job stress or job satisfaction. The final study,<sup>1321</sup> which had follow up from only 7.7% of participants that had completed pre-treatment surveys, reported improvements in time management, mental-interpersonal relationships, and work output.

In summary, data regarding the efficacy of PAP in impacting workplace productivity is limited and confined to a few studies that consist of case series and low-quality cohort studies. They are limited by the lack of uniformity in the definition of OSA, lack of blinding,<sup>1310,1318-1321</sup> relatively small numbers of participants,<sup>1319-1321</sup> short follow up periods,<sup>1310,1318-1320</sup> use of non-validated<sup>1310,1320</sup> and subjective assessment tools,<sup>1310,1318-1321</sup> recall bias<sup>1310</sup> selection bias,<sup>1310,1318-1321</sup> and failure to fully control for adherence to PAP therapy.<sup>1310,1320,1321</sup>

### PAP to Improve Work Productivity

**Aggregate Quality of Evidence:** C (level 2c: 5 studies).

**Benefit:** Improvements in OSA-related symptoms may be related to improvements in work productivity, work-related absenteeism, mental demands, and inter-personal relationships.

**Harm:** Minor risks associated with PAP therapy and inconvenience or intolerance.

**Cost:** Low to moderate costs associated with PAP equipment and visits.

**Benefits-Harm Assessment:** Balance of benefit over harm. Low risk of harm, but the evidence to show clear benefit for CPAP impact on work productivity is limited.

**Value Judgments:** Although the aggregate grade of evidence is low, the potential benefits of CPAP in improving work productivity through reductions in OSA-related symptoms should be greatly valued by the patient, employers, and other stakeholders that support healthcare or benefit related costs.

**Recommendation Level:** Option

**Intervention:** In patients with OSA and sleepiness who experience work-related absenteeism, reduced productivity, or work-related accidents, treatment of OSA with CPAP should be considered.

Table VIII.B.8 PAP and Work Productivity

Study	Year	LOE (1a-5)	Study Design	Study Groups	Clinical Endpoints	Conclusion
Botokey, et al. <sup>1318</sup>	2019	4	Observational cohort	Participants with OSA adherent to CPAP (N=39);  Followup Assessment: 89 days (SD: 58)	WRFQ	OSA participants on CPAP had improvements in schedule management, productivity, mental demands, and social demands compared to pre-treatment scores.
Jurado-Gómez, et al. <sup>1319</sup>	2015	4	Observational cohort	Participants with OSA adherent to CPAP (N=54)  Followup assessment : 6 months	JCQ MBI-GS SMBQ Job satisfaction index IMPALA	OSA participants on CPAP demonstrated improvements in job productivity, professional efficacy, and burnout compared to pre-treatment scores.  No changes in job stress or satisfaction was observed with CPAP use.
Mulgrew, et al. <sup>1321</sup>	2007	4	Observational cohort	Participants with OSA (N=33 of 428)	WLQ	OSA participants on CPAP demonstrated

				initially surveyed) Followup assessment: 2 years		improvements in time management, mental-interpersonal relationships, and work output.
Scharf et al. <sup>1310</sup>	1999	4	Cross-sectional study with recall assessment	Participants with OSA (N=254 of 316 initially surveyed) Followup assessment: 6 months	“Rate your productivity at your job” (10-point Likert scale) “How many days of work have you missed because of illness, tiredness or sleepiness over the past 6 months”	OSA participants treated with CPAP demonstrated improvements in work-related absenteeism and job productivity
Ulfberg et al. <sup>1320</sup>	1999	4	Observational cohort	Participants with OSA (N=34) Followup assessment: 6 months	5-point Likert scale “Do you have difficulty doing your job due to sleepiness or tiredness” “How difficult is it for you to concentrate on new tasks?” “How difficult is it for you to learn new tasks?” “How difficult is it for you to	OSA participants treated with CPAP demonstrated improvements in job productivity and areas including concentrating on new tasks, learning tasks, and performing monotonous tasks

					perform monotonous tasks?"	
WRFQ = Work Role Functioning Questionnaire; JCQ = Job Content Questionnaire; MBI-GS = Maslach burnout inventory - general survey; SMBQ = Shirom-Melamed burnout questionnaire; IMPALA = índice de impacto de la enfermedad en la productividad laboral (job productivity questionnaire); WLQ = Work Limitation Questionnaire						

### VIII.B.9 PAP and Insomnia

Few studies addressed the question of whether CPAP improves insomnia in patients with OSA (See Table VIII.A.6.i).<sup>942,1322</sup> Evidence shows approximately 20-50% improvement in self-reported insomnia symptoms with use of PAP for OSA. Improvement in sleep maintenance difficulties occurred more commonly than improvement in difficulty with sleep onset or early morning awakening. There is high variability in study design, insomnia definitions, and duration of follow-up time between the studies.

**Table VIII.A.6.i PAP and Improvement in Insomnia**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Glidewell et al. <sup>1322</sup>	2014	4	Retrospective cohort study	Archival data from 68 PAP-treated sleep apnea patients	Insomnia Severity Index (ISI), PSG	For the 53 patients with pretreatment insomnia symptoms, ISI scores improved in 45.3% and persisted in 54.7% following PAP treatment.
Bjornsdottir et al. <sup>942</sup>	2013	3b	Prospective longitudinal cohort study	705 adults with OSA	Basic Nordic Sleep Questionnaire, HSAT	Symptoms of sleep maintenance insomnia improved significantly among patients using PAP (from 59.4% to 30.7%, $P < 0.001$ ). Symptoms of initial insomnia tended to persist regardless of PAP treatment, and symptoms of late insomnia were more likely to improve among patients not using PAP.

Sweetman et al. <sup>1189</sup>	2019	2	Prospective trial	73 adults treated with CPAP. Those who had CBTi were excluded	ISI (6-months)	CPAP therapy led to a 36% improvement in ISI.
---------------------------------	------	---	-------------------	---	----------------	---

### VIII.B.10 PAP and Obesity Hypoventilation Syndrome

Distinguishing OHS from eucapnic OSA is important as there are significant differences in clinical outcomes seen between the two groups. In addition to hypercapnic respiratory failure, people with OHS are more likely to develop chronic heart failure and pulmonary hypertension,<sup>1323,1324</sup> present with more comorbidities,<sup>1325</sup> utilize more health care resources,<sup>133,1326</sup> report poorer health-related quality of life (HRQoL), experience more socioeconomic deprivation<sup>1327</sup> and have lower survival rates compared to those with eucapnic OSA.<sup>1325,1328</sup> Positive airway pressure (PAP) therapy, in the form of CPAP or the various modes of bilevel ventilatory support (spontaneous (BVS-S), spontaneous-timed (BVS-ST) and volume-targeted pressure support (BVS-VTPS)) have formed the cornerstone of treatment for OHS. While the evidence supporting one mode of PAP over another has been limited, many patients have traditionally been managed with BVS despite its higher cost and need for greater expertise to set up and monitor. Studies evaluating the different modes of BVS, primarily BVS-ST against BVS-VTPS, have failed to show significant differences in clinical outcomes in the medium term (up to 3 months), so long as therapy is set up to deliver equivalent levels of tidal volume and/or CO<sub>2</sub> control.<sup>1329-1331</sup> Although CPAP does not directly address hypoventilation, it can relieve upper airway obstruction and reduce the work of breathing.<sup>1332</sup> Three RCTs<sup>86,1333,1334</sup> and two meta-analyses<sup>1335,1336</sup> comparing CPAP to bilevel therapy over the medium term in ambulatory OHS patients with concomitant OSA (OHS+OSA) found similar improvements in awake CO<sub>2</sub> and daytime symptoms between the two therapy modes. Nevertheless, as OHS is most commonly a life-long condition, it has been unclear if these early and equivalent improvements with CPAP would be maintained over a more extended period. Two recent long-term comparative studies have shed some light on this issue. A prospective cohort study following 252 newly diagnosed patients with OHS for at least 2 years<sup>1337</sup> reported better therapy adherence and larger improvements in depression scores in those prescribed BVS compared to CPAP. However, all other measures including resolution of awake hypercapnia, improvement in HRQoL and mortality were similar between therapies. In a long-term RCT with a median follow up period of 5 years, Masa et al<sup>1338</sup> reported the outcomes of 204 stable OHS patients with severe OSA allocated to CPAP or BVS. No significant difference between groups was observed for any outcome measured including hospitalization days, healthcare utilization, mortality, cardiovascular events, awake blood gases, health-related quality of life or symptoms. Hence, current data suggest that while improvements in some parameters such as awake PaCO<sub>2</sub> and cardiac function may occur more rapidly with BVS,<sup>1333,1339</sup> the longer-term efficacy of these PAP modalities is similar for stable OHS with OSA.<sup>1338</sup>

Given CPAP is more cost effective than BVS,<sup>1340</sup> and both PAP modalities provide similar long-term clinical outcomes,<sup>1336,1338,1341</sup> CPAP is now suggested as the initial therapy for stable patients with OHS and concomitant severe OSA.<sup>1336,1342</sup> Nevertheless, CPAP will fail in a proportion of individuals. Patients at the greatest risk of a suboptimal response are those with higher baseline PaCO<sub>2</sub> levels,<sup>1333</sup> more

restrictive spirometry and lower AHI.<sup>1343</sup> Consequently, close monitoring is needed to ensure an appropriate response to therapy is achieved.<sup>1342</sup>

Bilevel therapy remains the therapy of choice in OHS patients without severe OSA (ie AHI<30/hr). A randomized trial comparing BVS-VTPS to lifestyle changes alone in 98 stable patients with OHS without OSA showed that by 2 months only the BVS group showed significant improvements in CO<sub>2</sub>, sleepiness and PSG parameters.<sup>1344</sup> Extending follow up to at least 3 years, the authors found benefits favoring BVS in terms of improved blood gases and quality of life.<sup>1341</sup> However, no differences between groups in hospitalization days per year, other health resource use, cardiovascular events or mortality were observed. For those presenting with acute respiratory decompensation, bilevel therapy also remains the therapy of choice.<sup>1345,1346</sup> However, even in this latter group a proportion can be stepped down to CPAP after a period of clinical stability without compromising awake blood gases, quality of life or sleep quality.<sup>1347,1348</sup>

Adherence to therapy is an important modifiable factor influencing therapy response, irrespective of the PAP mode used. In a post-hoc analysis of data from their long-term PAP trial, Masa et al<sup>1338</sup> found patients with OHS+OSA who were more adherent to PAP (>4 hours/day) also experienced lower hospitalization days per patient-year, hospital and ICU admissions, emergency room visits, and mortality than those less adherent. The type of PAP used did not alter these outcomes. In a case-control study which included 206 OHS patients and 236 eucapnic OSA patients, Kreivi et al<sup>1325</sup> found that untreated or non-adherent OHS patients had an adjusted 5-year mortality rate of 27% compared to 2% in those adherent to PAP therapy and 4% in OSA patients who abandoned CPAP. Similarly, amongst OHS patients without severe OSA, higher adherence to bilevel therapy was associated with fewer emergency room visits and lower mortality.<sup>1341</sup> Unlike OSA, there is a lack of literature around strategies for improving adherence to PAP in patients with OHS.

While it appears from cohort studies<sup>1325,1328,1335,1349</sup> and long-term RCTs<sup>1338,1341</sup> death from respiratory failure is significantly reduced with PAP therapy, the impact on cardiovascular risk and overall mortality is less marked. Even with PAP therapy, OHS is associated with poorer survival compared to OSA alone.<sup>1328</sup> This highlights the need for early detection of this disorder before significant co-morbidities develop, along with the use of multimodal therapy beyond PAP therapy including weight loss programs and pulmonary rehabilitation to improve outcomes. Although weight loss is an obvious therapeutic target, there is a lack of good quality data around how best this can be achieved and maintained, and what target weight loss is needed to achieve clinically relevant benefits.<sup>1350,1351</sup>

#### VIII.B.11 PAP in Overlap Syndrome (COPD)

Concurrent OSA and chronic obstructive pulmonary disease (COPD) is known as overlap syndrome (OS).<sup>777</sup> Studies have shown that CPAP improves respiratory muscle function, work of breathing, gas exchange and functional status in OS patients.<sup>1352,1353</sup> Several mechanisms may explain these results, such as bronchodilation, reduction of respiratory load, improvement of ventilation/perfusion ratio, and changes in central chemoreceptor sensitivity. Two prospective cohort studies provided the best available evidence on CPAP and survival in patients with OS.<sup>1354,1355</sup> (Table VIII.7c) Marin et al evaluated CPAP on first-time hospitalization from COPD exacerbation and mortality in three groups; OS *with* CPAP, OS *without* CPAP, and COPD *without* OSA.<sup>1355</sup> All three groups had similar markers of COPD severity and received similar COPD management. At baseline, patients with OS had a higher incidence of COPD



exacerbations. The investigators reported a significant mortality increase and higher hospitalization rates in the OS group *without* CPAP compared to the OS group *with* CPAP and the COPD group. OS patients *without* CPAP carry a worse prognosis compared to OS with CPAP and COPD without OSA. Machado et al evaluated CPAP on OS patients with moderate-to-severe OSA and hypoxemic/hypercapnic COPD on long-term oxygen supplementation.<sup>1354</sup> The authors reported a 5-year survival benefit in the CPAP treated group versus the non-CPAP group.

Stanchina et al analyzed the relationship between CPAP adherence and survival in 227 OS patients.<sup>1356</sup> Multivariate analysis showed that more time on CPAP was associated with reduced risk of death in a dose dependent manner. A recent retrospective cohort study analyzed the effect of CPAP therapy on healthcare utilization in the 1-year pre- and 1-year post CPAP initiation in Medicare beneficiaries with OS.<sup>1357</sup> CPAP was associated with significant reductions in COPD related hospitalizations, particularly in older adults ( $\geq 75$  years), higher COPD complexity (defined by comorbid respiratory and procedures<sup>1358</sup>), and those with three or more medical co-morbidities.

Bilevel PAP therapy is widely accepted for acute COPD exacerbations and data also suggest benefit in stable hypercapnic COPD patients in the outpatient setting.<sup>1359-1361</sup> None of the studies however reported concurrent OSA diagnosis, so it is unclear if bilevel PAP would be as beneficial as CPAP in OS patients, particularly those with more severe gas exchange abnormalities including daytime hypercapnia. In a post hoc analysis of OS patients on CPAP versus bilevel PAP, those who benefited from bilevel PAP had a higher body mass index, lower FEV<sub>1</sub> and FEV<sub>1</sub>/FVC, and worse daytime gas exchange.<sup>1362</sup> Randomized clinical trials are needed to determine the role of bilevel PAP versus CPAP in OS.

In summary, there is overwhelming evidence that patients with comorbid OSA and COPD are at risk for increased morbidity and mortality compared with either disease alone. CPAP therapy seems to mitigate these risks, however, this has yet to be proven with randomized clinical trials. Also, further studies are needed to determine the role of bilevel PAP on clinical outcomes in OS.

#### **PAP to Improve COPD Outcomes and OSA in Overlap Syndrome**

Aggregate Quality of Evidence: B (Level 2A: 1 study; Level 2b: 7 studies, Level 4: 2 studies)

Benefit: Patients with comorbid OSA and COPD are at risk for increased morbidity and mortality. CPAP therapy seems to mitigate these risks.

Harm: The potential harms of CPAP are inconvenience (use nightly, maintenance/cleaning) and therapy-related side effects (including but not limited to discomfort of equipment, sleep disruption, airway dryness, nasal congestion, skin abrasion, and aerophagia).

Cost: There are low to moderate for treatment with PAP therapy, depending on the type of testing and PAP device used.

Benefits-Harm Assessment: The benefits of OSA treatment of patients with comorbid COPD outweigh the harm.

Value Judgments: There is overwhelming evidence about the worsened clinical outcomes in patients with both COPD and OSA compared to either COPD or OSA alone. CPAP therapy seems to mitigate these risks, but randomized clinical trials are needed, including those that assess for benefits in the subsets of patients with OSA and COPD (e.g. those with severe daytime gas exchange abnormalities, specifically chronic hypercapnia). Studies evaluating the role of bilevel PAP in these patients are much needed as well.

Recommendation Level: Recommendation

**Intervention:** Treatment with PAP therapy is recommended in patients with concomitant COPD and OSA.

**TABLE VIII.B.11 Positive Airway Pressure (PAP) Therapy and Clinical Outcomes in Overlap Syndrome**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Marin et al <sup>1355</sup>	2010	2b	Prospective cohort	1) 228 patients with Overlap on CPAP 2) 213 patients with Overlap not on CPAP 3) 210 patients with COPD only	1) Mortality and first-time hospitalization from COPD exacerbation in Overlap Syndrome  2) Effect of CPAP on mortality and first-time hospitalization	Overlap Syndrome patients had higher incidence of hospitalization from COPD exacerbations; (RR 1.70; 1.21-2.38).  Overlap Syndrome is associated with increased mortality compared with COPD alone; (RR 1.79; 1.16-2.77).  CPAP improves mortality in Overlap Syndrome patients compared to Overlap patients without CPAP.
Machado et al <sup>1354</sup>	2010	2b	Prospective cohort	Overlap Syndrome patients with moderate-severe OSAS and severe COPD on LTOT  (N=95)	Effect of CPAP on survival	Significant 5- year survival advantage with CPAP (71%) treatment compared to no CPAP (26%); (P<0.01).

				1) Treatment with CPAP 2) No CPAP		
Singh et al <sup>1357</sup>	2019	2b	Retrospective cohort	5% national sample of Medicare beneficiaries with COPD and on CPAP therapy  1) Pre CPAP 2) Post CPAP	Effect of CPAP on emergency room visits and hospitalizations for all-cause and COPD related conditions in 1-year pre- and post- CPAP initiation	Hospitalization rates for COPD related conditions were lowered in 1-year post CPAP treatment compared to 1-year pre-CPAP.  Hazard ratio for death due to respiratory failure or cardiovascular disease between groups was 0.19 (95% CI 0.08–0.48).  No change in ER visits for COPD related conditions or for any cause.  CPAP was more beneficial in older adults, higher COPD complexity, and three or more medical comorbidities.
Stanchina et al <sup>1356</sup>	2013	4	Retrospective cohort (post hoc analysis)	Overlap Syndrome patients identified from large outpatient database analyzed for	Mortality	Greater hours on CPAP were associated with reduction in mortality; (HR 0.71, p<0.001).

				CPAP adherence		
Kuklisova et al <sup>1362</sup>	2018	2b	Retrospective cohort (post hoc analysis)	Post hoc analysis of large database with Overlap Patients using CPAP versus bilevel PAP	Determinants of CPAP failure	PCO <sub>2</sub> awake and CT90% predicted failure, bilevel PAP was well tolerated and effective.

CPAP=continuous positive airway pressure, COPD=chronic obstructive pulmonary disease, LTOT=long term oxygen therapy, ER=emergency room, PCO<sub>2</sub>=partial pressure arterial carbon dioxide, HR=hazard ratio, CT90%=sleep time with SPO<sub>2</sub><90%

### VIII.C Medical Management of OSA: Oral Appliances

#### VIII.C.1 Tongue Retention Devices

A tongue retaining device (TRD) uses suction force to anteriorly displace the tongue during sleep. Unlike other oral appliances, a TRD isolates the tongue and obviates the need to advance the mandible. However, combination devices do exist<sup>1363</sup>. Such devices can be acquired over the counter or can be customized. The first report of such therapy dates back almost four decades. TRD offer potential advantages relative to other therapies for OSA due to their portability and low cost. There are currently no Cochrane Review of clinical guidelines on the role of TRD in the management of OSA.

The literature on TRD for OSA is small, with only 16 published studies and one unpublished study, involving only 278 patients in total<sup>1364</sup>. The majority of reports are case series, with only 6 randomized controlled trials (RCTs). The predominant outcome has been the apnea-hypopnea index (AHI), but oxygen desaturation, arousal index, and snoring have also been assessed. A minority of studies explored patient reported outcomes, including daytime sleepiness and side-effects. All studies demonstrate a reduction in AHI, on average approximately 50% (range 13.5 – 67.4%)<sup>1364</sup>. Most studies have included OSA in the moderate to severe range and systematic review of 16 studies shows an average Pre-TRD AHI of 34 reducing to a Post-TRD AHI of 16<sup>1364</sup>. One study did not detect a difference in treatment outcome for mild, moderate, or severe OSA<sup>1365</sup>. Several studies have suggested a greater reduction in supine compared to non-supine AHI<sup>1366,1367</sup>, although OSA by body position has not been reported in most studies. A similar reduction in the oxygen desaturation index (ODI) has been observed across studies that assessed this outcome. The small number of studies that assessed subjective sleepiness, have demonstrated an improvement in the Epworth Sleepiness Scale (ESS). The treatment duration has generally only been for up to 6 months, and only a few case series in small numbers of patients have evaluated long term efficacy. A RCT compared TRD to mandibular repositioning device (MRD) and showed a similar reduction in mean AHI (15 events/hour, 55% reduction in AHI) with both therapies, but a higher proportion of patients achieving a complete or partial response with MRD treatment (68 vs 45%). Furthermore, compliance was poorer with TRD and 91% of patients preferred MRD treatment<sup>1365</sup>. Another study compared TRD to CPAP in a randomized cross-over study and revealed a significantly greater reduction in mean AHI as well as better improvement of sleep-related oxygen parameters with

CPAP therapy than with TRD. However, there was no significant difference between interventions for other sleep parameters, daytime sleepiness, and patient's quality of life<sup>1368</sup>. A majority of patients (48%) preferred CPAP to TRD due to their perceptions of greater efficacy and less side effects with CPAP therapy.

Side effects of TRD occur in approximately two thirds of patients and include tongue numbness, tongue pain, tooth or gum pain, and dry mouth<sup>1369</sup>, and likely contribute to device intolerance.

There are current gaps in knowledge regarding long term efficacy, adherence, and side effects, as well as patient characteristics associated with a beneficial outcome.

#### **Tongue Retention Devices for OSA**

**Aggregate Quality of Evidence:** C (Level 1a: 1 study; Level 1b: 3 studies; Level 2b: 1 study; Level 3b: 6 studies; Level 4: 5 studies).

**Benefit:** Improved AHI, ODI, and ESS.

**Harm:** Side effects including tongue numbness, tongue pain, tooth or gum pain, and dry mouth.

**Cost:** Low to moderate cost associated with device. Variable cost which is dependent on device type.

**Benefits-Harm Assessment:** Balance of benefit over harm.

**Value Judgments:** TRD can be used for OSA but has suboptimal effectiveness and tolerance, and objective verification of response is recommended.

**Recommendation Level:** Option.

**Intervention:** Tongue retention devices can be used to treat OSA, though other treatment options, including other oral appliances, demonstrate better effectiveness and tolerability.

**Table VIII.C.1: Summary of Evidence for Tongue Retention Devices for OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Banhirian W <i>et al.</i> <sup>1368</sup>	2019	2b	RCT (cross-over)	1) TRD 2) CPAP 27 Subjects	1) AHI (WatchPAT) 2) FOSQ 3) ESS 4) Side effects 5) Adherence	TRD reduced AHI less than CPAP, no difference in ESS or FOSQ scores.
Chang <i>et al.</i> <sup>1364</sup>	2017	1a	Systematic Review	TRD 242 Subjects	1) AHI 2) LSAT 3) ESS 4) ODI	Reduced AHI and ODI, increased LSAT, and decreased ESS

Deane S.A. <i>et al.</i> <sup>1365</sup>	2009	1b	RCT (crossover)	1) TRD 2) MRD 22 Subjects	1) AHI 2) ESS 3) Snoring (subjective) 4) Sleep quality 5) Side effects 6) Treatment preference	Similar AHI reduction for TRD and MRD, but higher proportion achieving complete or partial response with MRD treatment (68 vs 45%).
Lazard D.S. <i>et al.</i> <sup>1369</sup>	2009	4	Retrospective case series	TRD 55 Subjects	1) AHI 2) Snoring 3) ESS	AHI improvement at 5 years.

AHI – Apnea hypopnea Index, CPAP – Continuous Positive Airway Pressure, ESS – Epworth Sleepiness Score, FOSQ – Functional Outcomes of Sleep Questionnaire, LSAT – lowest oxygen saturation, MRD – Mandibular Repositioning Device, ODI – Oxygen desaturation Index, RCT – Randomized Controlled Trial, TRD – Tongue Retaining Device

### VIII.C.2 Mandibular Repositioning Devices (MRD)

Mandibular Repositioning Devices (MRD) attach to the upper and lower dental arches and secures the mandible in a more anterior, or protruded, position relative to the maxilla. They are also commonly referred to as mandibular advancement splints, appliances, or devices (MAS/MAA/MAD), or mandibular repositioning devices (MRD) or oral appliances (OA). They are generally the preferred oral appliance type for treatment of OSA, owing to stronger evidence of effectiveness and great patient acceptance compared to TRD. The forward positioning of the mandible while wearing MRD increases the pharyngeal airway space and reduces collapsibility, representing key mechanisms for improvement in OSA. Current clinical guidelines of the American Academies of Sleep Medicine and Dental Sleep Medicine recommend that MRD should be prescribed, rather than no therapy, for adult OSA patients who are intolerant of CPAP or who prefer alternative therapy<sup>808</sup>.

MRD are manufactured from impressions (digital or physical) of an individual's dentition and hence are customized devices. Prefabricated or 'boil and bite' devices also exist. A meta-analysis of three crossover trials compared customized and prefabricated MRDs in a total of 129 participants<sup>1370</sup>. Customized MRDs were superior in AHI reduction, as well as the proportion of treatment responders (AHI<5/hr or 50% reduction in AHI)<sup>1370</sup>. Additionally, in crossover trials patient preference and self-reported adherence was in favor of the customized MRD<sup>1370</sup>. Therefore, customized devices offer clear advantages for clinical effectiveness, as reflected in the clinical guidelines<sup>808</sup>. We provide a summary of the evidence for the effect MRD have on AHI, subjective and objective health outcomes, and therapy side effects.

#### MRD Candidacy - Dentition evaluation

Dental contraindications to MRD therapy have been found to present in up to 34% of 100 consecutive patients undergoing polysomnography<sup>1371</sup>. The dentist conducts an odontologic examination, including patient history and examination to characterize oral diseases and occlusal conditions. To be suitable for MRD therapy, candidates generally require sufficient healthy teeth and alveolar ridge to retain the device, the absence of temporomandibular disorders (TMD), and adequate protrusive jaw function<sup>1372</sup>. The presence of 8 to 10 teeth in each arch and a minimum 5mm protrusive capacity of the mandible are

usually considered necessary for optimal results from MRD treatment. However, lack of sufficient teeth may not be an absolute contraindication as the use of a dental implant-retained MRD has been reported in edentulous and partially dentate patients<sup>1373</sup>. Moreover, tongue retaining devices (TRDs) have also been proposed as a treatment alternative for edentulous patients. The periodontal status of OSA patients warrants consideration. Periodontal disease may pose a contraindication to MRD therapy due to substantial tooth mobility<sup>1371,1372</sup>. Dental or periodontal care may be required before the use of MRD (estimated in some 16% of patients)<sup>1371</sup>.

#### **MRD Candidacy - TMJ/associated disorders**

A comprehensive temporomandibular joint (TMJ) assessment is an important prerequisite to treatment with MRD. The prevalence of temporomandibular disorder (TMD) in OSA patients varies from 2% to 52%<sup>1371,1374</sup>, with 50% of subjects complaining of myofascial pain associated with and without limited mouth opening and arthralgia<sup>1374</sup>. Another study highlights the association between the two disorders, finding a 28.4% OSA prevalence rate in 53 TMD patients, highlighting the need to consider diagnostic sleep testing in TMD patients complaining of sleep disturbances<sup>1375</sup>.

There have been numerous studies that have collectively reported TMD as a result of MRD use. However, in an MRI study, translation of the mandibular condyle (movement out of the glenoid fossa of the temporal bone) with MRD therapy was equal to or less than that observed with maximum jaw opening in the absence of significant TMJ morphological alterations<sup>1376</sup>. Nonetheless, many patients experience TMJ related pain in the initial stages of treatment which is usually transient and not a contraindication to MRD use. To date, two studies advocate the use of mandibular jaw exercises to manage TMJ side effects with MRD use<sup>1374,1377</sup>.

#### **MRD Outcomes - Polysomnographic indices**

Pre-post comparison of customized MRD therapy in thirty-three studies (n=1,259) show a mean reduction in AHI (or RDI) of 13.9 events/hour<sup>808</sup>, as. Twenty-one studies (n=904) demonstrated a modest increase in minimum oxygen saturation. Only 6 studies (n=399) evaluated change in oxygen desaturation index and showed a mean reduction 12.8 events/hour. Arousal index was measured in only 16 studies (n=704) and showed a mean reduction of 10.8 per hour<sup>808</sup>. Additionally, 16 studies (n=675) evaluated REM sleep and noted a small but statistically significant increase in REM sleep; clinical significance of this increase is unknown and furthermore, no change in sleep efficiency between the two study nights with and without MRD was detected<sup>808</sup>. A meta-analysis of cross-over trials of MRD versus control appliance (i.e., inactive device that does not produce mandibular advancement) showed improvements in AHI, minimum oxygen saturation, and arousal index with MRD, indicating mandibular advancement is key to efficacy (4 studies, n=155)<sup>1378</sup>.

#### **MRD Outcomes - Daytime sleepiness (Epworth Sleepiness Score)**

A 2015 network meta-analysis of the effects of OSA therapy on ESS identified 5 studies (n=271) assessing MRD versus inactive control and 3 studies (n=244) which compared CPAP, MRD and an inactive control<sup>1379</sup>. In both pairwise and network analysis MRD reduced ESS versus inactive control (-1.7 points;  $p < 0.0001$ )<sup>1379</sup>.

#### **MRD Outcomes - Blood pressure**

Blood pressure is the most common objective health outcome reported in MRD studies. A 2015 network meta-analysis of the effects of OSA therapy on blood pressure assessed MRD versus inactive control (6 studies, n=473)<sup>1207</sup>. Compared to inactive control, MRD were associated with a reduction in systolic

blood pressure (SBP) of 2.1 mm Hg ( $p=0.002$ ) and in diastolic blood pressure (DBP) of 1.9 mm Hg ( $p=0.008$ )<sup>1207</sup>.

### MRD Outcomes - Health-related quality of life

The 36-Item Short Form Health Survey (SF-36) is widely used to evaluate health-related quality of life. The SF-36 has multiple domains to evaluate different aspects of quality of life. A systematic review and meta-analysis of RCTs incorporating the SF-36 identified two RCTs (one parallel; 25-29 participants, one cross-over; 83 participants) which compared SF-36 between MRD and inactive control device<sup>1380</sup>. Pairwise meta-analysis demonstrated improvement in the mental component score for MRD versus control (2.7 points;  $p=0.041$ )<sup>1380</sup>. The physical component score did not show a significant improvement versus control device (1.3 points;  $p=0.18$ )<sup>1380</sup>.

### MRD Side effects

Long-term use of MRD is associated with progressive but generally minor tooth movements, but not craniofacial changes. A systematic review and meta-analysis to evaluate dental and skeletal changes associated with MRD included twelve studies in meta-analysis (follow-up periods 2 to 7 years). In a single study ( $n=489$ ), tooth movements were associated with ongoing MRD usage, with decreases in overjet after MRD treatment ( $-0.99$  mm;  $p<0.00001$ ) and overbite ( $-1.00$  mm;  $p<0.00001$ )<sup>1381</sup>. No significant changes in skeletal relationships (craniofacial angles between landmarks sella-nasion line and point A on the maxilla [SNA], sella-nasion line and point B on the mandible [SNB], point A-nasion line and point B [ANB]) or mandibular rotation were evident. Additional side effects of MRD use include pain and sensitivity of the teeth, mouth dryness, occlusion changes, and TMJ exacerbation or pain.

### Factors related to MRD efficacy

Inter-individual variability in AHI reduction with MRD is common and several studies have sought to describe patient factors associated with AHI reduction using MRD. A recent meta-analysis suggests 'responders' to MRD therapy tend to have the following characteristics: lower age ( $n=998$ ;  $-3.1$  years;  $p<0.0001$ ), female gender, lower BMI ( $n=970$ ;  $-1.96$  kg/m<sup>2</sup>;  $p<0.00001$ ), smaller neck circumference ( $n=688$ ;  $-1.04$  cm;  $p<0.0001$ ), and lower baseline AHI ( $n=914$ ;  $-4.56$  events/hour;  $p<0.00001$ ), as well as some craniofacial characteristics (retracted maxilla and mandible, narrower airway and shorter soft palate)<sup>1382</sup>. It is also suggestive that MRD are more effective in positional OSA than non-positional OSA patients (4 out of 5 studies)<sup>1382</sup>. Although these average differences are statistically significant, the narrow mean differences do not make these factors useful as clinical selection tools.

### Mandibular Repositioning Devices for OSA

Aggregate Quality of Evidence: A (Level 1a: 8 studies).

Benefit: Improved AHI, ODI, arousal index, ESS, and blood pressure.

Harm: Side-effects include risk for tooth movement and pain associated with use.

Cost: Device cost is moderate and coverage varies by practice location.

Benefits-Harm Assessment: Preponderance of benefit over harm.

Value Judgments: MRD is considered an effective treatment option for OSA for reducing OSA severity and improving sleep symptoms. Effectiveness of therapy is variable.

Recommendation Level: Strong Recommendation

Intervention: MRD is an effective treatment option in selected patients with OSA.



Table VIII.C.2 Summary of Evidence for Mandibular Repositioning Devices

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Araie T. <i>et al.</i> <sup>1381</sup>	2018	1a	Systematic Review and Meta-analysis	MRD 12 studies (489 subjects)	Cephalometry, dental casts	Long-term use associated with dental changes
Bratton D.J. <i>et al.</i> <sup>1379</sup>	2015a	1a	Network meta-analysis	1) MRD 2) Control 3 studies (271 subjects)	Epworth Sleepiness Score	MRD reduces daytime sleepiness (ESS) compared to inactive control
Bratton D.J. <i>et al.</i> <sup>1207</sup>	2015b	1a	Network meta-analysis	1) MRD 2) Control 3 studies (229 subjects)	Blood pressure	MRD reduce blood pressure compared to inactive control device
Chen H. <i>et al.</i> <sup>1382</sup>	2020	1a	Systematic Review and Meta-analysis	MRD 41 studies (1854 subjects)	1) Age 2) Gender 3) BMI 4) Neck circumference 5) Cephalometry 6) AHI	On average MRD 'responders' are younger, female, less obese, with lower baseline AHI
Johal A. <i>et al.</i> <sup>1370</sup>	2017	1a	Systematic Review and Meta-analysis	1) Customized MRD 2) Prefabricated MRD 3 studies (129 subjects)	1) AHI 2) Proportion treatment responders	Customized devices have definable advantages including greater efficacy and patient preference and adherence
Kuhn E. <i>et al.</i> <sup>1380</sup>	2017	1a	Systematic Review and Meta-analysis	1) MRD 2) Inactive Control 3 studies (177 subjects)	SF-36 (mental and physical components)	MRD was associated with improvement in both physical and mental component scores, but only 2 studies

Lim J. <i>et al.</i> <sup>1378</sup>	2006	1a	Cochrane Systematic Review and Meta-analysis	1) MRD 2) Inactive Control 13 studies (553 subjects)	1) AHI 2) LSAT 3) Arousal Index	MRD reduce polysomnographic indices of OSA versus inactive control devices
Ramar K. <i>et al.</i> <sup>808</sup>	2015	1a	Clinical Practice Guideline	1) Pre and Post MRD 2) MRD versus sham-MRD 3) MRD versus CPAP 42 studies (1307 subjects)	1) AHI 2) LSAT 3) ODI 4) Arousal Index 5) REM% 6) Sleep Efficiency	It is recommended that MRD is prescribed for adult OSA patients, rather than no therapy, who are intolerant of CPAP or prefer alternate therapy

AHI - Apnea Hyponea Index; BMI – Body Mass Index; CPAP – Continuous Positive Airway Pressure; ESS – Epworth Sleepiness Score; LSAT – lowest oxygen saturation; MRD – Mandibular repositioning device; ODI – Oxygen Desaturation Index; OSA – Obstructive Sleep Apnea; %REM – percent of total sleep time spent in Rapid Eye Movement sleep stage; SF-36 - 36-Item Short Form Health Survey.

### VIII.C.2.a MRD Efficacy versus CPAP

Many studies have compared the effects of MRD versus CPAP, reporting on efficacy of treatment and subjective and objective health outcomes.

#### Efficacy (AHI)

Efficacy of both MRD and CPAP depends on compliance to therapy. Most data on MRD compliance has been limited to self-report.<sup>1383</sup> Patient acceptance and comfort levels have direct implications for successful therapy. CPAP is better at reducing AHI, as illustrated by a meta-analysis of 12 RCTs (n=824) showing greater average AHI reduction (8.2 events/hour;  $p < 0.001$ ).<sup>1384</sup>

#### Treatment usage (hours per night)

Six RCTs comparing CPAP and MRD included self-reported MRD usage, as well as either objective or self-report CPAP usage<sup>1384</sup>. There was evidence of high heterogeneity between studies. Overall CPAP compliance was found to be significantly lower than self-report MRD compliance by 1.1 hours per night<sup>1384</sup>. An additional assessment of MRD versus CPAP for adherence included 11 studies (n=442), with adherence favoring MRD by 0.7 hours per night, again with high study heterogeneity<sup>808</sup>. Eight studies were included in a meta-analysis of dropouts for each treatment (CPAP, MRD) and did not find a difference<sup>1384</sup>.

#### Daytime Sleepiness (ESS)

A 2015 network meta-analysis of 67 studies (n=6873) compared CPAP, MRD and inactive control devices for effect on ESS<sup>1379</sup>. CPAP treatment produced greater reductions in ESS than MRD by 0.8 points ( $p = 0.015$ ). A meta-analysis of twelve RCTs comparing CPAP and MRD did not find a statistically significant improvement in ESS score, with a difference in means of only 0.6 points ( $p = 0.203$ )<sup>1384</sup>. There

was statistical heterogeneity detected between studies and a sensitivity analysis concluded more studies with balanced baseline ESS values are needed to understand if there truly is a statistical difference in ESS between treatments or not<sup>1384</sup>.

### Blood Pressure

Network meta-analysis (N=4888 participants) confirms both CPAP and MRD reduce blood pressure relative to control<sup>1207</sup>. There was no significant difference between CPAP and MRD in their association with change in SBP (-0.5 mmHg; p=0.55) or in DBP (-0.2 mm Hg; p=0.82).

### Quality of life

In meta-analysis of the effect of CPAP versus control treatment (11 studies), CPAP improved both the mental (1.6 points; p=0.047) and physical component (1.8 points; p=0.005) scores of the SF-36 questionnaire<sup>1380</sup>. There was no difference between CPAP and MRD in pairwise and network meta-analysis of the physical and mental component scores for health-related quality of life<sup>1380</sup>. However, the authors acknowledge the limited data on MRD and wider confidence intervals, and although this study is suggestive that MRD may be just as effective, further RCTs comparing CPAP and MRD are ultimately needed. The Functional Outcomes of Sleep Questionnaire (FOSQ) assesses disease specific quality of life. Four RCTs (N=559) of MRD and CPAP found no difference in FOSQ changes between CPAP and MRD (difference in means of 0.03; p=0.788)<sup>1384</sup>; however, quality of evidence (GRADE) is moderate due to risk of bias<sup>1384</sup>.

### Cognitive function

There have been two trials comparing CPAP and MRD that have used trail making B test (n=244), which assesses executive functioning. Statistical heterogeneity between studies was not found. No difference in mean cognitive performance was detected using this test (mean difference of -3.5; p=0.395)<sup>1384</sup>; however, quality of evidence (GRADE) is very low due to risk of bias, inconsistency and imprecision<sup>1384</sup>.

### MRD Compared to CPAP for OSA

**Aggregate Quality of Evidence:** A (Level 1a: 5 studies).

**Benefit:** MRD and CPAP are associated with similar outcomes for quality of life improvement, improved blood pressure and cognitive function. MRD has potential for improved compliance rates compared to CPAP.

**Harm:** Inconsistent efficacy in AHI reduction with MRD relative to CPAP.

**Cost:** Device cost is moderate and coverage varies by practice location.

**Benefits-Harm Assessment:** Balance of benefit over harm.

**Value Judgments:** CPAP more effectively reduces OSA severity, but MRD is associated with improved compliance. Patient preference and likelihood of device use should be considered in choosing MRD vs. CPAP for OSA therapy.

**Recommendation Level:** Option.

**Intervention:** MRD is an effective alternative to CPAP in OSA.

**Table VIII.C.2.a: Summary of Evidence for Mandibular Repositioning Device Efficacy versus CPAP**

Study	Year	LOE (1a to	Study Design	Study Groups	Clinical Endpoint	Conclusion
-------	------	------------	--------------	--------------	-------------------	------------

		5)				
Bratton D.J. <i>et al.</i> <sup>1379</sup>	2015a	1a	Network meta-analysis	1) MRD 2) CPAP 3) Control 67 studies 6873 subjects	Epworth Sleepiness Score	CPAP more effective than MRD in reducing ESS (although possibility of publication bias in favor of CPAP that may contribute to difference)
Bratton D.J. <i>et al.</i> <sup>1207</sup>	2015b	1a	Network meta-analysis	1) MRD 2) CPAP 3) Control 51 studies 4888 subjects	Blood pressure	Both MRD and CPAP reduce BP relative to control. There was no difference in BP reduction between CPAP and MRD
Kuhn E. <i>et al.</i> <sup>1380</sup>	2017	1a	Systematic Review and Meta-analysis	1) MRD 2) CPAP 23 studies 2342 subjects	SF-36 (mental and physical components)	Suggestive that MRD may be similarly effective to CPAP, but more RCTs needed
Ramar K. <i>et al.</i> <sup>808</sup>	2015	1a	Clinical Practice Guideline	1) MRD 2) CPAP 15 studies 491subjects	Poly-somnographic indices, adherence, side effects, blood pressure, quality of life, sleepiness	It is recommended that MRD is prescribed for adult OSA patients, rather than no therapy, who are intolerant of CPAP or prefer alternative therapy
Schwarz M. <i>et al.</i> <sup>1384</sup>	2018	1a	Systematic Review and Meta-analysis	1) CPAP 2) MAS 12 (824) [AHI] 6 (525) [compliance] 4 (559) [FOSQ] 10 (950) [ESS] 2 (244) [cognitive function]	1) AHI 2) Compliance 3) FOSQ 4) ESS 5) Cognitive function	CPAP better reducing AHI. No difference SF-36, FOSQ, cognitive performance. ESS potentially favors CPAP, adherence greater in MRD

AHI - Apnea Hyponea Index; BP – Blood Pressure; CPAP – Continuous Positive Airway Pressure; ESS – Epworth Sleepiness Score; FOSQ – Functional Outcomes of Sleep Questionnaire; MRD – Mandibular repositioning

#### VIII.D Medical Management of OSA: Behavioral and Adjunctive Therapies

##### VIII.D.1 Positional Therapy for Positional OSA

In patients with positional OSA, disease severity depends on the total sleeping time (TST) in the supine position. Positional therapy (PT) aims at preventing patients from sleeping in the supine position in order to improve or resolve positional OSA. The majority of early studies on PT used the so-called tennis ball technique (TBT) where a bulky mass is strapped to the patient's back.<sup>1385</sup> TBT is effective in reducing the overall AHI and the percentage of TST in supine position, but long-term compliance is poor. This is due to discomfort and no improvement, or even deterioration of sleep quality and/or daytime alertness.<sup>1386,1387</sup> Compliance rates of TBT reported in the literature range from 40-70% in the short-term to only 10 % in the long-term.<sup>1386-1389</sup>

A new generation of small, lightweight, battery-powered vibrotactile smart devices, which are either attached to the trunk (or neck) was introduced. Almost all research is with chest-worn devices (Table VIII.D.1 ). When the patient moves to the supine position, these sleep position trainers (SPT) provide a vibrating stimulus aiming to turn the patient to a non-supine sleeping position without awakening the user. In a recent meta-analysis, data from studies reporting on the effect of new-generation SPT devices were included. Data from 6 studies showed that mean AHI was significantly reduced from a mean 21.8 to 9.9 events/hr (54% change) and AHI SMD was -1.94 (large effect). Pooled mean reduction in percentage of TST in the supine position also declined from 40.1% to 6.5% (84% reduction).<sup>1390</sup> Short-term compliance (4 weeks to 3 months of therapy) is high, varying from 76% to 96%, when defined as at least 4 hours of use per night during 7 days a week.<sup>1390-1401</sup>

Long-term compliance of SPT varies between 64.4 and 75.5%.<sup>1390-1401</sup> The impact of compliance on SPT effectiveness is illustrated in a RCT study where 55 patients were treated with either SPT or TBT. Both SPT and TBT were equally effective in reducing respiratory events in those with mild positional OSA with a normal ESS. However, compared to TBT, sleep quality, QOL, and compliance was significantly greater in the SPT group.<sup>1395</sup>

In a recent RCT the effectiveness of mandibular advancement device (MAD) versus PT was compared.<sup>1391,1394</sup> The effect after 3 and 12 months was the same but there were more treatment-related side effects in the MAD arm. Two RCTs compared CPAP and SPT in the treatment of mild positional OSA. In the first study APAP was compared with PT in a randomized crossover trial format. SPT was found to be noninferior in treatment efficacy and greater adherence.<sup>1392</sup> A total of 117 participants were randomized (58 SPT first, 59 APAP first). The AHI with PT was higher compared to APAP (mean  $\pm$  standard deviation,  $7.29 \pm 6.8$  versus  $3.71 \pm 5.1$  events/h,  $P < .001$ ). The mean AHI difference (SPT-APAP) was 3.58. The average nightly adherence (all nights) was greater with PT ( $345.3 \pm 111.22$  versus  $286.98 \pm 128.9$  minutes,  $P < .0001$ ). Participants found the SPT to be more comfortable and easier to use, and 53% reported a preference for PT assuming both devices were equally effective. In the other, smaller (N=40) RCT, a neck SPT was used and compared to CPAP. ESS difference with SPT did not meet the noninferiority margin.<sup>1402</sup>

Others have looked at combination therapy with PT and mandibular advancement device therapy.<sup>1403</sup> In one study of persistent POSA with MAD therapy, patients underwent consecutive randomized PSG tests with SPT and with SPT + MAD. The effects of MAD and PT were comparable with approximately a 50% reduction of the AHI, but then a further 25% reduction was reported when MAD and PT were combined. A recent Cochrane review was generalized to all categories of OSA and included both TBT and SPT devices.<sup>1404</sup> The review described a greater improvement in AHI with CPAP compared to PT, but no difference in ESS or quality of life between the groups. Studies that compared PT to an inactive control group showed improved ESS and AHI in the PT group.

### Positional Therapy with Sleep Position Trainers for Positional OSA

**Aggregate Quality of Evidence:** B (Level 1: 6 studies; level 2: 6 studies).

**Benefit:** New generation sleep position trainers are effective in reducing OSA severity and symptoms in those with positional OSA.

**Harm:** Serious side effects of newer generation positional devices have not been reported. Older TBT techniques are associated with back discomfort. Risk for variable efficacy in treating OSA and variable compliance. Studies are limited to date (small, short-term and examine a limited range of outcomes).

**Cost:** Cost and coverage vary based on insurance.

**Benefits-Harm Assessment:** Benefits outweigh the harms.

**Value Judgments:** New generation positional therapy device use for positional OSA can be effective without serious side effects. It can be used as primary treatment or in combination with other treatments and may have better adherence than classic positional therapy with TBT.

**Recommendation Level:** Recommendation.

**Intervention:** For positional OSA, positional therapy is an effective intervention. New generation sleep position therapy may have better adherence rates than classic positional therapy (TBT).

**Table VIII.D.1 Evidence for Positional Therapy for Positional OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Eysvogel <sup>1395</sup>	2015	2b	RCT	55 patients with positional OSA ( defined as supine AHI $\geq$ 2 times nonsupine AHI and non-supine AHI $<$ 10) with chest worn device (n=29, SPT, NightBalance) vs. tennis ball technique (n=26)	AHI, Compliance (use $\geq$ 4 hours/day and $\geq$ 5 days/week)	Equal reduction AHI (SPT: 11.4 vs. 3.9, TBT: 13.1 vs. 5.8), better compliance in SPT arm (SPT: 75.9% vs. TBT:42.3%, p=0.01).
Laub <sup>1396</sup>	2017	1b	RCT	101 patients with positional OSA ( defined as supine AHI $\geq$ 2 times nonsupine AHI, supine AHI $>$ 10 and non-supine AHI $<$ 10) with chest worn device (n=52, SPT, NightBalance) vs no treatment	AHI, % supine sleep, sleepiness, compliance (SPT use $>$ 4 hours/night all week)	At 2 months, AHI improved in the SPT group (from 18.1 to 10.4 on per-protocol analysis, p=0.008) and remained unchanged in the control group (p=0.2). Percentage of time supine improved in both groups and ESS did not change in either group. Compliance with SPT was 75.5%.

				(n=49)		
Benoist <sup>1391</sup>	2017	2b	RCT	99 patients with positional OSA ( defined as supine AHI $\geq$ 2 times nonsupine AHI) with chest worn device (n=48, SPT, NightBalance) vs. oral appliance therapy (n=51)	AHI, Compliance	SPT and oral appliance equally effective. At three months, AHI decreased in both groups (SPT: 13.9 to 8.7, oral appliance: 13.2 to 8.1, p<0.001 for both). Only SPT decreased percentage of time in supine sleep (42.4 to 14.2, p<0.001).
De Ruiter <sup>1394</sup>	2017	1a	RCT	58 patients with positional OSA (defined as supine AHI $\geq$ 2 times nonsupine AHI) with chest worn device (n=29, SPT, NightBalance) vs. oral appliance therapy (n=29)	AHI, Compliance	SPT and oral appliance equally effective. At 12 months, AHI decreased in both groups (SPT: 13.2 to 7.1, oral appliance: 13.4 to 5.0, p<0.001 for both). Only SPT decreased percentage of time in supine sleep (41.6 to 12.7, p<0.001).
Berry <sup>1392</sup>	2019	1b	Non inferiority RCT, cross over	117 patients with positional OSA (defined as AHI $\geq$ 15 or AHI 10-15 with ESS>10 and supine AHI $\geq$ 2 times nonsupine AHI) with CPAP vs chest worn device (SPT, NightBalance) followed by crossover	Adherence, AHI, PROMs	SPT non inferior to CPAP with improved AHI in both groups (SPT: 21.5 to 7.3, CPAP: 21.5 to 3.7). SPT had greater nightly adherence than CPAP (345.3 vs 286.98 minutes, p<0.0001).
Mok <sup>1402</sup>	2020	2b	Non inferiority RCT, crossover	40 patients with ESS 10-16, positional OSA (defined as supine AHI $\geq$ 2 times nonsupine AHI, supine AHI>10 and non-supine AHI<10)	AHI, ESS	With regard to decrease in AHI, PT inferior to CPAP (PT: 23.4 to 13.0, CPAP: 23.4 to 4.0, p<0.001) With regard improvement in ESS, PT noninferior to CPAP.

				with CPAP vs neck worn device (Night Shift)		
Srijithesh <sup>1404</sup>	2019		SR, Cochrane	323 patients with OSA treated with positional therapy vs. CPAP (n=72) or positional therapy vs. inactive control (n=251)	AHI, ESS	Positional therapy was less effective than CPAP for reducing AHI (6.4 fewer events per hour with CPAP, 95% CI 3.00 to 9.79; low-certainty evidence) but compliance may be higher. Positional therapy was more effective than inactive control in reducing AHI and ESS.
Van Maanen <sup>1400</sup>	2013	2b	Single arm	36 patients with positional OSA ( defined as supine AHI > 2 times nonsupine AHI) with chest worn device (Sleep Position Trainer [SPT]NightBalance)	AHI, sleep efficiency, ESS, FOSQ, compliance	At 1 month, the median percentage of supine sleeping time decreased from 49.9 % to 0.0 % (p<0.001) and median AHI decreased from 16.4 to 5.2 (p<0.001).
Van Maanen <sup>1401</sup>	2012	2b	Single arm	36 patients with positional OSA ( defined as supine AHI > 2 times nonsupine AHI) with simple neck worn device	AHI, sleep quality	Mean AHI decreased from 27.7 to 12.8 (p<0.01) and mean percentage of supine sleeping time decreased from 40% to 19% with use of the device.
Van Maanen <sup>1399</sup>	2014	2b	Single arm	106 patients with positional OSA ( defined as supine AHI > 2 times nonsupine AHI) and data from chest worn device (SPT, NightBalance)	Sleep efficiency, ESS, FOSQ, compliance.	Long term reduction of percentage of supine sleep from 21% to 3% (p<0.001) at 6 months and improvement of ESS and QoL.
Levendowsky <sup>1397</sup>	2014	1b	Single arm	30 patients with positional OSA (	AHI, SO <sub>2</sub> , depression	Improvement of mean AHI from 24.7 to 7.5



				defined as supine AHI $\geq$ 1.5 times nonsupine AHI) with neck worn device (NightShift)	score, sleep architecture	( $p < 0.00001$ ), decrease in percentage of time O2 sat $< 90\%$ (from 4.2 to 1.2, $p < 0.01$ ), and improved sleep architecture.
Beyers <sup>1393</sup>	2019	1b	Single arm	58 patients with positional OSA (defined as supine AHI $\geq$ 2 times nonsupine AHI) with chest worn device (SPT, NightBalance)	Long term AHI, % supine sleep, sleep quality, compliance	At 1 year, 85% of patients were still using the device and 75% reported subjective improvement in sleep quality. Mean AHI improved from 16.4 to 6.2 ( $p < 0.001$ ), percentage of time in supine sleep was reduced from 37.1% to 1.4% ( $p < 0.001$ ).
Dieltjens <sup>1403</sup>	2015	1b	RCT	20 patients with residual positional OSA after mandibular advancement device use (defined as supine AHI $\geq$ 2 times nonsupine AHI, supine AHI $> 10$ and non-supine AHI $< 10$ ) with chest worn device (SPT, NightBalance) vs combination of chest worn device and mandibular advancement device	AHI, Compliance	SPT and MAD equally effective at reducing AHI and ODI, combination more effective with decrease in AHI from 20.9 to 5.5, $p < 0.008$ .

### VIII.D.2 Weight Management for OSA

The role of weight loss on severity of obstructive sleep apnea (OSA) has been studied. A total of 8 papers were identified that reported results of RCTs of medical weight loss interventions against controls, of which 7 were RCTs on adult patients and one was a meta-analysis (Table IX.1.b)<sup>122,1405-1410</sup>.

Study durations ranged from 4 weeks to 1 year. All RCTs included a small number of participants that ranged from 11 to 264. Low calorie diet was compared to control in 6 RCTs<sup>1406,1407,1409-1412</sup>, diet and exercise were compared to control in 2 RCTs<sup>122,1408</sup> and inpatient rehabilitation program group (including individualized exercise training, education activities sessions, and dietary management) was compared to control in 1 RCT. One RCT demonstrated efficacy of the Mediterranean diet for reduction in cardiovascular endpoints, weight loss and has been shown to reduce the REM-related AHI at 3 months<sup>1413</sup>. The meta-analysis included is the most recent American Thoracic Society (ATS) Clinical Practice Guideline for the role of weight management in the treatment of adult OSA<sup>1414</sup>. Medical weight loss was superior to control in reducing AHI in all included studies.

The mean difference in weight change with weight loss in the 6 RCTs ranged from -5 kg to -18.7 kg. The resultant mean difference in AHI ranged from -4 to -25<sup>122,1405-1408,1410</sup>. One RCT only reported mean difference in BMI (-1.8kg/m<sup>2</sup>) and percent change in AHI (-16.9%)<sup>1409</sup>. In the ATS meta-analysis there were only 4 RCTs that examined the impact of weight loss on OSA severity, and the mean difference (or reduction) in AHI was -8.5 events/hour (95% CI -10.8 to -6.2)<sup>1414</sup>. Given the benefits of weight loss programs, and their limitations related to their role in the management of OSA, the ATS made a strong recommendation for comprehensive weight loss programs, but underlined that this recommendation is of very low certainty in the estimated effect.

Neither serious adverse effects nor deaths were reported in any of the included studies. Cost analysis was not performed in any of the studies.

Weight loss medications can be beneficial in some patients. The Endocrine Society recommends weight loss agents as adjunctive therapy for patients unsuccessful in losing weight despite lifestyle modifications, diet, and exercise<sup>1415</sup>. The benefits of pharmacologic weight loss in patients with OSA has been explored, although only two RCTs have measures related to OSA specific outcomes<sup>1416,1417</sup>. A new medication for weight loss includes glucagon-like peptide-1 receptor agonists (GLP-1 RA) such as semaglutide (15). GLP-1RA medications stimulate insulin secretion and reduce glucagon and may also delay gastric emptying.<sup>1418</sup> A recent randomized, double-blind study looked at the effects of semaglutide combined with intensive behavioral therapy and low-calorie diet. When compared to placebo, once-weekly subcutaneous semaglutide resulted in a 10.3% greater decrease in body weight and more participants lost at least 5% of their body weight.<sup>1419</sup> Daily liraglutide demonstrated reduction in AHI (-6.1 events per hour) which was associated with the degree of weight loss in post hoc analysis.<sup>1416</sup> Overall, there are limited data showing that weight loss medications improve measures of outcomes related to OSA. However, given the benefits of weight loss in general, these medications should be considered to promote weight loss in patients who cannot achieve weight loss goals with calorie restriction regimens.

### Weight Loss for Improvement in OSA Severity

**Aggregate Quality of Evidence:** B (Level 2a: 2 studies; level 2b: 9 studies).

**Benefit:** Medical weight loss is effective in reducing OSA severity.

**Harm:** No deaths were reported in any of the trials. There was no difference in reported adverse events.

**Cost:** Cost analysis not performed. Low to moderate dependent on recommended restricted calorie plan and exercise regimen.

**Benefits-Harm Assessment:** Preponderance of benefit over harm. Studies demonstrate that weight loss is effective at reducing the AHI.

**Value Judgments:** Small number of RCTs with small numbers of subjects demonstrated effectiveness of weight loss.

Recommendation Level: Recommendation.

Intervention: Weight loss programs should be suggested in overweight or obese patients with OSA.

**Table VIII.D.2** Evidence for the role of weight loss in the management of obstructive sleep apnea (OSA).

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
López-Padrós et al. <sup>1411</sup>	2020	2b	RCT	<p>1.Intensive weight loss program with low (600–800 kcal/day) calorie diet for 15 days followed by a 1,200 kcal/day diet during the remainder of the initial 12 weeks, and a 1,200–1,800 kcal/day Mediterranean diet for the last 36 weeks (n=22)</p> <p>2.Control group (n=20)</p>	AHI (PSG)	<p>In obese patients with severe OSA (AHI&gt;30), an intensive weight loss program is superior to control in reducing weight and OSA severity.</p> <p>Diet group: MD in weight at 3 months: -10.5kg 12 months: -8.2 kg MD in AHI at 3 months: -23.7 12 months: -19.4</p> <p>Control group: MD in weight at 3 months: -2.3 kg at 12 months: -0.1 kg, MD in AHI at 3 months: -9 at 12 months: -13.5</p>
Hudgel et al. <sup>1414</sup>	2018	2a	SR with meta-analysis	4 RCTs that examined the impact of weight loss on OSA	AHI	<p>MD in weight was -11.6 kg; MD in BMI was -4.1 kg/m<sup>2</sup></p> <p>AHI MD -8.5 ESS MD -2.4 points</p> <p>For patients with OSA who are overweight or obese, suggest a reduced-calorie diet (with or without exercise/increased physical activity) rather than no diet (conditional recommendation, very low certainty in the estimated effect).</p>
Fernandes et al. <sup>1406</sup>	2015	2b	RCT	800 Cal diet group (n=11)	pAHI (with WatchPAT)	Weight loss superior to control in improving OSA severity. Mean differences

				Control group (n=10) Age (20-55)		below.  Diet group: Change in weight: -5.57kg Change in pAHI: -7.22  Control group: Change in weight: 0.43kg Change in pAHI: 0.13 (p=0.04)
Make-Nunes et al. <sup>1408</sup>	2015	2b	RCT	Hypocaloric diet (decrease of 500 kcal/day) and exercise training group (n=16)  Control group (n=8)	AHI (PSG)	Hypocaloric diet and exercise training superior to control in improving OSA severity. Mean differences below.  Hypocaloric diet and exercise training group Change in weight: -5 kg Change in AHI: -16  Control group: Change in weight: 1 kg Change in AHI: 11  Change in body weight was associated with change in AHI.
Ng et al. <sup>1409</sup>	2015	2b	RCT	Dietician led lifestyle modification program (diet) group (n=61)  Control group: Usual care (n=43)	AHI	In patients with moderate to severe OSA, lifestyle modification was superior to usual care in reducing the severity of OSA.  Dietician led lifestyle modification program (diet) group: Change in BMI: -1.8 kg/m <sup>2</sup> Percent change in AHI: -16.9%  Control group: Change in BMI: -0.6 kg/m <sup>2</sup> Percent change in AHI + 0.6%
Desplan et al. <sup>1405</sup>	2014	2b	RCT	Inpatient rehabilitation program group including	AHI, ODI (PSG)	In patients with moderate to severe OSA, intervention was superior to control in reducing AHI and ODI.

				<p>individualized exercise training, education activities sessions and dietary management (n=11)</p> <p>Control group: one-month education activity sessions (n=11)</p>		<p>Inpatient rehabilitation program: Change in BMI: -0.8kg/m<sup>2</sup> Change in AHI: -12.6 Change in ODI: -5.5</p> <p>Control group: Change in BMI: 0 kg/m<sup>2</sup> Change in AHI: 5.6 Change in ODI: 5.2 Change in arousals: 6.7</p>
Papandreou et al. <sup>1413</sup>	2012	2b	RCT	<p>Mediterranean diet, CPAP, and lifestyle intervention (n=20)</p> <p>Prudent diet, CPAP, and lifestyle intervention (n=20)</p>	AHI (PSG)	In patient with moderate to severe OSA (AHI >15) and BMI ≥ 30 kg/m <sup>2</sup> , Mediterranean diet was only superior to control in reducing AHI during REM sleep. Otherwise, there were no significant differences in other sleep parameters between the two groups. Changes in weight and BMI did not reach statistical significance between the two groups.
Foster et al. <sup>122</sup>	2009	2a	RCT	<p>Intervention group: Diet, exercise and training (n=125)</p> <p>Control group: 3 group sessions for diabetes management (n=139)</p>	AHI, ODI (unattended overnight PSG)	<p>Intervention superior to control in reducing AHI reported as adjusted mean differences.</p> <p>Diet and exercise group: Change in weight: 10.8kg Change in BMI: -3.8kg/m<sup>2</sup> Change in AHI: -5.4 Change in ODI: -5.5</p> <p>Control group: Change in weight: 0.6kg Change in BMI: 0.2kg/m<sup>2</sup> Change in AHI: 4.2 Change in ODI: 1.2</p>
Johansson et al. <sup>1407</sup>	2009	2b	RCT	Intervention group: Very low calorie (2.3 MJ/day) liquid diet	pAHI, ODI (WatchPAT)	Very low calorie diet superior to usual diet in reducing pAHI. Low energy diet

				(n=30) Control group: Usual diet (n=33)		improved OSA in obese men, with the greatest effect in patients with severe disease. Mean differences below.  Intervention group: Change in weight: -18.7 kg Change in BMI: -5.7 kg/m <sup>2</sup> Change in pAHI: -25 Change in ODI: -19  Control group: Change in weight: 1.1 kg Change in BMI: 0.3 kg/m <sup>2</sup> Change in pAHI: -2 Change in ODI: -1
Tuomilehto et al. <sup>1410</sup>	2009	2b	RCT	Intervention: Very low calorie diet program 600–800 kcal/day (with supervised lifestyle modification (n=35)  Control: Routine lifestyle counseling (n=37)	AHI, mean Sa <sub>O2</sub>	Intervention superior to control in reducing AHI in mild OSA, and improving mean oxygen saturation, together with weight loss. Mean differences below.  Diet group: Change in weight: -10.7kg Change in BMI: -3.5 kg/m <sup>2</sup> Change in AHI: -4.0 Change in mean Sa <sub>O2</sub> : 0.8  Control group: Change in weight: -2.4kg Change in BMI -0.8kg/m <sup>2</sup> Change in AHI: 0.3 Change in mean Sa <sub>O2</sub> : -0.3
Nerfeldt et al. <sup>1412</sup>	2008	2b	RCT	Intervention: weight reduction program consisting of a low-calorie diet and group meetings (n=6)  Control: expectancy followed by crossover after 8 weeks (n=5)	AHI, ODI (Micro Digi trapper-type 3)	Intervention was superior to control in reducing ODI in males with BMI ≥30. Mean differences below.  Diet group: Change in weight: -18.5 kg Change in BMI: -4.8 kg/m <sup>2</sup> Change in ODI: -50  Control group: Change in weight: -13kg Change in BMI: -3.7 kg/ m <sup>2</sup> .

						Change in ODI: -1
Pharmacotherapy						
Blackman et al. <sup>1416</sup>	2016	1b	RCT	Liraglutide 3 mg with diet (500 kcal/day) and exercise (n=180)  Placebo with diet (500 kcal/day) and exercise (n=179)	AHI (PSG)	Intervention was superior to placebo in reducing AHI in patients with obesity (BMI $\geq 30$ kg/m <sup>2</sup> ) and mild-moderate OSA (AHI $\geq 15$ ). Mean differences below.  Liraglutide group: Change in weight: $-6.7$ kg $\pm$ 0.5 Change in BMI: $-2.2 \pm 0.2$ kg/m <sup>2</sup> Change in AHI: $-12.2 \pm 1.8$  Placebo group: Change in weight: $-1.9$ kg $\pm$ 0.4 Change in BMI: $-0.6 \pm 0.1$ kg/m <sup>2</sup> Change in AHI: $-6.0 \pm 2.0$  Significant treatment difference in AHI, weight, SBP and HbA1c between groups.
Winslow et al. <sup>1417</sup>	2012	2b	RCT	Phentermine 15 mg plus extended-release topiramate 92 mg (n=22)  Placebo (n=23)	AHI (PSG)	Treatment was superior to placebo in reducing AHI. Mean Differences below.  Phentermine and topiramate group: Change in weight: $-11.0 \pm 1.24$ kg Change in AHI: $-31.5 \pm 4.2$  Placebo group: Change in weight: $-4.5 \pm 1.21$ kg Change in AHI: $-16.6 \pm 4.5$

AHI= apnea hypopnea index; CWLP= comprehensive weight loss program; EDS= excessive daytime sleepiness; ESS= Epworth sleepiness score; MD= mean difference; N= number;  
ODI= oxygen desaturation index; OSA= obstructive sleep apnea; pAHI=PAT AHI; PAT=Peripheral arterial tonometry; RCT= randomized controlled trial; Sa<sub>o2</sub>= oxygen saturation; SBP: systolic blood pressure; SR= systematic review

### VIII.D.3 Sedative Medications and Effect on OSA

A sedative is defined as “A drug taken for its calming or sleep-inducing effect” and are often used by people who are struggling to fall or stay asleep.<sup>1420</sup> Early in the history of obstructive sleep apnea, case reports suggested that some sedatives worsened breathing during sleep.<sup>1421,1422</sup> Benzodiazepines, commonly used sedative medications, likely affect respiration through multiple mechanisms, including sedation, muscle relaxation, and increasing N2 sleep.<sup>1423</sup> A 2015 Cochrane review reviewed 14 randomized controlled studies of patients with OSA and ten opiate, hypnotic, and sedating medications including: remifentanyl (infusion), eszopiclone, zolpidem, brotizolam, flurazepam, nitrazepam, temazepam, triazolam, ramelteon and sodium oxybate. The findings demonstrated that no evidence that the pharmacological compounds assessed have a deleterious effect on the severity of OSA as measured by change in AHI or ODI, though some statistically significant decreases in oxygen level were observed with remifentanyl, zolpidem and triazolam.<sup>1424</sup>

Alcohol is often considered a sedative and has effects similar to that of benzodiazepines. Alcohol use in a 1982 case report dramatically worsened sleep-disordered breathing in 7 patients with known snoring and/or obstructive sleep apnea.<sup>1425</sup> However, in contrast to the benzodiazepine data above, alcohol increased in the severity of OSA in a statistically significant manner, both in terms of apnea-hypopnea index (AHI) and mean blood oxygen level in a 14-study meta-analysis.<sup>1426</sup> Most of the studies in the meta-analysis used between 2-3 standard alcohol drinks as the tested dosage.

Sedating anti-depressants including trazodone, protriptyline, mirtazapine, paroxetine, and fluoxetine have been studied without evidence that they negatively impact OSA severity.<sup>1427</sup> Suvorexant, a newer medication with an orexin antagonism mechanism did not impact OSA severity in a study of 26 patients with mild-moderate OSA.<sup>1428</sup> Antihistamines are often used as over-the-counter sedative medications; no evidence has suggested that these medications are respiratory depressants or that they impact the ventilatory response.<sup>1423</sup>

Sedative medications are frequently used in the perioperative setting, both before and after surgery. Scientific data suggest that patients with OSA are at higher risk for adverse events in the peri-operative setting.<sup>467</sup> In specific, patients with OSA and high arousal thresholds may be particularly sensitive to sedatives and narcotic medications with an increased risk of respiratory arrest in the peri-operative period. Limiting sedative use as possible and close monitoring is suggested in patients with OSA undergoing surgery.<sup>1427</sup>

While the majority of this section has focused on the potential worsening of sleep-disordered breathing with use of sedatives, there is some data suggestive that sedative medications may be helpful in some patients with OSA. For instance, one study of eszopiclone use in patients with OSA demonstrated a statistically significant reduction of AHI.<sup>399</sup> One current theory suggests that in appropriate patients, sedatives may increase the arousal threshold to facilitate the experience of sufficient magnitude of respiratory stimuli for an adequate duration which activates pharyngeal dilator muscles and thus stabilizes breathing. With fewer arousals and stabilized breathing, deeper sleep may be obtained further reducing the occurrence of respiratory events. Thus, for the sedative to be an effective treatment, the sedative must increase the arousal threshold, and the patient must have a mild to moderately collapsible upper airway, responsive and effective upper airway dilator muscles, and a low to moderate arousal threshold.<sup>1427</sup>



#### VIII.D.4 Nasal Obstruction and Sinusitis Management for OSA Treatment

The evaluation and management of nasal obstruction plays an important role in OSA as the nose regulates nasal resistance and stimulates ventilation<sup>1429</sup>. Nasal obstruction is thought to contribute to OSA and is known to interfere with treatment options including CPAP and oral appliances<sup>1430</sup>. Addressing nasal obstruction can be done with surgical management (septoplasty, inferior turbinate reduction, and endoscopic sinus surgery), medical management (nasal corticosteroid sprays, nasal decongestants, oral antihistamines, leukotriene antagonists and internal or external nasal dilators) or a combination of surgery and medical management. The medical management of nasal obstruction investigated is primarily limited to studies examining the use of intranasal corticosteroid sprays and/or mechanical stents to hold the nasal cavity open during nasal respiration. Although there are a number of randomized control trials (RCTs) evaluating the above medical therapies, data consist of short follow up times, heterogenous patient populations and the inherent challenge of establishing an objective measurement of nasal obstruction.

The conglomeration of literature overall suggests an improvement in both subjective and objective sleep in patients with rhinitis and OSA with the use of intranasal corticosteroids (Table 1). Craig et al. evaluated the effect of intranasal corticosteroid use on multiple patient-reported sleep symptoms using pooled data from three randomized placebo-controlled, cross-over trials and found that improved nasal congestion in patients with perennial allergic rhinitis correlated highly with improved sleep ( $p < 0.01$ ) and daytime sleepiness ( $p = 0.01$ )<sup>890</sup>. In the only systematic review published on this topic, Liu et al. demonstrated that intranasal corticosteroid sprays were effective in decreasing AHI (SMD standardized mean difference  $-0.73$ ) in patients with OSA<sup>1431</sup>. However, the overall effectiveness of intranasal corticosteroid therapy for decreasing OSA severity is still undetermined. Kiely et al. performed a randomized placebo-controlled, cross-over study demonstrating improved sleep outcomes using intranasal corticosteroids in patients with allergic rhinitis and OSA. AHI was significantly reduced in 13 patients with OSA and rhinitis treated with fluticasone for 4 weeks as compared to placebo (23.3 vs 30.3  $p < 0.05$ ). Despite improvements, most patients continued to have significant OSA<sup>894</sup>. In divergence, Smith et al. in 2019 performed a randomized placebo controlled double blind investigation examining patients with an AHI less than 15, demonstrating fluticasone and montelukast did not significantly decrease AHI or ESS<sup>1432</sup> while the total sleep time and % of REM sleep improved. The role of intranasal corticosteroids in improving CPAP adherence in patients with OSA also remains undetermined. In a meta-analysis of two randomized controlled trials evaluating corticosteroid use and objective CPAP compliance, Charakorn et al. found that while CPAP use increased by an average of 0.4 hours per night in treated patients, this benefit did not reach statistical significance and there was no change in percentage of nights with CPAP use<sup>1178</sup>.

Clarenbach et al. performed a randomized placebo-controlled, cross-over study examining the benefits of acutely improving nasal obstruction by using a decongestant (oxymetazoline). They demonstrated AHI significantly decreased at the time of maximal pharmacological effect (30-210 minutes) (27.3 vs 33.2), but overall AHI did not change<sup>899</sup>. Despite these short-term AHI reductions, routine nasal decongestant use is not recommended secondary to known rebound congestion and architectural changes in the sinonasal epithelium.

#### Chronic Rhinosinusitis

There are limited data evaluating the impact of medical therapies (topical nasal corticosteroid sprays, saline irrigations, oral antibiotics and oral corticosteroids) on patient sleep quality outcome measures in CRS. In a study by Alt et al.,<sup>1433</sup> patients undergoing both medical and surgical therapy for CRS were

followed longitudinally after each intervention. Patients in the surgical cohort were found to have greater improvement in Pittsburgh Sleep Quality Index as compared with their medical therapy counterparts. Additional study is required to confirm these findings.

### Allergic Rhinitis

Oral antihistamines and leukotriene inhibitors have also been investigated as medical therapies for comorbid allergic rhinitis and OSA, though data are limited. Acar et al. evaluated the impact of desloratadine treatment in both the presence and absence of concomitant mometasone nasal sprays in a 2013 RCT. No additional benefit was noted in objective sleep parameters when desloratadine was added<sup>1434</sup>. Similarly, Smith et al. evaluated the combination of montelukast and fluticasone as compared to placebo on AHI in mild OSA patients in a double-blind placebo RCT. While there was no significant reduction in AHI, total sleep time and percentage of REM sleep improved<sup>1432</sup>. The potential sedative effect of oral antihistamine treatment in OSA patients warrants consideration if antihistamine therapy is considered for management of comorbid allergic rhinitis. Further study is needed to delineate the role of oral antihistamine and leukotriene inhibitors for OSA therapy.

### Medical Treatment of Nasal Obstruction and Sinusitis for OSA Severity

Aggregate Quality of Evidence: B: Level 1A (2 studies) Level 1B (13 studies) Level 3B (3 studies) Level 4 (11 studies).

Benefit: Improvements in sleepiness and small reductions in AHI and O2 saturations.

Harm: Risks associated with topical nasal corticosteroid use include: epistaxis, nasal discomfort/burning, dryness, crusting, foul taste, headache, and sore throat.

Cost: Low monthly cost associated with topical nasal corticosteroid use.

Benefits-Harm Assessment: Balance of benefit and harm due to mixed evidence on changes in OSA severity.

Value Judgments: Topical nasal corticosteroids are associated with improvement in nasal obstruction and sleep symptoms in allergic rhinitis patients with OSA and may produce a small change in AHI.

Recommendation Level:

Topical Corticosteroids: Option

Topical Decongestants: Recommend Against

Oral antihistamines and leukotriene inhibitors: No Recommendation due to insufficient evidence.

Intervention: Topical nasal corticosteroids are an option for treatment of allergic rhinitis and as adjunct therapy for OSA. While adverse events and side effect profiles of topical nasal corticosteroids are minimal, the small reductions seen in objective sleep parameters suggests that they should not be used as definitive therapy for OSA.

**Table VII.D.4: Evidence for Medical Therapies for Nasal Obstruction and Obstructive Sleep Apnea**

Study	Year	LOE	Study Design	Study Groups/Intervention	Clinical Endpoints	Conclusion
Topical corticosteroids, oral antihistamines, leukotriene inhibitors						
Kiely JL, Nolan P, McNicholas WT <sup>894</sup>	2004	1b	RCT	1. OSA: AHI>10 fluticasone	1. AHI 2. NAR	AHI was significantly reduced in 13 patients

				2. No OSA Intervention: Fluticasone spray x 4 weeks	3. EpSS 4. Snoring	with OSA and rhinitis treated with fluticasone for 4 weeks as compared to placebo (23.3 vs 30.3). Despite improvements, most patients continued to have significant OSA.
Stuck et al. <sup>891</sup>	2004	3b	Prospective controlled cohort	1. Seasonal AR patients 2. Non-AR patients  Intervention: None – study designed to evaluate the impact of AR on sleep	PSG SF-36 Daytime sleepiness	In patients with AR during allergy season, AHI significantly worsened as compared to non-AR patients. This difference was not clinically meaningful.
Lavigne et al. <sup>893</sup>	2013	3b	Prospective cohort	1. OSA w AR 2. OSA w/o AR  Intervention: Mometasone spray x 10-12 weeks	PSG EpSS	Decrease in oxygen nadir in AR pts with OSA. Significant improvement in supine AHI in OSA patients with AR. Improvement in nasal symptom scores.
Tam et al. <sup>1435</sup>	2019	4	Case series	OSA  Intervention: Fluticasone spray x 4 weeks	PSQI EpSS NOSE	Decreases in PSQI, EpSS, and NOSE after 4 weeks of fluticasone.
Meltzer et al. <sup>1436</sup>	2010	1b	RCT Double blind placebo-controlled	Moderate to severe perennial AR  Intervention: Mometasone spray	PSG TNSS RQLQ EpSS	No significant difference in AHI in perennial AR patients AHI with mometasone (increase in AHI from 2.57 to 3.53) TNSS, RQLQ, EpSS significantly improved.
Acar et al. <sup>1434</sup>	2013	1b	RCT Double blinded placebo controlled	Groups: 1. Mometasone spray 2. Mometasone spray + desloratadine 3. Desloratadine 4. Placebo  Duration: 6 weeks	PSG EpSS	Nasal corticosteroid spray significantly reduced AHI (29->24). There was no additional benefit of adding the oral antihistamine. EpSS improved

Smith et al. <sup>1432</sup>	2019	1b	RCT Double blinded placebo control	OSA with AHI greater than 5 and less than 15  1. Montelukast + fluticasone 2. Placebo	PSG EpSS	Fluticasone and Montelukast did not significantly decrease AHI or Epss. AHI in patients with chronic rhinitis (n=4) significantly worsened. Total sleep time and %REM sleep improved
Liu et al. <sup>1431</sup>	2016	1a	SR and Metanalysis of RCTs	Intranasal corticosteroids for OSA: 5 RCTs included – 2 adult studies (Acar and Kiely)	PSG	Intranasal corticosteroid was effective for OSA in decreasing AHI (SMD - 0.73). Effectiveness of intranasal corticosteroid therapy for decreasing OSA severity is undetermined.
Craig et al. <sup>890</sup>	2005	1a	RCT Double blind placebo- controlled crossover	Perennial AR without OSA  Intervention: 1. Budesonide, flunisolide, or fluticasone 2. Placebo	PSG Sleepiness and nasal congestion severity based on symptom diaries.	Intranasal corticosteroid decreased nasal congestion and sleepiness. Changes in PSG (fluticasone group only) were not statistically significant.
Charakorn et al. <sup>1178</sup>	2017	1a	SR and Metanalysis of RCTs	Intranasal corticosteroids for OSA treated with CPAP: 2 RCTs included	CPAP compliance	Intranasal corticosteroid increased CPAP usage 0.4 h per night, but this was not statistically significant. Percentage of nights with CPAP use did not change.
<b>Nasal Decongestants</b>						
Clarenbach et al. <sup>899</sup>	2008	1b	RCT placebo- controlled crossover	OSA with nasal congestion  Intervention: Oxymetazoline	PSG	In 12 patients with OSA, AHI significantly decreased at time of maximal pharmacological effect (30-210 minutes) (27.3 vs 33.2), but overall AHI was not significantly different between oxymetazoline and placebo
Mclean et al. <sup>902</sup>	2005	1b	RCT single blind placebo-	OSA and nasal obstruction. Nasal obstruction defined	Nasal resistance PSG	Nasal resistance was significantly decreased. AHI fell 12 points with

			controlled crossover	by turbinate hypertrophy +/- nasal valve collapse  Intervention: Breathe right (external dilator) Oxymetazoline x 2		oxymetazoline and external dilator. This was statistically significant but did not provide a clinically effective treatment
Kerr et al. <sup>901</sup>	1992	4	Case series	10 OSA patients of varying severity  Intervention: Vestibular dilator, oxymetazoline	PSG Nasal resistance	Improvement in arousals/hour and sleep quality. No change in apnea.
Koutsourelakis et al. <sup>1437</sup>	2013	1b	RCT Double blinded crossover	OSA with AHI>10  Intervention: Nasal tramazoline and dexamethasone spray BID	PSG Nasal resistance EpSS	Mean decrease in AHI of 21% (-6.1) after one week of therapy compared to placebo

#### VIII.D.5 Nasal Dilators for OSA

Internal and external nasal dilators have been studied as a treatment option for snoring and obstructive sleep apnea. While many studies have shown some benefit with snoring, the vast majority of studies have not found improvement in obstructive sleep apnea.<sup>903,1430,1438-1440</sup>

A systematic review by Camacho et al. examined nasal dilators (both internal and external) and their effect on snoring and OSA.<sup>1441</sup> Fourteen studies were analyzed, with 5 studies utilizing internal dilators and 9 studies using external dilators; only 2 studies showed that nasal dilators reduced obstructive sleep apnea parameters. A meta-analysis showed that both internal and external nasal dilators did not have an effect on the apnea hypopnea index (AHI) or sleep architecture but internal nasal dilators did have a small improvement on the apnea index (AI).<sup>1441</sup>

In the study by Hoijer et al, ten patients underwent two sleep studies with and without an internal nasal dilator (Nozovent) with a reduction in the apnea index by 47%.<sup>1442</sup> However, it is important to point out that 3 out of the 10 patients had a pre-treatment apnea index less than 5 and one patient worsened with the use of the nasal dilator. The study excluded other measures of OSA such as apnea hypopnea index (AHI) and respiratory disturbance index (RDI). A study of external nasal dilators (Breathe right strips) on patients with obstructive sleep apnea in 26 patients<sup>1443</sup> showed that 19 out of 26 patients had a reduction in RDI, and sub-analysis of the patients that benefited showed a positive effect in patients with nasal obstruction, minor or no pharyngeal obstruction, and age under 55 years.<sup>1443</sup>

In a randomized crossover study comparing external nasal dilator strips to placebo strips, no reduction in AHI was noted. Within this study a subset of patients with severe nasal obstruction, based on rhinometry, did experience a significant but small reduction in AHI (7.4 to 5.4) and improved mean SpO<sub>2</sub>

(92.4 to 96.7).<sup>900</sup> Other studies showed an increase in nasal cross sectional area and reduction in nasal resistance with nasal dilators but without effects on objective obstructive sleep apnea outcomes such as AHI.<sup>901,1438,1444</sup>

The evidence suggests that nasal dilators do not improve objective sleep parameters in patients with obstructive sleep apnea, especially in patients in the moderate to severe OSA.<sup>1441</sup> However, it does appear that a small subset of patients with severe nasal obstruction and obstructive sleep apnea may potentially benefit from nasal dilators.<sup>900,1443</sup> While nasal dilators (internal and external) are not recommended as monotherapy for obstructive sleep apnea, they may still play a role as an adjunct treatment, as it has been shown that nasal dilators could reduce the amount of pressure required by CPAP devices which may improve adherence.<sup>1179,1445</sup>

### Nasal Dilators for Treatment of OSA

Aggregate Grade of Evidence: B (level 1a: 1 study; level 2b: 5 studies; level 3b: 1 study; level 4: 7 studies).

**Table VIII.D.5: Evidence for Effects of Nasal Dilators on OSA.**

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical End-point	Conclusion
Yagihara et al. <sup>1440</sup>	2017	2b	Randomized crossover study	26 patients with severe OSA randomized to either 1 month of nasal dilator strips or nasal CPAP and then crossover after 2 weeks.	Sleep architecture, AHI, arousal index, oxygen saturation, sleep questionnaires	Nasal dilator strips in patients with severe OSA had no effect on objective sleep outcomes (sleep architecture and respiratory events).
Camacho et al. <sup>1441</sup>	2016	1a	SR	14 studies (5 internal dilators, 9 external dilators). Most of the studies were individual case-control or prospective case-series.	Effect of nasal dilators on sleep stages, AHI, apnea index, lowest oxygen saturation, snoring, sleepiness, and sub-analysis comparing internal to external dilators.	Nasal dilators did not improve AHI or most PSG metrics except for internal nasal dilators which had a mild improvement on the apnea index.
Amaro et al. <sup>1446</sup>	2012	2b	Randomized crossover study	12 patients with acromegaly and moderate to severe OSA underwent a randomized crossover study using CPAP and nasal dilator strips	Sleep architecture, apnea index, hypopnea index, apnea hypopnea index, central apnea, oxygen saturation, sleep questionnaires	Nasal dilator strips had no reduction on objective sleep parameters; subjective sleep improvement, but less than in the CPAP group.
Djupesland	2001	2b	Randomized	18 patients with	Nasal patency,	Improvement in AHI

et al. <sup>900</sup>			crossover study	nocturnal nasal obstruction, severe snoring, and without severe OSA (mean AHI 9.3) underwent a randomized crossover study comparing external nasal dilator strips vs placebo strips.	AHI, oxygen saturation, sub-analysis based on nocturnal nasal dimensions.	and oxygen saturation was noted only by a subset of patients with severe nasal obstruction based on rhinometry.
Pevernagie et al. <sup>903</sup>	2000	2b	Double-blind crossover RCT	Effect of external nasal dilators on chronic rhinitis patient with snoring. Mean AHI for the group was 6.	Effect on snoring, sleep architecture, objective sleep parameters	External nasal dilators improved snoring but had no effect on objective sleep apnea measures.
Schonhofer et al. <sup>1430</sup>	2000	4	Individual case series	21 patients with OSA who used the internal nasal dilator (Nozovent) for 1 month.	Effect on snoring, sleep architecture, objective sleep parameters, sleep questionnaires.	No effect on objective sleep parameters or snoring.
Gosepath et al. <sup>1443</sup>	1999	4	Individual case series	26 patients undergoing polysomnography with and without an external nasal dilator (Breathe right nasal strips).	Effect on RDI, correlation with other factors such as comorbidities, age, and rhinologic factors.	19 out of the 26 patients experienced a reduction in RDI.
Bahammam et al. <sup>1438</sup>	1999	2b	Double-blind crossover RCT	18 patients in a double blinded crossover RCT comparing external nasal dilators to placebo	Effect on nasal airway, sleep architecture, AHI, oxygen saturation	External nasal dilators had no effect on AHI
Redline et al. <sup>1309</sup>	1998	3b	Prospective cohort	Effect of CPAP vs nasal dilators and conservative management.	Snoring, RDI, oxygen saturation, sleep questionnaires	CPAP was superior to conservative therapy (included nasal dilators).
Wenzel et al. <sup>1439</sup>	1997	4	Individual case series	1) 30 patients with OSA 2) 20 patients with snoring without OSA	Effect on objective sleep parameters and snoring	Neither the degree of OSA or snoring in patients without OSA was changed
Hoffstein et al. <sup>1447</sup>	1993	4	Individual case series	15 patients underwent sleep study with and without	Snoring, apneas, hypopneas, oxygen saturation	Internal nasal dilator had a weak effect on snoring and no effect

				an internal nasal dilator (Nozovent)		on obstructive sleep apnea measures
Hoijer et al. <sup>1442</sup>	1992	4	Individual case series	10 patients used an internal nasal dilator (Nozovent) for 10 nights, and then they had two sleep studies one with and one without the device at a random order	Rhinomanometry, apnea index, oxygen saturation, snoring noise, questionnaires	Internal nasal dilator reduced the apnea index, severity of oxygen desaturation, and snoring noise.
Metes et al. <sup>1444</sup>	1992	4	Individual case series	Effect of internal nasal dilator (Nozovent) on nasal resistance and sleep outcomes in a subset of patients who are heavy snorers with OSA	Nasal resistance, snoring, apnea index, hypopnea index, oxygen saturation	Internal nasal dilators improved nasal resistance significantly but there was no effect on objective sleep outcomes in a subset of patients who heavy snorers and have OSA
Kerr et al. <sup>901</sup>	1992	4	Individual case series	10 OSA patients treated with a nasal dilator and topical nasal vasoconstriction	Rhinomanometry, sleep architecture, oxygen saturation, AHI, apnea index	Despite a 73% mean drop in nasal resistance, there was no improvement in objective obstructive sleep apnea measures

#### VIII.D.6 Surfactants for OSA Treatment

Multiple physiologic and anatomical factors contribute to the presence and severity of obstructive sleep apnea. Surface tension of the upper airway lining is one potential target for the treatment of obstructive sleep apnea. In awake patients, it has been shown that by applying surfactant to the upper airway and reducing surface tension, less intraluminal pressure is required to reopen a closed pharynx.<sup>1448</sup> This led to studies of the effects of upper airway surface tension on obstructive sleep apnea.

There are a limited number of studies looking at the role of surfactants in obstructive sleep apnea treatment. Three studies have been found which demonstrated a modest improvement in obstructive sleep apnea after surfactant administration.<sup>1449-1451</sup> Jokic et al studied the effect of surfactant on obstructive sleep apnea in a double-blinded crossover randomized controlled trial in 10 patients.<sup>1449</sup> The patients underwent two sleep studies, one night with a placebo and the other night with surfactant. The mean apnea-hypopnea index (AHI) on the surfactant night was 14 compared to 24 on the placebo night (95% CI 6-13).<sup>1449</sup> Of note, this was the only published randomized controlled trial studying the effect of surfactant on obstructive sleep apnea.

The two other studies identified were both prospective cohort studies.<sup>1450,1451</sup> Kirkness et al. demonstrated that surfactant decreased the surface tension of the upper airway lining as well as the severity of the respiratory disturbance index (RDI), and the correlation between the two was statistically significant.<sup>1450</sup> This study involved nine patients who underwent two separate sleep studies, one diagnostic



and the other interventional. The RDI decreased from 51 on the diagnostic night to 35 ( $p < 0.03$ ) on the test night when surfactant was administered.<sup>1450</sup> Morrell et al performed a prospective cohort study recruiting nine patients with obstructive sleep apnea to study the effect of surfactant on the respiratory disturbance index (RDI) by comparing it to saline. The protocol involved studying patients on two separate nights with one night collecting data on pre and post saline instillation while the second night involved pre and post surfactant administration. Seven patients were able to complete the study and the data collected showed that the RDI was reduced with surfactant administration (pre surfactant RDI 79.7 versus post surfactant RDI 59.6 ( $p < 0.05$ )) whereas saline did not decrease RDI (pre saline 75.3 versus post saline 79.9).<sup>1451</sup>

One concern with surfactant is the practicality of administration by patients given that the studies published report instillation via nasal catheters targeting the nasopharynx positioned above the level of the soft palate. Perhaps a more practical form of application that could be considered is delivery via a nasal spray or an inhaler. Additionally, while surfactant appeared to reduce OSA severity in the studies discussed, OSA was not cured in any of those studies, and the improvement was modest. Surfactant may potentially play a role as an adjunct treatment or be a suitable monotherapy option for individuals with mild OSA, however, the evidence is still lacking. Larger randomized control trials are needed to further elucidate the utilities of surfactant in obstructive sleep apnea management and define appropriate roles in treatment.

#### Use of Surfactants for Treatment of OSA

Aggregate Grade of Evidence: C (level 2b: 1 study; level 3b: 2 studies)

**Table VIII.D.6: Evidence for the role of surfactant in obstructive sleep apnea treatment**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Kirkness et al. <sup>1450</sup>	2003	3b	Prospective cohort	9 patients with OSA	Effect of surfactant on surface tension of the upper airway lining and severity of OSA	Surfactant reduced the surface tension of the upper airway lining and RDI.
Morrell et al. <sup>1451</sup>	2002	3b	Prospective Cohort	1. 19 Asymptomatic adult snorers 2. 9 Adults with OSA	1. Effect of surfactant on upper airway mechanics in snorers. 2. Effect of surfactant compared to saline on OSA	Surfactant reduced airway resistance at peak inspiratory pressure. Surfactant reduced OSA severity while saline did not.

Jokic et al. <sup>1449</sup>	1998	2b	Double-blind crossover RCT	<ol style="list-style-type: none"> <li>10 OSA patients receive surfactant</li> <li>Same 10 patients crossover to receive placebo</li> </ol>	AHI scores, sleep architecture, arousal index	Surfactant reduced OSA severity compared to placebo but there was no effect on sleep architecture.
------------------------------	------	----	----------------------------	---	---	--

### VIII.D.7 Supplemental Oxygen for OSA Treatment

Supplemental oxygen has been investigated as a therapy for intermittent nocturnal hypoxia in OSA for over 30 years, particularly for those patients that are intolerant to CPAP. Approximately 25 – 50% of patients with OSA have been shown to either refuse CPAP therapy or experience intolerance<sup>1452</sup>. While administration of oxygen has been shown to consistently improve the mean oxyhemoglobin saturation to levels comparable to CPAP<sup>1453</sup>, long term oxygen therapy can prolong the duration of apnea hypopnea events due to suppression of hypoxic ventilatory drive, worsen carbon dioxide retention and lead to respiratory acidosis<sup>1454</sup>. Oxygen therapy has not been shown to improve subjective sleep quality or daytime functioning<sup>1455,1456</sup>, or reduce the frequency of apnea hypopnea events<sup>1453</sup>. Short-term oxygen therapy was evaluated for post-operative patients for 3 days and was shown to reduce AHI, oxygen desaturation index and improve oxygen saturation<sup>1457</sup>.

The effect of oxygen therapy on blood pressure in patients with OSA has been recently evaluated with well-designed randomized studies<sup>1458-1460</sup>. Patients with OSA are at increased risk for nocturnal fluctuations in blood pressures and daytime hypertension. Recurrent nocturnal hypoxemia increased sympathetic stimulation and alteration of the renin angiotensin aldosterone system are the proposed mechanisms for elevation in blood pressure and increased cardiovascular risk in these patients. Norman et al studied 46 patients with moderate and severe OSA who were randomized to receive 2 weeks of placebo, CPAP or supplemental oxygen. Patients were monitored with 24-hour ambulatory blood pressure monitoring at the end of treatment period. Patients in the oxygen group experienced an improvement in the mean saturation and nadir saturation but oxygen did not lower daytime or nighttime blood pressure<sup>1459</sup>. Gottlieb et al. conducted the Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT) study and randomized patients with moderate to severe sleep apnea to receive CPAP or nocturnal supplemental oxygen or education on sleep hygiene for 12 weeks<sup>1458</sup>. At the end of the study, patients randomized to CPAP experienced a significant reduction in mean 24-hour blood pressure as compared to supplemental oxygen. The results of these 2 randomized studies suggest that nocturnal oxygen therapy does not significantly impact blood pressure in patients with sleep apnea, however both studies used low flow oxygen at 2-3 liters/min and excluded patients with most severe sleep apnea. The recently published SOX (Supplemental Oxygen during CPAP Withdrawal) trial was a single center, double blind, and crossover trial with randomized treatment order. The results demonstrated that supplemental oxygen at 5 L/min eliminated the morning rise in blood pressure

experienced by patients with moderate to severe sleep apnea after CPAP withdrawal, as compared with room air. Patients were not excluded based on sleep apnea or hypoxia severity<sup>1460</sup>. Larger, multi center studies are needed before any treatment recommendations can be made in the use of supplemental oxygen in sleep apnea.

Oxygen therapy may have a role in obstructive sleep apnea co-morbid with other conditions (e.g. heart failure, COPD) but rigorous studies are lacking.

In this era of precision and personalized approach to medicine, identifying patients most likely to benefit from oxygen therapy is prudent. Sands et al demonstrated that elevated loop gain in combination with greater pharyngeal patency could be used to predict responsiveness to oxygen therapy in their cohort of patients with moderate to severe OSA that underwent diagnostic polysomnography<sup>1461</sup>. In a proof of concept study, Wang et al determined that a 10-minute awake ventilatory chemoreflex test to assess response to hypercapnia and hypoxia could indicate response to low flow oxygen therapy in patients with OSA<sup>1462</sup>. Future research on the role of oxygen therapy in OSA must focus on recognizing oxygen responders. Larger studies are needed to establish the duration and dose of oxygen therapy and long-term outcomes. Additionally, safety of long-term oxygen therapy in patients with OSA should be ascertained given concerns for carbon dioxide retention and acidosis.

#### Supplemental Oxygen for Treatment of OSA

Aggregate Quality of Evidence: B (1b: 8 studies, 1a: 1 study)

Benefit: Oxygen improves oxygen saturation in patients with OSA. May reduce blood pressure in certain patient populations receiving higher levels of oxygen supplementation.

Harm: Risk of carbon dioxide retention and respiratory acidosis.

Cost: Moderate to high cost of treatment with supplemental oxygen and related to increased health care utilization.

Benefits-Harm Assessment: Harms exceed benefit.

Value Judgments: Oxygen therapy improves oxygen saturation in patients with OSA but does not benefit sleep quality, daytime functioning, duration or frequency of apnea and hypopnea events. Inconsistent effects of treatment with supplemental oxygen on blood pressure are reported.

Recommendation Level: Recommend against.

Intervention: Oxygen therapy should not be used as a treatment for OSA.

**Table VIII.D.7 Evidence on Supplemental Oxygen and OSA Treatment**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Phillips et al <sup>1456</sup>	1990	1b	Randomized Crossover	1.Nasal Oxygen 2.Nasal air 3.Nasal CPAP	SDB events and Oxygen saturation  Sleep architecture and daytime sleepiness	Oxygen did not improve daytime sleepiness or SDB events but improved oxygen saturation.

Loredo et al <sup>1455</sup>	2006	1b	Randomized, double blind, placebo controlled parallel study	1.CPAP 2.Placebo CPAP 3.Oxygen at 3 L/min	Sleep architecture and arousals  Daytime Sleepiness	Oxygen did not improve sleep quality when compared to CPAP, it improved oxygen saturation .
Norman et al <sup>1459</sup>	2006	1b	Randomized double blind, placebo controlled study	1.CPAP 2.Placebo CPAP 3.Oxygen at 3 L/min	Change in 24 hour ambulatory BP monitoring  AHI, ODI, Mean oxygen saturation, average SPO2 nadir during desaturations, time with saturation < 90%	Oxygen did not improve 24-hour ambulatory BP parameters.  Both the CPAP and oxygen groups had a higher mean nocturnal SpO <sub>2</sub> compared with the placebo group.
Mehta et al <sup>1453</sup>	2013	1a	Systematic review and meta analysis	14 studies that included O2 therapy and/or CPAP as a study intervention	Effects of oxygen on AHI, apnea duration and nocturnal hypoxemia	Oxygen improved O2 saturation, but may increase duration of apnea hypopnea events.
Gottlieb et al <sup>1458</sup>	2014	1b	Randomized controlled trial	1.CPAP 2.Oxygen at 2 L/min 3.Education on sleep hygiene and healthy lifestyle	24 hour mean arterial blood pressure at 12 weeks	24 hour mean BP was lower in the CPAP group, no significant difference was noted in the oxygen group.
Liao et al <sup>1457</sup>	2017	1b	Randomized controlled study	1.Oxygen at 3 L/min for 3 post operative nights 2.Control group (no oxygen)	Oxygen saturation  PSG data	Supplemental oxygen improved oxygenation, AHI without increasing duration of respiratory events.
Sands et al <sup>1461</sup>	2018	1b	Single-blinded randomized-controlled crossover	1.40% supplemental oxygen 2.Room Air	PSG variables  Blood pressure and self reported sleep quality	Increased loop gain in combination with improved airway could be used to predict response to oxygen therapy in

						patients with OSA that were off CPAP treatment.
Wang et al <sup>1462</sup>	2018	1b	Randomized parallel group double-blind placebo-controlled clinical trial	1.Oxygen at 3 L/min 2. Air	Ventilatory response threshold test  PSG parameters	10 mins wakefulness test predicted response to oxygen therapy.
Turnbull et al <sup>1460</sup>	2019	1b	Randomized double blind crossover trial after CPAP withdrawal	1.Oxygen at 5 L/min 2.Air	Change in home morning BP  Home morning HR, Office BP and HR, levels of urine sympathetic metabolites, AHI, ESS, OSLEP test	Oxygen improved the morning rise in BP and improved oxygen saturation. It did not improve objective or subjective sleepiness.

#### VIII.D.8 Myofunctional Therapy for OSA

Upper airway dilator muscles are thought to be crucial in maintaining airway patency, and muscle training whilst awake via myofunctional therapy (MT) can reduce airway collapsibility in patients with Obstructive Sleep Apnea (OSA).<sup>1463</sup> MT exercises involve the patient performing a series of prescribed isotonic and isometric oropharyngeal exercises to improve muscle tone and soft tissue position in the oropharyngeal airway. These exercises include vowel sound repetition, tongue movements along the hard palate and floor of mouth, exerting facial musculature and swallow/breathing techniques.<sup>1463,1464</sup>

The majority of well-designed studies, where MT was analysed against a control group, report a positive effect of MT in lowering polysomnographic (AHI, oxygen saturation parameters) measures, as well as improvements in secondary outcomes such as Epworth Sleepiness Score (ESS), snoring, CPAP compliance and subjective quality of life scores. A systematic review by Camacho et al, found MT provides an AHI reduction of approximately 50% in selected adults<sup>1464</sup>.

Within the literature, the prescription of MT exercise type and duration is non-standardized, leading to difficulty in ascertaining where the treatment effect lies. Most randomized controlled trials (RCTs) are not powered for multiple outcome measures, and might better be described as ‘exploratory’ rather than ‘conclusive’. The most comprehensive description of MT exercises lies within the Guimaraes et al (2009) paper – where soft palate vowel maneuvers, tongue exercise, facial muscle movements, breathing and chewing exercises are all combined<sup>1463</sup>. Patients were prescribed intensive and detailed sequences of exercises with some observed by speech pathologists which may not be practical in real life paradigms. Unfortunately, follow-up protocols between studies varied significantly, making generalizability a challenge.

The pathophysiological mechanism of improvement after treatment with MT is not well defined. MT may improve airway dilator tone, resisting collapse, as well as improve airway volume through tongue fat reduction and neck adiposity reduction. A significant neck circumference reduction was observed in a treatment group *without* significant AHI reduction<sup>1463,1465</sup>. However, this finding was not reproduced in other studies<sup>1466</sup>. The mechanism accounting for reported increased CPAP compliance also needs further investigation<sup>1467</sup>.

Based on the available evidence MT may have a role in the armamentarium of treatment options for mild/moderate OSA – perhaps as an adjunct to more definitive treatments. Further data is needed to isolate the mechanism of action of MT, as well as the optimal exercise regime and duration, which may be too involved and nuanced to be practical. A paucity of long term studies with clinical significance exists, thus further research is warranted.

### Myofunctional Therapy for OSA Treatment

Aggregate Grade of Evidence: B (Level 1: 5 studies)

Table VIII.D.8: Evidence on Myofunctional Therapy to Treat OSA

Study	Year	LOE	Study Design	Study Groups	Clinical End Point	Conclusion
Guimaraes KC et al <sup>1463</sup>	2009	1b	RCT, age 25-65 recent diagnosis moderate OSAS n= 31	1) 3 months Sham therapy (n =15, control) 2) 3 months Oropharyngeal exercises - tongue, soft palate, oropharyngeal wall, facial muscles (n=16, treatment group)	1) PSG (AHI) 2) Snoring (Berlin questionnaire) 3) Subjective Sleepiness (ESS) 4) Sleep Quality (Pittsburgh Questionnaire)  ** Note anthropometric measures similar pre-post treatment, <i>except</i> significant reduction in neck circumference (cm) in treatment group 39.6±3.6 to 38.5±4.	1) AHI significantly reduced in treatment group, 22.4±4.8 to 13.7±8.5. <i>No significant change in control group.</i> 2) Reduced snoring frequency and intensity in treatment group. 3) Reduced ESS in treatment group 14±5 to 8±6. 4) Improved sleep quality in treatment group.
Camacho et al <sup>1464</sup>	2015	1a	Systematic review	Included data from total 9 studies:	1) Polysomnography data	1) MT provides a reduction in AHI of approximately 50% (24.5±14.3 to 12.3±11.8)

				<p>2 RCTs 3 Prospective Case series (no controls) 2 Retrospective Case Series 1 Retrospective Case Report 1 Abstract</p> <p>* Combined, 120 adult patients studied</p>	<p>2) Snoring 3) Subjective Sleepiness (ESS)</p>	<p>2) Reduction in snoring scores (72%) 3) Reduction in ESS in post MT (<math>14.8 \pm 3.5</math> to <math>8.2 \pm 4.1</math>)</p>
Diaferia et al <sup>1468</sup>	2013	1b	RCT, 185 consecutive male patients with no previous OSAS treatment	<p>3 months of treatment: 1) Placebo (sham therapy) 2) MT 3) CPAP without MT 4) Combination Group – treated with both MT and CPAP</p>	<p>1) Polysomnography (AHI) 2) Subject Sleepiness (ESS) 3) Quality of Life questionnaires (FOSQ, WHOQoL-Bref, SF-36)</p>	<p>1) Significant reduction in AHI in MT group vs placebo: <math>28.0 \pm 22.7</math> to <math>13.9 \pm 18.5</math>. 2) CPAP compliance superior in combination group (hrs per night): <math>5.1 \pm 2.3</math> versus CPAP alone <math>3.6 \pm 1.8</math> (<math>p=0.02</math>) 3) QoL scores improved in all questionnaires.</p>
Ieto V et al <sup>1466</sup>	2015	1b	RCT, 39 patients in final analysis. Primary snoring, or mild-moderate OSA included	<p>3 months treatment: 1) Control group (sham). n=20 2) Therapy group: Daily MT n=19.</p>	<p>1) Snoring primary measure a) Snore Index/hr as measured in PSG b) Bed partner subjective score 2) Pre and post treatment AHI, SpO2 minimums 3) Sleepiness (ESS)/Sleep quality (Pittsburgh index)</p>	<p>1) Therapy group had significantly lower snore index 2) Non Significant difference in pre-post therapy AHI in treatment group 3) Pittsburgh sleep quality index significantly better in treatment group. 4) Non Significant change in ESS.</p>
Diaferia et	2015	1b	RCT, 100	3 months	1) CPAP	1) CPAP adherence was 30%

al <sup>1467</sup>			patients in final analysis.	treatment 4 Treatment groups  1) Placebo (neck exercises). n=24 2) MT (3x 20 min sessions. Each day). n=27. 3) CPAP. n=27 4) Combination CPAP + myofunctional therapy. n=22	adherence  2) AHI/SpO2 min  3) Subjective Sleepiness (ESS)	in CPAP only group vs 65% in combined group. Non Significant difference in CPAP pressures.  2) Myofunctional therapy alone group significant reduction in AHI (28 to 13.9, P=< 0.001)  3) Significant reduction in ESS in myofunctional therapy alone, and combination groups
--------------------	--	--	-----------------------------	---	--	---

MT – Myofunctional therapy; RCT – Randomized Controlled Trial; ESS – Epworth Sleepiness Score; PSG – Polysomnogram; SpO2 min – minimum oxygen saturation

## IX. Surgical Treatment for OSA

### IX.A Surgical Candidacy

#### IX.A.1 Evaluation of PAP Failure Prior to Surgery

As CPAP is considered the primary first-line treatment for OSA, defining CPAP failure is crucial to determining surgical candidacy. CPAP nonadherence is complex and multifactorial, influenced by many factors including patient knowledge, perception of treatment and disease state, bed partner involvement and mask interface.<sup>1469</sup> A widely accepted definition of adequate CPAP adherence is based on the U.S. centers for Medicare and Medicaid decision memo describes greater than 4 hours of use per night for greater than 70% of nights.<sup>21,1470</sup> Despite inherent problems with this arbitrary definition, it has remained the standard since early papers on CPAP adherence were published in the 1990s.<sup>1090,1471,1472</sup>

Evidence has emerged on patient adherence to CPAP and what constitutes adequate treatment. Treatment outcomes differ based on the outcome metric selected (i.e. self-reported clinical outcomes, polysomnogram generated data, and cardiovascular/disease-oriented outcomes). Weaver et al. observed a linear dose response relationship in objective daytime sleepiness as well as patient self-reported sleepiness and quality of life with increasing levels of CPAP use.<sup>1097</sup> Stradling et al. showed a similar dose response relationship in a RCT of CPAP use.<sup>1473</sup> Neither study identified a treatment threshold. Campos Rodriguez et al. in a prospective cohort associated at least 1 hour/night with a lower mortality.<sup>1474</sup> Antic et al. showed CPAP improved neurocognitive and behavioral outcomes with increased CPAP use.<sup>1475</sup> In summary, evidence varies on the effectiveness of CPAP with different levels of use, different patient populations, and different treatment outcome measures. No true definition of CPAP failure exists.<sup>1106,1195</sup> Overall, despite extensive evidence that CPAP is the most definitive way to resolve OSA, there is minimal data to define CPAP failure based on adherence. Determining which



patients require surgery to effectively treat their OSA may require more than fitting them into a strict criteria of CPAP usage time.

When counseling patients about surgical candidacy and surgical options, individualized discussion on experiences with CPAP and acceptance of CPAP as a long-term solution for OSA are important components of the shared-decision making process.

### Evaluation of CPAP Non-Adherence for Surgical Candidacy

Aggregate Grade of Evidence: B (level 1b: 4 studies; level 3b: 5 studies; level 5: 3 studies).

Table IX.A.1 Evidence for defining CPAP non-adherence

Study	Year	LOE	Study design	Study groups	Clinical end-points	Conclusion
Faccenda et al. <sup>1476</sup>	2001	1b	RCT crossover study	1. Control placebo pill (n=70) 2. CPAP use group (n=71)	Change in BP, ESS, FOSQ	Patients on CPAP with use > 3.5h/night had a drop in BP 1.5 mmHg
Redline et al. <sup>1309</sup>	1999	1b	RCT	RDI < 30 and nonsleepy patients randomized 1. Control conservative therapy (n=52) 2. CPAP users (n=59)	Change in ESS, mood, MSLT, functional status, neuropsychologic testing	Average CPAP use 3.1h/night, CPAP group had significant improvements in RDI, MSLT, O2 nadir and ESS score. Improvement in O2 saturation and RDI was significantly greater in CPAP than control group.
Barbé et al. <sup>38</sup>	2012	1b	RCT	Nonsleepy (ESS < 10) OSA patients with AHI > 20 1. No intervention (n=366) 2. CPAP (n=357)	Change in BP and cardiovascular events	No significant difference found between groups, but in those with CPAP use > 4h/night, there was a significant decrease in the incidence density ratio of hypertension or cardiovascular events.
Stradling et al. <sup>1473</sup>	2000	1b	RCT	1. Therapeutic CPAP 2. Subtherapeutic CPAP as control	1. CPAP adherence 2. Post treatment neurocognitive	Degree of improvement correlated significantly with amount of CPAP use in the therapeutic CPAP group, but did not in the

						and behavioral tests	subtherapeutic CPAP group.
Kribbs et al. <sup>1090</sup>	1993	3b	Cohort	CPAP users (n=35)	CPAP adherence	CPAP adherence	Average use 4.88h/night, and only 46% of the patients met criteria for regular use of > 4h/night. Very few patients, 2 of the 35, used CPAP for > 7h/night
Engleman et al. <sup>1471</sup>	1994	3b	Cohort	CPAP users (n=54)	CPAP adherence	CPAP adherence	CPAP use < 5 hours/night, and did not correlated with OSA severity
Reeves-Hoche et al. <sup>1472</sup>	1994	3b	Cohort	CPAP users (n=38)	CPAP adherence	CPAP adherence	Mean hours of CPAP use at effective pressure was for 4.3 hours/night
Weaver et al. <sup>1097</sup>	2007	3b	Cohort	Moderate to severe OSA	1. CPAP adherence 2. Post treatment neurocognitive and behavioral tests	1. CPAP adherence 2. Post treatment neurocognitive and behavioral tests	Increased CPAP usage is associated with increased objective and subjective sleepiness measures. In thos with severe OSA, greatest propotion normalized ESS scores with 4h/night of CPAP, analysis shows further improvement can be obtained with more hours of use.
Antic et al. <sup>1475</sup>	2011	3b	Cohort	Moderate to severe OSA	1. CPAP adherence 2. Post treatment neurocognitive and behavioral tests	1. CPAP adherence 2. Post treatment neurocognitive and behavioral tests	Increasing CPAP adherence improves behavioral and neurocognitive outcomes in a linear fashion, even highly compliant patients may not attain normal functional status.
Schwab et al. <sup>1195</sup>	2013	5	Expert opinion	None	None	None	There is insufficient evidence to support 4h/night for 70% of nights in a consecutive 30 day period as the definition of

						adherence.
Campos-Rodriguez et al. <sup>1474</sup>	2005	3b	Case-control	1. Noncompliant CPAP use, < 1h/night 2. Mildly compliant, 1-6h/night 3. Compliant, >6h/night	Mortality rate	Patients who use CPAP >1h/night have a significantly lower mortality than those who use it <1h/night.
Zimmerman et al. <sup>1477</sup>	2006	3b	Case-control	1. CPAP poor users, < 2h/night (n=14) 2. CPAP moderate users, 2-6 hours/night (n=25) 3. CPAP optimal users, > 6h/night (n=19)	Memory performance measured by HVLT-R	Patients with OSA and memory impairment have improvement in memory scores if they used CPAP > 6h/night.
Aloia et al. <sup>1478</sup>	2010	3b	Cohort	CPAP users with neuropsychologic testing prior to starting treatment and 3-6 months after (n=150)	Changes in neuropsychologic tests before and after CPAP treatment	Based on the reimbursement criteria for CPAP of 4h/night for 70% of nights during consecutive 30 day period during the first 3 months of use, 37% of patients would be considered nonadherent. However, both adherent and nonadherent patients experienced similar improvements in neuropsychologic testing, and these improvements accumulated at the 6 month point

Krakow et al. <sup>1479</sup>	2016	3b	Case control	1. Noncompliant CPAP use, < 2h/night (n=13) 2. Subcompliant CPAP use, 3-4h/night (n=21) 3. Compliant CPAP use, > 4h/night (n=59)	Changes in insomnia, sleepiness, and nocturia based on CPAP adherence	Both compliant and subcompliant CPAP users had improvements in insomnia, sleepiness, and nocturia. Patients exhibited a dose dependent response to CPAP use.
Sawyer et al. <sup>1106</sup>	2011	5	Expert opinion	None	None	The historical level of CPAP use of 4h/night is not necessarily relevant given the evidence of a dose response relationship between CPAP use and benefits
Brown et al. <sup>21</sup>	2010	5	Expert opinion	None	None	The CMS guidelines for reimbursement of CPAP, 4h/night for > 70% of nights during consecutive 30 day period during the first 3 months of use, is inappropriate considering the evidence of a dose response to CPAP use
Ravesloot et al. <sup>1480</sup>	2011	5	Expert opinion	None	None	Using mean AHI instead of arbitrary compliance rates for CPAP use is a more effective way of measuring CPAP adherence, as worsened OSA severity requires higher CPAP usage to be deemed effective

### IX.A.2 BMI Criterion for Surgical Candidacy

Surgery for obstructive sleep apnea (OSA) is considered a second line treatment for patients who fail continuous positive airway pressure (CPAP).<sup>1481,1482</sup> With CPAP non-adherence rates of 30-40%, alternative therapies to CPAP, including upper airway surgery may be considered in treating a significant portion of OSA patients.<sup>1469,1483</sup> This section delves further into candidates for upper airway surgery

based on BMI criteria, what constitutes CPAP failure, and which patients could be considered for primary surgery for OSA.

Elevated BMI plays a crucial role in the development and severity of OSA. Obesity increases airway collapsibility, contributes to mechanical changes, and decreases neuromuscular tone.<sup>802</sup> The prevalence of OSA in morbidly obese (BMI > 40 kg/m<sup>2</sup>) patients is 40-90%, with BMI being a major predictor of AHI severity.<sup>349</sup> In addition, a 10% weight loss has been linked to a corresponding 30% decrease in AHI.<sup>188,802</sup>

BMI has also been shown to play a role in upper airway surgery success in management of OSA. Much of our knowledge on this subject is based on post-hoc analysis of cohorts to see if BMI differences affects surgical success. Studies suffer significant selection bias with morbidly obese patients (BMI > 36-40 kg/m<sup>2</sup>) often excluded due to a mostly accepted belief that limited upper airway surgery is inadequate.<sup>813</sup>

The effect of BMI on OSA surgery outcomes is not universally accepted. Friedman et al. in 2003 produced a 4-level staging system for determining candidates for palate and tongue surgery for OSA based on tongue position in the mouth, with stage 4 representing morbidly obese patients that were not appropriate for surgery. However, this study showed that BMI in patients without morbid obesity (BMI < 40 mg/kg<sup>2</sup>) had no significant effect on surgical success.<sup>813,1484</sup> Furthermore, in a group with BMI < 34 mg/kg<sup>2</sup> and anatomically favorable patients with Friedman staging 1-2, Browaldh et al. showed no effect of BMI on the success rate of UPPP and a systematic review by Choi et al. showed that BMI was not a significant negative predictor of success after UPPP.<sup>1485,1486</sup> In contrast, a study by Shie et al. retrospectively analyzed the effect of obesity on a cohort of patients with severe OSA (AHI > 30) and found it to be a significant negative predictor of success.<sup>526</sup> A systematic review of long term outcomes of UPPP showed BMI was a significant factor in surgical failure.<sup>811</sup>

Hypoglossal nerve stimulation therapy (HGNS) is one surgical therapy that has focused on excluding patients with severely elevated BMI due to the belief it may have decreased effectiveness in more obese patients. One of the original exclusion criteria for the clinical trial for the device was a BMI < 32 kg/m<sup>2</sup>.<sup>382,1487</sup> However, in a small population, Huntley et al. in 2018 found no difference in short term surgical success for patients with BMI between 32 and 34mg/kg<sup>2</sup>.<sup>1488</sup> However, this continues to be a source of controversy.

For non-palatal surgery, a systematic review by Camacho et al. compiled papers on maxillomandibular advancements (MMA) and tracheostomies performed on patients with BMI ≥ 40 kg/m<sup>2</sup>. Despite a small number of patients, MMA showed success in this population. Tracheostomy is considered a last resort and often confined to this population, and it does show good evidence of improving OSA.<sup>1489</sup>

Conflicting published evidence exists to use BMI as a criteria for surgical candidacy. Heterogeneity of outcomes by procedure is highly likely and for many procedures the data on outcomes on patients with higher BMI does not exist. For this reason, higher BMI should be considered a poor predictor of surgical success other than tracheostomy. Inadequate data is available to make recommendations on lesser degrees of obesity, but it is suggested that other clinical and anatomic features should be considered before excluding surgical therapy.

### **BMI and Candidacy for Upper Airway Sleep Surgery**

**Aggregate Quality of Evidence:** C (level 2a: 3 studies; level 2b: 1 study; level 3b: 3 studies; level 4: 4 studies).

**Benefit:** Improvement in sleep apnea severity and symptoms, as well as CPAP tolerance after sleep surgery.

**Harm:** Higher rates of surgical failure and likelihood for persistent sleep apnea in patients who are morbidly obese. Risks specific to surgery type, increased perioperative risks related to obesity and respiratory complications, and long term surgical complications.

**Cost:** Moderate cost associated with surgery, recovery and time off work.

**Benefits-Harm Assessment:** Balance of benefit and harm

**Value Judgments:** Properly selected patients with appropriate anatomy can have substantial improvement in OSA severity regardless of their BMI; insufficient data exists to determine surgical success in patients with BMI > 40 kg/m<sup>2</sup>.

**Recommendation Level:** Option

**Intervention:** BMI level should be considered in determining surgical candidacy.

**Table IX.A.2: Evidence for BMI as a criterion for surgical candidacy**

Study	Year	LOE	Study design	Study groups	Clinical end-points	Conclusion
Choi et al. <sup>1485</sup>	2016	2a	Systematic review	OSA patients who underwent single level UPPP (n=15 studies)	Surgical success as determined by AHI < 20 and AHI decrease by 50%	BMI does not affect surgical success in the immediate period; only Friedman 3 and low hyoid were negative predictors
He et al. <sup>811</sup>	2019	2a	Systematic review	Studies of patients with OSA who had single level UPPP (n=11 studies)	Surgical success as determined by AHI < 20 and AHI decrease by 50%	BMI negatively affects long term surgical success
Camacho et al. <sup>1489</sup>	2015	2a	Systematic review	Studies of morbidly obese patients with OSA who underwent MMA or tracheostomy 1. MMA (n=34 patients) 2. Tracheostomy (n=14 patients)	Surgical success determined by AHI < 20 and decrease by 50%.	AHI significantly improved after MMA or tracheostomy in morbidly obese patients. However, studies are limited, making it difficult to draw definitive conclusions

Browaldh et al. <sup>1486</sup>	2013	2b	RCT	Moderate to severe OSA patients with BMI < 36 kg/m <sup>2</sup> , Friedman stage 1-2. Separated by Friedman stage and BMI 30 kg/m <sup>2</sup> 1. Control group, no intervention (n=33) 2. Intervention, UPPP (n=32)	Primary outcome change in AHI	Intervention resulted in mean 60% improvement in AHI compared to 11% in control, and this was independent of BMI, tonsil size, or Friedman stage
Huntley et al. <sup>1488</sup>	2018	3b	Case control	OSA patients undergoing hypoglossal nerve stimulation 1. BMI < 32 kg/m <sup>2</sup> 2. BMI > 32 kg/m <sup>2</sup>	Surgical success, > 50% reduction in AHI and AHI < 20 post operatively	There was no difference in surgical success between the 2 groups
Heiser et al. <sup>1487</sup>	2019	3b	Case control	OSA patients who underwent hypoglossal nerve stimulation in the ADHERE registry (n=508)	Analysis of predictors of surgical success and failure	On posthoc analysis, for each 1 unit increase in BMI, there was a 9% decrease in odds of surgical success. Increasing age was a positive predictor for success.
Shie et al. <sup>526</sup>	2013	3b	Case control	Patients with severe OSA, failed CPAP, and underwent UPPP 1. BMI < 27 kg/m <sup>2</sup> (n=56) 2. BMI > 27 kg/m <sup>2</sup> (n=61)	Surgical success, > 50% reduction in AHI or AHI < 20 post operatively	Obesity was a significant negative predictor of treatment success

Li et al. <sup>1490</sup>	2006	3b	Case control	OSA patients who underwent UPPP (n=110)	Surgical success as determined by AHI < 20 and AHI decrease by 50%	Friedman staging had a significant predictive value on surgical success, and BMI was not predictive (no patients with BMI 40)
Martino et al. <sup>1491</sup>	2006	4	Case series	Obese, OSA patients with average BMI of 36 kg/m <sup>2</sup> and tonsillar hypertrophy (n=7)	Posttreatment reduction in AHI compared to baseline.	6 of 7 patients had reduction in AHI by at least 50%
Vicente et al. <sup>1492</sup>	2006	4	Case series	Severe OSA patients who underwent tongue base suspension and UPPP (n=54)	Surgical success as determined by AHI < 20, AHI decrease by 50%, and ESS < 11	78% of patients experienced surgical success at 3 years follow up, and BMI at baseline was the only predictor of surgical success
Friedman et al. <sup>1484</sup>	2002	4	Case series	Patients with OSA undergoing UPPP (n=151) 1. Friedman stage 1 (n=31) 2. Friedman stage 2 (n=79) 3. Friedman stage 3 (n=74)	Surgical success as determined by RDI < 20 and RDI decrease by 50%	Lower Friedman stages at any BMI < 40 kg/m <sup>2</sup> did not affect outcome
Chandrashekariah et al. <sup>1493</sup>	2016	4	Case series	OSA patients who had undergone UPPP, obese (average BMI 41 kg/m <sup>2</sup> ), and had persistent elevated AHI (n=11)	Improvement in CPAP adherence	8 of 11 patients had improvement in PAP adherence, with increased mean of 48.6 minutes per night



### IX.A.3 Surgery as Primary Treatment for OSA

In most patients CPAP continues to be considered the first line treatment of severe OSA. Primary surgery as first line therapy remains a strategy with an absence of high level data to support its use. Despite this, primary surgery is advocated for some patients with mild or moderate OSA (where comparable clinical outcomes are observed) or in selected patients with appropriate anatomic features (such as craniofacial abnormalities or marked tonsil hypertrophy).<sup>1494</sup>

A systematic review by Rotenberg et al. explored both studies evaluating CPAP and surgical therapies, commenting specifically on trials that compared the two. Two trials, one randomized controlled trial by Woodson et al. and another nonrandomized controlled trial by Ceylan et al., compared temperature controlled radiofrequency tissue ablation (TCRFTA) of the tongue and palate to CPAP, both finding minimal differences between the two on objective PSG parameters and subjective parameters such as the Epworth sleepiness scale (ESS).<sup>1494-1496</sup> Another study by Weaver et al. compared a cohort of patients who had undergone UPPP versus continued CPAP treatment and found that the CPAP patients had a 31% higher mortality.<sup>1497</sup> Despite limitations, these data suggest that there may be a phenotype of patient who may benefit from interventions other than CPAP as the first line.

Certain anatomic features predispose patients to surgical success. Hypertrophic tonsils and a low tongue position, with the combination encompassed in the Friedman staging system, portend a good result for palate surgery.<sup>546</sup> A study by Rotenberg et al. explored palate surgery for Friedman stage 1 patients, which showed a success rate (based on Sher's criteria) of 87.5%.<sup>1498</sup> A systematic review of tonsillectomy for OSA by Camacho et al. revealed that isolated tonsillectomy is effective as a treatment for patients with hypertrophied tonsils and mild-moderate OSA.<sup>334</sup> A study by Senchak et al. showed substantial improvement in the AHI of a population of young adults with large tonsils undergoing primary tonsillectomy for reasons other than OSA.<sup>1499</sup> Though the number of patients with such favorable anatomy is small, it does raise the point that surgery can provide a simple and efficient way to treat OSA in the appropriate situation and patient population.

Maxillomandibular advancement (MMA) is another technique where anatomic factors can make primary surgery favorable. The original Stanford protocol by Riley et al. in 1993 kept MMA as a phase 2 surgery to be performed after a more conservative approach such as palatoplasty failed.<sup>1500,1501</sup> However, there is minimal data on using it as a primary surgical approach in OSA. A randomized control trial by Vicini et al. compared primary MMA to CPAP on patients with severe OSA (AHI > 30). They found MMA to be non-inferior to CPAP as a treatment.<sup>1502</sup> Liu et al. in a retrospective review showed that MMA was effective for stabilizing lateral pharyngeal wall collapse, an area that is difficult to treat with intrapharyngeal surgery.<sup>1503</sup> Patients with dentofacial abnormalities, specifically class II occlusion, are also good candidates for primary MMA.<sup>1504</sup>

In general, for the majority of patients, CPAP represents the best primary option. Practice parameters for surgery for OSA published by Aurora et al. in 2010 and Kent et al. in 2021 continue to recommend CPAP as the primary option given the lack of good evidence showing surgery as a primary modality to treat OSA.<sup>1481,1505</sup> Further research is necessary to explore primary surgery for OSA.

#### Surgery as Primary Treatment of OSA

**Aggregate Quality of Evidence:** B (level 1a: 1 study; level 1b: 2 studies; level 2a: 2 studies; level 2b: 2 studies; level 3b: 4 studies)

**Benefit:** Proceeding to surgery first in appropriate patients may result in resolution of OSA and related health issues and avoids the cost and inconvenience of using CPAP long-term.

**Harm:** Postoperative pain, possible surgical failure and delay of appropriate treatment for OSA; perioperative risks and complications.

**Cost:** Moderate cost of surgery and recovery compared to CPAP device costs.

**Benefits-Harm Assessment:** Balance of benefit and harm.

**Value Judgments:** Certain patients with appropriate anatomic parameters may benefit from proceeding directly to surgery rather than attempting CPAP first. However, conservative medical treatment should still be the default given the lack of strong evidence favoring surgery over CPAP and low risk related to CPAP use.

**Recommendation Level:** Option.

**Intervention:** Primary surgery for OSA may be considered in specific patients with appropriate anatomic features such as tonsil hypertrophy or craniofacial abnormalities. In this group, shared decision making regarding the risks, benefits, and tradeoffs of primary surgery vs. CPAP treatment is suggested to weigh individual patient symptoms, preferences, and comorbidities.

**Table IX.A.3 Evidence for Surgery as a Primary Treatment for OSA**

Study	Year	LOE	Study design	Study groups	Clinical end-points	Conclusion
Sundaram et al. <sup>1482</sup>	2005	1a	Cochrane systematic review	Surgical RCTs for treatment of OSA (n=709 patients combined)	Effectiveness of surgery for OSA	There is insufficient evidence to support surgery being consistently effective for OSA management. More RCTs are necessary to specify subgroups that would benefit most from surgery.
Woodson et al. <sup>1496</sup>	2003	1b	RCT	Patients with mild to moderate OSA randomized to 1. Sham-placebo (n=30) 2. CPAP (n=30) 3. Temperature controlled radiofrequency tissue ablation, TCRFTA (n=30)	AHI, quality of life measures	Both CPAP and TCRFTA had significant improvement over sham-placebo. There was no significant difference in outcomes between CPAP and TCRFTA

Vicini et al. <sup>1502</sup>	2010	1b	RCT	Patients with severe OSA (AHI > 30) randomized to 1. APAP group (n=25) 2. MMA group (n=25)	Reduction in AHI and ESS	MMA is a viable alternative surgical therapy to CPAP, with a noninferior success rate.
Rotenberg et al. <sup>1494</sup>	2016	2a	Systematic review	1. Systematic review of CPAP trials (n=82 trials) 2. Systematic review of surgery trials (n=69 trials) 3. Systematic review of CPAP vs. Surgery trials (n=3 trials)	Comparison of success between CPAP and surgery for OSA	Lack of long term follow up and low adherence in CPAP trials, along with evidence of surgical success, should change our thought that surgery cannot be a primary treatment in OSA.
Aurora et al. <sup>1481</sup>	2010	2a	systematic review	Review of effectiveness surgical trials (n=79 trials)	Publishing of practice parameters for surgical management of OSA	Due to lack of strong evidence favoring surgical management of OSA, CPAP should always be considered as the initial treatment for OSA.
Walker-Engstrom et al. <sup>1506</sup>	2002	2b	RCT	Patients with mild to moderate OSA 1. Dental appliance group (n=32) 2. UPPP group (n=40)	PSG parameters at 1 and 4 years follow up, surgical success determined as AHI < 10	Oral appliance had better success rate of 62% over UPPP, with success rate of 33%. Compliance with oral appliance was 62% at 4 year follow up.
Lojander et al. <sup>1507</sup>	1996	2b	RCT	1. Nasal CPAP vs. conservative treatment (n=44) 2. UPPP with or without mandibular osteotomy vs. conservative treatment (n=32)	ESS and post treatment ODI	CPAP was successful but compliance was an issue. Surgery also showed significant improvement compared to control. No comparison can be made in this study between CPAP and surgery.

Weaver et al. <sup>1497</sup>	2004	3b	Cohort	VA Patients with OSA 1. Using CPAP (n=18,754) 2. Underwent UPPP (n=2072)	Post treatment overall survival	Patients on CPAP had a 31% higher probability of mortality at any time relative to patients who underwent UPPP.
Senchak et al. <sup>1499</sup>	2015	3b	Cohort	Cohort of military patients undergoing tonsillectomy for reasons other than OSA.  Out of 156, n = 19 with OSA	Post treatment AHI	Patients had 82% reduction in AHI. In population of young overweight men with large tonsils and moderate OSA, tonsillectomy alone can be effective treatment.
Ceylan et al. <sup>1495</sup>	2009	3b	Case-control	Mild to moderate OSA 1. nasal CPAP group (n=21) 2. Temperature controlled radiofrequency tissue volume reduction group, TCRTVR (n=26)	ESS and post treatment PSG	No significant difference between success in the multilevel minimally invasive surgery group (TCRTVR) and nasal CPAP group.
Rotenberg et al. <sup>1498</sup>	2014	3b	Case-Control	Patients with moderate to severe OSA who failed CPAP and had favorable anatomy for palate surgery	1. 1 yr post treatment AHI 2. 1 yr post treatment ESS 3. 1 yr post treatment sleep apnea quality of life index (SAQLI-E) 4. 1 yr post treatment BP	By AHI, 85.7% of patients achieved surgical success. SAQLI-E scores improved significantly after surgery. A subset of patients can be managed more effectively with surgery than CPAP.
Kent et al. <sup>1505</sup>	2021	1a	Meta-analysis	Evaluation of 2 RCTs and 15 observational studies. For RCTs patients were randomized to surgery or no	AHI/RDI, ESS, LSAT, sleep-related QOL, snoring, ODI, blood pressure, death,	Recommend PAP as initial therapy for adults with OSA and a major upper airway abnormality. Harm for initial trial of PAP therapy is low. Recommendation

				treatment.	persistent side effects.	was conditional.
--	--	--	--	------------	--------------------------	------------------

## IX.B Perioperative Management of OSA

### IX.B.1 Anesthesia Considerations in OSA and Upper Airway Surgery

Patients with OSA are at increased risk for complications associated with anesthesia. Risks may be higher after upper airway surgery given anatomical changes to the airway and soft tissue edema postoperatively. Multiple large-scale studies have examined the associations between OSA and adverse perioperative outcomes (Table).<sup>465-467,1508-1510</sup> Although results are heterogeneous, studies focused on outcomes surrounding sleep surgery demonstrate that OSA is associated with multiple perioperative complications including difficult airway management, upper airway obstruction, and postoperative respiratory failure.

#### Difficult Airway Management

In evaluating difficult airway management, a qualitative systematic review to determine the influence of OSA on perioperative outcomes included 61 studies with a total of 413,304 OSA patients and 8,556,279 control patients;<sup>467</sup> the majority of studies reported that difficult intubation was more common for OSA patients than for controls. A review of 492,239 cases performed at four institutions documented a 0.4% rate of difficult mask ventilation (grade 3 or 4) combined with difficult laryngoscopy (grade 3 or 4 view) in patients with OSA. OSA was an independent predictor of difficult mask ventilation and laryngoscopy as were increased age, male sex, Mallampati III or IV, neck radiation, limited thyromental distance, and limited jaw protrusion.<sup>1511</sup> Two smaller studies in patients undergoing non-sleep surgery did not report a relationship between OSA and difficult airway management.<sup>1512,1513</sup> One limitation of the systematic reviews and meta-analyses is that they typically excluded patients undergoing sleep surgery. When populations of patients undergoing sleep surgery were examined, the majority of studies showed an association between OSA and difficult airway management.<sup>1509,1514-1517</sup> OSA patients who underwent uvulopalatopharyngoplasty (UPPP) had higher rates of difficult intubation when compared to age- and sex-matched controls.<sup>1515</sup> Furthermore, the rate of difficult intubation positively correlated with OSA severity, especially for patients with an apnea-hypopnea index (AHI) greater than or equal to 40 events/hour.<sup>1515</sup> Based on strong evidence supporting an association between OSA and difficult airway management, the American Society of Anesthesiologists (ASA) practice guidelines recommend that patients with known or suspected OSA be managed according to the Practice Guidelines for Management of the Difficult Airway: An Updated Report.<sup>1518,1519</sup> A recent consensus statement recommended modifications to management such as using a ramped position for induction and intubation, noninvasive positive pressure ventilation during induction, and weighing the advantages of rapid sequence induction against the risk of rapid oxygen desaturation and difficult airway management.<sup>1508,1520</sup>

#### Perioperative Sedatives and Opiates

Acute upper airway obstruction is another concern in the perioperative management of patients undergoing sleep surgery. Studies demonstrate an increased tendency for OSA patients to develop acute

upper airway obstruction in the setting of minimal sedation when compared to otherwise healthy adults. In particular, hypoglossal nerve activity is sensitive to minimal levels of anesthesia and inappropriate sedation can lead to loss of genioglossus tone and consequently upper airway patency.<sup>1521-1523</sup> In addition, postoperative complications and oxygen saturation may be associated with OSA severity. A retrospective cohort evaluation of patients who underwent UPPP with or without tonsillectomy demonstrated that 8.9% developed postoperative oxygen desaturation and the mean AHI of patients who developed complications was significantly higher than of those without complications (68.1 versus 49.3 events/hour, respectively).<sup>1524</sup> It is recommended that no sedating medications be given to at-risk OSA patients preoperatively. Intraoperatively, acute obstruction following extubation is positively correlated with the amount of opioid administered for patients with OSA.<sup>1525</sup> Thus, it is recommended that sedative pre-medications not be routinely used in OSA patients and if necessary, be delivered judiciously with close monitoring.<sup>1520</sup> Similarly, intraoperative opioid use should also be minimized to decrease the risk of difficult extubation and immediate postoperative respiratory failure. Proper care during extubation should be taken to ensure that the patient has completely recovered consciousness, neuromuscular blockade is fully reversed, and if possible, the patient placed into a semi-upright or lateral position.<sup>1520,1521</sup>

### Airway Edema Management

With regards to postoperative respiratory failure, systemic steroids are commonly used to address postoperative airway edema in patients undergoing sleep surgery despite the fact that the immediate postoperative effect of upper airway surgery on OSA severity is unclear. The use of steroids is supported by a small study (n=8) of postoperative edema following laser-assisted uvulopalatoplasty (LAUP) with pre- and post-operative polysomnography, magnetic resonance imaging (MRI), and videoendoscopy. These authors demonstrated that 48-72 hours after LAUP, mean respiratory disturbance index nearly doubled from 11.3 to 21.7 events/hour while cross-sectional area of the airway decreased slightly from 49.8 to 47.9 mm<sup>2</sup>.<sup>1526</sup> Similarly, a study of patients undergoing maxillomandibular advancement noted pharyngeal edema on nasopharyngolaryngoscopy after surgery in all 70 patients and hypopharyngeal hematoma in 6% of patients, though ultimately none had airway difficulty.<sup>1527</sup> In light of these findings, articles based on expert opinion recommend that systemic steroids should be considered to reduce airway edema with optimal dosing of one dose prior to surgery followed by several doses postoperatively.<sup>1520,1528</sup>

### OSA and Difficult Airway Management

**Aggregate Quality of Evidence:** B (Level 2a: 1 study, 2b: 3 studies, 3a: 1 study, 3b: 3 studies)

**Benefit:** Reduce rates of respiratory compromise and intraoperative loss of airway.

**Harm:** Increased time and potential increased cost of additional equipment necessary for intubation.

**Cost:** Low, dependent on necessary time and equipment for securing the airway.

**Benefits-Harm Assessment:** Benefits outweigh harm for consideration of difficult airway management plans in patients undergoing surgery for OSA.

**Value Judgments:** Overwhelming consistent evidence from observational studies show an association between OSA and difficult perioperative airway management.

**Recommendation Level:** Recommendation

**Intervention:** Contingency plans for difficult airway management, such as those provided by the ASA<sup>1519</sup>, should be implemented in OSA patients undergoing surgery.

### Perioperative Sedatives and Opiates and Acute Upper Airway Obstruction in OSA

**Aggregate Quality of Evidence:** C (Level 2b: 1 study, 1 case report)

**Benefit:** Reduced risk of oversedation and respiratory depression.

**Harm:** Inadequate anesthesia or patient discomfort/anxiety in the perioperative period.

**Cost:** Decreased cost associated with judicious use of pharmacologic agents.

**Benefits-Harm Assessment:** Benefits outweigh harm as judicious use of sedating medications preserves airway patency in OSA patients.

**Value Judgments:** Observational studies show an association between increased opioid use and airway instability in the perioperative period.

**Recommendation Level:** Recommendation

**Intervention:** Sedating and opiate medications should be used cautiously in the preoperative and intraoperative settings for patients with OSA undergoing upper airway surgery.

### **Steroids for Airway Edema Management After Upper Airway Surgery**

**Aggregate Quality of Evidence:** D (Expert opinion)

**Benefit:** Reduced upper airway edema in the postoperative period with systemic steroid use.

**Harm:** Adverse effects of acute systemic steroid administration including hyperglycemia, hypertension, acid reflux, immune suppression, and restlessness.

**Cost:** Increased cost of medication.

**Benefits-Harm Assessment:** Theoretical benefit and possible harm associated with systemic steroid use.

**Value Judgments:** Little evidence and reasoning from first principles suggest that upper airway edema occurs after soft tissue and MMA surgeries in the immediate postoperative period, which could potentiate increased airway obstruction and respiratory failure.

**Recommendation Level:** Option

**Intervention:** Systemic steroid administration in the perioperative period can be considered to reduce upper airway edema unless contraindicated. Optimal dosage based on expert opinion include once preoperatively and several doses postoperatively.

**Table IX.B.1a Evidence for Perioperative Outcomes Associated with OSA and Upper Airway Surgery**

Study	Year	LOE	Study design	Study Groups	Clinical endpoint	Conclusion
Opperer <i>et al.</i> <sup>467</sup>	2016	2a	SR	OSA (n=413,304) and non-OSA (n=8,556,279) patients undergoing non-sleep surgery with general/neuraxial anesthesia or sedation.	Varying postoperative outcomes including pulmonary complications, cardiac complications, oxygen desaturation, difficult airway management.	The presence of OSA is associated with an increased risk of postoperative complications.
Kaw <i>et al.</i> <sup>466</sup>	2012	2a	SR	Patients undergoing non-	Varying postoperative outcomes, primarily	The incidence of postoperative desaturation,

				cardiac, non-sleep surgery (n=3942).	cardiac/respiratory complications.	respiratory failure, postoperative cardiac events, and ICU transfers was higher in patients with OSA.
Hai <i>et al.</i> <sup>465</sup>	2014	2a	SR	Patients undergoing non-sleep surgery (n=7162).	Outcomes: acute respiratory failure, cardiac complications, postoperative ICU transfer.	OSA was associated with significant increase in risk of respiratory failure, cardiac events, and ICU transfer postoperatively
Vasu <i>et al.</i> <sup>1510</sup>	2012	2a	SR	Patients undergoing surgery, excluding bariatric and sleep-apnea procedures (n=108,968).	Varying perioperative complications.	Patients with OSA are at increased risk for perioperative complications.
Corso <i>et al.</i> <sup>1508</sup>	2018	2a	SR	Patients with OSA undergoing surgery (46 studies).	All articles containing relevant evidence on epidemiology, pathophysiologic mechanisms, and perioperative interventions on OSA.	Preoperative screening of OSA patients is of relevance given the increased perioperative morbidity of these patients.
Riley <i>et al.</i> <sup>1516</sup>	1997	2b	Retro specti ve Cohor t	OSA patients undergoing various upper airway procedures (n=182).	54 perioperative factors were analyzed.	Intraoperative airway risks can be reduced by use of fiberoptic intubation in patients with increased neck circumference and skeletal deficiency. Patients with OSA are at a significantly increased risk for hypertension. Nasal CPAP eliminated the postoperative risk of hypoxemia, which allowed the use of adequate analgesics.
Vest <i>et al.</i> <sup>1513</sup>	2013	3b	Retro Case- contr ol	90 adults with difficult tracheal intubation were compared with 81 gender-matched controls	Predictors of difficult intubation	In adult subjects, OSA history was not a predictor of difficult intubation. Other patient or anesthesiologist factors (lower BMI, higher Mallampati scores) should be assessed for their association with difficult intubation.
Iyer <i>et</i>	2011	2b	Retro	Consecutive series	The incidence of	Severe OSA and neck



<i>al.</i> <sup>1529</sup>			specti ve Cohor t	of patients who had undergone laparoscopic gastric banding (n=267).	difficult intubation, early postoperative complications and its attendant risk factors were studied.	circumference greater than 44 cm were factors associated with difficult intubation in morbidly obese patients who presented for bariatric surgery.
Kheterp al <i>et</i> <i>al.</i> <sup>1530</sup>	2009	2b	Prosp ective Cohor t	Consecutive of patients undergoing general anesthesia over 4-year period (n = 50,000).	The primary outcome was impossible mask ventilation defined as the inability to exchange air during bag-mask ventilation attempts, despite multiple providers, airway adjuvants, or neuromuscular blockade. Secondary outcomes included the final, definitive airway management technique and direct laryngoscopy view.	A total of 77 cases of impossible mask ventilation (0.15%) were observed. Neck radiation changes, male sex, sleep apnea, Mallampati III or IV, and presence of beard were identified as independent predictors.
Kim <i>et</i> <i>al.</i> <sup>1515</sup>	2006	3b	Retro Case- contr ol	Patients who had undergone UPPP (n=90).	OSA patients were compared with 90 age and sex-matched control patients with respect to the prevalence of difficult intubation.	The occurrence of difficult intubation can be predicted using AHI in patients who undergo UPPP surgery for OSAS.
Leong <i>et</i> <i>al.</i> <sup>1509</sup>	2017	3a	SR	Patients with (n=4,626) and without OSA (n=64,684) who underwent airway management for surgery.	Difficulty of airway management (mask ventilation, tracheal intubation, failed supraglottic airway device).	OSA was found to be a risk factor associated with difficult tracheal intubation and difficult mask ventilation. There was no association between OSA and difficult supraglottic airway use.
Corso <i>et</i> <i>al.</i> <sup>1514</sup>	2011	3b	Retro Case- contr ol	OSA patients (n=145) who underwent sleep surgery were compared with control patients (n=1263) who underwent other otolaryngologic surgery.	Difficult intubation	Difficult intubation occurred more frequently in patients with OSA. In OSA patients in whom difficult intubation was found, Body Mass Index (BMI), Apnea-Hypopnea Index AHI and LSAT were not different from values obtained in OSA patients who underwent easy intubation.

Siyam <i>et al.</i> <sup>1517</sup>	2002	3b	Retro Case-control	Anesthetic management of OSA patients (n=36 were compared with non-OSA controls (n=77))	Difficult intubation	Difficult intubation occurred more often in sleep apnea patients. No relationship was found between severity of OSA and the occurrence of difficult intubation.
Ulnik <i>et al.</i> <sup>1531</sup>	2000	2b	Prospective Cohort	Patients who underwent sleep surgery (n=38)	Postoperative course and occurrence of complications within 72 hours.	Within the first 72 hours after surgery, no complications were observed. Patients with BMIs greater than 35 were at increased risk for postoperative desaturations. The uncomplicated OSAS patient, one without significant comorbid factors, can be treated in a safe and prudent fashion outside of an intensive care unit.
Kim <i>et al.</i> <sup>1524</sup>	2005	2b	Retropective Cohort	OSA who underwent UPPP surgery with/without tonsillectomy under general anesthesia (n=90)	Apnea-hypopnea indices (AHI), preoperative lowest arterial saturation (LSAT-PREOP) levels, percentages of obstruction at the upper level of the uvula during apnea (AL-U), need for an airway in the postanesthesia care unit (PACU) or during the first postoperative night in a ward (POPN1), LSAT-PACU, LSAT-POPN1, and the incidence of postoperative bleeding or other complications.	Immediate postoperative complications and oxygen saturation are associated with OSAS severity and the level of obstruction, inducing apnea in those who have undergone UPPP for OSAS.
Talei <i>et al.</i> <sup>1532</sup>	2013	2b	Retropective Cohort	Patients who underwent UPPP with or without septoplasty for OSA (n=32).	Perioperative, clinical, and anesthetic records were reviewed for any complications and risks, defined as any adverse event delaying surgical progress or	Review of 32 patients failed to show any life-threatening risks or complications.

					recovery along with any additional risk to patient safety.	
--	--	--	--	--	--	--

**Table IX.B.1b Evidence for Reduction of Preoperative Sedative and Intraoperative Opiate Use**

Study	Year	LOE	Study design	Study Groups	Clinical endpoint	Conclusion
Raveslot et al. <sup>1520</sup>	2019	2a	SR and expert consensus	Studies on operative care of OSA patients (n=164)	Consensus of experts (n=12) on preoperative, intraoperative, and postoperative care topics	Strong recommendation to avoid use of sedatives (quality of evidence: very low) and opioids (quality of evidence: low).
Esclamado et al. <sup>1525</sup>	1989	2b	Retrospective Cohort	OSA patients who underwent sleep surgery (n=135)	Various patient demographics and perioperative complications, including difficulty intubating and failed extubation.	Acute obstruction with extubation was significantly and positively correlated with dose of narcotic analgesia intraoperatively.
Connolly et al. <sup>1521</sup>	1991	4	Case report	One patient who underwent UPPP and review of literature	Complications after anesthesia	Recommendation for limitation to regional anesthesia, inhaled anesthetic, and/or short-acting opioids when possible, and to avoid sedatives and opioids due to high sensitivity in OSA patients.

**Table IX.B.1c Evidence for Administration of Perioperative Systemic Steroids after Sleep Surgery**

Study	Year	LOE	Study design	Study Groups	Clinical endpoint	Conclusion
Raveslot et al. <sup>1520</sup>	2019	2a	SR and expert consensus	Studies on operative care of OSA patients (n=164)	Consensus of experts (n=12) on preoperative, intraoperative, and postoperative care topics	Weak recommendation for postoperative methods to reduce edema, including steroids (level of evidence: very low). If used, agents should be administered pre- and several times post-operatively.
Mickelson et al. <sup>1528</sup>	2007	5	Expert opinion	N/A	Postoperative airway edema	Recommendation for one dose of dexamethasone (5-10mg) pre- and several times post-operatively.

## IX.B.2 Perioperative CPAP Use and Sleep Surgery

Patients with OSA have been shown to have greater risks for perioperative adverse events, such as oxygen desaturation, difficult intubation, cardiac complications, and atrial fibrillation.<sup>467,1533</sup> In the outpatient setting, positive airway pressure (PAP) has been consistently demonstrated to be effective in controlling OSA symptoms and reducing consequent cardiopulmonary effects. In the perioperative setting, PAP reduces upper airway edema and increases lung functional residual capacity and volume.<sup>1508,1534</sup> Therefore, it is important to consider the effect of PAP use in the perioperative management of OSA patients undergoing surgery.

The immediate effect of upper airway surgery on the severity of OSA in the postoperative period is unknown as increased airway volume and stability may be counteracted by factors such as local tissue edema and the use of sedating medications.<sup>1520</sup> Presently, there are no studies specifically addressing the perioperative use of PAP in OSA patients undergoing upper airway surgery, likely because PAP failure is often a reason for surgery.<sup>1520</sup> A retrospective cohort study from 2001 showed that OSA patients undergoing elective hip/knee replacement surgery had a significantly increased risk of postoperative cardiopulmonary complications and that the subset of these OSA patients who used continuous PAP (CPAP) preoperatively had a lower rate of such complications.<sup>1535</sup> The current practice guideline recommendations regarding CPAP use for patients with OSA are based on expert opinion surveys of the American Society of Anesthesiologists (ASA); they suggest that providers consider the preoperative initiation of CPAP, particularly if OSA is severe.<sup>1518</sup>

There is a robust body of literature evaluating the benefits of postoperative PAP on cardiopulmonary outcomes in patients with OSA undergoing non-sleep surgery.<sup>1508,1534-1539</sup> In contrast, the literature on PAP use following sleep surgery specifically is limited.<sup>1540</sup> One randomized controlled trial (RCT) evaluating the effect of CPAP use in 16 patients after uvulopalatopharyngoplasty (UPPP) and septoplasty showed that CPAP was effective in preventing blood pressure elevation during sleep in the immediate postoperative period.<sup>1540</sup> A meta-analysis which included pooled data from 6 studies (3 observational studies, 2 RCTs, and 1 case series) concluded that there was no significant difference in postoperative adverse events between CPAP and non-CPAP groups.<sup>1534</sup> However, these studies were largely heterogeneous, the majority of patients did not undergo surgeries to specifically address OSA, and the 2 RCTs included were not designed to address the perioperative effects of CPAP.

A recent review and consensus statement by a group of upper airway surgery experts produced several recommendations surrounding the perioperative use of PAP in patients with OSA undergoing upper airway surgery.<sup>1520</sup> The following recommendations reached >90% expert consensus and are all based on “very low” quality of evidence based on the GRADE system:<sup>1541</sup>

1. Perioperative treatment with PAP should be considered to potentially reduce the risk of postoperative airway complications after upper airway surgery in patients with OSA without contraindications. A few relative contraindications include: un-cooperative patients, unstable cardiorespiratory status, facial trauma or burns, copious respiratory secretions, severe nausea and vomiting, and severe air-trapping diseases. Patients who have surgery that involves the skull base or the orbital wall should avoid PAP as it can be lead to pneumocephalus and/or air in the orbit.
2. PAP therapy should be used preoperatively in OSA patients already receiving PAP.

3. Full-face mask PAP in OSA patients may be used after nasal surgery if PAP is indicated, tolerated, and not contraindicated.
4. Recommend against the use of PAP after maxillofacial surgery.<sup>1520</sup>

There is high variability in the resumption of PAP use after nasal, sinus and skull base surgery in patients with OSA. This is principally related to the paucity of data on best practices including clinical outcomes and complications related to early or late resumption of PAP in patients with OSA. Generally, practitioners agree that for nasal surgery and sinus surgery without a skull base or orbital defect, resumption of CPAP within the first 2 weeks is appropriate. With a skull base or orbital defect, resumption of PAP is principally dependent on the size of the defect but can also be dependent on PAP pressure and individual patient dependence on PAP therapy. With Increasing size of skull base defects with a CSF leak, the delay in initiation of PAP therapy varies from 14+ days from small CSF leaks to 21+ days for more significant leaks.<sup>1542</sup>

In summary, although the perioperative use of PAP is generally encouraged in cases of non-upper airway surgery, especially cardiothoracic and major abdominal surgeries, PAP use in the patients undergoing upper airway surgery for OSA has not been well-studied and limited evidence has shown equivocal results.

#### Perioperative CPAP use and Sleep Surgery

**Aggregate Quality of Evidence:** D (Level 1b: 2 studies).

**Benefit:** Reduced postoperative cardiopulmonary complications with decreased likelihood of need for intensive monitored care with use of perioperative CPAP.

**Harm:** Rare procedure risk of subcutaneous, orbital, and/or intracranial emphysema in postoperative patients related to sinus and skull base surgery.

**Cost:** Low, dependent on length and type of PAP therapy prescribed.

**Benefits-Harm Assessment:** Balance of benefit and harm

**Value Judgments:** A limited number of studies show benefit of perioperative CPAP in patients with OSA undergoing surgery. Limited evidence for PAP management after upper airway surgery. Limited evidence for PAP management after upper airway surgery is predominantly based on expert opinion.

**Recommendation Level:** Option.

**Intervention:** Patients with OSA already receiving PAP should continue therapy preoperatively unless otherwise contraindicated or not tolerated. PAP therapy can be considered on a case-by-case basis postoperatively depending on the severity of OSA, nature of the surgery, and tolerance.

**Table IX.B.2: Evidence of the Effects of Perioperative CPAP Use and Sleep Surgery**

Study	Year	LOE	Study design	Population size (n) and Study Groups	Clinical endpoint	Conclusion
Ravesloot et al. <sup>1520</sup>	2019	1b	Review and consensus	164 articles published on or before December 31, 2011	47 questions covering preoperative, intraoperative, and postoperative care	Use of perioperative PAP may reduce airway complications after sleep surgery, if not otherwise contraindicated.

De Araújo <i>et al.</i> <sup>1540</sup>	2013	1b	RCT	OSA patients subjected to UPPP +/- septoplasty (n = 16) 1.CPAP (n=10) 2.Non-CPAP (n=6)	AHI Nocturnal blood pressure Nocturnal heart rate Nocturnal norepinephrine/epinephrine levels	AHI increased in patients without CPAP on postoperative day 1. Nocturnal blood pressure and catecholamine levels were increased in non-CPAP group
---	------	----	-----	--	--	---

### IX.B.3 Postoperative Disposition After Sleep Surgery

Postoperative monitoring is important in the OSA patient population and should involve metrics such as oxygen saturation levels, respiratory rate, and ideally, end-tidal carbon dioxide levels.<sup>1520</sup> Methods to specifically address postoperative upper airway edema, such as corticosteroid administration (see “Anesthesia Considerations”), head-of-bed elevation, and avoidance of supine positioning when possible are also recommended in the postoperative period.<sup>1520</sup>

The spectrum of surgeries available for OSA management varies widely and consequently postoperative disposition can include a combination of: intensive care units (ICU), step-down units, inpatient ward, post-anesthesia recovery units (PACU), and same-day discharge home. Decisions regarding postoperative disposition should take into account the type of surgery performed, patient comorbidities, OSA severity, and if applicable, adherent use of positive airway pressure (PAP).<sup>1520,1543</sup> A large-scale analysis of 3,130 adults who underwent uvulopalatopharyngoplasty (UPPP) showed that increased apnea-hypopnea index (AHI) (odds ratio [OR] 1.23,  $p = 0.05$ ), elevated body mass index (BMI) (OR 1.34,  $p = 0.04$ ), and the presence of medical comorbidities (OR 1.47,  $p = 0.002$ ) were each associated with increased rates of serious postoperative complications.<sup>1543,1544</sup>

Depending on the type of sleep surgery, there are varying levels of evidence regarding optimal postoperative disposition to minimize adverse events while preventing the waste of resources. Procedures that do not directly involve the oropharynx and hypopharynx, such as isolated nasal surgery and hypoglossal nerve stimulator implantation are generally safe to perform in an ambulatory setting. Current consensus guidelines propose that prolonged postoperative monitoring is not required in isolated nasal surgery.<sup>1520</sup> Hypoglossal nerve stimulation (HNS) surgery is unique compared to other surgical interventions for OSA in that the native airway anatomy is preserved and there is less postoperative pain compared to upper airway soft tissue surgeries. Therefore, HNS patients have been shown to be safely managed in an ambulatory setting and can typically be discharged home the same day following surgery provided the degree of OSA and severity of co-morbidities do not warrant overnight monitoring.<sup>814,1545-1547</sup> Minimally-invasive, office-based procedures including radiofrequency to the palate or base of tongue and palate suspension or implant placement, the use of local anesthetic alone allows patients to safely go home the same day.<sup>1548-1553</sup>

In the case of palatoplasty surgery, postoperative outcomes of UPPP and its modifications (transpalatal advancement, expansion pharyngoplasty) has been examined. Several cohort analyses examined complication rates in the immediate postoperative period and determined that there is often no need for routine ICU or inpatient prolonged postoperative monitoring.<sup>812,1554-1562</sup> Complication rates were generally low and serious events such as acute oxygen desaturations often occurred within a few hours

after surgery and could be addressed in the recovery room.<sup>1558,1560,1562</sup> Therefore, although postoperative monitoring, usually involving an overnight inpatient stay, has been recommended for patients with OSA undergoing UPPP, same-day discharge after a several-hour stay in the postoperative recovery room may be appropriate in select cases. Other factors to be considered should include the patients' severity of OSA, oxygen saturation nadir, comorbidities, and BMI.<sup>812,1520,1544,1556</sup>

Few studies evaluate postoperative protocols for hypopharyngeal sleep apnea surgery, such as base of tongue reduction, hyoid suspension, and transoral robotic surgery (TORS). Current data suggests that airway-related complication rates may be higher in hypopharyngeal surgeries.<sup>1549,1563</sup> However, existing literature on hypopharyngeal surgery lacks large-volume studies focused on specific procedures within the lower pharynx and results are inconclusive. One study of 22 patients who underwent hypopharyngeal surgery for OSA demonstrated no instances of postoperative desaturation, pulmonary edema, or airway compromise requiring re-intubation.<sup>1564</sup> Multilevel surgery may warrant augmented post-operative monitoring, though existing data on management do not provide a sufficient basis for management recommendations.

For maxillomandibular advancement (MMA), which involves advancement of the nasopharyngeal, retropalatal, and hypopharyngeal airway, there are few studies that examine the optimal immediate postoperative management regimen. Review of existing literature shows that patients generally require postoperative monitoring in ICU or inpatient hospital units.<sup>1563,1565</sup> Further research regarding these types of airway procedures is warranted and current expert consensus suggests patients undergoing hypopharyngeal airway surgery or MMA for OSA should at least have overnight postoperative monitoring in the hospital facility.<sup>1520</sup>

Overall, OSA patients are susceptible to multiple postoperative complications such as acute respiratory failure, oxygen desaturation, or inadequate pain control. The frequency and severity of postoperative issues are dependent on the type of surgery performed, patient comorbidities, and the severity of OSA. Postoperative disposition should be determined based on these same factors.

#### Postoperative Disposition After Sleep Surgery

Aggregate Grade of Evidence: C (1 level 1b; 12 level 2b studies)

Table IX.B.3: Evidence for Postoperative Disposition after Sleep Surgery

Study	Year	LOE	Study design	Study Groups	Clinical endpoint	Conclusion
Terris <i>et al.</i> <sup>1562</sup>	1998	2b	Retrospective cohort	OSA patients who underwent surgery (n=109).	Postoperative and follow-up complications and adverse events.	Routine postoperative intensive care monitoring for all adult patients undergoing sleep surgery is unnecessary. Although high-risk patients cannot always be identified preoperatively, significant complications generally emerge within 2 hours after surgery. A decision regarding the level of postoperative monitoring needed may be made with

						confidence during the period of time that the patient is in the recovery room.
Mickelson <i>et al.</i> <sup>1557</sup>	1998	2b	Retrospective cohort	OSA patients who underwent UPPP (n=347).	Postoperative complications and escalation of care.	Except for one patient, all complications that occurred on the surgical ward were treated without transfer to the intensive care unit. These findings suggest that UPPP is a safe procedure and that postoperative monitoring in an intensive care setting is not necessary for most patients.
Rocke <i>et al.</i> <sup>1544</sup>	2013	2b	Retrospective cohort	OSA patients (n=104) who underwent surgical treatment were triaged to ICU, routine ward bed, or discharge home based on preoperative patient factors and type of surgery.	Postoperative complications	A postoperative disposition protocol can be effectively used to triage patients to less than intensive postoperative care. In institutions like the Durham VA, where sleep apnea patients were routinely triaged to intensive care, postoperative resources will be more efficiently utilized.
Pang <i>et al.</i> <sup>1558</sup>	2012	2b	Retrospective cohort	OSA patients who underwent multilevel airway surgery (n=487).	Surgical complications.	Routine postoperative admission to the intensive care unit for all patients with OSA is unnecessary. These patients should be closely monitored in the post-anesthesia care unit area after surgery, and based on the outcome of this period, they can be observed overnight in either the high-dependency unit or the general ward.
Rotenberg <i>et al.</i> <sup>1559</sup>	2010	1b	Prospective cohort	OSA patients who underwent surgery (n=121).	1) incidence of respiratory complications requiring nursing intervention, 2) level of postoperative blood oxygen saturation	The incidence of respiratory events requiring intervention in the early postoperative course of OSA patients was low (3.4%). Routine postoperative inpatient monitoring may not be required in many cases.



Cillo <i>et al.</i> <sup>1554</sup>	2015	2b	Retrospective cohort	OSA patients who underwent surgery (intra- and extra-pharyngeal procedures) (n=267).	Surgical complications	The incidence of respiratory events requiring intervention in the early postoperative course of OSA patients was low (2.2%). Intraparyngeal complications 1.2% and extraparyngeal complications 3.8% .
Hathaway <i>et al.</i> <sup>1556</sup>	2006	2b	Retrospective cohort	OSA patients who underwent UPPP +/- tonsillectomy, septoplasty, or supraglottoplasty (n=110).	Admission rate and surgical complications.	Admission was required in 20 (18%) patients whereas 90 (82%) were discharged on the day of surgery. Admission due to desaturation was noted in 3 (3%) patients. Careful preoperative selection of patients should permit many patients to undergo UPPP as outpatient surgery. Factors requiring admission should be assessed in the early postoperative period.
Spiegel <i>et al.</i> <sup>1560</sup>	2005	2b	Retrospective cohort	OSA patients who underwent UPPP (n=117).	Postoperative complications.	The majority of complications after UPPP with or without additional procedures occur within 1-2 hours after surgery. Postoperative oxygen desaturation is usually no worse than that that was observed on preoperative polysomnography findings. A 2-3 hour observation period followed by same day discharge may be suitable for patients after UPPP although number studied was limited.
Strocker <i>et al.</i> <sup>1561</sup>	2008	2b	Retrospective cohort	Moderate to severe OSA patients who underwent UPPP (n=40).	Postoperative outcomes.	Patients with significant OSA safely underwent UPPP as an outpatient procedure in this small cohort.
Kandamy <i>et al.</i> <sup>812</sup>	2013	2b	Retrospective cohort	OSA patients who underwent UPPP (m=345).	Postoperative complications.	The incidence of post-UPPP complications is much lower than the literature has historically suggested. Selected patients should be able to safely undergo outpatient UPPP. Patients with higher AHI, higher BMI, or multiple comorbidities are at higher risk for postoperative complications and are most appropriate for

						overnight monitoring.
Gessler <i>et al.</i> <sup>1555</sup>	2003	2b	Retrospective cohort	OSA patients who underwent tonsillectomy and UPPP (n=130).	Postoperative complications.	Patients who undergo tonsillectomy and UPPP do not require monitoring in an intensive care unit postoperatively.
Glazer <i>et al.</i> <sup>1566</sup>	2014	2b	Retrospective cohort	Moderate to severe OSA patients who underwent TORS for OSA (n=166).	Major and minor complication rates.	All patients were admitted to ICU postoperatively with median days in the ICU and hospital 1 and 2, respectively. Complications are similar to those seen with other surgical treatments of OSA and were only predicted by ASA score and number of procedures performed.
Nelson <i>et al.</i> <sup>1564</sup>	2015	2b	Retrospective cohort	OSA patients who underwent hypopharyngeal surgery (n=22).	Postoperative complications.	No patient in this very small group experienced intra-operative complications, post-operative O2 desaturation <90%, prolonged admission for inadequate pain control, pulmonary edema, or airway compromise requiring re-intubation.

#### IX.B.4 Opioid Use for Pain Control After Sleep Surgery

Patients with OSA may be particularly susceptible to the respiratory depressant effects of common anesthetic agents and opioid pain medications.<sup>1518</sup> Existing literature lacks high-quality large-volume studies examining the influence of differing pain management regimens on the postoperative outcomes of patients undergoing sleep surgery. One Cochrane review did not find any significant effect of sedative and hypnotic medications on the AHI in a non-surgical setting. However significant decreases in oxygen saturation nadirs were observed with remifentanyl, zolpidem, and triazolam.<sup>1424</sup> The current recommendation, based on anecdotal evidence, first principles, and expert consensus, is to minimize or avoid perioperative opioid use in adult OSA patients when possible and instead, utilize alternative pain management options to augment patient comfort and reduce the need for opioids.<sup>1518,1520,1525,1528,1567</sup> An assessment of 42 patients who underwent uvulopalatopharyngoplasty (UPPP) and were treated with acetaminophen as the sole analgesic agent, reported no instances of significant oxygen desaturation in the immediate postoperative period, but pain scores were not recorded.<sup>1567</sup>

Although it is optimal to completely avoid opioids after sleep surgery, some upper airway procedures are associated with significant postoperative pain requiring multimodality therapy. If necessary, experts agree that opioids should be given in a setting where oximetry can be monitored, especially for

intramuscular or intravenous routes of opioid administration.<sup>1518</sup> Furthermore, if systemic opioids are administered through a patient-controlled device, background fixed-rate infusions should be avoided or strictly monitored.<sup>1518</sup>

Alternative pain medications are recommended to replace or reduce opioid requirement in the postoperative period after sleep surgery. Several randomized controlled trials (RCT) have compared the efficacy and safety of intranasal butorphanol, a synthetic opioid agonist-antagonist that does not cause dose-related respiratory depression, with commonly used medications such as meperidine and fentanyl. In the immediate postoperative period following UPPP, intranasal butorphanol was shown to be equally efficacious to oral mefenamic acid and intramuscular meperidine in pain relief<sup>1548,1568</sup> and additionally, reduced the incidence of postoperative cognitive dysfunction in patients undergoing sleep surgery.<sup>1568</sup>

Non-opioid analgesics, such as intravenous ketorolac, have also been shown to be safe and non-inferior to meperidine and mefenamic acid.<sup>1569</sup> Additionally for patients undergoing UPPP, the intraoperative and postoperative administration of a selective COX2 inhibitor, parecoxib, as well as the preemptive submucosal infiltration of ropivacaine have both been shown to reduce postoperative pain compared to placebo.<sup>1570,1571</sup> Local ropivacaine infiltration has also been shown to reduce postoperative patient-controlled consumption of morphine.<sup>1570</sup>

Multiple studies have demonstrated the safety and efficacy of dexmedetomidine in achieving analgesia in the intensive care unit setting and during non-airway surgeries<sup>1572-1574</sup>, but investigations in patients undergoing sleep surgery have not shown any reduction in opioid requirements with dexmedetomidine use.<sup>1575</sup>

In the tonsillectomy literature, two systematic reviews from 2011 and 2019 evaluated RCTs on postoperative analgesic regimens with overall recommendations supporting a multimodal strategy including acetaminophen, non-steroidal anti-inflammatory drugs, as well as dexamethasone.<sup>1576,1577</sup> Finally, other suggested pain control alternatives mentioned in the 2019 expert consensus statement include intraoperative ketamine, intraoperative/postoperative intravenous lidocaine, ice application, magnesium, and alpha-2 agonists.<sup>1520,1578-1581</sup>

### **Opioids for Pain Control After Sleep Surgery**

**Aggregate Quality of Evidence:** B (Level 1a: 4 studies; Level 1b: 5 studies)

**Benefit:** The use of non-opioid analgesic interventions reduces opioid usage and postoperative respiratory complications after sleep surgery.

**Harm:** Risk of inadequate analgesia and consequent effect on quality of life and hemodynamic instability.

**Cost:** Variable, dependent on medication selection and dosage.

**Benefits-Harm Assessment:** Slight benefit of opioid avoidance as oversedation can lead to dangerous postoperative complications however this is not well-studied.

**Value Judgments:** OSA patients are susceptible to respiratory obstruction in the postoperative period. Therefore, opioid-sparing pain management techniques are desirable but not well-established in existing literature.

**Recommendation Level:** Option.

**Intervention:** Opioids should be used judiciously in the postoperative pain regimen of OSA patients. When intravenous and high dose opioids are used, consider pulse-oximetry monitoring in the immediate postoperative period. Multimodal analgesic regimens, including local anesthetic infiltration, non-steroid anti-inflammatory drugs, acetaminophen, and dexamethasone, should be considered to achieve adequate analgesia and reduce opioid requirements.

**Table IX.B.4 Pain Management after Sleep Surgery**

Study	Year	LOE	Study design	Study Groups	Clinical endpoint	Conclusion
Diakos <i>et al.</i> <sup>1576</sup>	2011	1a	SR	RCTs (n=580) with adults undergoing tonsillectomy where peri-operative steroids were used.	Pain level compared dexamethasone use with control or placebo	Dexamethasone significantly reduced pain and postoperative nausea and vomiting in adults undergoing tonsillectomy.
Mason <i>et al.</i> <sup>1424</sup>	2015	1a	SR	RCTs (n=293) with adult OSA patients where participants were randomly assigned to use opiates or opioids, sedatives, hypnotics or placebo	Effect on OSA severity	No evidence suggests that the pharmacological compounds assessed have a deleterious effect on the severity of OSA as measured by change in AHI or ODI. Significant clinical and statistical decreases in minimum overnight SpO <sub>2</sub> were observed with remifentanyl, zolpidem 20 mg and triazolam 0.25 mg.
Tolska <i>et al.</i> <sup>1582</sup>	2019	1a	SR	RCTs (n=1816) reporting on analgesics and dexamethasone for post-tonsillectomy pain in adults and adolescents (>13 years)	Pain intensity	Paracetamol, gabapentinoids, and dexamethasone reduced pain on the day of surgery. Ketoprofen, ibuprofen, indomethacin, lornoxicam, parecoxib, rofecoxib, and dextromethorphan reduced pain intensity, need for rescue analgesics, or both on the day of surgery. Dexamethasone in multiple doses provided analgesia beyond the first postoperative day.

Titirung ruang <i>et al.</i> <sup>1577</sup>	2019	1a	SR	RCTs (n = 6,327) of steroids in adults and children who underwent tonsillectomy	Pain, nausea/vomiting, hemorrhage outcomes	IV steroids significantly decreased immediate postoperative pain severity, as well as nausea/vomiting.
Yang <i>et al.</i> <sup>1568</sup>	2015	1b	RCT	OSA patients (n=260, 65 in each group) who underwent H-UPPP  1. Intranasal butorphanol 2. Intravenous butorphanol 3. Intranasal fentanyl 4. Intravenous saline (control)	Postoperative day 1, 6, 12, 18, 24, 36, 48 – hour pain scores: VAS and Brureggemann comfort scale  Cognitive dysfunction evaluated by Mini-Mental Status Examination assessed one day before, and 1, 3, and 7 days postoperatively.	Intranasal administration of butorphanol is safe and effective, reducing postoperative usage of analgesic and the incidence of postoperative cognitive dysfunction in patients undergoing H-UPPP.
Huang <i>et al.</i> <sup>1548</sup>	2009	1b	RCT	OSA patients (n=12) who underwent UPPP 1. Transnasal butorphanol (n=7) 2. Oral mefenamic acid and intramuscular meperidine (n=5)	Pain scores at 12, 24, 72-hour postoperatively -VAS -Clinical Global Impression in Severity and Improvement -Postoperative pain-related morbidities (PRM) and quality of life in bodily pain (QOL-BP) were evaluated 72-hours postoperatively	Transnasal butorphanol can safely alleviate wound pain after UPPP. No significant difference in degree of pain relief was found between the two groups.

Lee et al. <sup>1569</sup>	2007	1b	RCT	<p>Patients who underwent surgical OSA treatments (n=90, 45 in each group)</p> <ol style="list-style-type: none"> <li>1. Intravenous ketorolac</li> <li>2. Oral mefenamic acid and intramuscular meperidine</li> </ol>	<p>Postoperative discomfort by self-assessment questionnaire on 1<sup>st</sup> and 3<sup>rd</sup> days after surgery.</p> <p>Patient satisfaction with postoperative pain treatment evaluated at 1 month postoperatively.</p>	<p>Short-term administration of intravenous ketorolac is noninferior to the conventional regimen and represents a safe treatment for wound pain after OSA surgery.</p>
Xie et al. <sup>1571</sup>	2013	1b	RCT	<p>UPPP patients (n=40, 20 in each group) randomized to 2 groups</p> <ol style="list-style-type: none"> <li>1. local block with ropivacaine + saline</li> <li>2. local block with ropivacaine + intra- and postoperative parecoxib infusion</li> </ol>	<p>VAS pain score at 24 and 48 hours after surgery; postoperative adverse effects</p>	<p>Intravenous parecoxib combined with incision-local ropivacaine provided effective postoperative analgesia.</p>
Li et al. <sup>1570</sup>	2014	1b	RCT	<p>UPPP patients (n=50, 25 in each group) randomized to 2 groups</p> <ol style="list-style-type: none"> <li>1. submucosal infiltration of ropivacaine + epinephrine</li> <li>2. submucosal infiltration of saline + epinephrine</li> </ol>	<p>Cumulative patient-controlled morphine consumption, VAS scores at 4, 8, 12, 24, 48 hours postoperatively at rest and with swallowing, opioid-related adverse effects</p>	<p>Patients who received preemptive submucosal infiltration with 0.33% ropivacaine expressed significantly decreased pain scores and also demonstrated lower morphine consumption postoperatively.</p>
Chawla et al. <sup>1575</sup>	2010	3b	Retrospective case-control	<p>Patients who underwent OSA surgery (n=268)</p> <ol style="list-style-type: none"> <li>1. Dexmedetomidine used (n=125)</li> <li>2. Dexmedetomidine not used (n=143)</li> </ol>	<p>Mean arterial pressure</p> <p>Use of anti-hypertensives</p> <p>Use of opioids</p>	<p>Dexmedetomidine improves hemodynamic stability in patients undergoing sleep surgery. No difference was noted in opioid dosage between case and control groups.</p>

### IX.C Surgical Planning: Level of Obstruction Assessment

#### IX.C.1 Physical Examination for Surgical Planning

Physical examination has long been considered a critical component in the assessment of patients pursuing surgical intervention for OSA. It is vital in identifying any anatomic abnormality that may contribute to upper airway obstruction. However, to date, the physical exam has had limited utility in determining the site and mechanism of obstruction. Here we identify the literature that describes physical examination findings for assessment of surgical treatment of OSA.

### **BMI**

Obesity, and an elevated body mass index (BMI) has long been known to be a factor in the pathophysiology of upper airway obstruction leading to obstructive sleep apnea and surgical outcomes related to its treatment. In Friedman's scoring system, a BMI above 40 is considered an exclusion criteria for patients undergoing UPPP.<sup>813,1484</sup> Part of the rationale behind this association is related to potential fat deposition in the tongue and parapharyngeal space. Cadaveric studies indicate that as BMI increases, adipose tissue may accumulate in the tongue, increasing the potential for hypopharyngeal obstruction.<sup>207</sup> Additionally, there is literature suggesting that increasing BMI is associated with greater tendency for complete concentric collapse of the velum on drug induced sleep endoscopy, which may predict an unfavorable phenotype in surgical outcomes.<sup>1583</sup> Patients with obesity often have other comorbidities such that bariatric surgery may be more appropriate and result in a greater likelihood in resolution of OSA.

### **Facial Exam**

External examination allows for identification of craniofacial abnormalities such as deformities of the external nose, midface hypoplasia, retrognathia, large neck circumference and low position of the hyoid relative to the mandibular plane. Exam findings of retrognathia and midface defects contribute to considerations for skeletal surgery and can be used in combination with cephalometry or cone beam CT imaging craniofacial analyses.<sup>1584</sup> While craniofacial abnormalities (such as a low hyoid to mandibular plane) have been studied in the context of alternative OSA treatments, there is conflicting data in their abilities to predict outcomes with both mandibular advancement devices and surgical intervention.<sup>1584,1585</sup>

### **Nasal Exam**

Nasal obstruction can play a significant role in the pathophysiology and management of obstructive sleep apnea. While correction of nasal obstruction alone does not significantly reduce the overall AHI, it can improve sleep quality and tolerance of CPAP (SECTION X).<sup>544,1586,1587</sup>

The nasal exam aims to identify anatomic abnormalities in patients with nasal obstruction. Examination of the external nasal structure as well as anterior rhinoscopy with a nasal speculum and headlight is an essential part of the nasal exam. This allows for identification of turbinate hypertrophy and evaluation of septal deviation, which can occur as a spur along the maxillary crest, a high septal deflection, or a caudal obstruction. The Cottle and modified Cottle maneuvers are useful in assessing for internal nasal valve collapse. Nasal examination can be further enhanced with use of nasal endoscopy, which may help identify nasal polyps, inflammation associated with chronic sinusitis, posterior nasal septal deviations, enlarged adenoid tissue and, in rare cases, masses.

### **Oral Cavity/Oropharyngeal Exam**

Examination of the oral cavity allows identification of the shape of the hard palate, size of the tongue, and presence and size of palatine tonsils. Identification of enlarged palatine tonsils may identify the oropharynx as the primary source of obstruction (both in children and adults) and suggest tonsillectomy

as a reasonable initial surgical option. Additionally, oral cavity and oropharyngeal examination allows assessment of Mallampati and Friedman tongue position (FTP) which in combination with tonsillar size has been used in the Friedman scoring system (FSS). Lower scores in the FSS have been associated with improved outcomes in uvulopalatopharyngoplasty and by extension may identify the oropharynx and palate as the principal source of upper airway obstruction.<sup>326,813,1588,1589</sup> Anthropometric measurement can be taken in the oropharynx and may have predictive value in severity of OSA.<sup>1590</sup> However, there remains no correlation with site and mechanism of collapse.

### Laryngoscopic Exam

Use of a fiberoptic endoscope can be used to examine the entire upper airway from the nose to the subglottis. It can be used at the level of the velum to identify maxillary constriction (narrowed distance between posterior edge of hard palate and posterior pharyngeal wall) as well as the oblique vs. vertically oriented palate.<sup>1591</sup> This technique can also be used to identify enlarged lingual tonsillar tissue<sup>556,1592,1593</sup> and epiglottis anatomy such as an omega shaped epiglottis.<sup>1594</sup> Other abnormalities of the upper airway, such as laryngeal stenosis, vocal fold paralysis, inflammatory supraglottic changes, and neoplastic masses can be identified with fiberoptic endoscopy.<sup>1595</sup> An adjunct to this exam is the Mueller maneuver which acts to simulate upper airway obstruction.<sup>1596</sup> However, the Mueller maneuver does not readily reproduce the pattern of airway collapse associated with physiologic sleep and has not been shown to correlate with surgical outcomes related to site of obstruction.<sup>1597-1599</sup>

Physical examination remains an important adjunct in the evaluation of patients pursuing options for treatment of obstructive sleep apnea. However, there is limited evidence that supports the use of awake physical examination for identifying the source or character of obstruction as a predictor for surgical intervention and OSA outcomes.

### Physical Examination for Level of Upper Airway Obstruction and Surgical Planning

Aggregate Grade of Evidence: C (Level 2b:5 studies; Level 2c: 3 studies; Level 3a:4 studies; Level 4: 4 studies; Level 5: 5 studies)

Table IX.C.1 Evidence for Physical Exam for Surgical Planning

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Friedman <sup>1484</sup>	2002	4	Retrospective cohort	Retrospective analysis without control group	Surgical success	Use of clinical staging system identifies potential for success or failure with UPPP.



Friedman <sup>813</sup>	2004	4	Prospective cohort	Prospective analysis without control group	Surgical success	Use of clinical staging system identifies potential for success or failure with UPPP and those for whom tongue base intervention should be added to intervention.
Kim <sup>207</sup>	2014	3a	Case control	Obese non-apneic (control) and obese apneic patients (study)	Volume of tongue fat	Increase deposition of tongue fat in apneics compared to obese non-apneic controls.
Vroegop <sup>1583</sup>	2014	4	Observational study	Patients undergoing DISE	Patterns of collapse identified during DISE	Overview of patterns of collapse in a large cohort of SDB patients who underwent DISE.
Denolf <sup>1584</sup>	2016	3a	Meta analysis	Review of available literature on cephalometry	Using cephalometry to predict outcomes of MAD	Cephalometric patterns cannot reliably predict treatment outcomes from MAD.
Hong <sup>1585</sup>	2016	3a	Systematic review	Review of available literature on upper airway evaluation in patients with OSA	Use of multiple modalities for evaluation of OSA	Physical examination cannot reliably predict site and mechanism of obstruction.
Ishii <sup>544</sup>	2015	3a	Meta-analysis	10 studies included	AHI, RDI, ESS	Isolated nasal surgery offered improvement in ESS and RDI.  No improvement in AHI.

Kim <sup>1586</sup>	2004	4	Case Series	Subjects undergoing nasal surgery  Pre and postoperative sleep study	RDI  Apnea Index (AI)  Oxygen desaturation index (ODI)	Significant improvement in RDI, AI, and OSI with nasal surgery.
Osborn <sup>1587</sup>	2013	5	Expert Opinion			Discussion of various medical and surgical treatment options for nasal obstruction.
Nuckton <sup>1589</sup>	2006	2b	Prospective Case series	Patients evaluated at Sleep Center	Likelihood of Mallampati score to predict OSA	Increased Mallampati score associated with risk of OSA diagnosis and increased severity.
Holmlund <sup>1588</sup>	2016	2b	Multicenter prospective interventional study	Adult patients with tonsillar hypertrophy and OSA undergoing Tonsillectomy	Resolution of OSA and reduction in AHI	Significant improvement in AHI.
Jara <sup>326</sup>	2018	2c	Retrospective cohort study	Patients undergoing tonsillectomy for OSA	Association between palatine tonsil (PT) grade and volume and OSA	PT grade associated with PT volume and AHI  PT volume not associated with AHI.

Friedman <sup>813</sup>	2004	2b	Prospective cohort study	One cohort of patients evaluated preoperatively using Friedman staging system and one cohort not	Surgical success rates	Cohort evaluated preoperatively with Friedman staging system and managed accordingly had improved surgical outcomes.
Olszewska <sup>1591</sup>	2019	5	Expert Opinion			Review of palate anatomy.
Dündar <sup>1592</sup>	1996	5	Case Report	Patient with OSA and lingual tonsillar hypertrophy	Surgical outcome	Improvement in disease severity.
Tang <sup>556</sup>	2018	2c	Retrospective cohort study	Patients with lingual tonsillar hypertrophy and OSA compared to those without OSA	Association of lingual tonsil size and OSA diagnosis	No significant correlation between lingual tonsil size and diagnosis of OSA.
Friedman <sup>1593</sup>	2017	5	Expert opinion			
Delakorda <sup>1594</sup>	2019	2c	Retrospective cohort study	Evaluation of epiglottis shape in patients with OSA undergoing DISE	Epiglottic shape in those patients with tongue base and epiglottic obstruction seen on DISE	Many patients with tongue base and epiglottic obstruction on DISE had abnormal epiglottis shape (flat).

Hsu <sup>1596</sup>	2004	2b	Prospective cohort study	Quantitative computer-assisted videoendoscopy performed in patients with OSA and compared to cohort without OSA	Retropalatal and retrolingual airway measurements and their association with OSA	Retropalatal and retrolingual measurements found predictive of OSA.
Fernández-Julián <sup>1597</sup>	2014	2b	Prospective cohort study	Comparison of surgical recommendations based on clinical evaluation vs DISE	Correlation of surgical recommendation and type of evaluation	DISE evaluation provided more information for surgical planning, particularly at the level of the hypopharynx and larynx.
Yegin <sup>1599</sup>	2017	2c	Retrospective cohort study	OSA patients undergoing evaluation with Muller's maneuver and DISE	Difference in upper airway obstruction findings with Muller's maneuver and DISE	DISE may have improved ability to diagnose site(s) and configuration of upper airway collapse when compared to Muller's maneuver.
Soares <sup>1598</sup>	2013	2c	Retrospective cohort study	Patients with OSA undergoing office evaluation with Muller's maneuver and DISE	Location in airway obstruction.	Significant difference in finding of severe retrolingual obstruction seen on DISE compared to Muller's maneuver.

### IX.C.2 Drug Induced Sleep Endoscopy (DISE)

#### IX.C.2a DISE Methods

This article is protected by copyright. All rights reserved.

Assessment of the site(s) of obstruction is critical to successful surgical treatment of obstructive sleep apnea (OSA). Multiple evaluation techniques have been developed to examine an individual's pattern of upper airway obstruction; each has important strengths and weaknesses. Traditional evaluation of the upper airway with physical examination techniques performed in the office are commonly performed during wakefulness and include largely static observations rather than dynamic assessments. As such, they may not be ideal methods to assess the upper airway during breathing and sleep.

Flexible fiberoptic endoscopy of the upper airway during natural sleep has been performed in research and limited clinical settings,<sup>1600-1603</sup> but logistical challenges have prevented broad clinical adoption. In 1991 Croft and Pringle described the technique of "sleep nasendoscopy" as the fiberoptic examination of the upper airway under conditions of spontaneous ventilation and pharmacologic sedation.<sup>1604</sup> This has been renamed drug-induced sleep endoscopy (DISE) by Hohenhorst,<sup>1605</sup> based on the use of sedation to achieve physiologic changes similar to natural sleep during the performance of endoscopy.

Consensus-based recommendations have been offered regarding many technical aspects of DISE, albeit mostly guided by expert opinion.<sup>1606</sup> This section will focus on the choice of sedative agent, as DISE has been performed with a variety of agents, most often using propofol or a combination of midazolam and propofol but with more-recent interest in dexmedetomidine.

Upper airway patency relies on pharyngeal dilator muscle tone and changes in lung volume that counteract collapsing forces, principally intraluminal negative pressure generated during inspiration and anatomical narrowing of the airway.<sup>1607</sup> OSA patients maintain pharyngeal patency with greater dilator (genioglossus) muscle tone during wakefulness, but sleep onset results in marked decreases in muscle tone due to loss of the wakefulness stimulus and decreases in negative pressure reflex activity and lung volume.<sup>395,1608-1613</sup> Because the purpose of DISE is to evaluate the pattern of obstruction in OSA, DISE's accuracy depends on reproducing the changes in upper airway physiology seen in natural sleep.

Most anesthetic agents have a wide spectrum of action from sedation to general anesthesia, with dose-dependent effects on muscle tone, airway collapsibility, responses to chemosensory input, and airflow. A recent review of sedative agents commonly used in DISE focused on propofol, midazolam, and dexmedetomidine and included a discussion of physiologic changes and their comparison to natural sleep.<sup>1614</sup> The interest in transition from wakefulness to unconscious sedation is based on the concept of a thalamocortical switch determining consciousness or unconsciousness (no response to verbal stimulation) that may be common to natural sleep and sedation.<sup>1615,1616</sup>

Hillman found that increasing levels of sedation with propofol are consistent with a switch, as changes in upper airway collapsibility, levels of EEG activity, and muscle tone occurred at this transition from consciousness to unconsciousness disproportionate to changes in propofol concentration.<sup>1617</sup> Unconscious sedation with propofol is associated with decreases in genioglossus tone to 10% of maximum awake activity,<sup>1617,1618</sup> which is one-half to one-third of tone seen during non-REM sleep in individuals with no sleep apnea,<sup>1609</sup> but greater than during REM sleep in patients both with and without OSA.<sup>186</sup> Rabelo showed that low doses of propofol have been associated with similar levels of sleep disordered breathing as seen in natural sleep,<sup>1619</sup> and this study and another by Berry showed that propofol did not induce snoring or airway obstruction in those without sleep disordered breathing during natural sleep.<sup>1619,1620</sup> Propofol does induce changes in electroencephalogram (EEG) waveforms,<sup>1621</sup> making a comparison to sleep staging difficult or impossible; it is unclear whether this is relevant to DISE as a surgical evaluation technique.

Midazolam also induces EEG waveform changes,<sup>1622</sup> but moderate doses of midazolam in a small study of males with OSA produced similar levels of sleep disordered breathing (apnea-hypopnea index, AHI) and upper airway collapsibility to those seen in natural sleep.<sup>1602,1623</sup>

Dexmedetomidine has been examined in DISE, based on its use in many procedures requiring sedation. Dexmedetomidine has demonstrated similar EEG waveforms compared to natural sleep in normals<sup>1624</sup> but likely does not produce the same changes in upper airway muscle tone that occur in natural sleep.<sup>1625</sup>

Two studies have examined potential associations between sedative agent and DISE findings using the VOTE Classification based on DISE performed in the same study participants with different sedative agents.<sup>1626</sup> Yoon showed excellent agreement between findings with propofol vs. dexmedetomidine,<sup>1627</sup> whereas Viana found a greater degree of tongue-related obstruction with propofol and midazolam vs. dexmedetomidine but otherwise found no differences.<sup>1628</sup>

Overall, propofol has been the most-studied sedative agent, with some similarities in upper airway physiology to those seen in natural sleep at the transition to unconsciousness. Studies performed with propofol, midazolam, or a combination have demonstrated validity<sup>1620,1629</sup> and moderate to good test-retest and inter-rater reliability.<sup>1630-1632</sup> However, more research with all sedative agents will help to define their roles in DISE.

### DISE Classification Scheme

For many years, surgical evaluation techniques focused on categorizing patients according to the Fujita classification system that encompasses the two primary regions of pharyngeal upper airway obstruction: the palatal/velopharyngeal and hypopharyngeal/retroglossal/retrolingual regions.<sup>1633</sup> However, there are two major limitations of region-based classifications. First, there is substantial anatomical overlap between these regions, including the extension of the lateral pharyngeal walls throughout the length of the pharynx and the physical overlap of the tongue and soft palate. Second, a region-based approach may not direct surgical treatment adequately. For example, in patients with hypopharyngeal/retroglossal/retrolingual obstruction, the oropharyngeal lateral walls, tongue, and epiglottis can each play a prominent role.

There has been a long-standing interest in describing the pattern of obstruction during DISE, and multiple groups have proposed grading systems with varying degrees of complexity.<sup>1604,1634-1636</sup> Initially, these focused on the regions outlined by Fujita<sup>1604,1635</sup> but some of these incorporated specific combinations of pharyngeal structures<sup>1634</sup> or the entire upper airway (Nose Oropharynx Hypopharynx and Larynx classification, or NOHL).<sup>1636</sup>

Because DISE is an examination of the pharynx and because pharyngeal procedures may exert differential effects on pharyngeal structures, distinguishing between the structural contributions may play a critical role in procedure selection and improvement of outcomes. In 2011, Kezirian, Hohenhorst, and de Vries developed the VOTE Classification (Table 1) to characterize the four most common structures that play a role in pharyngeal airway obstruction: the Velum, Oropharynx lateral walls, Tongue, and Epiglottis.<sup>1626</sup> The VOTE Classification encompasses these potentially-involved structures in various combinations of the degree of airway narrowing (none, partial, or complete) and configuration (anteroposterior, lateral, or concentric (combination of anteroposterior and lateral)). It is important to note that epiglottis-related obstruction can be defined as limited to those cases in which the epiglottis obstructs the airway independently or as occurring additionally in cases where another structure (such as the tongue) mechanically displaces the epiglottis to obstruct the airway in combination; it is not clear which definition is better, but any study should identify the choice and maintain consistency.

Although each of these structures represents a combination of numerous muscles and other tissue types, the VOTE Classification is based on the way these structures may be visualized during DISE. The VOTE Classification is used most commonly around the world, but ultimately the choice of a system or any improvements must be based on research identifying the specific DISE findings associated with treatment outcomes.

**Figure IX.C.2: The VOTE Classification.**

STRUCTURE	CONFIGURATION			DEGREE OF OBSTRUCTION*
	AP	LATERAL	CONCENTRIC	
Velum				
Oropharynx lateral walls				
Tongue				
Epiglottis				

AP: Anteroposterior

\* Degree of obstruction has one number for each structure

- 0 No obstruction (no vibration)
- 1 Partial obstruction (vibration)
- 2 Complete obstruction (collapse)
- X Not visualized

### DISE Findings and Associations

DISE findings differ from one individual to another, likely reflecting differences in the anatomical contribution to OSA across individuals. However, one might expect there to be associations between DISE findings and clinical characteristics, principally AHI and body mass index (BMI). Vroegop has provided the only study of sufficient size to explore these associations among 1249 study participants.<sup>1583</sup> Increasing AHI was associated with a greater odds of: obstruction related to multiple VOTE structures; complete vs. partial degree of obstruction related to the velum, oropharyngeal lateral walls, and tongue (especially complete concentric velum-related obstruction); and oropharyngeal lateral wall-related obstruction. In the same study, they also showed that increasing body mass index was associated with: greater odds of complete concentric velum-related obstruction; greater odds of oropharyngeal lateral wall-related obstruction; and lesser odds of complete tongue-related obstruction.

Cadaveric<sup>1637</sup> and live<sup>207,342</sup> human studies have demonstrated that fat deposition can occur in tissues surrounding the upper airway, especially within the tongue itself. While the tongue has been studied most thoroughly, it is likely that the same fat deposition occurs in other structures of the head and neck. Fat deposition would be expected to increase the volume of tissues, increasing OSA severity (AHI) and the contributions of the enlarged structures to airway obstruction. In this sense, it is somewhat surprising that increasing BMI was associated with a lesser odds of complete tongue-related

obstruction, but the apparent lesser odds may reflect an even greater odds of structure-related obstruction for other structures (such as the oropharyngeal lateral walls).

### IX.C.2.b DISE Findings Inform Surgical Outcomes

The key to any surgical evaluation technique is the extent to which findings are associated with outcomes of surgery. Despite almost 3 decades of experience with DISE, the literature on the association with surgical outcomes is limited (Table 2). Single-center cohort studies have examined AHI outcomes for palate surgery (almost all study participants) with or without additional procedures.<sup>1635,1638-1643</sup> These studies have generally (but not universally) shown that palate surgery outcomes are improved in the presence of velum-related obstruction only during DISE, with the exception of complete concentric velum-related obstruction that has been associated with poorer outcomes.

Unfortunately, these studies were limited by multiple concerns: single-center studies relying on the DISE scoring of the unblinded operating surgeon, small sample size and limited statistical power, and the incorporation of multiple combinations of procedures without the ability to perform statistical adjustment for the type of procedure. To address these limitations, two recent larger, multi-center cohort studies incorporated DISE video reviews by multiple surgeons blinded to the type of procedure and surgical outcome. Of note, both studies excluded adults with marked tonsillar hypertrophy (3+ or 4+ on the Brodsky<sup>1644</sup> or Friedman<sup>1484</sup> scales), where DISE may not be able to visualize other structures contributing to airway obstruction, aside from the tonsils themselves due to their large size. Both studies included adjustment for tonsil size, the factor most clearly associated with surgery outcomes.

The first study examined pharyngeal surgery and showed that complete or partial (vs. none) oropharyngeal lateral wall-related obstruction was associated with poorer surgical outcomes (adjusted odds ratio 0.51; 95% CI 0.27, 0.93).<sup>1645</sup> Complete tongue-related obstruction was associated with a lower odds of surgical response in moderate to severe OSA (adjusted odds ratio 0.52; 95% CI 0.28, 0.98), with findings that were similar but not statistically-significant in other analyses. Among numerous statistical analyses was the suggestion that tongue resection procedures may be associated with better outcomes in the presence of complete tongue-related obstruction. Surgical outcomes were not clearly associated with the degree and configuration of velum-related obstruction or the degree of epiglottis-related obstruction. Limitations of the study include an inability to differentiate specific palate surgery techniques to identify whether these techniques had differential associations with DISE findings (for example, whether newer palate surgery techniques can address oropharyngeal lateral-wall related obstruction).

The second study examined hypoglossal nerve stimulation and AHI outcomes on the post-implantation titration polysomnogram. Complete (vs. partial/none) tongue-related obstruction was associated with increased odds of treatment response (78% vs. 68%,  $p=0.043$ ).<sup>1646</sup> Complete (vs. partial/none) oropharyngeal lateral wall-related obstruction was also associated with lower odds of surgical response (58% vs. 74%,  $p=0.042$ ). Limitations of this study include the fact that the analysis was based on titration sleep study outcomes rather than full-night efficacy studies.

Both of these studies have limitations, and there will be benefits to additional research, including studies with larger sample sizes that may increase statistical power to analyze DISE findings for velum- and epiglottis-related obstruction. However, these two cohort studies provide higher-level evidence indicating that certain DISE findings are associated with surgical outcomes.



**DISE Findings Associated with Surgical Outcomes**

Aggregate Quality of Evidence: C (Level 2b: 2 studies; Level 4: 6 studies)

Benefit: Selected DISE findings are associated with outcomes of upper airway surgery and hypoglossal nerve stimulation. Other DISE findings are not clearly associated with outcomes.

Harm: Additional risk of anesthesia if done as a stand alone procedure; potential but small increase in anesthetic risk if performed at the same time as a planned surgery. Use of DISE does not always lead to improve surgical outcomes.

Cost: Increased time and effort to perform DISE before surgery.

Benefits-Harm Assessment: Balance of benefit and Harm

Value Judgments: Recent multicenter studies have identified specific DISE findings associated with outcomes of upper airway surgery and hypoglossal nerve stimulation. Additional research can evaluate whether newer palate surgery techniques can address potential limitations of upper airway surgery, such as oropharyngeal lateral wall-related obstruction.

Recommendation Level: Option

Intervention: DISE can be used to assess the upper airway for areas of collapse and can guide surgical intervention in selected cases.

**Table IX.C.2b: Association between DISE findings and Surgical Outcomes**

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical Endpoint	Conclusion
Iwanaga <sup>1635</sup>	2003	4	Cohort	Region(s) of obstruction during DISE (n=60)	Postoperative reduction in AHI	Anteroposterior velum- and tonsil-related obstruction associated with better outcomes after palate surgery than complete concentric velum-related obstruction or multilevel obstruction
Hessel <sup>1639</sup>	2004	4	Cohort	Region(s) of obstruction during DISE (n=55)	Postoperative AHI <20	Hypopharyngeal obstruction associated with poorer outcomes after palate +/- other procedures
Koutsourelakis <sup>1641</sup>	2012	4	Cohort	DISE findings based on VOTE Classification (n=49)	Postoperative AHI <10 and AHI reduction >50%	Complete circumferential velum-related obstruction and complete tongue-related obstruction associated with poorer outcomes after palate +/-

						other procedures
Soares <sup>1642</sup>	2012	4	Cohort	DISE findings based on VOTE Classification (n=34)	Postoperative AHI <20 and AHI reduction >50%	Complete oropharyngeal lateral wall-related obstruction and complete epiglottis-related obstruction associated with poorer outcomes after various procedures
Zhang <sup>1643</sup>	2015	4	Cohort	DISE findings based on VOTE Classification (n=43)	Postoperative AHI <20 and AHI reduction >50%	DISE findings not associated with outcomes of palate procedures
Blumen <sup>1638</sup>	2015	4	Cohort	DISE findings based on VOTE Classification (n=24)	Postoperative AHI <10 and AHI reduction >50%	Complete circumferential velum-related obstruction and complete tongue-related obstruction associated with poorer outcomes after tonsillectomy +/- palate surgery
Hsu <sup>1640</sup>	2017	4	Cohort	DISE findings based on VOTE Classification (n=38)	Postoperative AHI <20 and AHI reduction >50%	Complete circumferential velum-related obstruction associated with smaller, but still significant, AHI reduction following palate surgery compared to noncircumferential collapse
Green <sup>1645</sup>	2019	2b	Cohort	DISE findings based on VOTE Classification (n=275)	Postoperative AHI <15 and AHI reduction >50%	Oropharyngeal lateral wall-related obstruction (partial or complete) and complete tongue-related obstruction were associated with poorer outcomes, with and without adjustment for type of surgery
Huyett <sup>1646</sup>	2020	2b	Cohort	DISE findings based on VOTE Classification	Postoperative AHI <15 and AHI reduction >50%	Complete (vs. partial/none) oropharyngeal lateral wall-related obstruction was associated with poorer

				(n=343)		outcomes, and complete (vs. partial/none) tongue-related obstruction was associated with better outcomes of hypoglossal nerve stimulation.
--	--	--	--	---------	--	--

### IX.C.2.c DISE for Treatment Planning and to Improve Outcomes

Three studies have examined whether DISE changes the treatment plan for adults considering alternatives to positive airway pressure therapy, finding that DISE changed the treatment plan in a substantial proportion of study participants (Table IX.C.2.c.1).<sup>1597,1647,1648</sup> A more-important question is whether DISE improves surgical outcomes, a question addressed by two other studies (Table IX.C.2.c.2). One single-center study showed that DISE was potentially associated with more-aggressive surgery without a difference in outcomes.<sup>1649</sup> A multi-center study showed better AHI and blood pressure outcomes in a group undergoing surgery without DISE, compared to those undergoing DISE, in spite of the latter undergoing more tongue-directed procedures (but fewer nasal procedures).<sup>1650</sup> Importantly, there was statistical adjustment for age, gender, and body mass index in the latter study, but not for tonsil size.

Because DISE is an evaluation tool for treatment selection, sleep endoscopy is primarily indicated for those patients who do not tolerate positive airway pressure therapy who are considering multiple options, such as various procedures (and possibly the use of oral appliances). If BMI or other factors (eg large tonsils) would limit the choice of options to a single primary approach, DISE is not generally recommended because it may not inform treatment selection.

Ultimately, understanding when and how to use DISE is dependent on studies of the association between DISE findings and surgical outcomes. The recent multicenter studies may have more clearly delineated the role of DISE in procedure selection and, more importantly, counseling patients regarding surgical outcomes (e.g., recommending specific approaches or outcome expectations in the presence of complete oropharyngeal lateral-wall related obstruction). If so, systematic protocols and rigorous studies will determine better when and how to use DISE in improving treatment outcomes.

#### DISE and Treatment Outcomes

Aggregate Grade of Evidence: C (Level 2b: 1 study; Level 4: 4 studies)

**Table IX.C.2.c.1: Studies examining whether DISE changes the treatment plan**

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical Endpoint	Conclusion
Gillespie <sup>1648</sup>	2012	4	Case series	DISE findings based on multiple classifications.	Change in surgical treatment	Change in 62% (23/37) overall, including all with epiglottis-related obstruction during DISE

				(n=37)	plan	(n=14)
Eichler <sup>1647</sup>	2013	4	Case series	DISE findings based on VOTE Classification. (n=97)	Change in treatment plan (surgery and/or oral appliance)	Change in 78% (76/97) overall
Fernandez-Julian <sup>1597</sup>	2014	4	Cohort	DISE findings based on own classification. (n=162)	Change in surgical treatment plan	Change in >40% overall

**Table IX.C.2.c.2: Evidence for the association of DISE with improved outcomes**

Study	Year	LOE (1a to 5)	Study Design	Study Groups	Clinical Endpoint	Conclusion
Golbin <sup>1649</sup>	2016	4	Cohort	1) palate surgery +/- tonsillectomy without DISE (n=40) 2) palate surgery +/- tonsillectomy +/- partial glossectomy +/- partial epiglottectomy with DISE (n=64)	1) AHI 2) Epworth Sleepiness Scale score	Both groups showed a significant decrease in AHI and no change in the Epworth score. There were no differences between the groups in either endpoint.
Pang <sup>1650</sup>	2020	2b	Cohort	1) surgery without DISE (n=156) 2) surgery with DISE (n=170)	1) AHI 2) Systolic and diastolic blood pressure	Surgical success rate was greater in group without DISE, as were the decreases in systolic and diastolic blood pressure.

## IX.D Surgical Treatment for OSA

### IX.D.1 Sinus Surgery

Chronic rhinosinusitis and OSA have been demonstrated to negatively impact patient reported sleep quality.<sup>1433</sup> Endoscopic sinus surgery, in turn, has been shown to improve patient reported sleep quality for chronic rhinosinusitis (CRS) patients through an assortment of patient reported outcome measures

such as the Epworth Sleepiness Scale, the Pittsburgh Sleep Quality Index, and the Sinonasal Outcomes Test-22.<sup>914</sup> Despite patient reported improvements in validated patient reported outcome measures, data supporting the use of endoscopic sinus surgery as a surgical therapy to improve objective OSA measures is lacking. Studies examining the impact of endoscopic sinus surgery on polysomnography measures are plagued by small sample sizes, heterogenous patient populations (chronic rhinosinusitis without nasal polyposis, chronic rhinosinusitis with nasal polyposis) and variable surgical approaches (i.e. polypectomy vs complete/full endoscopic sinus surgery, concurrent septoplasty).<sup>1651</sup> Of the studies that evaluate objective parameters such as the apnea-hypopnea index, very few include endoscopic sinus surgery alone.<sup>919,1652-1654</sup> In the Tosun et al. case series, the mean AHI score did not significantly change following surgery. AHI scores decreased in 11 patients, increased in 11 patients, and did not change in 5 patients in the postoperative period. Jiang et al. found a statistically significant reduction in AHI in CRS patients with moderate OSA. Yalamanchali et al. investigated concurrent septoplasty and inferior turbinate reduction and endoscopic sinus surgery in 57 patients.<sup>920</sup> Patients with moderate and severe OSA were found to have statistically significant reductions in AHI, however no patient in this study achieved a reduction in their OSA severity category following surgery. In a systematic review of three articles evaluating AHI outcomes after endoscopic sinus surgery, the effect size, as measured by the standardized mean difference for sinus surgery was -0.20, indicating a trivial to small reduction in AHI for CRS patients with nasal polyposis undergoing sinus surgery.<sup>1651</sup> There is a paucity of high-quality data to support the use of endoscopic sinus surgery to improve objective measures of OSA severity.

In contrast to the nominal impact of endoscopic sinus surgery on AHI outcomes, data examining the impact of surgery on validated outcomes measures including the Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index are promising. Several prospective cohort studies have evaluated sleep outcomes with the Epworth Sleepiness Scale<sup>918-920</sup>. Each of these studies demonstrated significant improvement in subjective sleep as measured by the Epworth Sleepiness Scale. These results are best summarized in the meta-analysis from Sukato et al. in which the standardized mean difference was -0.94 indicating a large and statistically significant improvement following sinus surgery. Similarly, Alt et al.<sup>914,1433,1655</sup>, Little et al.,<sup>1656</sup> and Rotenberg and Pang<sup>918</sup> demonstrated statistically significant improvements in the Pittsburgh Sleep Quality Index. The standardized mean difference of -0.80 in the Sukato meta-analysis confirmed a large and statistically significant improvement in the Pittsburgh Sleep Quality Index. Together, these outcomes are consistent with a robust improvement in sleep quality for chronic rhinosinusitis patients undergoing endoscopic sinus surgery.

### Sinus Surgery for OSA Treatment

**Aggregate Quality of Evidence:** C (Level 3a: 1 study, Level 4: 6 studies)

**Benefit:** Possible small decrease in AHI and improvement in sleep symptoms with sinus surgery.

**Harm:** Risks of endoscopic sinus surgery including pain, bleeding, infection, orbital injury, cerebrospinal fluid leak, etc. Continued need for adjunctive OSA therapies.

**Cost:** Moderate to high costs associated with sinus surgery and indirect costs of time off work and recovery period.

**Benefits-Harm Assessment:** Preponderance of Harm over Benefit.

**Value Judgments:** While sinus surgery has been shown to improve sleep symptoms in chronic rhinosinusitis patients, sinus surgery alone should not be performed to significantly improve or cure sleep apnea.

**Recommendation Level:** Recommendation against.

**Intervention:** While endoscopic sinus surgery may improve subjective sleep quality in patients with chronic rhinosinusitis and concurrent SDB, SDB alone is not an indication to perform sinus surgery.

**Table IX.D.1: Evidence for Endoscopic Sinus Surgery for the Treatment of Obstructive Sleep Apnea**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Series et al. <sup>1657</sup>	1993	4	Case series	Patients undergoing nasal airway surgery or polypectomy	RDI Oxygen saturation REM Number of arousals Total Apnea Index Cephalometric measurements	Increase in REM. No differences in other measures.
Tosun et al. <sup>919</sup>	2009	4	Case series	CRSwNP with body mass index less than 28kg/m <sup>2</sup>	VAS (snoring) EpSS AHI Oxygen saturation Number of arousals % of sleep stages Rapid eye movement stage	Snoring VAS and EpSS significantly improved. No difference noted in AHI after polypectomy and sinus surgery. No difference in saturation, arousals, sleep stages or eye movement.
Gunhan et al. <sup>1652</sup>	2011	4	Case series	CRSwNP. OSA patients excluded	AHI Erectile Dysfunction	AHI Significantly reduced from 2 to 1.5.
Yalamanchali et al. <sup>920</sup>	2014	4	Case series	Mild OSA Moderate OSA Severe OSA	AHI Oxygen saturation Sleep efficiency Sleep parameters	AHI was statistically significantly reduced in severe and moderate AHI categories. "Successful surgery", defined as a reduction in AHI <20 or a 50% reduction in AHI was only achieved in 3.6% of patients. No patients achieved a change in OSA severity.
Uz et al. <sup>1654</sup>	2017	4	Case series	CRSwNP undergoing sinus surgery	1. PSQI 2. AHI	AHI decreased significantly from 13.3 to 11.2 at 6 mos post operatively
Sukato et al. <sup>1651</sup>	2018	3a	Systematic review of case series		1. AHI 2. PSQI 3. ESS	Random effects meta-analysis suggests small improvement after surgery.

Jiang RS, Liang KL <sup>1653</sup>	2019	4	Case Series	Non-OSA vs Mild, Moderate and Severe OSA	1. Sinonasal outcomes test -20 2. AHI	Increase in AHI in non-OSA patients. Statistically significant decrease in moderate OSA patients
Alt et al. <sup>1655</sup>	2014	4	Case Control	CRSwNP and CRSsNP	PSQI	Significant improvement in PSQI
Alt et al. <sup>1433</sup>	2017	4	Case Control	CRSwNP and CRSsNP Medical vs surgical management	PSQI	Significant improvement in PSQI in surgically managed group but not medically managed group
Rotenberg BW, Pang KP <sup>918</sup>	2015	4	Case series	CRSsNP	PSQI ESS	Significant improvement in both ESS and PSQI
Little et al. <sup>1656</sup>	2020	4	Case series	CRS	PSQI SNOT-22	Significant improvement in PSQI, SNOT-22

ESS: Epworth Sleepiness Scale, OSA: Obstructive Sleep Apnea, CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis, VAS: Visual Analogue Scale, PSQI: Pittsburgh Sleep Quality Index, AHI: Apnea/Hypopnea Index, RDI: Respiratory Disturbance Index, REM: Rapid Eye Movement

#### IX.D.2 Nasal Surgery

Nasal obstruction is a known contributor to OSA.<sup>274</sup> Studies have shown that airflow resistance in the nasal cavity is significantly higher in patients with OSA, suggesting that surgical correction of nasal obstruction may be an important treatment modality.<sup>1658</sup> The goal of nasal surgery is to correct anomalies in the nasal passage and to relieve clinical symptoms of nasal obstruction that have implications in OSA management.<sup>905</sup>

##### Impact on OSA Severity and Symptoms

Three meta-analyses have examined the role of nasal surgery as a treatment for OSA. These studies do not provide consensus on whether nasal surgery is effective at reducing AHI, but all showed significant improvement in ESS. Most studies included had small sample sizes and combined a variety of different nasal surgery procedures.

In a 2011 meta-analysis, Li et al.<sup>905</sup> found no significant change in AHI after nasal surgery. This study suggested that variance in pharyngeal anatomy may be a factor in surgical outcomes. The study did find a significant decrease in ESS. A 2015 meta-analysis of 10 studies by Ishii et al.<sup>544</sup> also found no significant improvement in AHI but did show significant improvement in RDI and ESS after nasal surgery. The studies analyzed included a variety of nasal surgery techniques and approaches including septoplasty alone, septoplasty with turbinate reduction, and septoplasty with turbinate reduction plus nasal valve reconstruction. The variability of nasal surgeries, along with variable methods for evaluating the response to nasal surgery among the studies, limited the analysis. The most recent 2017 meta-analysis by Wu et al.<sup>1659</sup> found a significant, but small, decrease in AHI following nasal surgery. This meta-analysis included 17 studies with pre- and post-operative quantitative data. There was a statistically significant improvement in AHI of -4.15 (95% CI = -6.48 to -1.83). ESS also improved significantly by -4.08 (95% CI = -5.27 to -2.88). This analysis included more recent studies and utilized an analysis that sub-grouped the collected data according to standard deviation of change.

It is important to note that all three meta-analyses found significant improvement in ESS, an important measure of daytime sleepiness related to OSA. Nasal surgery has been shown to improve subjective sleep quality, daytime sleepiness, snoring, and sleep-related quality of life measures in patients with nasal obstruction and sleep-disordered breathing. Most of the included studies were prospective or retrospective studies without controls with considerable heterogeneity and inconsistent patient selection criteria, increasing the potential for bias. Small sample sizes and short follow-up periods limit generalizability of the data.

Nasal surgery and role in improving PAP tolerance is addressed in Section VIII.A.5.g.

### **Nasal Surgery compared to Medical Therapy and Controls**

One non-randomized study compared surgery with septoplasty and inferior turbinate reduction versus medical therapy with sprays, saline lavage, and antihistamines. No significant changes were found in PSG metrics, but subgroup analysis showed patients with lower BMI and lower Friedman tongue position (FTP 1 or 2) were associated with better subjective outcomes for snoring and somnolence after nasal surgery.<sup>908</sup>

In the only RCT comparing results for patients who underwent septoplasty versus sham surgery, AHI remained unchanged but ESS scores decreased in the group that underwent septoplasty.<sup>1660</sup> There have not been any RCTs assessing the effect of turbinate reduction alone on AHI.

Overall, existing pooled analyses have shown mixed results in AHI change after nasal surgery in OSA patients, but certain patients may have a higher chance of surgical benefit. Non-obese BMI, lower Friedman tongue position, positional dependence of OSA, and baseline mild OSA may be potential predictors for significant improvements in OSA severity after nasal surgery.<sup>898,1661</sup>

### **Nasal Surgery for OSA**

Aggregate Quality of Evidence: Grade B (Level 1b: 1 study, Level 2a: 3 studies, Level 2b: 5 studies; Level 4: 1 study).

Benefit: Nasal surgery is associated with improved subjective nasal breathing, improved ESS, but only small improvements in AHI and RDI.

Harm: Risks and complications related to nasal surgery; persistent sleep apnea is likely for patients with moderate to severe OSA.

Cost: High costs for surgery and postoperative care.

Benefits-Harm Assessment: Balance of benefit and harm due to the evidence showing no significant changes in AHI and improvements in sleepiness symptoms. Benefits may outweigh harm for patients with symptomatic nasal obstruction.

Value Judgments: Nasal surgery to treat nasal obstruction that is refractory to medical management can improve ESS and RDI. Nasal surgery alone should not be used to cure moderate to severe OSA.

Recommendation Level: Option.

Intervention: Consider nasal surgery for patients with concurrent nasal obstruction and OSA for symptom improvement and PAP tolerance. Decision to treat should be based on clinical exam and goals of therapy.



Table IX.D.2 Evidence for Nasal Surgery to Treat OSA

Study	Year	LOE	Study Design	Study Groups	Clinical End-Point	Conclusion
Wu, J, et al. <sup>1659</sup>	2017	2a	Meta-analysis	17 studies (2002-2016): 1 RCT, 2 nonrandomized control, 11 prospective, 3 retrospective	Association of isolated nasal surgery with improvement in apnea-hypopnea index (AHI), ESS.	Both AHI and ESS improved significantly after nasal surgery. AHI change 4.15 (-6.5 to -1.8).
Ishii, L et al. <sup>544</sup>	2015	2a	Meta-analysis	10 studies: 2 RCTs, 7 prospective, 1 retrospective	AHI, RDI, ESS.	No significant improvement in AHI; significant improvement in RDI and ESS. RDI declined by 11 {-16 to -6}.
Li HY, et al. <sup>905</sup>	2011	2a	Meta-analysis	13 studies (1999-2009): 1 RCT, 1 nonrandomized control, 9 prospective, 2 cross-sectional	Changes in nasal resistance, AHI, ESS, snoring.	Changes in AHI after nasal surgery were not statistically significant; variable results in reduction of snoring; statistically significant reduction in ESS.
Koutsourelakis, I et al. <sup>1660</sup>	2008	1b	RCT	49 OSA patients with fixed nasal obstruction due to deviated septum	Association of septoplasty with increased nasal breathing epochs and reduction in AHI.	No significant decrease in AHI; change in AHI after surgery inversely related to change in nasal breathing epochs.
Shuaib SW, et al. <sup>910</sup>	2015	2b	Retrospective cohort	26 patients with septal and nasal valve obstruction	Association between functional septorhinoplasty and AHI.	Significant decrease of 35% in mean postoperative AHI.
Yalamanchali, S et al. <sup>920</sup>	2014	4	Case series	56 patients with mild, moderate or severe OSA	Association between combined nasal surgery and endoscopic sinus surgery on measurements of OSA and sleep	Small, statistically significant reduction in AHI in patients with moderate to severe OSA.

					architecture.	
Moxness, MH et al. <sup>1662</sup>	2014	2b	Prospective cohort	59 patients with OSA and clinically significant nasal obstruction	Association of either 1) septoplasty alone, or 2) septoplasty with turbinate reduction with OSA parameters. Evaluated 3 months postop.	Significant reduction in AHI in the group that had septoplasty with turbinate reduction (17.4 to 11.7 postop) Sleepiness improved in both groups.
Park, CY, et al. <sup>1658</sup>	2014	2b	Cohort	25 patients with reduced nasal cavity patency and narrowing of retroglottal or retropalatal airways with OSA	Association of septoplasty and turbinoplasty with improvement in OSA parameters (AHI, RDI, ESS).	Significant decrease in AHI and RDI; reduction in subjective symptoms. ESS improved even in those categorized as AHI non-responders.
Li, HY et al. <sup>908</sup>	2009	2b	Cohort	66 patients with OSA and chronic nasal obstruction	Association of nasal surgery with ESS, PSG parameters, AHI, Snoring (SOS).	Significantly improved SOS and ESS; insignificant changes in polysomnographic parameters.
Hu, B, et al. <sup>1663</sup>	2013	2b	Cohort	79 OSA/hypopnea syndrome patients with nasal obstruction	Association of nasal surgery with polysomnographic parameters (AHI), and nasal resistance.	Inconsistent decrease in AHI depending on severity of OSAHS; significant decrease in nasal resistance.

### IX.D.3 Tonsillectomy

Historically reserved as a treatment for recurrent infections or tonsillar malignancies, only a few studies have discussed the use of isolated tonsillectomy as a treatment for obstructive sleep apnea (OSA) syndrome. There is, however, a more substantial body of evidence supporting palatine tonsillectomy as part of uvulopalatopharyngoplasty (UPPP),<sup>1664-1669</sup> a common surgical treatment for adult OSA. The efficacy of UPPP is augmented when combined with tonsillectomy, resulting in additional improvement in the apnea-hypopnea index (AHI), daytime sleepiness, and snoring.<sup>1664-1669</sup>

Several publications have shown an association between the objective tonsil volume as well as the subjective tonsil grade, and AHI. A palatine tonsil (PT) grading scale has been used to predict OSA severity and the efficacy of tonsillectomy in treating OSA. A higher grade, which corresponds with larger

and more exophytic tonsils, corresponds with higher preoperative AHI values and a more significant reduction in AHI after removal<sup>1668,1670</sup>. A small series noted improvement in AHI in selected patients with small tonsils after tonsillectomy.<sup>1671</sup> Jara and Weaver<sup>326</sup> found a strong correlation between the subjective and objective tonsil measures that were consistent with the findings of previous studies, and they suggested that palatine tonsil grade, rather than volume, may be more predictive of the severity of OSA. Cahali et al. found a correlation between tonsillar hypertrophy and OSA but did not find a correlation between tonsillar size and OSA severity<sup>1672</sup>.

Tan et al. evaluated the efficacy of tonsillectomy as an isolated surgical treatment for the reduction of the RDI and other sleep study parameters in patients with OSA with significant tonsil hypertrophy (grade 3 to 4)<sup>1673</sup>. This study showed that in the group with RDI > 60, an average reduction of RDI by 57.6 was achieved. They concluded that tonsillectomy alone might be considered as an effective first-line surgical procedure in the treatment of OSA in patients with grade III or IV tonsils, reserving other upper airway procedures for a later stage if necessary.

A meta-analysis by Camacho et al.<sup>334</sup> reviewed 17 manuscripts analyzing isolated tonsillectomy for OSA in the adult population, but there was no manuscript with evidence level 3a or above. In their analysis, tonsillectomy for hypertrophied tonsils (or grade 2-4) resulted in AHI decrease of 65.2%. Surgical success was achieved in 85.2% of patients, and 57.4% of the patients were cured. All patients with AHI < 30 were successfully treated with tonsillectomy, while 84% were cured. They concluded that tonsillectomy can be a viable option as the sole treatment for patients with mild-moderate OSA and tonsil hypertrophy.

Holmlund et al.<sup>1588</sup> studied 28 patients (ages 18-59 years) with OSA who had an AHI of > 10 and large tonsils (grade 3-4) who underwent tonsillectomy. They found a significant decrease in the AHI as well as an improved ESS score. Senchak et al.<sup>1499</sup> chose an endpoint of reduction of at least 50% in AHI as well as absolute AHI of < 15 events/hour and found a beneficial effect for adult tonsillectomy. Nakata et al. examined the efficacy of isolated tonsillectomy in 30 patients with severe OSA and showed a success rate of 40%. In patients with BMI < 25, the success rate was 100%. Tonsillectomy did not affect snoring values<sup>1674</sup>. A subsequent study by Nakata et al.<sup>1675</sup> examined the role of tonsillectomy on nasal resistance and OSA and found that it was beneficial in reducing both nasal resistance and AHI. Tan et al.<sup>1673</sup> who examined the role of tonsillectomy as the sole treatment in 34 patients, as well as Verse et al. who treated 11 patients<sup>1676</sup> suffering from OSA, also reported positive results.

Tonsillectomy appears to be an effective treatment for obstructive sleep apnea in adults with tonsil hypertrophy. It was shown that tonsillectomy alone can significantly improve the quality of life and reduce the AHI in a select population of adults with obstructive sleep apnea and tonsillar hypertrophy.<sup>1677</sup> Tonsillectomy can be successful as a treatment for adult OSA, especially among patients with grade 3 or 4 tonsils and mild to moderate OSA<sup>334</sup>.

### Tonsillectomy for Treatment of OSA

**Aggregate Quality of Evidence:** C (level 3a: one study, level 3b: six studies, level 4: ten studies).

**Benefit:** Palatine tonsillectomy improves the severity of OSA in patients with tonsil hypertrophy.

**Harm:** Consequences of postoperative healing include pain and dysphagia and required time off work for recovery. Low risk for postoperative bleeding requiring treatment.

**Cost:** Moderate cost of surgical treatment and postoperative care including time off work.

**Benefits-Harm Assessment:** Benefits outweigh low risk of harm. Tonsillectomy for OSA patients with tonsil hypertrophy can improve OSA severity.

**Value Judgments:** Adults with tonsil hypertrophy can benefit from tonsillectomy to improve OSA severity and daytime sleepiness. Upon anatomic assessment, tonsillectomy can be combined with palatoplas-

ty techniques, however the additional benefit of palatoplasty in those with tonsil hypertrophy requires further study.

**Recommendation Level:** Recommendation.

**Intervention:** Assess for tonsil hypertrophy in patients with OSA and consider tonsillectomy as a treatment option for OSA especially in those with grade 3 or 4 tonsils and in those who cannot tolerate CPAP.

**Table IX.D.3 Evidence on Tonsillectomy for Treatment of OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Smith et al. <sup>1677</sup>	2017	4	CS	29 OSA patients	Sher's criteria	Tonsillectomy appears to be an effective treatment for OSA in a select population of adults with tonsillar hypertrophy.
Holmlund et al. <sup>1588</sup>	2016	3b	PCC	28 OSA patients with AHI > 10, Friedman grade III and IV tonsils	Change in AHI, ESS 6 months after surgery	Tonsillectomy may be an effective treatment for adult patients with OSA and large tonsils.
Camacho et al. <sup>334</sup>	2016	3a	SR/MA	NA	NA	Isolated tonsillectomy can be successful as a treatment option for adult OSA, especially among patients with large tonsils, and mild to moderate OSA (AHI < 30/hour).
Senchak et al. <sup>1499</sup>	2015	3b	PCC	19 OSA patients	Reduction of AHI by at least 50% to an absolute index of < 15	Adult tonsillectomy alone has a beneficial effect in the treatment of OSA.
Tan et al. <sup>1673</sup>	2014	3b	PCS	34 OSA patients	Sher's criteria	Tonsillectomy alone may be considered as an effective, first-line surgical procedure in the treatment of OSA.
Stow et al. <sup>1678</sup>	2012	4	RCS	13 OSA patients with tonsillar hypertrophy	Sher's criteria	In selected adult subjects, tonsillectomy with intercurrent nasal surgery should be considered an effective treatment for

						OSA.
Nakata et al. <sup>1675</sup>	2007	3b	PCS	20 OSA patients	AHI decrease	The reduction in nasal resistance induced by simple tonsillectomy could play an important role in improving OSAS, similar to nasal surgery and adenoidectomy.
Martinho et al. <sup>1491</sup>	2006	4	PCS	7 OSA patients with moderate obesity & tonsil hypertrophy	AHI decrease	Tonsillectomy for OSAHS in obese patients with obstructive palatine tonsil hypertrophy caused a significant reduction in AHI.
Nakata et al. <sup>1674</sup>	2006	3b	PCS	30 OSA patients with tonsillar hypertrophy	Sher's criteria	Simple tonsillectomy is a beneficial modality to treat OSA in selected patients (larger tonsils, low body mass index).
Verse et al. <sup>1676</sup>	2000	3b	PCS	11 OSA patients with tonsillar hypertrophy	Sher's criteria	In carefully selected patients, tonsillectomy should be considered an effective and safe surgical option for the treatment of OSA.
Miyazaki et al. <sup>1679</sup>	1998	4	RCS	10 OSA patients	PSG, AHI, 3 months postoperatively	Certain subjects can be effectively treated through tonsillectomy solely.
Houghton et al. <sup>1680</sup>	1997	4	RCS	7 OSA patients	PSG, 3 months postoperatively	Adult patients with tonsilomegaly may represent a subgroup of patients with OSA who would benefit from surgery aimed at the oropharynx.
Cheong et al. <sup>1681</sup>	1990	4	RCS	14 OSA patients	Postoperative PSG	Tonsillectomy offered a simple and effective therapy for patients with tonsillar hypertrophy.
Aubert-Tulkens et	1989	4	RCS	7 severe OSA	Postoperative AI	In adults with long-standing sleep apnea syn-

al. <sup>1682</sup>				patients		drome, surgical correction of nasal or pharyngeal abnormalities should not be expected to normalize sleep and breathing.
Moser et al. <sup>1683</sup>	1987	4	RCS	6 OSA patients with adenotonsillar hypertrophy	> 2 months post-operative AI	Many adults with OSA can clearly benefit from the removal of hypertrophied tonsils.
Rubin et al. <sup>1684</sup>	1983	4	RCS	23 moderate-severe OSA patients (7 underwent tonsillectomy, 16 treated by SMR)	Postoperative PSG, AI	Tonsillectomy improved the AI
Orr et al. <sup>1671</sup>	1981	4	RCS	6 OSA patients with tonsillar hypertrophy	ESS, PSG in 4 patients	Even relatively mild tonsillar enlargement can play an important role in the pathogenesis of obstructive sleep apnea.

CS – Case series, PCC – Prospective case-control study, SR – Systematic review, PCS – prospective cohort study, RCS – retrospective cohort study.

#### IX.D.4 Soft Palate Surgery

##### IX.D.4.a Uvulopalatopharyngoplasty (UPPP)

A standard or traditional uvulopalatopharyngoplasty (UPPP) was first described in the literature by Fujita in 1981. A standard UPPP is based on palate and uvula tissue resection. UPPP has typically included tonsillectomy and trimming of the free-edge of the soft palate and uvula with suture closure. UPPP is the most commonly performed surgery for the management of OSA. Studies examining the efficacy of surgical procedures for OSA have been case series that have been evaluated in several systematic review and meta-analysis studies<sup>811,1485,1633,1685-1687</sup>. Sher et al. was one of the first papers looking at the efficacy of UPPP for OSA. They found that the overall success rate based on greater than 50% reduction in the severity of AHI and an AHI of less than 20 (Sher criteria) was approximately 40%<sup>1633</sup>. When examining the differences between responders and non-responders, they found that patients with only retropalatal collapse (52% success rate) had higher success rates than those with retrolingual or mixed collapse (5% success rate). It should be noted, that the Sher criteria for success is limiting and modern studies examine the effect of surgery on AHI and ESS change.

Several studies show standard UPPP decreases overall AHI by 33%-50%.<sup>811,1685,1687</sup> The effect has mainly measured with short-term analyses, with mixed data on long term deterioration of respiratory

events.<sup>811,1687</sup> Aside from AHI, other studies have also looked at impact of UPPP on daytime sleepiness, cardiovascular events, cerebrovascular events, and overall mortality.

A metanalysis on isolated UPPP outcomes examined AHI change in RCTs and cohort studies, the majority of studies demonstrated a reduction in respiratory events and daytime sleepiness after UPPP.<sup>1687</sup> In two RCTs, UPPP groups had significant AHI and ESS reductions compared to controls with no treatment. Data before and after UPPP in 3 RCTs and 3 cohort studies (196 patients) showed significant 49.5% reduction in AHI from mean 35.4 to 17.2 events/hour (mean difference of -19.14). Similar significant AHI improvements were seen in prospective cohort studies. Predictors for treatment success included BMI, age, OSA severity, and clinical and anatomic staging systems.<sup>1687</sup> Choi et al. found that the greatest pre-operative predictor of surgical success for UPPP was location of oropharyngeal narrowing<sup>1485</sup>. Friedman Stage I was a strong predictor of success while Friedman stage III and low hyoid position were negative predictors after UPPP. Halle et al. published evidence that UPPP has beneficial effect on mortality, cerebrovascular disease, but not on cardiac arrhythmias.<sup>1686</sup>

Major complications related to UPPP surgery include upper airway edema, postoperative bleeding with or without the need for surgical intervention, velopharyngeal insufficiency (VPI) or nasal regurgitation. In comparison to modern variations of the UPPP (see section X), a standard UPPP appears to have lower surgical efficacy with potentially higher complication rates. Sher et al. found that the incidence of mild VPI 2 years after UPPP was as high 39.4%. More recent studies have found the VPI rates to be much lower due to changes in surgical techniques.<sup>1687</sup> Post-operative bleeding requiring return to the operating room ranged from 2-8%.<sup>1633,1687</sup> Velopharyngeal stenosis complication rates was found to be around 1.8%.<sup>1687</sup> Overall complication rate reported for UPPP is approximately 1.3%.<sup>1543</sup>

#### UPPP for OSA

Aggregate Quality of Evidence: B (Level 1: 1 study; Level 2: 2 studies; Level 3: 3 studies).

Benefit: Reduction in AHI, sleepiness and OSA severity seen after UPPP.

Harm: Overall success rates and amount of AHI reduction after traditional UPPP are variable and based on short-term studies. Side effects of UPPP include acute post-operative pain and temporary dysphagia. Complications include post-operative bleeding, acute airway edema, nasopharyngeal stenosis, and velopharyngeal insufficiency.

Cost: Moderate cost for surgery. Indirect costs associated with time -off work after surgery.

Benefits-Harm Assessment: Balance of benefit and harm.

Value Judgments: UPPP has the ability to improve OSA severity and daytime sleepiness. Traditional UPPP may have lower surgical success rates in comparison to newer palatoplasty techniques. Higher complication rates are related to tissue resection and make traditional UPPP less desirable compared to expansion palatopharyngoplasty.

Recommendation Level: Option.

Intervention: Traditional UPPP is an option as a treatment for OSA in a properly selected patients who cannot tolerate CPAP therapy.

**Table IX.D.4.a: Evidence for Uvulopalatopharyngoplasty for the Treatment for Obstructive Sleep Apnea.**

Study	Year	LOE	Study design	Study group(s)	Clinical Endpoints	Conclusions
He M et al. <sup>811</sup>	2019	2a	Systematic review and meta-analysis of 11 studies (8 standard UPPP, 1 submucosal UPPP, 1 extended UPPP, and 1 uvulopalatal flap)	1) UPPP or modified UPPP with short-term (<1 year, n=435 patients) and/or long-term (>34 months, n=368) follow-up	1. AHI 2. RDI 3. ODI 4. Lowest arterial oxygen sat (LO2Sat) 5. CT90 6. ESS 7. Snoring scores	Long-term outcomes showed an overall 46.1% (mean difference -15.4 events/hr ) decrease of AHI  Efficacy decreased between short and long-term follow-up with AHI increase by 12.3 and surgical response declined from 67% to 44% in long term group. BMI, LO2Sat, and CT90 were significantly correlated with long-term surgical response.
Stuck BA et al <sup>1687</sup>	2018	1a	SR of 53 studies (7 RCTs, 6 non-randomized controlled trials, and 40 prospective cohort studies) with meta-analysis.  Focus on isolated, standard UPPP. Modifications to UPPP and concomitant other surgeries were excluded.	1. UPPP with or without tonsillectomy 3. Control (n=49)  2 RCTs compared UPPP with control group.	1. AHI 2. ESS 3. Cardiovascular disease	Pooled analysis: After UPPP, AHI reduced from mean pre-surgery 35.3 to 17.9 (49.5%) and ESS score reduced from mean 11.7 to 7.3.  Compared to non-treated controls in 2 RCTs, UPPP improved both AHI (mean difference of -18.6, sig mean difference -1.03 = large effect) and ESS (significant mean difference of -5.37).  Before and after UPPP in 3 RCTs showed 49.5% AHI reduction, mean difference -20.4.  Mixed results from long term studies.  Complications of UPPP include upper airway edema, post-operative bleeding (0-7.8%), VPI (2-8%, all temporary), and velopharyngeal stenosis (1.8%).



Halle TR et al <sup>1686</sup>	2017	3a	Systematic Review	<ol style="list-style-type: none"> <li>1. UPPP (n=6,704)</li> <li>2. Tracheotomy (n=157)</li> <li>3. Skeletal Surgery (n=125)</li> <li>4. HGNS (n=46)</li> <li>5. Controls (n=6,394)</li> </ol>	<ol style="list-style-type: none"> <li>1.AHI</li> <li>2.Cardiovascular event</li> <li>3.Cerebrovascular disease</li> <li>4.Mortality</li> </ol>	<p>UPPP group had significant variability in success of reducing AHI.</p> <p>Lower level evidence suggests that UPPP has beneficial effect on mortality but not on cardiac arrhythmias compared to those not undergoing surgery. Several retrospective studies found no difference in survival between CPAP users and UPPP.</p> <p>Lower level evidence suggests that patients undergoing UPPP had a relative risk of 0.45 of incident cerebrovascular disease compared to those not undergoing surgery.</p> <p>Effect on blood pressure is undetermined.</p>
Choi et al <sup>1485</sup>	2016	3a	Meta-analysis of 15 Retrospective Case Series	UPPP	Predictors of success- age, BMI, preoperative AHI, Friedman stage, cephalometric measurements	Friedman stage I is strong predictor of >50% postoperative reduction in AHI after UPPP (OR [95% CI] 4.4 [2.3-8.5], p<0.001) while stage III and low hyoid position are negative predictors. Age, BMI, and preoperative AHI did not differ between patients with and without AHI reduction.
Caples SM et al <sup>1685</sup>	2010	2a	SR and meta-analysis of 15 observational studies	UPPP (n=950)	Percent reduction in AHI (95% CI)	Percent reduction in AHI was 33% (95% CI: 23%-42%). Postoperative residual AHI remained elevated, averaging 29.8/hour. Side effects of surgery include difficulty swallowing/nasal regurgitation, taste disturbances, and voice changes. 1-2% risk of a life-threatening adverse events

						and 0.2% risk of death following UPPP.
Sher et al <sup>1633</sup>	1996	3a	SR	UPPP (n=992)	1.AHI 2.Surgical success rate (>50% reduction in AHI or RDI)	Overall surgical success rate was 40%. Patients with only retropalatal collapse had higher success rates (mean AHI change -74.6%, mean RDI change -32.7%) than those with retrolingual or mixed collapse (mean AHI change -22.8%, mean RDI change -6.5%)  Mild VPI at 2 years was 39.4%.  Post-operative bleeding requiring return to the OR was between 2-5%.

#### IX.D.4.b Expansion Palatopharyngoplasty

Expansion sphincter pharyngoplasty (ESP) was first described by Pang and Woodson in 2007<sup>1688</sup>. The technique creates tension in the lateral pharyngeal walls and palatopharyngeus muscles in order to treat velopharyngeal collapse and attempt to prevent lateral oropharyngeal wall collapse as seen on DISE. The procedure, and its subsequent modifications, consists of a tonsillectomy and palatopharyngeus muscle rotation flap that is antero-supero-laterally rotated and secured to the hamulus of the hard palate or near the junction of the lateral hard palate edge. The palatopharyngeus muscle is isolated and left with its posterior surface partially attached to the posterior horizontal superior pharyngeal constrictor muscles. A partial uvulectomy (optional), and closure of the anterior and posterior tonsillar pillars completes the procedure.<sup>1688</sup>

When compared to a standard or traditional UPPP techniques, ESP has been shown to have significantly better surgical success rates based on the Sher criteria.<sup>1689,1690</sup> The vast majority of studies are case series in which surgical success rate of ESP ranges from 57% to 86.6%<sup>1689-1698</sup>. In a systematic review of five papers, the overall pooled success rate of ESP was 86.3%.<sup>1689</sup> The authors acknowledge that one of the limitations of their systematic review was the heterogeneity of the patient population, patient selection criteria, small sample sizes, and inclusion of ESP with multilevel surgery in some studies.

When looking at other clinical outcomes, ESP is associated with improved ESS.<sup>1698-1700</sup> One study examining ESP and cardiovascular events showed patients with successful outcomes after ESP also had a decrease in cardiac sympathetic activity. Another study suggested that ESP can improve C-Reactive Protein but only in patients with an AHI < 5 after surgery<sup>1692</sup>.

Several studies have looked at the efficacy of ESP in comparison to other UPPP variations, such as barbed pharyngoplasty, relocation pharyngoplasty, uvulopalatal flap, z-pharyngoplasty, and suspension pharyngoplasty<sup>1690,1696,1701</sup>. Surgical success rates are similar between ESP and these other UPPP variations. ESP appears to have the lowest complication rates amongst palatoplasty procedures in a retrospective case series<sup>1701</sup>. ESP has also been shown to be effective in treating lateral oropharyngeal collapse and circumferential palate collapse patterns seen on DISE<sup>1694,1702</sup>.

ESP is a well-tolerated surgical procedure that is effective in AHI and ESS reduction. Individual outcomes will vary depending on BMI, age, and anatomic clinical features.

### Expansion Palatopharyngoplasty for OSA

**Aggregate Quality of Evidence:** C (Level 2: 2 studies; Level 3: 1 study; Level 4: 13 studies).

**Benefit:** Reduction in AHI and OSA severity after surgery. Rate of complications may be less than traditional UPPP surgery. Small studies suggest improvements in CRP levels with effective palatoplasty surgery.

**Harm:** Moderate side effects and risks include acute post-operative pain, temporary dysphagia, risk for post-operative bleeding, velopharyngeal insufficiency, long term globus sensation, and persistent OSA. Minimal long-term complications.

**Cost:** Moderate cost for surgery. Indirect cost includes time -off of work after surgery (approx. 2 weeks).

**Benefits-Harm Assessment:** Balance of benefit and harm. Potential for benefits may outweigh risks for harm in patients with OSA who cannot use CPAP.

**Value Judgments:** ESP has the potential to significantly decrease OSA severity and improve daytime sleepiness. ESP has been shown to improve circumferential velopharyngeal collapse seen on DISE and may have lower complication rates compared to traditional UPPP. Surgery outcomes will depend on patient selection. Low quality evidence suggests outcomes may be better than traditional UPPP. Surgical approach and technique may vary by surgeon and depend on anatomic features.

**Recommendation Level:** Option.

**Intervention:** Expansion sphincter pharyngoplasty is an option for OSA patients who cannot use CPAP. Decision for surgery requires shared decision making to assess patient symptoms, clinical features of disease, and patients' goals and values for therapy.

**Table IX.D.4.b: Evidence for Expansion Sphincter Pharyngoplasty for OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical End Points	Conclusion
Pang KP et al. <sup>1689</sup>	2016	2a	SR and meta-analysis of 5 studies (1 cohort and 4 comparative cohort)	1. Expansion sphincter pharyngoplasty (n=155) 2. UPPP (n=63) 3. Adenotonsillectomy (n=25)	1. AHI 2. Surgical success rate (reduction of postoperative AHI >50%)	ESP had significantly lower postoperative AHI than UPPP (standardized mean difference -7.32, 95 % CI (-11.11, -3.52), p = 0.0002). Overall pooled success rate of ESP was 86.3%
Hong SN et al. <sup>1694</sup>	2019	4	Prospective case series	Expansion sphincter	AHI Cross-	Mean AHI decreased from 35.5 to 17.3

				pharyngoplasty patients with moderate or severe OSA (n=63)	sectional pharyngeal area	(mean difference, 18.1; 95% CI, 16.3-20.0). ESP. Change in lateral pharyngeal collapse in patients with moderate or severe OSA (based on cross-sectional pharyngeal retropalatal areas with CT scan). Postoperative DISE was not employed.
Plaza G et al. <sup>1700</sup>	2019	4	Prospective case series	Expansion sphincter pharyngoplasty (n=75)	AHI ESS Surgical Success Rate (Sher Criteria, AHI reduction >50% and to <20 events/hr).	Surgical success was 90% and 33% of patients were cured (AHI <5). Mean AHI decreased from 22.1 to 8.6 (p<0.001). Mean ESS decreased from 11.5 to 4.6 (p<0.001). Well-tolerated; no significant complications
Lorusso F et al. <sup>1697</sup>	2018	4	Prospective case series	Expansion Sphincter Pharyngoplasty in patients with moderate or severe OSA (n=20), with or without nasal surgery, tonsillectomy, and/or hyoid bone suspension	1. AHI 2. Surgical Success Rate (Sher Criteria, AHI reduction >50% and to <20 events/hr)	Surgical success rate was 65% (100% in the ESP+tonsillectomy group [n=4]). Mean AHI decreased from 41.7 to 17.4 overall and 24.2 to 8 in the ESP+tonsillectomy group.
Bosco G et al. <sup>1703</sup>	2019	4	Prospective case series	Expansion Sphincter Pharyngoplasty	Surgical Success Rate	Surgical success rate was 82.4%. Well-tolerated
Karakoc O et al. <sup>1696</sup>	2018	4	Prospective case series	1.Expansion sphincter pharyngoplasty (n=31) 2.Cahali lateral	AHI ESS Surgical Success Rate (AHI	Surgical success rate was 74% in expansion group. Mean AHI decreased in both the ESP group,

				pharyngoplasty (n=28) 3. Anterior palatoplasty (n=20)	reduction >50% and to <15 events/hr)	from 26.8 to 9.1 (p<0.001), and in the CLP group. Mean ESS decreased in all groups and from 11.1 to 4.3 (p<0.001) in the expansion group. Snoring also decreased significantly in all groups.
Despeghe AS et al. <sup>1699</sup>	2017	4	Prospective case series	Expansion sphincter pharyngoplasty in patients with 1. AHI<5 (n=16) 2. AHI≥5 (n=19)	AHI ESS	53% had reduction in AHI > 50%. AHI reduction of 22% (mild OSA), 31% (moderate OSA), and 58% (severe OSA). ESS improved from 10.4 to 5.8 at 3 months post-operatively and 5.9 1 year. Minimal post-operative complications
Pang KP et al. <sup>1698</sup>	2016	4	Prospective case series	Expansion sphincter pharyngoplasty with (n=61) or without (n=12) nasal surgery	AHI ESS Surgical Success Rate (Sher Criteria, AHI reduction >50% and to <20 events/hr)	Success rate was 86% (88.5% in combined nose/palate surgery and 75% in palate surgery alone, p=0.081). AHI improved in all patients and was statistically significant (26.3 to 12.6, p<0.001). ESS had statistically significant improvement (11.5 to 2.9, p<0.001).
Binar M et al. <sup>1692</sup>	2017	3	Prospective case series	1. Expansion sphincter pharyngoplasty (n=23) 2. CPAP (n=28)	AHI C-Reactive Protein Surgical Success Rate (AHI reduction >50% and to <20 events/hr)	Success rate of ESP was 69.6% and 26% of patients were cured (AHI <5). Mean AHI decreased from 32.3 to 11.8 (p<0.001). Only patients with AHI < 5 after surgery had improvement in CRP.

						CPAP group did not have significant change in CRP.
Liu SY et al. <sup>1702</sup>	2020	2b	Prospective Cohort Study	Expansion sphincter palatoplasty in patients with complete circumferential collapse (n=12)	AHI Collapse pattern	Mean AHI decreased from 54.0 to 33.1. All patients converted to either no collapse at the level of the velum (n=3), complete anterior-posterior collapse (n=7), or partial anterior-posterior collapse (n=2).
Babademez MA et al. <sup>1691</sup>	2019	4	Retrospective case series	1.Expansion sphincter pharyngoplasty with anterior palatoplasty (n=53) 2.Barbed palatoplasty (n=45)	AHI ESS Surgical Success Rate (AHI reduction >50% and to <20 events/hr)	Success rate was 86.6% in BP and 84.9% in ESP with anterior palatoplasty. Both surgeries significantly improved AHI (25.9 to 7.4 in BP, 28.5 to 9.1 in ESP with anterior palatoplasty, both p<0.001). No significant difference in success rate or AHI reduction ratios between the surgeries. Both surgeries significantly improved ESS (11.2 to 3.4 in BP, 12.6 to 4.1 in ESP with anterior palatoplasty, both p<0.001). Selecting a threshold of a 50% reduction in AHI and AHI less than 20 events/h, success rates were 86.6% in BP group and 84.9% in ESPwAP group
Pang KP et	2019	4	Retrospective	1.Expansion	Post-	Complication rates:

al. <sup>1701</sup>			case series	<p>sphincter pharyngoplasty (n=84)</p> <p>2.Barbed reposition pharyngoplasty (n=40)</p> <p>3.Relocation pharyngoplasty (n=8)</p> <p>4.Uvulopalatoflapp (n=11)</p> <p>5.Suspension pharyngoplasty (n=9)</p> <p>6.Modified UPPP (n=64)</p> <p>7.Z-pharyngoplasty (n=1)</p>	operative complications	<p>Dry throat (overall: 7.8%, ESP: 0%, mUPPP: 15.6%), globus sensation (overall: 11.5%, ESP: 0%, mUPPP: 15.6%)</p> <p>Throat phlegm (overall: 10.1%, ESP: 0%, mUPPP: 15.6%)</p> <p>Scar sensation (overall: 3.7%, ESP: 0%, mUPPP: 3.1%)</p> <p>Dysphagia (overall 0.5%, ESP: 0%, mUPPP: 0%)</p> <p>mUPPP, suspension pharyngoplasty, and relocation pharyngoplasty had highest symptom complaints. ESP had no symptom complaints.</p>
Guler I et al. <sup>1693</sup>	2018	4	Retrospective case series	Expansion Sphincter Pharyngoplasty (n=67)	AHI ESS Minimum O2 saturation Surgical success rate (AHI reduction >50% and to <20 events/hr)	Surgical success rate was 67.2%. Significant improvement in AHI from 18.3 to 8.0 (p=0.001). ESS improved from 8.3 to 5.6 (p=0.001) and minimum O2 saturation improved from 83.9% to 88.7% (p=0.02).
Huntley C et al. <sup>1695</sup>	2018	4	Retrospective case series	<p>1.Expansion Sphincter Pharyngoplasty (n=33)</p> <p>2. Upper Airway Stimulation (n=75)</p>	AHI ESS O2 nadir Surgical Success Rate (AHI reduction >50% and to <20 events/hr)	Surgical success of ESP was 63.6% versus 86.7% for UAS.
Rashwan MS et al. <sup>1690</sup>	2018	4	Retrospective case series	1.Expansion sphincter pharyngoplasty	AHI ODI LOS	Both BRP and ESP are more effective than UPPP in improving AHI

				(n=25) 2.Barbed reposition pharyngoplasty (n=25) 3.UPPP (n=25)		and ODI and lowest oxygen saturation. No difference in mean change in LOS between the three groups.
Suslu AE et al. <sup>1704</sup>	2017	4	Retrospectiv e case series	Expansion sphincter pharyngoplasty (n=28)	AHI Heart rate variability Surgical Success Rate (AHI reduction >50% and to <20 events/hr)	Surgical success rate of ESP was 57.1%. Patient with successful outcomes after ESP had a decrease in cardiac sympathetic activity.

#### IX.D.4.c Lateral Pharyngoplasty

Lateral pharyngoplasty (LP) involves dissection and repositioning of palatopharyngeus and superior pharyngeal constrictor muscles in order to splint lateral pharyngeal walls (LPW) and thus decrease upper airway collapsibility at the velopharynx and oropharynx.<sup>1705</sup> The repositioning of the muscle flaps promotes structural changes to the retropalatal space.<sup>1706</sup> In OSA patients, the LPW narrow the upper airway during wakefulness,<sup>199,318</sup> they further enlarge in volume in obstructed respiration during sleep,<sup>1707,1708</sup> and are particularly collapsible in severe OSA during natural sleep.<sup>1709</sup>

In the first description of LP for OSA treatment in 2003, Cahali<sup>1705</sup> found improvement in the apnea-hypopnea index (AHI), snoring complaints, amount of deep sleep and Epworth sleepiness scale (ESS) score in a median follow-up of 8 months. Patients included in this study had retropalatal collapse on awake examination. There have been three randomized parallel group trials comparing LP to uvulopalatopharyngoplasty (UPPP), and all included patients examined while awake.<sup>1706,1710,1711</sup> Two of these trials included cases with only retropalatal collapse,<sup>1706,1711</sup> and the outcome favored LP in one,<sup>1706</sup> whereas the other study reported 100% success in both groups.<sup>1711</sup> The third randomized trial included patients with retropalatal and retroglossal collapse and the outcome favored LP in patients with moderate OSA, without significant differences in the remaining groups.<sup>1710</sup>

By selecting surgeries according to the pattern of retropalatal collapse found on awake examination, Karacoc et al.<sup>1696</sup> reported that only LP and Expansion Sphincter Pharyngoplasty (ESP) reduced AHI, whereas Anterior Palatoplasty did not. All interventions decreased ESS score and snoring. In a retrospective case series including only patients with retropalatal collapse on drug-induced sleep endoscopy (DISE), Carrasco-Llatas et al.<sup>1712</sup> reported a 70% success rate (Sher's criteria<sup>1633</sup>) with LP.

Some modifications in LP technique were included, focusing on reducing the stretch of upper airway tissues. In one of them, De Paula Soares et al.<sup>1713</sup> reported decrease in blood pressure during sleep and over a 24-h period 6 months after LP, along with decrease in AHI. The reported success rate with LP varies widely from 50 to 100% with consistent decrease in AHI across the studies. By performing the most recent version of LP, Elzayat et al.<sup>1714</sup> reported a 70% success rate in a series of non-selected patients. These authors did DISE preoperatively (not for the purpose of selecting the procedure) and



repeated DISE in surgical failures and found that, by excluding patients with complete hypopharyngeal collapse on DISE, LP improves 75% of patients with OSA with a success rate of 90%.<sup>1714</sup>

Bleeding and swallowing function are important considerations when performing any palatopharyngoplasty. Only one study reported 2 cases of postoperative bleeding after LP, which did not require return to the operating room.<sup>1696</sup> The rate of bleeding after LP seems similar to other palatopharyngoplasties.<sup>1696</sup> A few studies reported cases with transient dysphagia, which resolved after 1 to 6 months after LP<sup>1696,1705,1706</sup>

### Lateral Pharyngoplasty for OSA

Aggregate Grade of Evidence: B (Level 1b: 2 studies; Level 2b: 5 studies; Level 3b: 1 study; Level 4: 1 study).

Table IX.D.4.c: Evidence on Lateral Pharyngoplasty for OSA

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusion
Cahali <sup>1705</sup>	2003	2b	Prospective cohort	LP (n = 10) Oral findings and Müller maneuver: only retropalatal collapse, bulky lateral pharyngeal tissues	PSG ESS	LP significantly reduced median AHI (from 41.2 to 9.5, p=0.009), snoring, ESS (from 13 to 5, p=0.011) and increased slow wave sleep (from 5.3% to 16.3% of time, p=0.037). Success <sup>a</sup> of LP was 60%.
Cahali et al <sup>1706</sup>	2004	1b	Randomized parallel group trial	1 LP (n = 15) 2 UPPP (n = 12) Oral findings and Müller maneuver: only retropalatal collapse, bulky lateral pharyngeal tissues	PSG ESS CT scan	Only LP significantly reduced mean AHI (from 41.6 to 15.5, p=0.002) and increased slow wave sleep (from 9.8% to 16.3% of time, p=0.03). Significant decrease in AHI in LP vs UPPP (p=0.05). Both interventions significantly reduced ESS. No differences in postoperative upper airway CT measurements. Success <sup>a</sup> of LP was 53.3%.
Tunçel et al <sup>1715</sup>	2012	4	Retrospective case series	1 LP (n = 9) 2 ZP (n = 13) 3 LP or ZP plus TBS (n = 13) Oral findings and Müller maneuver: only retropalatal collapse for LP	PSG	AHI significantly reduced in all groups (LP: 9 to 4, p=0.007; ZP: 15 to 6, p<0.001; combined surgery: 18 to 8, p=0.002). Greater improvement with multilevel intervention. Success rates <sup>a</sup> are not available.

De Paula Soares et al. <sup>1713</sup>	2014	2b	Prospective cohort	LP (n = 18) Oral findings: clearly identifiable posterior tonsillar pillars	PSG ABPM	LP significantly reduced AHI (from 33.5 to 20.9, p=0.02), arousal index (31.6 to 16.7, p=0.005) and T90% (10.6% to 0.9%, p=0.008). LP significantly reduced systolic (7.4 mmHg decrease, p=0.006) and diastolic blood (4.2 mmHg decrease, p=0.03) pressure during sleep and over a 24-h period. Success <sup>a</sup> of LP was 50%.
Chi et al. <sup>1710</sup>	2015	1b	Randomized parallel group trial	1 LP plus UPPP (n = 25) 2 UPPP (n = 29) Oral findings and Müller maneuver: retropalatal and retroglottal collapse	PSG	Significant decrease in AHI in LP with UPP (30.7%) vs UPPP (10.8%, p=0.02) in moderate OSA. Similar but nonsignificant reduction in AHI in mild and severe OSA. Success rates <sup>a</sup> non available.
Carrasco-Llatas et al. <sup>1712</sup>	2015	3b	Retrospective case series	1 LP (n = 10) 2 PPR (n = 22) 3 UPPP (n = 7) 4 ZP (n = 4) 5 ESP (n = 10) Oral findings and DISE: only retropalatal collapse	PSG	All interventions significantly reduced AHI. AHI decreased in LP group from 48.0 to 15.2 (p<0.05) and success <sup>a</sup> of LP was 70%.
Dizdar et al. <sup>1711</sup>	2015	2b	Randomized parallel group trial	1 LP (n = 14) 2 UPPP (n = 9) Oral findings and Müller maneuver: only retropalatal collapse, bulky lateral pharyngeal tissues	PSG ESS	Both interventions significantly reduced AHI (LP: 23.4 to 11.3, p<0.05) and ESS (LP: 15.3 to 6.8). Success <sup>a</sup> of both interventions were 100%.
Karacoc et al. <sup>1696</sup>	2018	2b	Prospective cohort	1 LP (n = 28) 2 ESP (n = 31) 3 AP (n = 20) Oral findings and Müller maneuver: only retropalatal collapse. For LP: bulky lateral	PSG ESS Snoring	Only LP and ESP significantly reduced AHI, (LP: 17.69 to 12.05, p=0.004). All interventions significantly decreased ESS (LP: 13.2 to 8.3) and snoring. Success <sup>a,b</sup> of LP was 64%.

				pharyngeal tissues and primarily lateral wall collapse		
Elzayat et al. <sup>1714</sup>	2020	2b	Prospective cohort	LP (n = 40) Non-selected (excluded previous palatal surgery)	PSG DISE	LP significantly reduced AHI (from 34.7 to 16.6, p<0.001) and increased baseline and min O2 saturation during sleep. Success <sup>a</sup> was 70%. Complete postoperative hypopharyngeal collapse occurred in 83.3% of non-responders. By excluding cases with preoperative complete hypopharyngeal collapse (25% of cases), success <sup>a</sup> would be 90%.

(a) Success based on Sher's criteria<sup>1633</sup> = reduction in AHI  $\geq$  50% with final AHI < 20/h (or <sup>(b)</sup> <15/h). ABPM = ambulatory blood pressure monitoring; AP = anterior palatoplasty; CT = computed tomography; DISE = drug-induced sleep endoscopy; ESP = expansion sphincter pharyngoplasty; ESS = Epworth sleepiness scale; LP = lateral pharyngoplasty; PPR = partial palate resection; PSG = polysomnography; T90% = percentage of total sleep time with oxyhemoglobin saturation < 90%; TBS = tongue base suspension; UPPP = uvulopalatopharyngoplasty; ZP = Z-palatoplasty.

#### IX.D.4.d Transpalatal Advancement Pharyngoplasty

First described by Woodson et al (1993), transpalatal advancement pharyngoplasty (TPA) was originally described for OSA patients who had failed the traditional UPPP surgery<sup>1716</sup> and were found to have continued retropalatal collapse. These patients typically have a long bony palate antero-posteriorly and a narrow retropalatal region. The (TPA) involves targeted excision of a bony window near the posterior edge of the bony hard palate, leaving a small strip of bone adherent to the soft palate aponeurosis. The soft palate aponeurosis is then pulled and sutured forward anteriorly, thereby widening the retropalatal space. Woodson et al<sup>1716</sup> demonstrated in 11 patients the success rate was 67%. In the successful group the RDI decreased from 52.8 +/- 12.2 to 12.3 +/- 2.8. When examining the whole cohort, RDI decreased from 73.3 +/- 29.4 to 25.1 +/- 28.2 (p<0.001). The main complications included a transient oronasal fistula (ONF), transient dysphagia, and serous otitis media. Woodson<sup>1717</sup> also showed a significant increase in the retropalatal area in 7 patients after the TPA with area increase by 220% from 61.5 to 135.0 mm<sup>2</sup> (p<0.001), and retropalatal closing pressure decreased 9.2 cmH2O from 5 to -4.2 cmH2O (p<0.001). Woodson et al<sup>1718</sup> then studied success rates of TPA against traditional UPPP surgery. Both were associated with improvement in RDI, however, TPA was associated with a larger RDI reduction (TPA: 48.3 +/- 24.6 to 19.8 +/- 16.8, p<0.0001; UPPP: 47.9 +/- 30.0 to 30.9 +/- 24.2, p<0.0001). In the TPA group, the postoperative AHI change was greater (30.9 +/- 24.2 points versus 19.8 +/- 16.8, p<0.02). For patients with Friedman stage 3 tongue position, the odds ratio of 50% or greater AHI reduction to level <20 events per hour with TPA compared with UPPP was 3.80 (p<0.013).

As the most difficult complication to treat is the oronasal fistula (ONF), Shine et al<sup>1719</sup> demonstrated in 89 patients who underwent TPA, the type of incision used made a significant difference in incidence of postoperative ONF after adjusting for age, sex, previous tonsillar and UPPP surgery, smoking histories and pre-operative disease severity. Another study<sup>1720</sup> on 59 TPA patients (single surgeon data), showed

overall complication rate was 25.4% (15/59), the most common of which was transient velopharyngeal insufficiency (VPI) (8/59, 13.6%). ONF was seen in 4/59 (6.8%) of patients. The only significant contributing factor for the development of ONF was the presence of a high-arched palate.

A meta-analysis by Volner et al.<sup>1721</sup> analyzed 199 OSA patients (5 studies) who underwent the TPA. The mean preoperative and postoperative AHI (199 patients) an overall relative reduction of 64.8 % although the studies demonstrated significant heterogeneity. The standardized mean difference (SMD) for TPA demonstrated a large magnitude of effect on AHI -1.76 [95 % CI -2.4, -1.1]. LSAT (70 patients) also improved with after TPA with a mean difference of 3.55 percentage points (p=0.07).

### Transpalatal Advancement for Treatment of OSA

Aggregate Grade of Evidence: : D (Level 3: 2 studies; Level 4: 2 studies).

Table IX.D.4.d Evidence for Transpalatal Advancement Surgery for OSA

Study	Year	LOE	Study Design	Study groups	Clinical End Point	Conclusion
Woodson et al. <sup>1716</sup>	1993	4	Retrospective	Previous UPPP failures (n=11)	RDI	TPA led to RDI reduction from 73.3 +/- 29.4 to 25.1 +/- 28.2 (p<0.001). Main complications included transient oronasal fistula (ONF), transient dysphagia, and serous otitis media.
Woodson et al. <sup>1717</sup>	1996	4	Retrospective cohort study	TPA UPPP	Quantitative Endoscopic Area Assessment	TPA results in an increase in velopharyngeal area from 61.5 to 135.0 mm <sup>2</sup> (p<0.001).
Woodson et al. <sup>1718</sup>	2005	3	Retrospective cohort study	TPA (n=30) UPPP (n=44)	AHI	AHI reduction was greater with TPA vs. UPPP. Postop AHI was lower in TPA group (17.1 +/- 30.1) versus the UPPP group (28.5 +/- 25.6, p<0.04). TPA group had larger AHI change (30.9 +/- 24.2 points versus 19.8 +/- 16.8, p<0.02).
Volner et al. <sup>1721</sup>	2017	3a	Systemic review with Metanalysis (5 studies)	TPA (n=199)	AHI LSAT	1.AHI reduction from 54.6 ± 23.0 to 19.2 ± 16.8; mean difference -36.3 2.LSAT improved from 81.9 ± 8.1 to

						85.4 ± 6.9.
--	--	--	--	--	--	-------------

#### IX.D.4.e Radiofrequency Palatoplasty

Radiofrequency (RF) surgery of the soft palate was first introduced by Powell et al. in 1998 as a treatment in habitual snoring and/or mild OSA.<sup>1722</sup> The RF technique utilizes heating of the tissue via a RF electrode to create a precisely controlled submucosal scar, stiffening of the targeted tissue, and volume reduction in the applied area. Literature has shown volumetric tissue reduction of the soft palate and further amelioration of the symptoms following treatment.<sup>1723-1725</sup> Due to the simple technique requiring only local anesthesia, this procedure can be done in an office outpatient setting.<sup>1726</sup>

The efficacy of RF surgery has been demonstrated in numerous prospective clinical trials. The short-term efficacy of this treatment includes reduction in snoring, excessive daytime sleepiness, and OSA severity.<sup>1723,1727-1734</sup> A systematic review by Bäck demonstrated that RF of the soft palate could reduce symptoms of snoring, at least in the short term.<sup>1735</sup> On the contrary, the latest randomized controlled trial conducted by Holmlund's group reported no significant clinical benefit on daytime sleepiness, snoring, or apnea severity one year after RF palatoplasty.<sup>1736</sup> Modifying factors that impact the success of RF have been reported. Ferguson, et al. reported that multi-lesion RF with higher energy levels per treatment increased the efficacy compared to single-lesion therapy.<sup>1737</sup> A study by Bäck et al. revealed that RF surgery of the soft palate is not recommended as a single-stage approach in mild OSA.<sup>1738</sup> RF may be suitable as a first-step treatment particularly due to its minimally invasive nature, but additional treatment sessions may be needed to increase long-term efficacy.<sup>1739-1741</sup> Adverse events reported were minimal and included mucosal sloughing, pain, localized edema of the tissues and oronasal fistulization.<sup>1742</sup> There was no significant impact on vowels and voice quality after RF surgery of the soft palate.<sup>1743,1744</sup>

#### Radiofrequency Palatoplasty for OSA Treatment

**Aggregate Quality of Evidence:** B (level 1b: 4 studies; level 2a: 1 study; level 2b: 5 studies; level 3a: 7 studies; level 3b: 4 studies; level 4: 2 studies).

**Benefit:** Minimally invasive surgery that can be performed in the clinic. Reduction in snoring in the short term.

**Harm:** Short-term post-operative pain with relatively low complication rates. Risks for superficial mucosal erosion, edema, oronasal fistula and sloughing.

**Cost:** Moderate cost of equipment and surgical fees which may not be covered by insurance; minimal time off of work.

**Benefits-Harm Assessment:** Balance of benefit and harm.

**Value Judgments:** RF palatoplasty may provide short-term benefits in selected OSA patients who prefer minimally invasive treatment. Patients should be aware that improvement in sleep apnea and snoring may be limited and repeated treatments may be needed.

**Recommendation Level:** Option.

**Intervention:** RF palatoplasty is an option with short-term efficacy for patients with primary snoring or mild OSA.

**Table IX.D.4.e: Radiofrequency Palatoplasty for OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Bäck et al. <sup>1723</sup>	2001	3a	Prospective, non-randomized	21 healthy men with habitual snoring for at least 1 year	Epworth Sleepiness Scale (ESS), visual analogue scale (VAS) scores of symptoms, cephalometric analysis, inflammatory laboratory parameters	RF thermal ablation of the soft palate seems to be effective for snoring and excessive daytime sleepiness.
Bäck et al. <sup>1724</sup>	2002	3a	Prospective, non-randomized	20 non-obese habitual snorers	Snoring, daytime sleepiness, soft palate dimensions on magnetic resonance imaging (MRI)	Significant changes in the soft palate dimensions and in the T1-signal intensity were seen on MRI, along with decreased snoring and daytime sleepiness, after RF palatoplasty.
Bäck et al. <sup>1738</sup>	2009	1b	Randomized single-blinded placebo-controlled	32 patients with mild OSA	Primary measures: apnea/hypopnea index (AHI), ESS, and a 36-item short-form quality-of-life (QOL) questionnaire.  Secondary measures: soft tissue airway parameters in cephalometric radiographs, snoring scores, and rates of adverse events.	RF surgery of the soft palate is not recommended as a single-stage treatment in mild OSA. AHI did not differ between patients after RF surgery (11.0 preoperatively vs 13.0 postoperatively) vs. placebo (12.0 preoperatively vs 11.0 postoperatively, $p=0.63$ )
Bäck et al. <sup>1735</sup>	2009	1b	Systemic review	30 controlled or prospective studies of RF palatoplasty in snoring with at least 10 adults without moderate/severe OSA	ESS, AHI snoring severity, post-operative discomfort	RF surgery is a safe operative procedure, which may reduce symptoms of snoring in short-term follow-up. Of six studies reporting AHI and/or RDI, none reported significant change following RF.

Balsevičius et al. <sup>1742</sup>	2015	3a	Prospective, non-randomized	28 patients with mild/moderate OSA who underwent two sessions of RF within the interval from 6 to 8 weeks.	VAS scores of symptoms, AHI, Sleep Apnea Quality of Life Index, Beck Depression Inventory—second edition (BDI-II), ESS	RF with nine lesions to the soft palate seems to be an effective and safe treatment modality associated with low morbidity in selected mild/moderate OSA. Mean AHI decreased from $13.7 \pm 5.9$ to $8.3 \pm 4.9$ ( $p < 0.01$ ) and 60.7% of patients experienced an AHI reduction >50%.
Tatla et al. <sup>1734</sup>	2003	3b	Prospective, non-randomized study	10 patients with chronic habitual snoring or mild OSA	BMI, PSG, snoring VAS, subjective assessment of pain	RF palatoplasty has minimal morbidity, high patient acceptability, minimal analgesia requirements and little inconvenience to patients. Decrease in AHI was not significant.
Powell et al. <sup>1722</sup>	1998	2b	Prospective non-randomized	22 patients with sleep-disordered breathing	PSG, cephalometric radiographs, VAS scores of symptoms (pain, speech, snoring, and swallowing), and infrared thermal imaging	There was documented tissue reduction and improvement in symptoms in all patients. Apnea and hypopnea indices initially worsened in the 48-72 hours immediately following treatment but decreased to pre-treatment levels by 10-12 weeks; long term decrease was not significant.
Sher et al. <sup>1731</sup>	2001	2b	Prospective, non-randomized multicenter	113 patients with habitual disruptive snoring who had a respiratory disturbance index	VAS scores of symptoms (pain, snoring and sleep quality) and ESS	The multiple lesion RF protocol was the most successful. Temperature-controlled RF was

			study	(RDI) < 15 and minimum oxygen saturation not less than 85%		found to be a minimally invasive, well-tolerated procedure. Mean RDI increased from 6.4 to 8.7 for the overall cohort ( $p < 0.0031$ ).
Boudewyns et al. <sup>1728</sup>	2000	2b	Prospective, non-randomized multi-center clinical study	45 non-apneic snorers	ESS, snoring index	RF ablation applied at the midline of the soft palate, with a maximum of 3 treatment sessions, improves snoring and ESS in the majority of patients without serious adverse events.
Hofmann et al. <sup>1740</sup>	2006	2b	Prospective clinical trial	79 patients with primary snoring or mild OSA (47: uvulopalatopharyngoplasty [UPPP]; 32: RF palatoplasty).	Subjective snoring scores and AHI	The success rate of RF surgery of the soft palate is clearly lower compared to UPPP. Snoring scores improved in both groups, while AHI and HI only improved in the UPPP group.
Holmlund et al. <sup>1736</sup>	2014	1b	Randomized controlled trial	35 men with snoring and mild/no OSA	ESS, Basic Nordic Sleep Questionnaire, AHI with home sleep study	RF soft palate has no significant effect on daytime sleepiness, snoring, or AHI 1 year after surgery.
Hukins et al. <sup>1729</sup>	2000	3b	Prospective, non-randomized	20 adults with loud habitual snoring without clinically significant OSA	VAS scores of symptoms (snoring intensity, pain, difficulty in swallowing), and changes in speech, polysomnography and lateral cephalometry	RF palatoplasty is well tolerated with very low morbidity. It is associated with subjective improvement in snoring in most patients. Change in AHI is not significant.
Birkent et al. <sup>1743</sup>	2008	3a	Prospective, non-randomized	26 habitual snorers and mild OSA patients (AHI <10)	Acoustic evaluation made by the Multidimensional	RF of the soft palate as a treatment for snoring and mild OSA does not have a



					Voice Program	significant impact on voice quality.
Hultcrantz et al. <sup>1730</sup>	2009	3b	Prospective, non-randomized	29 patients with habitual snoring; 10 of 29 patients underwent electromyography (EMG) of palatoglossal muscles	Snoring VAS, bedpartner estimated hours of sleep and EMG changes of palatoglossal muscles	RF treatment for snoring may lead to long-term improvement in one out of four cases. Pre-evaluation with EMG may predict the outcome.
Ferguson et al. <sup>1737</sup>	2001	2b	Prospective, non-randomized	47 habitual snorers without symptoms suggestive of OSA (16: single-lesion treatments, 31: multilesion treatments)	VAS scores for snoring and pain	Multilesion RF palatoplasty using higher energy levels per treatment is safe and has increased efficacy without increased complications relative to single-lesion therapy.
Blumen et al. <sup>1727</sup>	2013	4	Retrospective review	105 subjects with simple snoring or mild OSA	To determine whether snoring intensity measured after the first session of soft palate RF predicts the final treatment outcome	Snoring intensity after the first RF session helps predict the final outcome of RF-assisted stiffening of the soft palate for simple snoring.
Haraldsson et al. <sup>1744</sup>	2002	3a	Prospective, non-randomized	16 habitual snorers (all patients had an oxygen desaturation index <6)	Objective (nasal-oral ratio meter) and subjective (speech-language pathologist) speech evaluation	RF soft palate for snoring did not show any significant adverse effect on velopharyngeal function and voice quality.
Kermadec et al. <sup>1739</sup>	2014	4	Observational retrospective study	77 patients underwent soft palate RF treatment for snoring with AHI <20 (at least 3 years' follow-up)	A postal questionnaire including snoring VAS, demographics, cardiovascular risk factors (body weight, hypertension and diabetes)	Relapse of snoring was observed in nearly all patients. Most patients did not comply with the follow-up instructions and did not seek other forms of treatment when

						recurrence occurred.
Stuck et al. <sup>1732</sup>	2004	2a	Systemic review	Habitual snorers and mild OSA (22 original articles published in peer-reviewed journals)	Snoring VAS and snoring index	RF surgery of the soft palate leads to a significant reduction of subjective snoring, and snoring is reduced to a tolerable level.
Stuck et al. <sup>1733</sup>	2005	1b	Randomized, placebo-controlled trial	26 patients with primary snoring (AHI < 15, BMI < 35) divided into treatment and placebo arms	Bed partner with snoring VAS	Snoring scores for the RF arm were significantly better than the placebo arm, although the reduction in snoring was only moderate.
Stuck et al. <sup>1741</sup>	2009	3a	Prospective clinical trial	19 patients with primary snoring (AHI < 15, BMI < 32) 18 months post-procedure	Questionnaire on snoring VAS, and the overall satisfaction with the procedure	A relapse in snoring can be expected in some patients after RF-assisted uvulopalatoplasty (RF-UPP).
Emery et al. <sup>1726</sup>	2000	3b	Prospective, non-randomized	43 snoring and/or mild OSA patients whose snoring intensity was bothersome to their bed partner	Safety, character of pain, and effects on speech, swallowing, and snoring severity	RF palatoplasty is well-tolerated and not painful.
Blumen et al. <sup>1725</sup>	2002	3a	Prospective, non-randomized	30 patients with simple snoring or mild OSA having soft palate obstruction	Efficacy and tolerance of RF and laser-assisted uvulopalatopharyngoplasty (LAUP)	RF was as effective as LAUP in reducing snoring in the short-term, and was better tolerated.

#### IX.D.4.f Pillar Implants

Pillar implants were initially introduced in 2003 for the treatment of snoring and were later approved for mild OSA. Three implants consisting of non-resorbable woven polyethylene terephthalate (each 18mm long and 2mm in diameter) are inserted into the soft palate, one in the midline of the junction between the hard to soft palate and one lateral to either side with a space of 3mm in-between. The procedure is performed under local anesthesia in an office setting.

The intention is to extend the hard palate by stiffening the soft palate through chronic inflammatory, fibrous capsule formation around the implant and thereby to prevent a retropalatal collapse. This process should also reduce tissue vibrations during respiration.

In the majority of studies a significant positive effect on AHI, snoring intensity, LSAT and daytime sleepiness (ESS) was observed selecting patients with the following criteria: mild to moderate OSA, BMI  $\leq 32$  kg/m<sup>2</sup>, no sign of airway collapse other than palate, a length of  $\geq 20$ mm of the soft palate<sup>1745-1752</sup>. In two of the three RCT a significant postoperative improvement of the AHI and the superiority of the implant over placebo was shown<sup>1747,1749,1751</sup>, one RCT showed elevation in AHI in both treatment and placebo groups.<sup>1751</sup>

An initial significant improvement in AHI after the first 90 days showed consistency for the follow up after 12-15 months<sup>1753,1754</sup>, whereas patients without improvement did not show any improvement either after 15 months<sup>1754</sup>. A long-term follow-up with up to 36 months also showed a permanent significant improvement in AHI and ESS but also a significant change in BMI which was not described further<sup>1755</sup>. Other studies, however, showed no significant improvement in AHI in mild to moderate OSA after implantation.<sup>1756,1757</sup>

When implanted in patients with moderate to severe OSA, the implant showed nearly no effect or a significant but clinically meaningless improvement regarding RDI and ESS<sup>1758,1759</sup>. AHI was unchanged, but the implantation significantly reduced the needed CPAP-pressure and increased CPAP-adherence: 11.2 cm H<sub>2</sub>O vs. 9.2 cm H<sub>2</sub>O ( $p < 0.001$ ), and 5.7h vs. 6.4h ( $p < 0.001$ ). Body weight was not measured postoperatively<sup>1758</sup>. However, these results could not be confirmed in a subsequent RCT at constant body weight<sup>1760</sup>. There is no objective data on other sleep parameters.

The above stated effects have to be measured against the morbidity of the surgery: In the vast majority the occurring mild pain, speech and swallowing difficulties were self-limiting within the first 24-72 hours up to 3-6 Months<sup>1756,1761</sup> or did not occur at all<sup>1746</sup>. Dysphagia in 14.8% and foreign body sensation in 25.9% persisted in one study<sup>1757</sup> and was self-limiting in most other cases<sup>1756,1759-1761</sup>. Infections occurred in 0%<sup>1749</sup> to 2%<sup>1751</sup> and irritations or ulcerations in 7.5%<sup>1752</sup>, and only one needed antibiotics. There is only one isolated report of an abscess<sup>1755</sup>. Extrusion rates were published between 0%<sup>1749,1759,1760</sup>, 4%<sup>1751</sup> and 9.9%<sup>1752</sup> to 14.3%<sup>1753</sup> of implanted patients. Complete resolution was reached after 2 weeks<sup>1752</sup>.

In summary, pillar implants can be recommended as sole therapy if the above selection criteria are fulfilled, or as part of a multimodality and multilevel treatment plan, since the potential benefits outweigh the possible harm. It cannot be recommended in patients with severe OSA or obesity. The costs may be significant and should be measured against other therapeutic options and the possible need to treat a persisting OSA.

### Pillar Implants for OSA Treatment

**Aggregate Quality of Evidence:** B (1a: 1 study; Level 1b: 4 studies; Level 4: 12 studies)

**Benefit:** Easy to perform in the office under local anesthesia with excellent patient tolerance and limited morbidity. Small changes in AHI, improved ESS and snoring in certain patients with snoring or mild to moderate OSA.

**Harm:** Self-limited mild pain, foreign body sensation, and swallowing difficulties for 72 hours, risk for ulceration and implant extrusion.

**Cost:** Moderate to high, often not covered by insurance. Minimal time off work.

**Benefits-Harm Assessment:** Balance of benefit and harm.

**Value Judgments:** Short term improvements in symptoms and AHI in patients with BMI  $< 32$  with mild to moderate OSA. There is minimal morbidity and efficacy is variable.

**Recommendation Level:** Option.

**Intervention:** Pillar implants can be considered in patients with primary snoring or mild to moderate OSA and suspected soft palate collapse for improvements in snoring, sleepiness, and small changes in AHI.

**Table IX.D.4.f: Evidence on Pillar Implants for Sleep Apnea**

Study	Year	LOE	Study Design	Study Groups	Clinical endpoint	Conclusion
Maurer et al. <sup>1749</sup>	2012	1b	<ul style="list-style-type: none"> <li>• randomized, double-blind, placebo-controlled trial</li> </ul>	Mild to moderate OSA (study group n=11, placebo group n=11) <ul style="list-style-type: none"> <li>• AHI 10-40/h</li> <li>• BMI <math>\leq 32 \text{ kg/m}^2</math></li> <li>• soft palate length <math>&gt; 25 \text{ mm}</math></li> <li>• tonsil size <math>&lt; 50\%</math> of the airway</li> <li>• no signs of retrolingual obstruction in clinical exam</li> <li>• no previous history of upper airway surgery other than nasal, adenoid, or tonsil</li> <li>• no other relevant disorders affecting sleep or daytime performance</li> <li>• tonsil size <math>&lt; 50\%</math> of the airway</li> </ul>	90 days follow up of AHI, snoring, LSAT and ESS	AHI, snoring and LSAT with significant improvement.  Placebo group: No significant difference in AHI and ESS.
Steward et al. <sup>1751</sup>	2008	1b	<ul style="list-style-type: none"> <li>• randomized, double-blind, sham-placebo-controlled, multi-institutional study</li> </ul>	Mild to moderate OSA (study group n=50, placebo group n=50) <ul style="list-style-type: none"> <li>• BMI <math>&lt; 32 \text{ kg/m}^2</math></li> <li>• AHI 5-40/h</li> <li>• tonsil size <math>&lt; \text{III}</math></li> </ul>	3 Months follow up of AHI and ESS, LSAT and PVT, snoring	Increase of AHI in both groups, pre- and post-interventional: study vs. placebo ESS and LSAT improved compared to placebo (No significant change in PVT or snoring.
Hu et al. <sup>1759</sup>	2018	4	<ul style="list-style-type: none"> <li>• retrospective, single-institutional</li> </ul>	Severe OSA with retropalatal collapse (n=10) <ul style="list-style-type: none"> <li>• RDI <math>&gt; 30/\text{h}</math></li> <li>• no nasal obstruction</li> <li>• tonsil size <math>&lt; \text{III}</math></li> <li>• soft palate length 30-40mm</li> </ul>	33 Months follow up, ESS, snoring, RDI, LSAT, sleep efficiency. RDI reductio	Improvement in snoring, ESS, RDI and LSAT

					n of <20/h and a reduction of ≥50%	
Bertoletti et al. <sup>1758</sup>	2009	4	<ul style="list-style-type: none"> <li>• non-randomized, single-institutional pilot-study</li> </ul>	<p>Moderate to severe OSA with CPAP-therapy and palatal implant (n=21)</p> <ul style="list-style-type: none"> <li>• titrated CPAP pressure &gt;10 cm H2O</li> <li>• AHI &gt;20/h</li> <li>• BMI &gt;30kg/m<sup>2</sup></li> </ul>	90 days follow up, CPAP pressure	<p>No significant difference of pre- and postoperative AHI and SpO<sub>2</sub>.</p> <p>Significant difference between average CPAP pressure levels (mean reduced from 11.2 to 9.3 cm H2O)</p>
Server et al. <sup>1757</sup>	2016	4	<ul style="list-style-type: none"> <li>• retrospective, non-randomized study</li> </ul>	<p>Mild OSA and simple snoring (n=27)</p> <ul style="list-style-type: none"> <li>• BMI &lt;30kg/m<sup>2</sup></li> <li>• AHI &lt;15/h</li> <li>• tonsils size &lt;50% of the airway</li> <li>• nasal passage's being open</li> <li>• implant's staying for more than one year</li> <li>• being together with the same bed-partner for six years</li> <li>• tonsil size &lt;50% of the airway</li> <li>• extrusion excluded patients</li> </ul>	6 Years follow up considering snoring, ESS, mouth dryness, foreign body sensation in the throat	<p>Snoring decreased significantly.</p> <p>No significant change of AHI or ESS.</p>
Friedman et al. <sup>1747</sup>	2008	1b	<ul style="list-style-type: none"> <li>• Randomized, double-blinded, placebo-controlled, clinical trial</li> </ul>	<p>Mild to moderate OSA (study group n=31, placebo group n=31)</p> <ul style="list-style-type: none"> <li>• AHI 5-39/h</li> <li>• BMI &lt;32kg/m<sup>2</sup></li> <li>• soft palate length ≥20mm but &lt;35mm</li> <li>• tonsil size &lt;III</li> </ul>	3 Months follow up of AHI, QOL (SF-36), snoring, ESS	Significant improvement of AHI (from 23.8 to 15.9 in treatment group), QOL, snoring, and ESS.
Nordgård et al. <sup>1750</sup>	2006	4	<ul style="list-style-type: none"> <li>• prospective, non-randomized study</li> </ul>	<p>Mild to moderate OSA (n=25)</p> <ul style="list-style-type: none"> <li>• AHI 10-30/h</li> <li>• BMI ≤30kg/m<sup>2</sup></li> <li>• Soft palate length &gt;25mm</li> <li>• Tonsil size &lt;50% of the airway</li> <li>• No significant nasal stenosis</li> <li>• Bed partner present</li> </ul>	3 Months follow up of AHI, ESS and snoring	Significant reduction of AHI, ESS and snoring.
Walker et al. <sup>1752</sup>	2006	4	<ul style="list-style-type: none"> <li>• prospective, non-</li> </ul>	<p>Mild to moderate OSA (n=53)</p> <ul style="list-style-type: none"> <li>• Palatal contribution to OSA</li> </ul>	3 Months	Significant improvement of AHI, ESS and snoring

			randomized study conducted at 5 clinical sites	<ul style="list-style-type: none"> <li>• AHI 10-30/h</li> <li>• BMI <math>\leq 32\text{kg/m}^2</math></li> <li>• soft palate length can accommodate 18mm implant with no previous surgery</li> <li>• no nasal obstruction or palatal surgery</li> <li>• bed partner</li> </ul>	follow up of AHI, ESS and snoring intensity (VAS), LSAT	
Choi et al. <sup>1756</sup>	2015	4	<ul style="list-style-type: none"> <li>• non-randomized study conducted at 5 clinical sites</li> </ul>	<p>Simple snoring to mild OSA (n=29)</p> <ul style="list-style-type: none"> <li>• AHI &lt;15/h</li> <li>• BMI &lt;25kg/m<sup>2</sup></li> <li>• Tonsil size grade 1 or 2</li> <li>• Palate-tongue position 1 or 2</li> <li>• Suspected retropalatal obstruction</li> <li>• Soft palate length &gt;25mm</li> <li>• tonsil size &lt;III</li> </ul>	3-6 Months follow up of Snoring (VAS), ESS	Significant improvement of snoring and ESS No significant change in AHI, RDI, LSAT or snore loudness. Improvement in AHI for patients with mild OSA.
Friedman et al. <sup>1761</sup>	2006 b	4	<ul style="list-style-type: none"> <li>• Non-randomized, retrospective review</li> </ul>	<p>Snoring and OSA (n=125), Groups: PIT only (n=29), adjunctive nasal procedure (n=37), adjunctive oropharyngeal procedure (n=55), failed previous UPPP (n=4)</p> <ul style="list-style-type: none"> <li>• BMI 19.5-39kg/m<sup>2</sup></li> </ul>	6 Months follow up of Snoring, ESS, AHI and AHI.	No significant improvement in AHI Significant improvement of AHI in combination with nasal airway procedures in mild OSA
Goessler et al. <sup>1748</sup>	2007	4	<ul style="list-style-type: none"> <li>• prospective, non-randomized study</li> </ul>	<p>OSA (n=16)</p> <ul style="list-style-type: none"> <li>• AHI 10-30/h</li> <li>• BMI <math>\leq 30\text{kg/m}^2</math></li> <li>• Soft palate length &gt;25mm</li> <li>• tonsils size &lt;50% of the airway</li> <li>• no previous pharyngeal surgery, nasal or retrolingual obstruction</li> </ul>	3 Months follow up on AHI, Snoring (VAS), ESS	Significant improvement of AHI, snoring and ESS
Choi et al. <sup>1745</sup>	2013	1a	<ul style="list-style-type: none"> <li>• Meta analysis of seven studies including 2 RCTs.</li> </ul>	OSA (total n=363)	3-29 Months of follow up of AHI, ESS, snore sound loudness and extrusion rate	Significant improvement of snoring sound loudness, ESS and AHI Extrusion rate was 9.3%.  AHI change was significant in most studies, pre-treatment AHI for all studies was < 25, post treatment mean AHI was elevated > 10 in most studies (significant mean difference -0.378, % change from 12-50%).

Walker et al. <sup>1754</sup>	2007	4	<ul style="list-style-type: none"> <li>• prospective case series conducted at four clinical sites</li> </ul>	<p>Continuation (Walker et al. 2006) of follow up (n=22/52)</p> <ul style="list-style-type: none"> <li>• Palatal contribution to OSA</li> <li>• AHI 10-30/h</li> <li>• BMI <math>\leq 32\text{kg/m}^2</math></li> <li>• soft palate length can accommodate 18mm implant with no previous surgery</li> <li>• no nasal obstruction or palatal surgery</li> <li>• bed partner available</li> </ul>	15 Months follow up of AHI, ESS and snoring intensity	<p>Patients with a significant decrease in AHI after 90 days (13/22) maintained this decrease, patients without a decrease in AHI after 90 days did not show any improvement. Snoring intensity remained improved in all patients. ESS in patients without AHI decrease returned to baseline level (after 15 months) from initial significant improvement after 90 days Those with AHI decrease remained improved</p>
Nordgård et al. <sup>1753</sup>	2007	4	<ul style="list-style-type: none"> <li>• prospective case series</li> </ul>	<p>Mild to moderate OSA (n=26)</p> <ul style="list-style-type: none"> <li>• AHI 10-30/h</li> <li>• BMI <math>\leq 30\text{kg/m}^2</math></li> <li>• Soft palate length <math>&gt;25\text{mm}</math></li> <li>• tonsils size <math>&lt;50\%</math> of the airway</li> <li>• no significant nasal stenosis and available bed partner</li> </ul>	1 Year follow up on AHI, ESS, snoring intensity and Pain	Significant improvement in AHI ESS and snoring after 3 and 12 Months compared to baseline
Neruntarat <sup>1755</sup>	2011	4	<ul style="list-style-type: none"> <li>• Prospective study</li> </ul>	<p>Mild to moderate OSA (n=92)</p> <ul style="list-style-type: none"> <li>• AHI <math>\leq 30/\text{h}</math></li> <li>• BMI <math>\leq 30\text{kg/m}^2</math></li> <li>• Soft palate length <math>&gt;20\text{mm}</math></li> </ul>	26-32 Months follow up on AHI, ESS, snoring intensity and LSAT	Significant decrease in AHI, ESS, snoring intensity and LSAT
Gillespie et al. <sup>1760</sup>	2011	1b	<ul style="list-style-type: none"> <li>• Randomized, double-blind, placebo-controlled multicenter study in four different</li> </ul>	<p>Moderate to severe OSA with pressure related CPAP-complaints (study group n=26, placebo group n=25)</p> <ul style="list-style-type: none"> <li>• AHI <math>&gt;15/\text{h}</math> prior to CPAP-use</li> <li>• Prescribed CPAP pressure <math>\geq 7\text{ cm H}_2\text{O}</math></li> <li>• Intolerance due to high pressure, mouth leak or mouth dryness</li> <li>• Soft palate length <math>\geq 25\text{mm}</math></li> <li>• No nasal obstruction</li> </ul>	90 days follow up of CPAP pressure after PI, adherence and CPAP-satisfaction	<p>At constant weight no significant reduction of CPAP pressure and no increase in CPAP compliance was detected Only CPAP-satisfaction was significantly better in study group vs. placebo</p>

			referral centers	<ul style="list-style-type: none"> <li>• CPAP-titration at baseline to identify lowest optimal pressure</li> <li>• tonsil size &lt;III</li> </ul>		
Friedman et al. <sup>1746</sup>	2006a	4	<ul style="list-style-type: none"> <li>• prospective, non-randomized study</li> </ul>	Persistence of mild to moderate OSA and snoring after UPPP (n=23) <ul style="list-style-type: none"> <li>• history of UPPP-surgery</li> <li>• AHI 5-40/h</li> <li>• Residual palate ≥20mm</li> </ul> Persistent retropalatal obstruction	6 Months follow up on AHI, snoring levels, ESS, QOL and LSAT	Significant decrease in snoring level and ESS. Improvement of AHI and LSAT

#### IX.D.4.g Palate Suture Suspension

The use of sutures to achieve an antero-apical suspension of the soft palate and lateral stabilization of the pharyngeal walls presents a fairly new surgical technique in treating sleep apnea, which has been developed with the intention of reduced morbidity and increased efficacy. Predecessors such as expansion sphincter pharyngoplasty or UPPP have shown to be effective, nonetheless they present more invasive techniques compared to those using suture suspension.<sup>1762</sup>

To date, there are several similar techniques using suspending sutures: barbed reposition pharyngoplasty<sup>1763</sup>, barbed suspension pharyngoplasty<sup>1764</sup>, the barbed roman blinds technique<sup>1765</sup>, the Alianza technique<sup>1766</sup>, barbed anterior pharyngoplasty<sup>1767</sup>, barbed expansion sphincter pharyngoplasty<sup>1768</sup>, expansion pharyngoplasty by simple suture suspension<sup>1769</sup>, modified barbed soft palatal webbing flap palatopharyngoplasty using barbed sutures<sup>1770</sup>.

The aim behind a suture suspension technique is an anterior-lateral soft palate displacement and stabilization of lateral pharyngeal wall by anchoring the sutures to fibrous and bony holds (i.e, pterygomandibular raphe or hamulus pterygoideus) without needing any fibromuscular resection or relocation. Most techniques use a self-locking bidirectional barbed suture that is inserted in a certain manner into the soft palate and both pillars including the tonsillar fossa.

The target group presents with retropalatal and lateral pharyngeal wall collapse as documented in drug-induced sleep endoscopy. Studies included patients with BMI < 35kg/m<sup>2</sup> or <30kg/m<sup>2</sup> and sleep apnea severity ranging from mild to severe. All studies suggest an effective treatment of OSA patients ranging from mild to severe cases, a statistically significant reduction in endpoints such as AHI, ODI, LSAT, ESS, and reduction of snoring. Some studies suggest the barbed reposition pharyngoplasty to be equally effective as ESP and more effective than UPPP.<sup>1762</sup> In 2019, Vicini et al published results of a randomized controlled trial (RCT) comparing the BRP to a control group (observation) where the surgical BRP group had nasal surgery, tonsillectomy and BRP. The 6-months follow-up showed a significant reduction in AHI and other relevant endpoints in patients that underwent surgery.<sup>1690</sup> Most studies and techniques include simultaneous or prior tonsillectomy and some studies included surgery at other levels.

The post-operative morbidity of patients who underwent suture suspension surgery is reported as low. Common short-term complications were post-operative pain, dysphagia and in some cases suture



extrusion. All papers stated an overall well-performable intervention with minor side-effects.<sup>1701,1771-1773</sup> Further data is needed to evaluate the long-term outcomes.

Unfortunately, the level of evidence of most existing studies is low as, except for the RCT by Vicini et al, most studies were either non-randomized single-arm studies or retrospective studies. Furthermore, the often-performed multi-level surgery in addition to suture suspension prohibits a conclusion about the specific effectiveness of suture suspension techniques.

In summary, suture suspension surgery appears to be an effective approach, when performed on selected patients. Compared to other surgical techniques, such as UPPP or ESP, suture suspension seems less invasive.

### Palate Suture Suspension for Treatment of OSA

Aggregate Grade of Evidence: C (Level 1: 1 study; Level 3: 1 study; Level 4: 9 studies).

Table IX.D.4.g: Evidence on Palate Suture Suspension for OSA

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Askar et al <sup>1774</sup>	2018	4	Single-center, prospective, uncontrolled case series	<ul style="list-style-type: none"> <li>- 29 patients</li> <li>- OSA (AHI&gt;15/h)</li> <li>- Surgical technique: double suspension suture + modified anterior palatoplasty</li> <li>- Tonsillectomy in patients with tonsil grade 2-4 (n=17)</li> <li>- history of tonsillectomy (n=8)</li> <li>- Mean BMI 24.1kg/m<sup>2</sup></li> <li>- Pre-op DISE: retro-palatal collapse</li> </ul>	<ul style="list-style-type: none"> <li>- 10-18 months follow-up</li> <li>- AHI</li> <li>- LSAT</li> <li>- ESS, VAS for snoring</li> <li>- Increase in retropalatal space measured during surgery</li> </ul>	<ul style="list-style-type: none"> <li>- Mean AHI dropped from a mean of <math>_{pre}28.6 \pm 5.5</math> to <math>_{post}8.3 \pm 2.96</math></li> <li>- AHI &lt;10/h was achieved in 98.65% (n=26)</li> <li>- The mean LSAT increased significantly from <math>79.4 \pm 3.5</math> to <math>93.1 \pm 3.1</math></li> <li>- ESS showed significant improvements (<math>_{pre}14.5 \pm 2.4</math> to <math>_{post}3.4 \pm 1</math>)</li> <li>- VAS for snoring significantly decreased from <math>_{pre}7.9 \pm 1.3</math> to <math>_{post}1.9 \pm 1.2</math>)</li> <li>- Retropalatal space widened significantly (<math>p &lt; 0.05</math>) at the end of surgery</li> </ul>
Askar et al <sup>1775</sup>	2018	4	Single-center, prospective single-arm study	<ul style="list-style-type: none"> <li>- 22 patients</li> <li>- OSA (AHI &gt; 5/h)</li> <li>- Surgical technique: double palatal suspension sutures technique</li> <li>- BMI &lt; 30 kg/m<sup>2</sup></li> <li>- Pre-op DISE: retro-palatal obstruction</li> </ul>	<ul style="list-style-type: none"> <li>- 6-months follow-up</li> <li>- AHI, LSAT</li> <li>- ESS</li> <li>- VAS for snoring</li> </ul>	<ul style="list-style-type: none"> <li>- Significant improvement of AHI (<math>_{pre} 29.7 \pm 5.5</math> to <math>_{post} 7.9 \pm 3.7</math> (<math>P &lt; 0.0001</math>), LSAT (<math>_{pre}80.34 \pm 4.42</math> to <math>_{post}90.3 \pm 4.75</math>), ESS (<math>_{pre}12.3 \pm 3.7</math> to <math>_{post}4.6 \pm 1.9</math>)</li> <li>- Snoring disappeared in 86.4% of patients and was reduced in 13.6%</li> <li>- mean inter-pillar distance</li> </ul>

						and the retropalatal distance increased significantly ( $P < 0.0001$ ) after completion of the procedure
Babade mez et al <sup>1691</sup>	2019	4	Single-center retrospective comparative chart review	<ul style="list-style-type: none"> <li>- Mild-moderate OSA</li> <li>- Surgical technique: BRP (n=45), ESP with AP (n=53)</li> <li>- simultaneous tonsillectomy performed</li> </ul>	<ul style="list-style-type: none"> <li>- Mean follow-up 18.8 months</li> <li>- Surgical success rate*</li> <li>- AHI</li> <li>- ESS</li> </ul>	<ul style="list-style-type: none"> <li>- Overall success rate* was 85.7%, with no significant statistical difference between BP and ESPw/AP.</li> <li>- AHI reduction in ESPw/AP from <math>_{pre}28.5/h</math> to <math>_{post}9.1/h</math> (<math>P = 0.000</math>) and in BRP from <math>_{pre}25.9/h</math> to <math>_{post}7.4/h</math> (<math>P = .000</math>)</li> <li>- BP group required less post-operative analgesic treatment</li> </ul>
Babade mez et al <sup>1776</sup>	2019	4	Prospective, non-randomized two-armed study	<ul style="list-style-type: none"> <li>- 34 patients</li> <li>- Mild-moderate OSA</li> <li>- Surgical technique: BRP (n=17) vs. mBRP involving barbed uvula lift (n=17)</li> <li>- All patients received tonsillectomy</li> <li>- Pre-op DISE: retro-palatal obstruction of any type, no hypopharyngeal obstruction</li> <li>- BMI <math>&lt; 35\text{kg/m}^2</math></li> <li>- No nasal obstruction, tonsillar hypertrophy <math>&lt; \text{grade } 2</math></li> </ul>	<ul style="list-style-type: none"> <li>- Mean follow-up 6-9 months</li> <li>- AHI, ESS, Snoring</li> </ul>	<ul style="list-style-type: none"> <li>- 82% and 95% success rate* for BRP and mBRP respectively, with no significant difference between the two procedures (<math>p&gt;0.05</math>)</li> </ul>
Camaroto et al <sup>1762</sup>	2017	4	Retrospective, comparison study	<ul style="list-style-type: none"> <li>- 30 patients</li> <li>- OSA (mean AHI <math>&gt; 30/h</math>)</li> <li>- BRP (n=10) or UPPP (n=10) or ESP (n=10) + TORS with supraglottoplasty (SGP) and temporary tracheostomy, tonsillectomy and septo-turbinoplasty in all patients</li> <li>- BMI <math>&lt; 30 \text{ kg/m}^2</math></li> </ul>	<ul style="list-style-type: none"> <li>- At least 6-months follow-up</li> <li>- AHI</li> <li>- ESS</li> </ul>	<ul style="list-style-type: none"> <li>- All patients received the same multi-level surgical procedure except for the palatal surgery, which was different</li> <li>- surgical success rate in BRP (and ESP) was 90% (50% in UPPP)</li> <li>- AHI reduction in BRP (<math>p = 0.005</math>) and ESP, ESS reduction in all patients (<math>p = 0.008</math>)</li> </ul>
El-Ahl	2016	4	Single-	<ul style="list-style-type: none"> <li>- 24 patients</li> </ul>	<ul style="list-style-type: none"> <li>- 6-months fol-</li> </ul>	<ul style="list-style-type: none"> <li>- Mean AHI dropped signif-</li> </ul>

et al <sup>1769</sup>			center prospective uncontrolled case series	<ul style="list-style-type: none"> <li>- OSA (AHI &lt; 15/h)</li> <li>- Surgical technique: expansion pharyngoplasty by simple suture suspension</li> <li>- No tonsillectomy was performed</li> <li>- Tonsil size grade 0-2</li> <li>- BMI &lt; 30kg/m<sup>2</sup></li> <li>- Pre-op DISE: retro-palatal obstruction of any type, lateral pharyngeal wall collapse, no retroglossal collapse</li> </ul>	<ul style="list-style-type: none"> <li>- low-up</li> <li>- AHI, LSAT, ESS, VAS for snoring</li> </ul>	<ul style="list-style-type: none"> <li>- ically (<math>P &lt; 0.001</math>) from <math>28.6 \pm 4.2</math> preoperatively to <math>8.9 \pm 4.9</math> postoperatively</li> <li>- Mean LSAT level increased significantly from <math>79.25 \pm 4.12</math> to <math>89.29 \pm 5.28</math> (<math>P &lt; 0.001</math>)</li> <li>- Mean ESS decreased from <math>pre\ 11.7 \pm 2.9</math> to <math>post\ 5.1 \pm 2.2</math></li> <li>- VAS for snoring reduced significantly (<math>P &lt; 0.0001</math>). Snoring completely disappeared in 75%.</li> </ul>
Elbassiony et al <sup>1770</sup>	2016	4	Single-center prospective uncontrolled case series	<ul style="list-style-type: none"> <li>- 21 patients</li> <li>- OSA</li> <li>- Surgical technique: Modified barbed soft palatal webbing flap palatopharyngoplasty using barbed sutures</li> <li>- included tonsillectomy where tonsillar collapse was documented in DISE (n=4, 19%)</li> </ul>	<ul style="list-style-type: none"> <li>- 6-months follow-up</li> <li>- AHI, LSAT</li> <li>- VAS for snoring</li> </ul>	<ul style="list-style-type: none"> <li>- 95% surgical success rate*.</li> <li>- Significant reduction in AHI (<math>pre\ 45.7 \pm 2.6</math> to <math>post\ 12.3 \pm 3.9</math> <math>p &lt; 0.005</math>), increase in LSAT (<math>pre\ 74 \pm 4</math> to <math>post\ 89 \pm 2\%</math>)</li> <li>- Only 3 patients had residual lateral wall collapse in post-operative DISE</li> </ul>
Mantovani et al <sup>1765</sup>	2015	4	Pilot longitudinal single-arm study	<ul style="list-style-type: none"> <li>- 32 patients</li> <li>- Severe OSA (AHI &gt; 30/h)</li> <li>- Surgical technique: barbed roman blinds technique</li> <li>- Pre-op DISE: retro-palatal lateral obstruction</li> <li>- All patients had formerly undergone tonsillectomy</li> <li>- BMI &lt; 30kg/m<sup>2</sup>, BMI-variation &lt; 0.2 within follow-up</li> </ul>	<ul style="list-style-type: none"> <li>- Mean follow-up 12 months</li> <li>- Success rate*</li> <li>- AHI</li> <li>- <math>t &lt; 90\% spO_2</math></li> <li>- ESS</li> </ul>	<ul style="list-style-type: none"> <li>- surgical success rate* of 84.4%</li> <li>- significant reduction in AHI (<math>pre\ 36.9 \pm 4.5/h</math> to <math>post\ 13.7 \pm 4.5/h</math> (<math>P &lt; 0.001</math>)), <math>t &lt; 90\%</math> and ESS (<math>P &lt; 0.001</math>)</li> </ul>
Mantovani et al <sup>1766</sup>	2017	4	Single-arm, non-randomized, pilot study	<ul style="list-style-type: none"> <li>- 19 patients</li> <li>- OSA (AHI 5-30/h)</li> <li>- Surgical technique: Alianza technique</li> <li>- DISE: concentric</li> </ul>	<ul style="list-style-type: none"> <li>- 6-months follow-up</li> <li>- AHI, ESS</li> <li>- VAS for snoring</li> </ul>	<ul style="list-style-type: none"> <li>- Significant reduction in AHI (<math>pre\ 22.4 \pm 5</math> vs. <math>post\ 7.4 \pm 9.4</math>, <math>p = 0.002</math>), <math>ESS_{pre}\ 11.3 \pm 5</math> vs. <math>ESS_{post}\ 3.9 \pm 4</math>, <math>p &lt; 0.001</math>)</li> </ul>

				<ul style="list-style-type: none"> <li>pharyngeal collapse at velum</li> <li>- All patients post-tonsillectomy</li> <li>- BMI &lt; 30kg/m<sup>2</sup></li> </ul>		<ul style="list-style-type: none"> <li>- reduction in snoring (pre 9.5 ± 0.7 vs. post 2.1 ± 1.7; p &lt; 0.01)</li> </ul>
Rashwan et al <sup>1690</sup>	2018	3b	Interventional comparative study	<ul style="list-style-type: none"> <li>- 75 patients</li> <li>- Moderate-severe OSA</li> <li>- Pre-op DISE: palatal obstruction with lateral pharyngeal wall collapse</li> <li>- surgical techniques: BRP (n=25), UPPP (n=25), ESP (n=25)</li> <li>- BMI &lt; 35kg/m<sup>2</sup></li> <li>- All patients received tonsillectomy and nasal surgery (turbinoplasty and/or septoplasty)</li> </ul>	<ul style="list-style-type: none"> <li>- 6-months follow-up with PSG</li> <li>- Delta(Δ)-AHI, -ESS, -ODI, -LSAT</li> </ul>	<ul style="list-style-type: none"> <li>- Significant reduction of all end-points in all groups (P &lt; 0.05)</li> <li>- Mean AHI reduction highest in BRP group (: Δ-AHI: BRP -15.76±14.5/h vs. ESP: -10.1±5.3/h vs. UPPP: 6.1±5.5)</li> <li>- Mean ESS reduction highest in BRP group (Δ-ESS: BRP: -5.52±4.1 vs. ESP: -4.84±3.3 vs. UPPP: 1.36±1.9; P &lt; 0.005)</li> <li>- No significant difference in reduction of LSAT between the three groups</li> </ul>
Vicini et al <sup>1763</sup>	2019	1b	single-center prospective randomized two-armed controlled trial	<ul style="list-style-type: none"> <li>- 50 patients (Group A: 25 BRP, Group B: 25 observation)</li> <li>- Diagnosis: moderate-severe OSA (AHI &gt;15/h)</li> <li>- Surgical technique: BRP</li> <li>- All patients received tonsillectomy and nasal surgery</li> <li>- age 18-65 years</li> <li>- BMI &lt; 35kg/m<sup>2</sup></li> <li>- Pre-op DISE: severe circular palatal collapse and severe transversal pharyngeal collapse with none or mild tongue collapse</li> </ul>	<ul style="list-style-type: none"> <li>- 6-months follow-up</li> <li>- AHI, ODI, LSAT</li> <li>- ESS</li> </ul>	<ul style="list-style-type: none"> <li>- Significant reduction of AHI, ODI, LSAT, and ESS (p&lt;0,05) in BRP group.</li> <li>- AHI and ODI in BRP group superior to observation (Δ-AHI BRP: -15.75±14.7 vs. control: -5±13.75, P = 0.01; Δ-ODI BRP: -15.1±17.9 vs control: -2.84±14.55 P = 0.01),</li> <li>- LSAT improvement not significant</li> <li>- ESS reduction not significantly different</li> <li>- No significant changes in control group observed</li> <li>- higher baseline AHI predicts more significant postoperative absolute AHI reduction</li> <li>- Both groups showed no significant change in BMI</li> </ul>

Table 1: \*Surgical success defined as 50% reduction in AHI and AHI < 20 (if not indicated otherwise); DISE: drug induced sleep endoscopy, BRP: barbed reposition pharyngoplasty, mBRP: modified barbed reposition pharyngoplasty, ESP: expansion sphincter pharyngoplasty, AP: anterior palatoplasty, UPPP: uvulo-palato-pharyngoplasty, TORS: transoral robotic tongue base reduction, LSAT: Lowest oxygen saturation

## IX.D.5 Tongue and Hypopharyngeal Surgery

### IX.D.5.a Tongue Base Radiofrequency Ablation

Tongue base radiofrequency (TBRF) was first described by Powell *et al.*<sup>1777</sup> Energy delivered through a radiofrequency or coblation device causes submucosal coagulation and ablation which leads to soft tissue fibrosis. While it was initially proposed that its effect would occur primarily through volumetric tissue reduction, Stuck *et al.*<sup>1778</sup> and Blumen *et al.*<sup>1779</sup> could not find any tongue base volume changes in Magnetic Resonance Imaging scans after TBRF, and these authors suggested that the benefits of TBRF were the result of the scar formation process.<sup>1780</sup>

A systematic review of TBRF outcomes is challenging, due to significant variability of devices, techniques used, presence or absence of procedures performed simultaneously, patient selection criteria, outcomes measured and paucity of data on long term results.

As the available evidence is most commonly focused on multilevel surgery, the assessment of a sole effect of each intervention is challenging. In this review we only selected studies in which individual analysis for TBRF was performed. We excluded papers where other procedures were performed but no individual role of TBRF was assessed, and those with duplicate results. This review included 12 articles, including one systematic review and meta-analysis.<sup>1781</sup>

Three techniques regarding TBRF have been described: transoral through the dorsal tongue, transoral through the ventral aspect of the tongue, and the transcervical approach. The first is the most commonly used technique. With the exception of den Herder *et al.*<sup>1780</sup>, all papers found a positive role for TBRF, despite significant methodological heterogeneity. Two articles suggested a decrease in efficacy over time.<sup>1782,1783</sup>

A metanalysis by Baba *et al.* included three non-randomized, parallel group comparative trials (CPAP, SMILE and lingual suspension), and seven prospective case series.<sup>1781</sup> They found 40% reduction on respiratory disturbance index (RDI) ( $p < 0.0001$ ), statistically significant improvement in lowest oxygen saturation (LSAT) ( $p = 0.002$ ), and improved Epworth sleepiness score ( $p < 0.00001$ ) with short term (< 12 months) follow-up.

It must be noted that none of the included studies had a placebo or non-treated control group though Woodson *et al.*<sup>1784</sup> had a cohort of non-surgical patients under CPAP treatment. Two articles compared UPPP alone and UPPP plus TBRF.<sup>1785,1786</sup> and both found a higher AHI reduction with the addition of TBRF. Friedman *et al.* found that specifically stage III patients (tongue base obstruction) were not significantly improved by UPPP alone (control group) but were significantly improved by UPPP plus TBRF (experimental group).

Two studies compared TBRF with other techniques.<sup>1782,1787</sup> Friedman *et al.* found a statistically significant difference favoring SMILE, in patients with stage III anatomy (tongue base obstruction) and patients with severe OSA.<sup>1787</sup>, however SMILE presented a higher complication rate. Fibbi *et al.* compared TBRF with tongue base suspension and found no difference between the groups.<sup>1782</sup>

There is significant heterogeneity on inclusion criteria among studies, not allowing a pooled analysis. While some articles studied subjects who failed prior surgeries or severe cases,<sup>1779,1784,1788</sup> others include primarily mild or moderate cases<sup>1789</sup>. Some authors used DISE to indicate surgery,<sup>1786</sup> while others only relied only on physical examination. Obesity, another variable assessed differently among selected studies, was a predictor of failure as shown by several authors<sup>1788,1790</sup>.

Woodson *et al.* found that TBRF was useful in mild OSA patients.<sup>1784</sup> This finding was also highlighted by Fibbi *et al.*, who observed 75% success rate after 6 months, and 33% after 2 years, concluding that their high ratio of success was attributed to the sample selection (mild OSA with AHI < 20 and tongue base obstruction Fujita III).<sup>1782</sup> Riley *et al.* found that a lower preoperative AHI and higher LSAT are statistically related to better response.<sup>1788</sup>

Available evidence suggests low complication rates. Major complications include, severe tongue edema, lingual artery lesion, hypoglossal nerve injury and tongue abscess. While Babae *et al.* analysed complications in their meta-analysis, no cumulative data for complications was provided.<sup>1781</sup> It is worth mentioning that Blumen *et al.* performed a transcervical approach with ultrasonography guidance to prevent lingual artery and hypoglossal nerve lesions.<sup>1779</sup>

In summary, the available literature suggests that TBRF has the ability to improve OSA as an adjuvant treatment in well selected patients with tongue base obstruction and without severe OSA. However, there remain questions about the optimal patient selection and the long-term effects.

### Tongue Base Radiofrequency for OSA Treatment

Aggregate Grade of Evidence: C (Level 3: 1 study; Level 4: 11 studies)

**Table IX.D.5.a: Evidence on Tongue Base Radiofrequency for OSA Treatment**

Study	Year	LOE	Study design	Study group(s)	Clinical Endpoints	Conclusions
Babae RY <i>et al.</i> <sup>1781</sup>	2015	3a	Systematic review and meta-analysis	TBRF alone (n: not reported)	RDI, AHI, LSAT, ESS, VAS	RDI 40% reduction (p<0.0001). LSAT RoM=1.05 (p=0.02) ESS reduction RoM= 0.59 (p<0.00001) and VAS snoring RoM=0.48 (p<0.00001)
Fibbi A <i>et al.</i> <sup>1782</sup>	2009	4	Cohort	TBRF (n=13) Lingual suspension (n=13)	Surgical success (AHI >50% decrease, final < 20); AHI, AI, LSAT, Change in ESS and	Success 75% with TBRF at 6 months; 33% at 24 months.  Reduction in AHI after 6 months (14.8 to 4.7) and

					VAS.	24 months (8.7).  ESS and VAS improved at 6 & 24 months.  No sig difference between techniques.
VandenBroek E et al. <sup>1786</sup>	2008	4	Retrospective Cohort	UPPP alone (n=38) UPPP +TBRF (n=37)	Surgical success (>50% decrease and AHI < 20)	42% success in UPPP alone vs. 49% in combined group, no sig difference.
Den Herder C et al. <sup>1780</sup>	2006	4	Quasi-experimental	TBRF pre (n=22) and post treatment (n=10)	Surgical success (>50% decrease AHI < 20 or AI < 10), AHI, ESS, VAS	33% success No significant change in AHI, ESS post procedure.  Improved snoring.
Blumen MB et al. <sup>1779</sup>	2006	4	Quasi-experimental	TBRF before (n=10) and after treatment (n=10)	RDI, AI, HI, LSAT, snoring volume, ESS, tongue volume on MRI	RDI improved (52 to 33.6, p=0.016); AI LSAT, ESS, Snoring VAS improved.  No change in tongue volume on MRI
Riley RW et al. <sup>1788</sup>	2003	4	Quasi-experimental	TBRF before (n=20) and after treatment (n=19)	AHI, LSAT, ESS, VAS (speech and swallow)	Significant AHI improvement (35.1 to 15.1); LSAT (82% to 86.3%); ESS (12.4 to 7.3); No difference in VAS for speech and swallow.
Friedman M et al. <sup>1785</sup>	2003	4	Retrospective cohort	UPPP alone (n=134)  UPPP + TBRF (n=143)	Surgical success (>50% decline to RDI < 15)	UPPP alone success rates by Friedman Stage I: 80.6%; Stage II: 37.9%; Stage III: 8.1%;  UPPP+TBRF

						Stage II: 55.1% Stage III: 33% Significant difference
Stuck BA et al. <sup>1789</sup>	2002	4	Quasi-experimental	TBRF before (n=20) and after treatment (n=18)	Success >50% decline to RDI < 15; RDI, mean O2 sat, ESS, VAS for snoring	Success in 33%; Responders 55% Improved ESS and VAS for snoring (significant).  No difference in RDI, mean O2 sat.
Li KK et al. <sup>1783</sup>	2002	4	Quasi-experimental	TBRF before (n=18) and after treatment (n=16)	RDI, AI, HI, LSAT, ESS, SF-36 in short and long term	Short term: sig improvements in RDI, AI, LSAT  Long term: Improved RDI, AI, LSAT, ESS, VAS snoring, and SF-36 scores.
Woodson BT et al. <sup>1784</sup>	2001	4	Quasi-experimental	TBRF before (n=73) and after treatment (n=56)	Success >50% decline AHI < 20, AHI, AI, LSAT, SF36, SNORE-25, ESS, FOSQ	Success: 20% Sig improvements in AHI, AI, ESS, FOSQ, VAS Snoring.
Powell NB et al. <sup>1777</sup>	1999	4	Quasi-experimental	TBRF before (n=18) and after treatment (n=18)	RDI, AI, HI, LSAT; Tongue volume on MRI, SF-36, ESS	Sig improvement in RDI, AI, LSAT, ESS; 40% cure rate; Reduced tongue volume.

#### IX.D.5.b Genioglossus Advancement

In 1986, Riley et al. first described the inferior sagittal osteotomy of the mandible with hyoid myotomy and genioglossus muscle advancement (GA) for the treatment of Obstructive Sleep Apnea (OSA).<sup>1791</sup> The objective for this procedure was to stabilize the hypopharyngeal airway by moving the genioglossus muscle forward, reducing its collapse and subsequently increasing the pharyngeal airway during sleep. Since the initial description, the procedure has undergone several modifications.

Genioglossus advancement with or without hyoid surgery (HS) was designed to increase the retrolingual space.<sup>1633</sup> Because GA is rarely performed in isolation and more commonly performed in conjunction



with other surgeries to address different levels of airway collapse, there is limited evidence evaluating the sole effect of GA. There can be significant heterogeneity in surgical techniques, thereby limiting a systematic analysis. Several osteotomy designs have been used to advance the genioglossus musculature, including standard genioplasty, inferior sagittal osteotomy, circular genioplasty, mortised genioplasty or genial bone advance trephine system. Variations in osteotomies may impact nearby muscles including the geniohyoid, digastric, and/or mylohyoid to enhance the advancement of the upper airway. In this literature review, studies in which individual analysis for GA with or without hyoid surgery or tongue base reduction were selected.

Eight papers suggest a positive impact of GA on OSA outcomes; however, evidence for genioplasty and genioglossus advancement is limited by heterogeneity in patient selection and surgical technique.<sup>1792</sup> A case series by Song et al. evaluated the individual role of GA and identified a mean AHI reduction from 37.6 (24.2) to 20.4 (15.1) (41.7% reduction).<sup>1793</sup> After GA with HS, mean AHI reduced from 34.5 (22.1) to 15.3 (17.6) (55.7% reduction).<sup>1793</sup>

One of the inherent limitations of studying GA outcomes is variation in patient selection, and available data on clinical characteristics and candidacy for surgery is limited. For example, Chen et al. selected subjects who declined CPAP<sup>1794</sup> as compared to Wootten et al. who selected pediatric subjects who failed adenotonsillectomy.<sup>1795</sup> Other authors had stricter criteria and indicated GA only after cephalometry,<sup>1791,1796,1797</sup> or DISE<sup>1798</sup>.

Despite the absence of clear practice guidelines, several predictive factors have been described. Riley et al. suggested that patients with normal skeletal development are the best candidates for GA; however, patients with mandibular deficiency can be candidates<sup>1799</sup>. Troell et al. suggested a positive correlation between the length of advancement and AHI improvement.<sup>1800</sup> Kezirian et al. found BMI and AHI to be predictors of outcome.<sup>1801</sup> Consequently, Foltán et al. excluded patients with an BMI over 30.<sup>1802</sup> Vilaseca et al. observed that AHI severity predicted outcomes, and best results were seen in patients with mild OSA.<sup>1797</sup>

Finally, another important factor is the difference in the follow-up periods, for surgical benefit may wane with time. There is significant heterogeneity among selected papers, varying from 3<sup>1791</sup> to 12 months<sup>1794</sup>. There is no long-term follow-up data for GA.

While limited, the available data suggests that GA surgery can have a positive impact on AHI; however, there is significant heterogeneity in patient selection criteria, use of simultaneous procedures, operative techniques and length of follow-up.

### Genioglossus Advancement for OSA Treatment

Aggregate Grade of Evidence: C (Level 2a: 1 study; Level 4: 6 studies).

Table IX.D.5.b: Evidence on Genioglossus Advancement for OSA

Study	Year	LOE	Study design	Study Groups	Clinical endpoint	Conclusion
Song <sup>1803</sup>	2016	2a	Systematic Review and Meta-Analysis	1. GA (n=24) 2. GA-HS (n=50)	1. AHI 2. LSAT	1. GA: 45.7% AHI reduction, (P<0.005). No significant LSAT improvement.

						2. GA-HS: 55.7% AHI reduction, (P < 0.001). LSAT improved from 80% to 88%, (P<0.002).
Kuscu <sup>1804</sup>	2015	4	Case Series	1. GA (n=17)	AHI, ESS, minimum and mean O2 saturation variation.	53% success rate. Statistically significant differences in AHI, mean SpO2 and ESS score.
Chen <sup>1794</sup>	2014	4	Nonrandomized prospective cohort study	1. UPPP (n=27) 2. UPPP + GA (n=24) 3. UPPP +TBA (n=26)	Sleep Stage, AHI, LSAT, CT90	All significantly improve S3 sleep, mean AHI, LSAT, and CT90 scores. No statistical comparison made.
Foltan <sup>1802</sup>	2007	4	Case Series	1. GA (n=31)	ESS, RDI, ODI, duration of the desaturation, basal O2 saturation, and average desaturation variation.	74% success rate. Improved ESS, RDI, ODI (p<0.01)
Richard <sup>1798</sup>	2006	4	Case-Control	1. Multilevel surgery with GA (n=14) 2. Multilevel surgery without GA (n=8)	1. AHI 2. ODI 3. ESS	No significant difference outcomes between groups.
Riley <sup>1796</sup>	1993	4	Case Series	1. GA-HS (n=6) 2. GA-HS + UPPP (n=233) 3. UPPP (n=10)	Success rate	1. 66% success 2. 60% success 3. 80% success No statistical comparison performed.

Riley <sup>1791</sup>	198 6	4	Case Series	1- GA-HS (n=5)	1. AHI, RDI, success	1. 60% success 2. AHI decreased for all patients 3. RDI decreased for all patients by 46- 85%
-----------------------	----------	---	-------------	-------------------	-------------------------	--

Legend: AHI (apnea-hypopnea index). CT90 (percentage of time with saturation below 90%). ESS (Epworth sleepiness scale). GA (genioglossus advancement). HS (hyoid surgery). LSAT (lowest oxygen saturation). ODI (oxygen desaturation index). RDI (respiratory disturbance index). UPPP (uvulopalatopharyngoplasty).

#### IX.D.5.c Tongue Suture Suspension

Surgical intervention for obstructive sleep apnea must target the area of collapse to improve outcomes<sup>1805,1806</sup>. Evidence found that those with hypopharyngeal or tongue base collapse did not respond to palatal surgery alone and had poorer outcomes with success rates as low as 5%<sup>1633,1807</sup>. In 2006, approximately 19% of sleep surgery was performed to target the hypopharynx including tongue base<sup>1808</sup>.

Tongue suture suspension has been developed to increase the anterior to posterior space of the hypopharynx with minimal morbidity and recovery time. The surgery involves placing a bone anchored screw into the lingual cortex of the mandibular symphysis, placing an anchoring nonabsorbable suture through the base of the tongue and securing it to the screw. Initially, a technique was utilized which placed a screw directly through the oral mucosa along the lingual surface of the mandible. This technique allowed for a minimally invasive, reversible intervention. Modifications have since been made involving a submental cutaneous approach, positioning a suspension suture in the mandibular symphysis without the use of a screw with successful outcomes<sup>1809</sup>. For the purposes of this review, surgical success, unless otherwise specified, is defined by Sher's criteria as 1) a 50% decrease in Respiratory Disturbances Index (RDI) or Apnea-Hypopnea Index (AHI) and 2) RDI or AHI <20<sup>1633</sup>.

The largest systematic review to date<sup>1810</sup> estimated surgical success of isolated tongue suspension to be 36.6%, ranging from 0-87%<sup>1811-1813</sup>. However, it is important to note that tongue suspension is uncommonly performed as an isolated surgery and is more often performed in combination with or following palate surgery, and therefore, success rate estimations quoted in the literature more often reflect multilevel surgery. When combined with uvulopalatopharyngoplasty, tongue suspension success rates increased to 62.3%, ranging from 40-81%<sup>1814,1815</sup>.

The main challenge with tongue suspension surgery is titrating the tension on the tongue to optimize the anterior to posterior diameter of the hypopharynx without causing discomfort or tissue strangulation. Overall complications from this procedure are low at about 8%<sup>1810</sup>, including sialadenitis, pain, and infection. There were reports of mandibular fractures with early use of bone anchored screws, however, modifications using adapted screws<sup>1811</sup> or a no-screw technique<sup>1809</sup> have not reported fracture complications. There has been concern regarding longevity of surgical outcomes due to risk of suture migration given that most of the studies published have limited follow-up between 2 months and 2 years.

Success rates vary based on the patient selection criteria. Across studies, surgical success for isolated tongue suture suspension ranged from 21-75% when average BMI of the selected sample was less than 30, but trended towards 30-32% when average BMI exceeded 30<sup>1810</sup>. When looking at the subjective quality of life outcomes after tongue suspension, one small study of 23 patients found no significant change in subjective sleepiness or quality of life two months after surgery<sup>1813</sup>. One review found significantly higher success rates in symptom improvement; however, the study included shorter postoperative follow-up periods from 3-12 months<sup>1816</sup>.

Overall, previous systematic reviews<sup>1810,1816</sup> have supported a grade C recommendation for tongue suspension. The wide variation in success rates across studies illustrates the importance of careful patient selection.

### Tongue Suture Suspension for OSA Treatment

Aggregate Grade of Evidence: C (Level 1b: 1 study; Level 2a: 3 studies; Level 2b: 1 study; Level 4: 1 study).

Table IX.D.5.c: Evidence for Tongue Suture Suspension for OSA

Study	Year	LOE 1-5	Study Design	Study Groups	Outcome	Conclusion
Handler <sup>1</sup> 810	2014	2a	Systematic Review and Meta-analysis	1. TS (6 studies, n=82) 2. TS + UPPP (8 studies, n=167)	1. AHI	TS: Mean Preop AHI: 32, Postop: 19, 41% AHI reduction, 36.6% success <sup>(a)</sup> TS + UPPP: Mean Preop AHI: 44, Postop: 17, 62% AHI reduction, 62.3% success.
Kezirian <sup>1</sup> 801	2006	2a	Systematic Review	TS (6 studies, n=77)	1. AHI 2. ESS	1. Significant change in AHI. Mean preop AHI: 33-45, postop: 17-24. 20-57% success <sup>(a)</sup> 2. 3/6 studies reported sig. improved ESS.
Bostanci <sup>1</sup> 1816	2016	2a	Systematic review	1. TS (7 studies, n=113) 2. TS + UPPP (10 studies, n=300)	1. AHI 2. ESS	TS: Significant change in mean AHI preop: 18-45, postop: 5-28. 48% success <sup>(b)</sup> (11-77%). Significant decrease in ESS. TS+UPPP: Sig change in mean AHI preop: 29-53, postop: 9-24. 70% success <sup>(b)</sup> (20-89%).

						Significant decrease in ESS.
Woodso n <sup>1817</sup>	2010	2b	Prospective case series	TS for moderate to severe OSA (n=42)	1. AHI, ESS, FOSQ,	1. Significant change in mean AHI preop: 35, postop: 27 2. Sig. change in ESS preop 12, postop: 8. 3. Sig change in FOSQ preop: 16, postop:18.
Tsou <sup>1818</sup>	2018	4	Prospective case series	Patients with large tongues, small tonsils who underwent UPPP and TS (n=36)	1. AHI 2. REM sleep 3. Sleep efficiency	1. Significant change in mean AHI preop: 25, postop: 18. 66% success <sup>(a)</sup> 2. No change in ESS. 3. Increased REM and sleep efficiency in success group.
Thomas <sup>1</sup> 815	2003	1b	Randomized trial	UPPP with 1. TA (n=9) or 2. GA (n=8)	1. AHI 2. ESS	Group 1. Significant change in mean ESS preop: 12, postop: 4. 57% (4/7) success <sup>(a)</sup>  Group 2. Significant improvement in ESS preop: 13, Postop: 5. 50% (2/4) success <sup>(a)</sup>

<sup>(a)</sup> Success based on Sher's criteria = reduction in AHI  $\geq$  50% with final AHI < 20/h;<sup>(b)</sup> Success not defined; AHI = Apnea Hypopnea Index; ESS = Epworth sleepiness scale; FOSQ = Functional Outcomes of Sleep Questionnaire; GA = genioglossus advancement, hyoid myotomy; OSA = Obstructive Sleep Apnea; TS = tongue suspension; UPPP = uvulopalatopharyngoplasty

#### IX.D.5.d Hyoid Suspension

In 1996, Sher and colleagues revealed that overall surgical success of uvulopalatopharyngoplasty decreased from 52% of those with retropalatal collapse, to 5% for those with mainly hypopharyngeal collapse<sup>1633</sup>. Consequently, it became clear that the field of sleep surgery required additional surgical interventions to try and address hypopharyngeal obstruction. One technique included anterior repositioning of the hyoid to increase the anteroposterior dimension of the hypopharynx and subsequently reduce tongue base obstruction<sup>1819</sup>. Hyoid suspension or hyoidthyroidpexy can be performed alone or in combination with other surgeries including genioglossus advancement or maxillomandibular ostomy to target hypopharyngeal obstruction.

Hyoid suspension was first described in 1984, at which time, the hyoid bone was isolated from the strap musculature attachments and suspended to the inferior border of the mandible using fascia lata<sup>1820</sup>. This

technique was then modified to isolate the hyoid from the suprahyoid musculature and suspend the center of hyoid arch anteroinferiorly to the thyroid lamina, which was found to have less morbidity<sup>1821</sup>.

In the largest review of isolated hyoid myotomy and suspension to date, AHI improved by 38% (range of 7 to 83%) for a mean AHI reduction from 37 to 23<sup>1803</sup>. In this study, three of the four studies evaluating subjective quality of life found modest improvement in sleepiness, as measured by the Epworth Sleepiness Scale (ESS). Another study found that surgical success, as defined by Sher's criteria<sup>1633</sup>, ranged from 17-87% across studies evaluating isolated hyoid suspension<sup>1550,1797,1801,1819,1822</sup>. For the studies in which the sample population's average BMI fell below 30, success rates ranged from 52-78%<sup>1550,1797,1819</sup>; however, success rates decreased to 17% when the population's BMI was above 30<sup>1822</sup>, illustrating the impact of careful patient selection on surgical success rates.

Given concern for immediate obstruction upon induction and extubation, hyoid myotomy and suspension under local anesthesia was developed. One study of 32 patients undergoing hyoid suspension and uvulopalatal flap under local anesthesia found a 78% success rate by decreasing RDI by 50% with postoperative RDI < 20<sup>1550</sup>. Symptomatically, ESS scores decreased from an average of 14 to 8. Complications included mild intraoperative pain, transient dysphagia with aspiration, seroma, and infection. However, the higher success rate may have been due to careful patient selection for surgery under local anesthesia given the patient sample had lower average BMI as compared to other studies.

In practice, it is common to perform multilevel surgery as isolated hypopharyngeal obstruction is rare in OSA. Several studies have shown significantly higher success rates when combined with palatal surgery<sup>1669,1801,1819</sup>. One study found that surgical success of hyoid suspension increased from 22% to 78% with concomitant tonsillectomy<sup>1669</sup>. Similarly, ESS decreased by 45% with concomitant tonsillectomy as compared to 27% without.

There has yet to be a randomized control trial evaluating efficacy of hyoid suspension as an isolated procedure or as part of a multilevel surgery. There is significant heterogeneity across studies due to large variation in patient inclusion criteria, surgical interventions, duration of follow-up and outcome measures. Consequently, there are no published meta-analyses evaluating hyoid suspension outcomes.

#### Hyoid Suspension for Treatment of OSA

Aggregate Grade of Evidence: C (Level 2a: 3 studies; Level 2b: 1 study; Level 4: 1 study).

**Table IX.D.5.d: Evidence on Hyoid Suspension for OSA**

Study	Year	LOE (1A-5)	Study Design	Study Groups	Clinical Endpoint	Conclusion
Kezirian <sup>1801</sup>	2006	2a	Systematic Review of retrospective studies	1. HS (4 studies, n=101) 2. HS + GA and palate surgery (7 studies,	AHI EDS	1. Preop AHI: 32-48, Postop: 15-37. Sig decrease in 2/4 studies. 17-78% success. EDS with sig decrease in ¾

				n=328)		<p>studies.</p> <p>2. Preop AHI: 27-71, Postop: 10-57. Sig decrease in 2/7 studies.</p> <p>18-77% success.</p> <p>EDS with sig decrease in ¾ studies.</p>
Verse <sup>1669</sup>	2015	2a	Prospective controlled clinical trial	<p>UPPP with</p> <p>1. Lingual tonsillectomy (n=58)</p> <p>2. HS+RFA (n=50)</p>	AHI	<p>1. Mean AHI preop: 35, AHI postop: 17, 59% success. ESS decreased from 10 to 6, (p&lt;0.001).</p> <p>2. Mean AHI preop: 50, AHI postop: 29, 54% success. ESS decreased from 12 to 8, (p&lt;0.001)</p> <p>No significant difference between groups.</p>
Verse <sup>1823</sup>	2006	2b	Prospective cohort study	<p>Multilevel surgery</p> <p>1. With HS (n=23)</p> <p>2. Without HS (n=12)</p>	AHI ESS	<p>1. Mean preop AHI: 39, postop: 21, (p&lt;0.001). ESS decreased from 9 to 7, (p&lt;0.05).</p> <p>2. No significant decrease in AHI. ESS showed decrease from 9 to 4, (p&lt;0.05).</p>
Song <sup>1803</sup>	2016	2a	Systematic review and metaanalysis	Isolated HS (9 studies, n=101)	AHI ESS	<p>Mean AHI reduced 38% from 37 to 23 (p&lt;0.001). 7-83% reduction in AHI</p> <p>Mean ESS decrease from 10 to 3 (p&lt;0.003).</p>
Askar <sup>1824</sup>	2019	4	Case series	DISE confirmed hypopharynge	AHI	Mean AHI decreased from 48 to 12, (p<0.001).

				al collapse (n=21)		
--	--	--	--	-----------------------	--	--

Success based on Sher's criteria = reduction in AHI  $\geq$  50% with final AHI  $<$  20/h; AHI: apnea hypopnea index; DISE = drug-induced sleep endoscopy; EDS = Excessive daytime sleepiness; ESS = Epworth sleepiness scale; HS = hyoid suspension; RFA = radiofrequency ablation; Sig = significant

#### IX.D.5.e Lingual Tonsillectomy

It is important for the practitioner to perform an assessment of the potential for lingual tonsillar hypertrophy in retroglossal airway obstruction. This may be accomplished by indirect examination with a flexible laryngoscope, cross sectional imaging with either CT or MRI, or drug-induced sleep endoscopy. The practitioner may be guided by a grading system for lingual tonsillar hypertrophy such as suggested by Friedman et al.<sup>555</sup> Patients with Friedman Grade 3 or 4 would be more likely to obstruct. A limitation to the Friedman grading system is that one cannot assess depth of tonsillar tissue, or, alternatively, the component of tongue base enlargement and retroglossal airway compromise that is rather due to macroglossia. Often lingual tonsillectomy in conjunction with palate surgery as a form of multi-level airway surgery.

Many tools for performing lingual tonsillectomy have been reported, including: CO2 laser, electrocautery, harmonic scalpel, coblation, radiofrequency ablation, and a microdebrider. There are several methods of visualizing the base of tongue and lingual tonsils including direct visualization with a laryngoscope or indirect approach with an angled endoscope, operating microscope, or more recently, transoral robotic surgery (TORS) with a DaVinci robot (Intuitive Surgical; Sunnyvale, CA). The robotic approach offers superior visualization, instrument access, and more precise tissue resection which can result in larger volumes of tissue removal.<sup>1825</sup> Friedman et al found TORS to be superior to radiofrequency ablation of the tongue base and submucosal minimally invasive lingual incision in terms of AHI reduction and surgical success rates.<sup>1826</sup> Coblation and TORS appear to have similar success rates, though no prospective, randomized trial has been performed to date. There is a suggestion in the literature that coblation is less painful than electrocautery, but no prospective, randomized trial has been performed to assess this.<sup>1827</sup>

When base of tongue obstruction from lingual tonsils is seen, evidence suggests that there is an additional benefit to lingual tonsillectomy over palate-level surgery alone<sup>1828,1829</sup>. Success rates (traditionally defined as a reduction of AHI  $>$ 50% and a postoperative AHI  $<$ 20) across multiple studies are in the range of 66.4 to 68.4% versus 40.7% for UPPP alone. This is also true for other measures of success, such as a lower Epworth Sleepiness Scale (reduction of 5.4 -7.1 points) and improvement in oxygen saturation nadir (increase of 5.1-5.4%). Complications of lingual tonsillectomy are rare, but include bleeding, dysphagia, globus sensation, dysgeusia, tongue numbness and soreness, and scarring.<sup>1830</sup> There is a body of evidence that suggests that outcomes after sleep surgery, including lingual tonsillectomy, are better with BMI  $<$ 30, pre-operative AHI  $<$ 60, and absence of lateral velopharyngeal wall collapse.<sup>1831</sup>

It should be emphasized that there is no clear phenotype for successful base of tongue surgery, including patients with lingual tonsillar hypertrophy. The studies examined in these systematic reviews have much heterogeneity, both in patient evaluation, and in surgical technique. As there are no randomized controlled trials for this surgery, a strong recommendation cannot be given. However, lingual tonsillectomy can be recommended with a preponderance of benefit over harm for adult OSA



patients with lingual tonsil hypertrophy (Friedman Grade 3 or 4). The individual practitioner must weigh the considerations of anatomy, severity of OSA, BMI, surgical training and familiarity with available surgical equipment when deciding whether to proceed with lingual tonsillectomy.

### Lingual Tonsillectomy for Treatment of OSA

**Aggregate Quality of Evidence:** B (level 2a: 2 studies).

**Benefit:** Lingual tonsillectomy results in reduction of AHI, an increase in O<sub>2</sub> saturation nadir and improved sleepiness

**Harm:** Potential complications of surgery include: bleeding, dysphagia and globus sensation, dysgeusia, tongue numbness, pain, and pharyngeal scarring.

**Cost:** Moderate to high costs associated with surgery and post-operative healing time (typically 2-3 weeks of time off from work).

**Benefits-Harm Assessment:** Balance of benefit and harm.

**Value Judgments:** The addition of lingual tonsillectomy can provide additional benefit to palate-level surgery for select OSA patients with multi-level obstruction involving the tongue base. Patients must have clear evidence of lingual tonsil hypertrophy and associated obstruction at the tongue base. This may be assessed by indirect exam, cross-sectional imaging or drug-induced sleep endoscopy.

**Recommendation Level:** Option.

**Intervention:** Lingual tonsillectomy is an option for properly selected OSA patients. Specifically lingual tonsillectomy can be considered when lingual tonsillar hypertrophy causes a component of upper airway obstruction in OSA patients who cannot use CPAP

**Table IX.D.5.e Evidence on Lingual Tonsillectomy for OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Miller et al <sup>1828</sup>	2017	2a	SR and meta-analysis	Adult patients with OSA (n=353)	1. AHI 2. Epworth Sleepiness Scale 3. O <sub>2</sub> nadir 4. Snoring visual analogue scale 5. Surgical success rate (AHI reduction >50% and to <20 events/hr) 6. Cure rate (AHI <5)	TORS BOT reduction decreases AHI (44.3±22.4 to 17.8±16.5, p<0.01) and symptoms of sleepiness (ESS:12.9±5.4 to 5.8± 37, p<0.01) and is considered successful in a majority (68.4%) of cases
Samutsakorn et al <sup>1829</sup>	2017	2a	SR and meta-analysis	Adult patients with OSA with multilevel obstruction (n=107)	1. AHI 2. O <sub>2</sub> nadir 3. Epworth Sleepiness Scale	Lingual tonsillectomy with palatal surgery reduces AHI by 18.5 events/hr (p=0.006), increases O <sub>2</sub> nadir

						(mean increase: 5.3, p=0.05), and reduces daytime sleepiness (mean reduction: 5.4, p=0.001) in select patients with OSA.
--	--	--	--	--	--	--

#### IX.D.5.f Epiglottis Surgery

The role of the epiglottis in adult Obstructive Sleep Apnea (OSA) has been studied comparatively little in the adult arena. With the increasing prevalence of drug-induced sleep endoscopy (DISE), sleep surgeons have come to recognize that epiglottic collapse can play a role in airway obstruction. However, data that is available is conflicting. One early study by Catalfumo et al showed a 12% incidence of epiglottic collapse during awake endoscopy.<sup>1832</sup> A systemic review by Torre et al, found a much broader potential range of epiglottic collapse in OSA, ranging from 15% to 73.5%.<sup>1833</sup> A more recent study by Vonk et al showed that epiglottic collapse noted on DISE may be subject to body position. In 324 patients, a floppy epiglottis was noted in 18.5%, but when rotated to the lateral head or trunk position, only one patient had evidence of obstruction.<sup>1834</sup>

Whether or not identification of epiglottic collapse on DISE is relevant is also of debate. Kwon et al found epiglottic obstruction during DISE in 43.7% of patients undergoing multilevel surgery. No epiglottic intervention was performed. There was no difference in success rates in those that had epiglottic obstruction (44.4%) and those that did not (40.7%).<sup>1835</sup> Primary epiglottic obstruction may be a reason for CPAP intolerance. Dedhia et al found that 15% of adult patients who were CPAP failures had DISE findings of primary epiglottic obstruction.<sup>1836</sup> It is prudent for the DISE surgeon to determine whether epiglottic collapse is from a posterior displacement of the epiglottis due to concurrent collapse of the tongue base or whether epiglottic collapse occurs in isolation. This may help guide surgical decision-making.

A variety of epiglottic procedures have been described including epiglottoplasty<sup>1837</sup>, partial epiglottectomy<sup>1838</sup>, and epiglottopexy<sup>1839</sup>. Golz et al<sup>1838</sup> used laser partial epiglottidectomy alone as a treatment for OSA in 27 adult patients with epiglottic-malacia, and reported a significant reduction of RDI from 45 +/- 14.6 to 14 +/- 5.1 events/hour, and an improvement in oxygen saturation nadir from 66% to 95%. These procedures are typically done in conjunction with base of tongue surgery and/or palatal surgery, making it difficult to assess the contribution from the epiglottis to a patient's outcome.<sup>1840,1841</sup> While there is no clear guidance from the adult literature as to when to include the epiglottis in surgical planning, there is clear recognition amongst sleep surgeons that the epiglottis has a role to play in OSA. Surgical procedures to ameliorate that component are well described in the literature and should be considered in surgical planning.

#### IX.D.6 Maxillary and Mandibular Surgery

##### IX.D.6.a Maxillary Expansion

Maxillary expansion as a treatment for obstructive sleep apnea (OSA) has mostly been studied in the pediatric population with only a few studies in adults. It is an orthopedic modality used by orthodontists to expand the palate by laterally forcing apart the two halves of the maxillary bone. During this process,

the intermaxillary suture is stretched and an osteogenic process ensues. By activating an expansion screw, Rapid Maxillary Expansion (RME) has the effect of both widening the bony alveolar housing for teeth and increasing the maxillary dental arch length. It can be used to correct dental malocclusions, including posterior crossbites, dental crowding, and transversely deficient maxillary arches. Etiology of transversely deficient maxillae include genetic predisposition, parafunctional oral habits, and inadequate labial/buccal force applied by the tongue during craniofacial development. This last etiology is often the result of increased nasal resistance, leading to mouth breathing, due to an inferior position of the tongue<sup>1842</sup>. Craniofacial anomalies that are common in patients with OSA include mandibular deficiency, narrowed posterior airway space, steep mandibular plane angle, and long anterior facial height<sup>233,1843</sup>. Benefits of maxillary expansion include increased nasal cavity volume, improved ability to breathe through the nose<sup>1844-1846</sup>, and increased width of the palate resulting in enhanced oral cavity volume<sup>1847</sup>. This allows the tongue to posture appropriately (antero-superiorly) at rest and while swallowing. An additional benefit of maxillary expansion is the increased tension of the palatal tissues, reducing laxity and tissue collapse in the oropharynx<sup>1848,1849</sup>. RME is a legitimate and effective in the treatment of OSA, with improvements/ reductions in the apnea/ hypopnea index, or AHI<sup>1850-1854</sup>.

### Technique

Micro-Implant Rapid Palatal Expander (MARPE) describes an appliance which employs dental micro-implants to engage the maxillary bone for more skeletal expansion than dental tipping. A MARPE allows an orthodontist to apply transverse forces directly to the skeleton through the use of micro-implants which engage both halves of the maxilla. While MARPE design, case selection, and protocol is essential to success, it allows the clinician to expand the maxillae in much older patients. Skeletally borne expanders allow for a more translational expansion while reducing bone bending and buccal tooth tipping<sup>1855</sup>. When buttressing forces of the maxillary sutures are too strong to be overcome by RME alone, surgical interventions can guarantee successful expansion. These adjunctive procedures are known as SARPE (Surgically Assisted Rapid Palatal Expansion) and DOME (Distraction Osteogenesis Maxillary Expansion). They involve surgical corticotomies and with initial activation of the expander intraoperatively to confirm intermaxillary separation.<sup>1856</sup> Further activation of the expander is delayed for a short latency period (approximately 1 week), which allows a healing callous to form in the suture. A callous has been shown to readily ossify, so expansion (0.25-1mm a day) is then resumed after the latency period is complete<sup>1857</sup>.

In addition to the craniofacial abnormalities mentioned previously, children with OSA often exhibit daytime sleepiness, enuresis, morning headaches, and parasomnias.<sup>1853</sup> Patients with OSA and maxillary constriction are the best candidates for RME<sup>1858,1859</sup>. RME was shown up to result in a 70% reduction in AHI in children, and in 95% reduction in AHI when performed in addition to adenotonsillectomy (T&A) or when tonsils are not hypertrophied. Children with small or surgically removed tonsils benefit more from expansion than do those with large tonsils that undergo RME without T&A<sup>1850</sup>.

### Maxillary Expansion for OSA

#### Aggregate Grade of Evidence:

Adult OSA: D (level 3: 1 study)

Pediatric OSA: C (level 2: 3 studies; level 3: 2 studies).

## IX.D.6.a Summary Table for Maxillary Expansion for OSA

Study	Year	LOE	Study Design	Study Group(s)	Clinical Endpoints	Conclusions
<b>Adults with OSA</b>						
Vinha, P. P., Eckeli, A. L., Faria, A. C et al. <sup>1854</sup>	2016	3a	Case series	16 adults with maxillary transverse deficiency and OSA	AHI reduction of 56.2%; RDI reduction of 55%; ESS improvement; reduced desaturation and microarousals	SARME promotes an improvement in OSA symptoms, decreases the rates of respiratory disturbances, microarousal, and desaturation, and reduces daytime sleepiness.
Yoon, A., Guilleminault, C., Zaghi, S. et al, <sup>1856</sup>	2019	3a	Retrospective cohort study	75 adult patients with OSA and narrow maxilla/nasal floor	Reduction of AHI from 17 to 8	DOME treatment reduced the severity of OSA, refractory nasal obstruction, daytime somnolence, and increased the percentage of REM sleep
<b>Pediatric Patients with OSA</b>						
Camacho, M., Chang, E. T., Song, S. A. et al, <sup>1850</sup>	2017	2a	Systematic review and Meta-analysis	314 children with transverse maxillary deficiency and OSA	AHI decrease of 70%; Cure rate (AHI <1/hr.) for 90 patients was 26%; Improved LSAT; More improvement in children after T&A or small tonsils	Improvement in AHI and lowest oxygen saturation has consistently been seen in children undergoing RME.
Machado-Junior, A. J., Zancanella, E., & Crespo, A. <sup>1852</sup>	2016	2a	Systematic review and Meta-analysis	215 Children 0-12 y/o with OSA	Mean change in AHI after follow up was -6.9	RME is an effective treatment for OSA
Vale, F., Albergaria, M., Carrilho, E, et al. <sup>1853</sup>	2017	2a	Systematic review and Meta-analysis	Children younger than 18 years old with OSA that	Statistically significant reduction in AHI after RME	RME reduced AHI in children with OSA, making RME therapy an appropriate alternative treatment option for these

			s	underwent RME		patients
Cistulli, P. A., Palmisano, R. G., & Poole, MD. <sup>1851</sup>	1998	3a	Case study	10 young adults with mild to moderate OSA and maxillary constriction	90% of participants had improved snoring and hypersomnolence. Reduction in AHI from 19 to 7	RME may be a useful treatment alternative for selected adults with OSA
Quo, S. D., Hyunh, N., & Guilleminault, C. <sup>1859</sup>	2017	3a	Retrospective Study	45 children age 3-14 years with Sleep Disordered Breathing	The majority of children showed improvement in sleep scores and symptoms after bimaxillary expansion	Bimaxillary expansion is a treatment option for improving respiratory parameters in children with Sleep Disordered Breathing

#### IX.D.6.b Maxillomandibular Advancement

Maxillomandibular advancement (MMA) is one of the most effective surgical interventions for OSA<sup>1799</sup>. The earlier indications for MMA included moderate to severe OSA, morbid obesity, severe mandibular deficiency, and failure of other forms of therapy<sup>1860</sup>. Current workup of OSA prior to surgery includes the use of drug induced sleep endoscopy (DISE). Concentric collapse of the velum is a contraindication for hypoglossal nerve stimulator implantation and lateral pharyngeal wall collapse is difficult to manage with soft tissue surgery alone.<sup>1799</sup> MMA is effective in addressing circumferential velum and lateral oropharyngeal wall collapse patterns.<sup>1799,1860</sup>

Previous algorithms considered MMA if patients had inadequate response to phase I multilevel surgery that involved soft tissue surgical approaches such as the uvulopalatal flap and genioglossus advancement<sup>1861</sup>. The phased approach remains a reasonable option, with expansion of phase 1 procedures to include various modifications of uvulopalatopharyngoplasty (UPPP), lingual tonsillectomy, maxillary expansion, and upper airway stimulation. In the contemporary approach for surgical decision making, MMA can be recommended prior to other procedures in: 1) patients with any degree of OSA, with dentofacial deformity, or 2) patients presenting with complete concentric collapse of the velum and/or lateral oropharyngeal wall collapse as seen on DISE, or 3) after failure of one or more of these surgeries.<sup>566,1565,1861</sup>

MMA results in a high surgical success rate and modest cure rate. Surgical success for sleep procedures is defined as a reduction in the AHI by more than 50%, or with an less than 20 events/hour. Cure is defined as AHI < 5.<sup>1862</sup> Holty et al. performed the largest meta-analysis by examining 22 studies with 627 patients who underwent MMA for OSA and reported a mean decrease in AHI from 63.9 to 9.5 events per hour. The surgical success and cure rates were 86.0% and 43.2%, respectively.<sup>1792</sup> Another large meta-analysis performed by Zaghi et al. which included 45 studies with 528 patients and showed that mean postoperative changes in AHI and respiratory disturbance index (RDI) after MMA were 47.8 and 44.4 events per hour, respectively. They reported success and cure rates of 85.5% and 38%, respectively<sup>1565</sup>.

MMA for OSA is typically accomplished with maxilla and mandible advancements of 8 - 14 mm<sup>1861</sup>. Such numbers need to be interpreted with caution as the landmarks can be inconsistent, and rotations of the maxillomandibular complex to achieve facial balance may further skew the interpretation. Barrera et al. examined differences in anatomic dimensions between patients with and without OSA<sup>566</sup>. Skeletal and soft tissue dimensions were measured with cephalometry and magnetic resonance imaging. Compared to controls, patients with OSA demonstrated: 1) increased mandibular plane-hyoid (MP-H) distance, 2) increased tongue volume, and 3) smaller posterior airway space. Gottsander-Wolf et al. performed a systematic review of posterior airway changes following MMA using lateral cephalometry and cone beam computed tomography<sup>1862</sup>. In 5 studies, where a third reported ranges for maxillary and mandibular advancements, there was an increase of 8.1 to 9.8 degrees for SNA and 9.5 to 11.0 degrees for SNB.

Caples et al<sup>1685</sup> reviewed surgical modifications of the upper airway for treatment of OSA in 2010 to update the American Academy of Sleep Medicine (AASM) on upper airway surgery. Of 1,383 studies reviewed, 9 studies on MMA were included. MMA resulted in the greatest reduction in AHI of 87% (95% CI 80% to 92%), with a mean postoperative AHI of 7.7.

Secondary measures, such as sleepiness or quality of life were reported in one study as a reduction in the Epworth score from 17.8 to 4.7<sup>1863</sup> and another reported significant decline in mean blood pressure at 6 months after surgery.<sup>1864</sup>

There is a need to better characterize surgical morbidity and adverse events after MMA. As MMA is generally performed in patients significantly older than corrective jaw surgery (orthognathic) patients, rates of malocclusion, malunion, and prolonged paresthesia are likely to be higher than seen in orthognathic surgery. Systematic reviews report the rates of major complications such as airway compromise at 1%, and other complications such as malunion at 5%. A less described but frequently encountered side effect from MMA surgery is nasal obstruction requiring corrective surgery. With classic MMA techniques, persistent nasal obstruction is reported to be as high as 18.7% from 379 patients over 15 years.<sup>1685</sup> Nasal obstruction rates can be reduced to 6.5% with modifications including pre-MMA maxillary expansion, concurrent septoplasty, piriformplasty, and emphasis on post-operative nasal and sinus rinsing.<sup>1865</sup> There is a need to update evidence on adverse events in contemporary MMA.

### Maxillomandibular Advancement for OSA Treatment

Aggregate Quality of Evidence: B (Level 2a: 6 studies; Level 2b: 3 studies)

Benefit: MMA offers significant AHI reduction and improvement in ESS.

Harm: Serious adverse events are rare. MMA is a lengthy and technically challenging procedure with surgical risks for dental malocclusion, facial neurosensory deficits and cosmetic changes.

Cost: High costs related to surgery, and visits. Indirect costs: time off work, recovery time varies from 4 – 6 weeks, may need orthodontic management before and after surgery often with out-of-pocket costs.

Benefits-Harm Assessment: Preponderance of benefit over harm.

Value Judgments: MMA surgery is efficacious for patients with moderate to severe OSA in lowering AHI. It may improve the oxyhemoglobin saturation as well as systemic blood pressure.

Recommendation Level: Recommendation

Intervention: MMA is indicated for patients with moderate to severe OSA who have failed CPAP. It is indicated in patients with skeletal-dental abnormalities and craniofacial anomaly.

Table IX.D.6.b: Summary Table for Maxillomandibular Advancement

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusions
Caples SM. et al. <sup>1685</sup>	2010	2a	Systematic review and meta-analysis	Review of 1,383 studies with 9 MMA studies	MMA has low surgical morbidity and adverse events Improvement in AHI is greatest with MMA	Overall reduction in AHI of 87% (95% CI 80% to 92%) with a mean postoperative AHI of 7.7
Liu SY et al.. <sup>1799</sup>	2019	2b	Retrospective Study	Patient selection criteria reviewed based on retrospective experience.	Historical review of MMA surgery at Stanford	Outlines the contemporary approach for MMA in the treatment of OSA. It details a stepwise approach for the procedure.
Riley RW et al. <sup>1860</sup>	1990	2b	Retrospective study	40 adults with OSA evaluated based on AHI	MMA has a higher success rate than genioglossal advancement and hyoid suspension	MMA is effective in treating moderate to severe OSA.
Barrera JE. <sup>1861</sup>	2018	2b	Systematic Review	Clinical Technique and Systemic Review based on AHI outcomes	MMA success increases with advancements over 10 mm. Success rate over 86%	This review highlights the variety of skeletal surgery offered for the treatment of OSA, including MMA as the gold-standard
Zaghi S et al. <sup>1565</sup>	2016	2a	Systematic review and meta-analysis	Success and cure rate	45 studies and 518 patients with surgical success and cure rates of 85.5% and	Meta-analysis of MMA showing surgical success with surgery.

			analysis		38% respectively	
Gottsauer-Wolf S et al. <sup>1862</sup>	2018	2a	Systematic review and Meta-analysis	Review of 15 publications With average advancements compared	Average advancement of the mandible were 8.1 to 9.8 mm and 9.5 to 11.0 mm	Systematic review analyzed posterior airway changes after MMA for OSA. They showed significant advancements for both the maxilla and mandible
Holty and Guilleminault <sup>1866</sup>	2010	2a	SR and MA	MMA (n=627 adults)	AHI, ESS, QOL	MMA sig improved AHI (63.9 to 9.5), reduced daytime symptoms and improved QOL. Success and cure rates were 86.0% and 43.2% respectively.  Younger, lower weight and AHI and greater maxillary advancement were predictive of increased surgical success.  Major complication rate: 1.0% Minor complication rate: 3.1%
Camacho et al. <sup>1867</sup>	2019	2a	SR and MA	MMA (n=120)	AHI, ESS, LSAT	Improvements in AHI, sleepiness, and lowest oxygen saturation were maintained in the long term (4 to <8 years). Mean AHI increased to moderate OSA in the very long term ( $\geq$ 8 years).
Awad M. et al. <sup>1792</sup>	2019	2a	Systematic review and	Review of 414 studies	MMA has highest success and cure rates.	This systematic review analyzed current trends in skeletal surgery for treatment of OSA.



			Meta - analy sis			They report that MMA is the most widely studied and efficacious multi-level surgery for OSA.
--	--	--	---------------------------	--	--	--

### IX.D.7 Hypoglossal Nerve Stimulation (HNS)

Hypoglossal nerve stimulation (HNS) is an emerging surgical treatment for obstructive sleep apnea (OSA). A few companies have produced HNS systems, but only the Inspire II (Inspire Medical Systems, MN USA) has obtained FDA approval. The Apex device (Apnex Medical, MN USA) produced promising Phase II data, but failed to complete a Phase III trial.<sup>1868</sup> The ImThera device (LivaNova, London UK) has shown promising results in a Phase II trial and is currently under investigation in an ongoing phase III trial.<sup>1869</sup> The Nyxoah Genio device is a bilateral hypoglossal nerve stimulation system with external battery with preliminary data showing improvement in AHI post-implant.<sup>1870</sup> Therefore, the bulk of literature regarding candidacy, efficacy, and usage of HNS comes from cohorts implanted with the Inspire II device.

#### IX.D.7.a Candidacy for HNS

Current clinical candidacy criteria for hypoglossal nerve stimulation (HNS) or upper airway stimulation are based on early feasibility studies and STAR trial which formed the basis for Federal Drug Administration (FDA) candidacy recommendations for Inspire II (Inspire Medical Systems, MN USA).

Criteria for patient enrollment in the pivotal STAR (Stimulation Therapy for Apnea Reduction) trial were based on feasibility trials that suggested improved outcomes with BMI  $\leq 32$  kg/m<sup>2</sup> and AHI  $\leq 50$  events/hour<sup>1871</sup> along with two small studies (N of 7 and 21 patients) that suggested HNS was not effective in patients with palate level complete concentric collapse (CCC) on drug-induced sleep endoscopy (DISE) prior to implantation. A statistically significant difference in AHI reduction was seen in the group without palate CCC leading the authors to conclude the absence of CCC can predict HNS success and DISE was recommended as a tool for patient selection.<sup>1871,1872</sup> The STAR trial involved a multi-institutional single group trial with 126 patients who were not adherent to CPAP with enrollment criteria: BMI  $<32$  kg/m<sup>2</sup>, with AHI greater than 20 and less than 50, central/mixed apnea events less than 25% of all apneic events, AHI in non-supine position  $> 10$  events/hour. Patients with tonsil size 3 or 4<sup>1644</sup> or palate CCC on DISE were excluded from the trial. The trial demonstrated therapy success based on the Sher criteria ( $\geq 50\%$  reduction in AHI from baseline and post-treatment AHI  $<20$ ) in 66% of the patients.<sup>381</sup> Effectiveness of HNS therapy in patients with a larger AHI range ( $> 15$  and  $<65$  events/hour), and BMI  $<35$  kg/m<sup>2</sup> along with absence of palate CCC on DISE was further demonstrated by several post-approval outcomes studies, meta-analyses and ADHERE registry<sup>1487,1488,1547,1873-1875</sup>.

Current candidacy criteria for HNS requires further evaluation. Mwenge et al. evaluated effectiveness of HNS in 13 patients with wider inclusion criteria for AHI and BMI 25-40 kg/m<sup>2</sup> and did not use DISE as a screening tool. Successful AHI reduction was demonstrated in 69% (9 out of 13) of patients at 12 months after implantation. Kezirian et al. looked at HNS in patients with selection criteria AHI 20-100 events/hour, BMI  $<40$  kg/m<sup>2</sup> and reported that 55% (17 out of 31) patients achieved Sher treatment success criteria.<sup>1868</sup>

FDA indications for HNS do not consider BMI as a definitive candidacy criterion. The STAR trial only included patients with BMI  $<32 \text{ kg/m}^2$ , thus this criterion has persisted for post-approval HNS patient selection by some insurance coverage policies. Data from most recent ADHERE post-implant follow up studies have suggested an inverse association of BMI and HNS therapy effectiveness.<sup>1487,1875</sup> However the appropriate cutoff for BMI level is not clear. Kezirian et al. demonstrated that patients with BMI  $< 35$  had greater AHI reduction with HNS. Huntley et al. found no difference in HNS therapy Sher success rate between BMI  $> 32 \text{ kg/m}^2$  and BMI  $< 32 \text{ kg/m}^2$  groups.<sup>1488</sup>

Current evidence demonstrates effectiveness of the HNS therapy in patients with absence of CCC. However, evidence level for CCC as a predictor of HNS outcomes is low quality and based on two very small case series.<sup>1871, 1872</sup> There are no multi-institutional studies demonstrating HNS therapy success rate in larger population of patients with CCC.

HNS therapy is indicated for treatment of a subset of adult patients 18 years of age and older with moderate-to-severe OSA  $15 \leq \text{AHI} \leq 65$  of which  $< 25\%$  are central/mixed apneas, who have failed or cannot tolerate PAP treatment and do not have a complete concentric collapse at the soft palate level. Current evidence supports HNS therapy success in patients with BMI  $\leq 35 \text{ kg/m}^2$ . As of 2021, the current HNS implant is not FDA approved for entry into many types of magnetic resonance imaging (MRI) including no body MRI and only 1.5T scanners for head and neck MRI.

When considering HNS therapy, clinical judgment should be used to assess patients' candidacy based on a comprehensive sleep medicine history, polysomnographic findings, upper airway anatomy and pathophysiology, body mass and fat distribution, medical and psychiatric comorbidities, physical and cognitive limitations, comorbid sleep disorders, other available treatment alternatives, presence of other implantable devices, occupation, and anticipated needs for MRI imaging.

#### IX.D.7.b Efficacy of HNS

The phase III trial STAR cohort (Stimulation Therapy for Apnea Reduction) demonstrated median apnea-hypopnea index (AHI) reduction by 68% from 29.3 to 9.0.<sup>381</sup> The randomized controlled therapy withdrawal portion of the STAR trial demonstrated that responders to HNS reverted to baseline OSA levels when the therapy was removed, and improved again when it was restarted.<sup>1876</sup> Over a period of five years, the STAR trial cohort demonstrated significant improvements in objective measures of OSA such as AHI, oxygen desaturation index (ODI), and percentage of sleep spent under 90% saturation<sup>382,814,1877</sup> as well as significant improvements in subjective daytime sleepiness (Epworth sleepiness scale, ESS), snoring level (bed partner visual analog score), and sleep-related quality of life (FOSQ). ESS decreased by 4.4 units on average with 78% of subjects below 10, indicating normal daytime sleepiness.<sup>382,814,1546,1877,1878</sup> At the 5-year mark, 75% of the remaining cohort met Sher's criteria. When including the last known values for those lost to follow up, the surgical success rate was approximately 63%.<sup>382</sup>

Post-approval single-center and multi-institutional cohort studies further confirm significant improvement in both objective and subjective measures with HNS. In the phase IV German Post-Market Study (GPMS), median AHI decreased from 28.6 to 10 at 3 years. In addition, 67% of the original cohort demonstrated an AHI  $< 10$ .<sup>1547,1879,1880</sup> An ongoing prospective observational study (ADHERE Registry), which serves as a registry of Inspire patients around the world, demonstrates significant improvements

in AHI and ESS, as well as better treatment adherence than PAP. Mean AHI decreased from 35.6 to 10.2 and ESS from 11.9 to 7.5.<sup>1881</sup> Overall, 69% met Sher's criteria at 12 months.<sup>1875</sup>

Several retrospective case-control studies observed that HNS outperformed uvulopalatopharyngoplasty and transoral robotic tongue surgery, with regard to significant improvement in both AHI and Sher's criteria.<sup>1882,1883</sup> Prior sleep surgery does not influence outcomes of HNS, and HNS non-responders can likewise be considered for further therapy, including surgery, if needed to optimize care.<sup>1884-1886</sup> Smaller retrospective cohorts show that HNS improves sleep architecture with lower arousal index, reduced light (N1) sleep, and increased deeper (N2 and N3) sleep.<sup>1887,1888</sup>

Several systematic reviews have demonstrated that HNS is effective in improving moderate-to-severe OSA.<sup>1873,1874,1889,1890</sup> Constantino et al., when analyzing the major cohorts of Inspire, Apnex, and ImThera, found that a majority of patients met Sher's criteria at rates of 72%, 55%, and 77%, respectively for each system at 12 months.<sup>1889</sup> In a review of 600 Inspire patients, Kent et al. observed that 77% met Sher's criteria and 42% obtained OSA cure with an AHI < 5, while the ESS decreased to less than 10 in 75% of included patients.<sup>1890</sup>

Despite the potential for HNS to improve OSA, there remain subsets of nonresponders who fail to meet predetermined AHI improvement. Evidence demonstrates nonresponders may still benefit from HNS. In the ADHERE registry, even though 31% did not meet Sher's criteria at 12 months, over 90% of patients were satisfied with their HNS, and would choose it again.<sup>1875</sup> The German Post-Market Study cohort demonstrated that among AHI nonresponders, the ESS and FOSQ significantly improved and over 90% continued to utilize their device.<sup>1547,1880,1891</sup>

Investigation continues into eligibility criteria for HNS since the literature postulates that a wider variety of patients may benefit from HNS than were included in the STAR trial. In a retrospective case series of 31 Veterans Affairs patients, of whom 61% did not meet the FDA's proposed criteria, Sher's criteria was met in 90%, with 72% achieving an AHI less than 5.<sup>1892</sup> In addition, patients with isolated retropalatal collapse achieve similar results from HNS when compared to patients with other airway collapse patterns.<sup>1893</sup> Withrow and colleagues' analysis of the ADHERE registry found that patients 65 years and older are more likely to have greater AHI reductions and higher device usage.<sup>1894</sup> Yet, previous ADHERE studies call into question whether age is an independent factor in outcomes.<sup>1875</sup> A German cohort found no differences in outcomes between patients younger and older than 65 years.<sup>1895</sup> Female sex and lower BMI has been suggested to increase odds of reaching surgical success.<sup>1875</sup> In contrast, a retrospective case control study found equivalent results in patients with BMI above and below 31.<sup>1488</sup> A smaller retrospective series demonstrated that higher baseline AHI is associated with greater overall AHI reductions.<sup>1896</sup>

The impact of HNS on common complications of obstructive sleep apnea is currently under investigation. Within the STAR cohort, Inspire responders had reduced heart rate variability suggesting lower sympathetic tone and improved cardiovascular health.<sup>1897</sup> In non-diabetic patients, HNS reduced insulin resistance and improved oral glucose tolerance.<sup>1898</sup> A retrospective study comparing ADHERE and a PAP cohort found HNS improved systolic and mean arterial pressures of baseline hypertensive patients, whereas PAP improved pressure measures in all groups, especially diastolic and mean arterial pressure.<sup>1899</sup>

## Hypoglossal Nerve Stimulation for Treatment of OSA

**Aggregate Quality of Evidence:** B (Level 1b: 1 study; Level 2a: 4 studies; Level 2b: 22 studies; Level 3a: 1 study; Level 3b: 7 studies; Level 4: 16 studies).

**Benefit:** Improvement in objective and subjective measures of OSA.

**Harm:** Surgical risks, device malfunction, potential for nonresponse requiring additional therapy, MRI limitations.

**Cost:** Moderate to high. HNS may be cost effective through mitigation of OSA complications when considering patient population non-adherent to PAP, but no studies of HNS impact on long-term major adverse health consequences of OSA have been published that would permit cost-utility analysis.

**Benefits-Harm Assessment:** Preponderance of benefit over harm

**Value Judgments:** HNS can significantly improve moderate to severe OSA in patients that are nonadherent to PAP. Approximately 70-75% of patients will respond as defined by AHI (>50% AHI reduction and overall AHI<20) and up to half may have a complete response (AHI<5). Follow-up with full night studies or HST for long-term therapeutic AHI measures is recommended

**Recommendation Level:** Recommendation

**Intervention:** HNS is an effective therapy for select patients with moderate-to-severe OSA that are intolerant of PAP and meet clinical criteria for therapy.

**Table IX.D.7.b Evidence on HNS Therapy for OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoint	Conclusions
Kent et al. <sup>1890</sup>	2019	2a	SR and meta-analysis of prospective and retrospective self-controlled cohort studies	Inspire implantation (n=584)	1. AHI 2. ESS 3. FOSQ 4. O2 nadir	HNS leads to significant improvements in objective and subjective measures of OSA and QoL. AHI decreased by mean 25.2 (6 months) and 16.5 (12 months). ESS decreased to <10 in 75% patients. 77% met Sher's criteria and 42% obtained OSA cure. Greater improvement seen in patients with greater pre-operative OSA.
Costantino et al. <sup>1889</sup>	2020	4	SR and meta-analysis of prospective self-controlled cohort studies	HNS patients: - Inspire: 239 - ImThera: 59 - Apnex: 52	1. AHI 2. ESS 3. ODI	HNS is safe and effective for moderate-to-severe OSA. Inspire and ImThera had surgical success rate ≥ 75%. AHI reduction of 56% (Inspire), 54% (ImThera), and 44% (Apnex) at 12 months and 59% (Inspire) at 60 months. ESS and ODI significantly improved.

Kompelli et al. <sup>1874</sup>	2018	4	SR and meta-analysis of self-controlled cohort studies	HNS patients (381)	1. AHI 2. ESS 3. ODI 4. FOSQ 5. SAQLI	HNS is safe and effective treatment for CPAP refractory OSA with significant improvements in objective and subjective measures. Mean AHI reduction of 23.5 and 21.2 at 6 and 12 months, respectively.
Certal et al. <sup>1873</sup>	2015	4	SR and meta-analysis of self-controlled cohort studies	HNS patients (200)	1. AHI 2. ODI 3. ESS	HNS is safe and effective treatment of moderate-to-severe OSA in patients who failed CPAP. Clinically significant decreases in mean AHI, ODI, and ESS as well as QoL through 12 months.
Strollo et al. <sup>381</sup>	2014	2b	STAR Trial Prospective, self-controlled cohort study; randomized controlled therapy-withdrawal trial	Inspire implantation (n=126) STAR cohort	1. AHI 2. ODI 3. ESS 4. FOSQ 5. % sleep under 90% SaO <sub>2</sub>	HNS results in clinically significant reductions in OSA severity and subjective OSA measures at 1 year, confirmed by withdrawal trial. More favorable effect with BMI 32 or lower and AHI 50 or less.
Woodson et al. <sup>1876</sup>	2014	1b	STAR Trial Prospective, randomized controlled therapy withdrawal study	Inspire responders -therapy withdrawn -therapy maintained STAR cohort	1. AHI 2. ODI 3. ESS 4. FOSQ 5. Snoring	Sleep parameters revert to baseline when therapy is withdrawn and improve when restarted. HNS benefit continued through 18 months.
Strollo et al. <sup>814</sup>	2015	2b	STAR Trial cont. Prospective cohort study	Inspire implantation at 12 and 18 months (n=124) STAR cohort	1. AHI 2. ODI 3. ESS 4. FOSQ 5. % sleep under 90% SaO <sub>2</sub>	HNS produces consistent and sustained therapy response in OSA severity, self-reported sleepiness, and QoL over 18 months.
Soose et al. <sup>1546</sup>	2016	2b	STAR Trial cont. Prospective, self-	Inspire implantation at 24 months (n=111)	1. ESS 2. FOSQ 3. Snoring	HNS produces clinically meaningful, significant improvements in subjective OSA measurements that are

			controlled cohort study	STAR cohort		consistent through 2 years
Woodson et al. <sup>1877</sup>	2016	2b	STAR Trial cont. Prospective, self-controlled cohort study	Inspire implantation at 36 months (n=116) STAR cohort	1. AHI 2. ODI 3. ESS 4. FOSQ 5. % sleep under 90% SaO2	HNS has lasting significant improvements in objective and subjective sleep measures at 36 months for CPAP intolerant, moderate-to-severe OSA patients.
Gillespie et al. <sup>1878</sup>	2017	2b	STAR Trial cont. Prospective, self-controlled cohort study	Inspire implantation at 48 months (n=91) STAR cohort	1. ESS 2. FOSQ 3. Snoring	HNS maintains sustained benefit on ESS, FOSQ, and snoring through 48 months.
Woodson et al. <sup>382</sup>	2018	2b	STAR Trial cont. Prospective, self-controlled cohort study	Inspire implantation at 5 years (n=97) STAR cohort	1. ESS 2. FOSQ 3. Snoring 4. AHI 5. ODI	At 5 years, HNS produces clinically meaningful and significant improvements in objective and subjective OSA measures. Adverse outcomes are rare and benign. Non-responders had higher AHI and ODI, and lower FOSQ scores at baseline.
Dedhia et al. <sup>1897</sup>	2019	4	Prospective, self-controlled cohort study	Inspire responders (n=32) STAR cohort	1. SDNN 2. LF 3. HF	HNS significantly improves heart rate variability during sleep similar to PAP usage suggesting lower sympathetic tone and improved cardiovascular health.
Thaler et al. <sup>1875</sup>	2019	2b	Prospective, Self-controlled cohort study	Inspire implantation (n=640) ADHERE Registry	1. AHI 2. Treatment success 3. ESS 4. Objective therapy use	HNS meets surgical success per Sher criteria in 83% and 69% of patients at 6 and 12 months, respectively. HNS significantly reduces AHI and ESS. Female sex and lower BMI increase odds of surgical success.

Steffen et al. <sup>1880</sup>	2020	2b	Prospective, multi-institutional self-controlled cohort study	Inspire implantation (n=41) G-PMS	1. AHI 2. ODI 3. ESS	HNS produces long-term control of objective and subjective OSA measures in CPAP-intolerant patients that met FDA inclusion criteria. 67% patients demonstrated AHI < 10/h at 3 years. Median AHI dropped from 28.6 to 10 at 3 years.
Withrow et al. <sup>1894</sup>	2019	2b	Prospective Cohort study	Inspire implantation 1. < 65 years (n=365) 2. ≥ 65 years (n=235) ADHERE	1. AHI 2. ESS 3. Therapy usage	Age ≥ 65 is independent factor for HNS success, with higher AHI reduction and therapy usage in older adults. It is safe and well tolerated among older adults.
Boon et al. <sup>1881</sup>	2018	2b	Prospective, Self-controlled Cohort study	Inspire implantation (n=301) ADHERE	1. Adverse events 2. AHI 3. ESS 4. Adherence	HNS provides objective success and satisfaction from surgeons and patients. Mean AHI decreased from 35.6 to 10.2, and mean ESS decreased from 11.9 to 7.5. Adverse events were rare and benign.
Steffen et al. <sup>1547</sup>	2018	2b	Prospective, multi-institutional self-controlled cohort study	Inspire implantation (n=60) G-PMS	1. AHI 2. ODI 3. ESS 4. FOSQ	HNS is effective therapy with durable results through 12 months. Median AHI decreased from 28.6 to 9.5 at 12 months. 73% patients met Sher criteria. Usage approached 40 hr/week. Nonresponders' ESS and FOSQ significantly improved, and all continued to utilize device.
Hasselbacher et al. <sup>1891</sup>	2018	2b	Prospective, multi-institutional self-controlled cohort study	Inspire implantation (n=60) G-PMS	1. ESS 2. FOSQ 3. Snoring 4. User experience	HNS leads to significantly improved daytime sleepiness and functioning, 73% and 59% reaching normal responses on ESS and FOSQ, respectively. Subjective improvement correlates with higher usage. 96% patient satisfaction.

Heiser, Maurer et al. <sup>1879</sup>	2017	2b	Self-controlled cohort study	Inspire implantation (n=60) G-PMS	1. AHI 2. ODI 3. ESS 4. FOSQ 5. Therapy usage	HNS achieved significant improvement in objective and subjective OSA measures at 6 months. 68% met Sher criteria, with average AHI reduction of 61%. Adherence was significantly higher than CPAP.
Shah et al. <sup>1883</sup>	2018	4	Retrospective case control study	Sleep surgery patients 1. Inspire (n=20) 2. UPPP (n=20)	1. AHI 2. ESS	HNS produced greater decrease in post-op AHI versus UPPP. 100% of HNS patients met Sher criteria versus 40% of UPPP patients. Previous sleep surgery did not have effect on AHI in either group.
Huntley, Topf et al. <sup>1882</sup>	2019	4	Retrospective case control study	Sleep surgery patients with BOT collapse 1. Inspire (n=76) 2. TORS BOT resection (n=24)	1. PSG outcomes 2. Complications 3. LOS and readmission	HNS significantly outperformed TORS for surgical success, AHI, O <sub>2</sub> nadir, hospital LOS, and no readmissions. 87% HNS patients reached Sher's criteria and 59% reached cure. HNS has largely replaced TORS for BOT obstruction at their institution.
Sarber et al. <sup>1892</sup>	2020	4	Retrospective case series	Veterans undergoing HNS (n=31)	1. PSG outcomes 2. ESS 3. Perioperative outcomes	In veterans with several medical and psychiatric comorbidities (61% did not meet FDA criteria), HNS significantly improved objective and subjective sleep measures, albeit higher complication risk. Sher criteria met in 90% of patients. 72% patients reached cure. No statistical difference in those with and without psychiatric disorders.
Walia et al. <sup>1899</sup>	2020	3b	Retrospective cohort study	OSA patients 1. HNS (n=278) 2. PAP (n=517)	1. Blood pressure 2. ESS	In matched patients, PAP had greater improvements in diastolic and mean arterial pressure. Only baseline hypertensive patients had BP improvement with HNS. HNS improved ESS to a greater degree.



Kezirian et al. <sup>1885</sup>	2019	2b	Self-controlled cohort study  ADHERE Registry	Inspire implantation 1. No prior sleep surgery (n=217) 2. Prior sleep surgery (n=82)	1. AHI	Previous upper airway sleep surgery is not associated with HNS efficacy HNS. These patients should be considered for HNS.
Bohorquez et al. <sup>1887</sup>	2020	4	Retrospective case series	Inspire responders (n=35)	1. Sleep architecture from PSG parameters 2. BMI	HNS responders had significant improvement in sleep architecture: reductions in N1 and arousal index, increases in N2 and N3. No changes in REM.
Evans et al. <sup>1896</sup>	2020	4	Retrospective case series	Inspire implantation (n=25)	Pre-operative clinical predictors of HNS success	Higher starting AHI was positively associated greater AHI reduction.
Mahmoud et al. <sup>1893</sup>	2019	4	Retrospective case series	Inspire implantation 1. Retropalatal collapse (n=25) 2. Any other collapse (n=57)	1. AHI 2. Nadir O2	Isolated retropalatal collapse performed similarly to other collapse types. HNS produced significant decreases in mean AHI and oxygen nadir.
Steffen, Chamorro et al. <sup>1898</sup>	2019	4	Prospective case series	Non-diabetic Inspire implantation (n=25)	1. AHI 2. ODI 3. ESS/FOSQ 4. Glucose metabolism 5. Appetite markers	HNS significantly improves AHI, ODI, and subjective measures of OSA. At 12 months, HgbA1C and BMI were similar, but insulin resistance and oral glucose tolerance improved. Hedonic food drive improved.
Huntley, Vasconcellos et al. <sup>1884</sup>	2018	3b	Retrospective case control study	Inspire implantation 1. No prior sleep surgery (n=141) 2. Prior "palate" surgery (n=23)	1. AHI 2. O2 nadir 3. ESS	Patients with persistent moderate-to-severe OSA after prior palate surgery should be considered for HNS. No statistical differences in outcomes in patients with and without prior palate surgery.

Huntley, Steffen et al. <sup>1488</sup>	2018	3b	Retrospective case control study	Inspire implantation 1. BMI > 32 (n=40) 2. BMI < 32 (n=113)	1. AHI 2. O2 nadir 3. ESS	Patients with BMI >32 had statistically similar outcomes with HNS compared to those with BMI <32. Over 92% patients met Sher criteria in both cohorts, and over 55% obtained cure.
Zhu et al. <sup>1895</sup>	2018	4	Prospective Cohort study	Inspire implantation 1. Age >64 years (n=31) 2. Age <65 years (n=31)	1. AHI 2. ODI 3. ESS	HNS leads to significant reductions in AHI, ODI, and ESS in older patients, statistically similar to younger patients.
Hofauer et al. <sup>1888</sup>	2017	4	Case series	Inspire implantation (n=26)	1. Sleep architecture from PSG parameters	HNS significantly decreased N1 sleep time and arousals.
Steffen, Abrams et al. <sup>1886</sup>	2019	4	Prospective case series	Inspire nonresponders 1. UAS followed by UPPP (n=7) 2. UAS preceded by UPPP (n=10) 3. UAS alone (n=8)	1. AHI 2. ODI 3. ESS	UPPP should be considered in HNS nonresponders if DISE demonstrates palatal collapse, as significant improvement in AHI, ODI, and ESS can be achieved in these patients.
Friedman et al. <sup>1869</sup>	2016	4	Self-controlled cohort study	ImThera implantation (n=46) Phase II study	1. AHI 2. ODI 3. Arousal index 4. ESS 5. Sleep apnea quality of life index	ImThera produced significant decreases in objective and subjective measures. Mean AHI decreased from 34.9 to 25.4 in all patients. In responders, mean AHI decreased from 35.7 to .5. Only 35% met Sher's criteria. 67 adverse events occurred.
Kezirian et al. <sup>1868</sup>	2014	4	Self-controlled cohort study	Apnex implantation (n=31)	1. PSG parameters 2. Compliance 3. Subjective improvement 4. Safety	Apnex produced significant improvements in objective and subjective measures of OSA. Mean AHI improved from 45.4 to 25.3. 55% met Sher's criteria.

### IX.D.7.c Titration of HNS

For hypoglossal nerves stimulation (HNS) therapy, proper titration of the electrical parameters is critical to comfort, use, and successful long-term outcomes. HNS therapy is an adjustable medical device that can be titrated in the clinic or sleep laboratory setting to optimize effectiveness and comfort longitudinally. HNS settings can be adjusted to maintain adequate disease control, as body weight or other pathophysiologic factors change over time. Prior studies have shown a graded increase in airflow and multilevel airway measurements with increasing stimulation amplitudes until a plateau is reached, balancing patient discomfort with therapeutic efficacy<sup>1900-1904</sup>. Although increasing amplitude may be associated with improved upper airway opening, a threshold is reached where further increases in amplitude are associated with therapy discomfort and subsequently detrimental to sleep-onset and sleep-maintenance.

Most research on HNS titration refers to the Inspire implantable hypoglossal nerve stimulation system (Inspire Medical Systems, MN USA). The STAR trial established the foundation for the current titration protocol which consists of: 1) device activation four weeks post-implant, 2) initial patient self-titration and accommodation period, followed by 3) laboratory-based overnight titration polysomnography two to six months postoperatively<sup>1903</sup>. Device activation is recommended with standard default stimulation settings (bipolar electrode configuration [+-+], pulse width=90 $\mu$ s, rate=33 Hz), confirmation of proper system function, and determination of the functional threshold – defined as the lowest amplitude at which tongue protrusion passes the mandibular incisors<sup>381,1905</sup>. Initial amplitude is set at or just below the functional threshold and includes a patient-control range of ten 0.1V increments (e.g. functional threshold=1.0V with a range of 0.8-1.7V with 0.1V increments)<sup>1906</sup>. Patients are asked to progressively increase the amplitude on their remote every few nights at home. This allows self-titration by patients to optimize their symptom while simultaneously balancing their comfort with the device.

When assessing treatment response, two types of polysomnography have been reported: 1) titration polysomnography which consists of an in-lab study with real-time therapy adjustments made by a sleep technician according to established laboratory protocols akin to CPAP titration studies, and 2) full-night efficacy polysomnography, either in-lab or via home portable monitoring, which measures the sleep outcomes at one setting all night. Although the STAR trial and German post-market study included titration studies between 2 and 6 months, the manuscripts reported outcomes from the subsequent full-night efficacy studies<sup>1879</sup>. Reports from the multicenter ADHERE global clinical registry, however, represent a combination of titration study data and full-night efficacy studies depending on the center and individual insurance coverage<sup>1487,1875</sup>. Three studies have reported HNS results from postoperative titration studies<sup>1545,1893,1907</sup>. As expected, the results from the titration studies showed more improvement in the final AHI when compared to full-night outcomes studies. In summary, variability exists in outcomes reporting based on study type. This variability underscores the importance of distinguishing between titration and full-night outcomes and the need for more full-night efficacy data in understanding long-term therapy outcomes<sup>1908</sup>.

For HNS patients with suboptimal OSA response or problems with device adherence, examination and implementation of best-practice approaches for device data download, patient education, targeted advanced titration and programming adjustments, and close clinical follow-up, may optimize long-term outcomes. For refractory cases with persistent OSA, there may be a role for awake endoscopy or drug-induced sleep endoscopy to further titrate therapy<sup>1909-1911</sup>. Industry-sponsored recommendations including sleep laboratory titration protocols, as well as office-based therapy troubleshooting and advanced titration protocols are available; however, peer-reviewed practice guidelines are still in

development. Additional research is needed to determine which titration protocols improve outcomes and which approaches have the most meaningful effects.

### HNS Titration for OSA

Aggregate Grade of Evidence: D (Level 2b: 1 study; Level 4: 3 studies)

**Table IX.D.7.c: Clinical studies with titration parameters of Hypoglossal Nerve Stimulation (HNS)**

Study	Year	LOE (1a-5)	Study design	Study groups	Clinical end-point	Conclusion
Strollo PJ et al. <sup>381</sup>	2014	2b	Multicenter prospective series of OSA patients CPAP intolerant and oral appliance therapy who underwent HNS implantation.	126 moderate to severe OSA patients who underwent HNS implantation.	Device use, sleep study parameters: AHI, ODI, ESS, FOSQ. Objective outcomes measured by in lab PSG (non-titration) at 12 months postoperatively	HNS provides significant improvement in OSA severity. AHI decreased from 32.0±11.8 to 15.3±16.1.
Kent DT et al. <sup>1545</sup>	2016	4	Single center retrospective case series of OSA patients CPAP intolerant and oral appliance therapy who underwent HNS.	20 patients with moderate to severe OSA who underwent HNS implantation	Objectively measured device use, adverse events, ESS, sleep study parameters: AHI, ODI. Objective outcomes were taken from the 2 month postoperative in-lab titration PSG	HNS can successfully be implemented with significant improvement in sleep outcomes. AHI decreased from 33.3±13.0 to 5.1±4.3
Huntley C et al. <sup>1907</sup>	2017	4	Comparison of two centers retrospective review of their OSA patients treated with HNS.	1. 48 moderate to severe OSA patients who underwent HNS implantation 2. 49 moderate to severe OSA patients who	Comparison between two different implant centers HNS results: Objectively measured	Study demonstrates reproducible improvement multiple sleep characteristics. Notably, AHI decreased from 35±17.3 to

				underwent HNS implantation at a different medical center.	device use, adverse events, ESS, sleep study parameters: AHI, ODI. Objective outcomes were taken from the 2 month postoperative in-lab titration PSG	6±8.3.
Mahmoud AF et al. <sup>1893</sup>	2018	4	Single center retrospective series of OSA patients CPAP intolerant and oral appliance therapy who underwent HNS. Compared patients who had undergone prior surgery for OSA and those who had not	1. 30 moderate to severe OSA patients with persistent OSA despite prior airway surgery who then underwent HNS implantation 2. 17 patients with moderate to severe OSA who had not undergone prior airway surgery for OSA	Objectively measured device use, adverse events, ESS, sleep study parameters: AHI, ODI. Objective outcomes were taken from the 2 month postoperative in-lab titration PSG	Prior airway surgery had no effect on ultimate outcomes. Overall, AHI decreased from 39.3±2.8 to 3.9±1.2

HNS= Hypoglossal Nerve Stimulation; OSA= obstructive sleep apnea; AHI= Apnea-Hypopnea Index; ODI=Oxygen desaturation index; ESS= Epworth Sleep Study; Functional Outcomes of Sleep Questionnaire (FOSQ)

#### IX.D.7.d Adherence in HNS Therapy

HNS outcomes are directly tied to therapy use – also referred to as therapy *compliance* or *adherence*. Furthermore, therapy adherence is influenced by therapy side effects, which include various device-related, stimulation-related, and/or psychosocial-related factors. Long-term adherence to OSA medical device therapies remains one of the biggest challenges in the treatment of OSA. The STAR trial reported 86% of participants using the therapy nightly at the 12-month mark; however, this adherence data represented self-report rather than objective analysis<sup>381</sup>.

Technology advances allowed for objective therapy use data to be downloaded from the pulse generator using the telemetry unit and clinician programmer. Early published objective adherence data was limited to total hours of therapy usage since the last device interrogation (reported as mean hours per night or week of use). At a mean 7.8 months follow-up, *Kent et al.* reported mean objective adherence of 7.0±2.2 hours/night<sup>1545</sup>. *Heiser et al.* reported similar high adherence rates with a mean of 6.6±2.7 hours/night at 12 months<sup>1879</sup>. Comparing HNS outcomes of 97 consecutive patients at two

centers, *Huntley et al.* also reported favorable adherence in the first year with 63.4% and 78.8% of the participants at the respective centers using the therapy over 40 hours/week<sup>1907</sup>.

Therapy side effects with negative potential impact on adherence have been reported in multiple studies. In the STAR trial, discomfort due to electrical stimulation was the most common non-serious adverse event reported and improved across the 5-year trial – 40% of patients noted an episode of discomfort during the first year but only 3.5% of patients reported discomfort during the fifth year<sup>381,382</sup>. Tongue abrasion from tongue movement against an adjacent tooth was reported in 21% of patients in the first year and was reduced to 4.1% of patients in the fifth year. The reduction in adverse stimulation-related side effects over time suggests a potential role for long-term therapy accommodation that includes patient education, therapy troubleshooting, targeted reprogramming, and close clinical follow-up.

More recently, *Heiser et al.* reported on 508 HNS patients from the multicenter international ADHERE registry with a mean objective nightly use of 6.4±2.0 hours/night at the first post-titration time point (n=344 patients; average=137± days postoperatively) and 5.7±2.2 hours/night at the final visit (n=229 patients; average=386±136 days postoperatively)<sup>1487</sup>. At both the post-titration and final visits, 23% of patients had a treatment-related adverse event, which most commonly consisted of stimulation-related discomfort, tongue abrasion, or insomnia/arousal. Furthermore, using a logistic regression model they showed increasing therapy adherence was associated with increasing age, lower body mass index (BMI), and increasing apnea-hypopnea index (AHI)<sup>1487</sup>. *Thaler et al.* published the results of 1,017 patients implanted with the HNS as part of the ADHERE registry<sup>1875</sup>. After 12-months, mean objective therapy use was 5.6±2.1 hours/night. Stimulation-related discomfort remained the most commonly reported adverse event and while adverse events typically decreased from their 6-month to 12-month time points, insomnia/arousals was the only event that increased (3% versus 5% of patients). These patients would likely benefit from advanced titration programs to increase the comfort of the device but there is a scarcity of evidence to guide practitioners.

More studies are needed to examine which specific treatment factors and patient factors most strongly impact therapy adherence and outcomes. For example, akin to other medical devices, comorbid insomnia may be a negative predictor of HNS therapy adherence and may benefit from concomitant insomnia and OSA management. Future investigations of HNS therapy should focus on patient education, patient selection, and post-implant troubleshooting algorithms to further optimize therapy comfort and adherence. Additionally, technology advances could provide clinicians with more detailed and granular, and even remotely-accessed, nightly adherence data for better longitudinal care.

#### HNS Adherence

Aggregate Grade of Evidence: C (2b: 1 study; 4: 7 studies)

**Table IX.D.7.d: Clinical studies looking at adherence and related adverse events of Hypoglossal Nerve Stimulation (HNS)**

Study	Year	LOE (1a-5)	Study design	Study groups	Clinical end-point	Conclusion
Strollo PJ et al. <sup>381</sup>	2014	2b	Multicenter prospective series of OSA	126 moderate to severe OSA patients who	Subjective adherence use. Adverse events at	86% of patients used device daily, 93% reported device us-

			patients CPAP intolerant and oral appliance therapy who underwent HNS implantation.	underwent HNS implantation. STAR trial	12 months postoperatively	age at least 5 days/week. Long term adverse events: 40% with stimulation discomfort and 21% with tongue soreness
Kent DT et al. <sup>1545</sup>	2016	4	Single center retrospective case series of OSA patients CPAP intolerant and oral appliance therapy who underwent HNS	20 patients with moderate to severe OSA who underwent HNS implantation	Objectively measured device use and adverse events at average follow up of 7.8 months	Mean time from surgery to last follow up= 7.6 ±3.3 months;  Mean adherence= 7.0 ±2.2 hours/night. Long term adverse events: 15% dry mouth; 5% with tongue abrasions
Heiser C et al. <sup>1879</sup>	2017	4	Single center prospective series of OSA patients CPAP intolerant and oral appliance therapy who underwent HNS	31 patients with moderate to severe OSA who underwent HNS implantation	Objectively measured device use and adverse events 12 months after surgery	Mean adherence= 6.6± 2.7 hours/night. No long term adverse events reported
Huntley C et al. <sup>1907</sup>	2017	4	Two center retrospective review of OSA patients treated with HNS	1. 48 patients with moderate to severe OSA who underwent HNS implantation as a single center 2. 49 patients with moderate to severe OSA who underwent HNS implantation at a different medical center	Comparison between two different implant centers HNS results: Objectively measured device use and adverse events.	Mean weekly adherence between centers: 63.4% and 78.8% used device >40 hours/week (43.75 ± 11.60 and 48.00 ± 10.24 hours/weekly) at 8.6 and 11.4 months post implantation. Long term adverse events: 4% patients had dry mouth, 3% had headaches, 2% with incisional discomfort, and 1% with tongue abrasion.
Hasselbacher K et al. <sup>1891</sup>	2018	4	Multicenter, prospective case series of HNS patients.	60 patients with moderate to severe OSA who	Objectively measured device use and long term adverse events at	Mean adherence= 5.6± 2.1 hours/night. No long term adverse events reported

				underwent HNS implantation	12 months postoperatively	
Woodson BT et al. <sup>382</sup>	2018	4	Multicenter, prospective case series of HNS patients	97 OSA patients treated with HNS, all of which were enrolled in the STAR trial	Objective device use and adverse events at 60 months after implantation	Median adherence= 6.6±2.7 hours/night. Compared to 12 months, stimulation discomfort and tongue abrasions decreased significantly (81 to 5 patients and 28 to 2 patients)
Heiser C et al. <sup>1487</sup>	2019	4	Multicenter, postmarketing observational, prospective case series of HNS patients	508 patients with OSA treated with HNS	Objectively measured device use and adverse events taken 12 months after implantation	32% complication rate with tongue discomfort being most common at 8-12%. Average adherence= 5.7±2.2 hours/night
Thaler et al. <sup>1875</sup>	2020	4	Multicenter, postmarketing observational, prospective case series of HNS patients	1017 patients with OSA treated with HNS	Objectively measured device use and adverse events 12 months after implantation	Average adherence =5.6±2.1 hours/night. Most common adverse event being stimulation discomfort (12% at posttitration visit and then 8% at 12 month follow up)

HNS = Hypoglossal nerve stimulation; OSA= obstructive sleep apnea; AHI= Apnea-Hypopnea Index; ODI=Oxygen desaturation index; ESS=Epworth sleepiness scale

#### IX.D.8 Multilevel Surgery

Multilevel surgery (MLS) for adults with obstructive sleep apnea (OSA) was popularized in the late 1990s following the recognition that single level surgery (with uvulopalatopharyngoplasty, UPPP) was successful in a minority of unselected cases.<sup>1633,1912</sup> This was found to be due to persistent retropalatal collapse but also untreated additional sites of obstruction.<sup>1642,1913</sup> As acceptance of the concept of multilevel upper airway collapse grew<sup>1583,1914</sup>, many centers around the world accordingly developed protocols to surgically treat multiple levels of the upper airway simultaneously. These protocols are collectively referred to as MLS and generically consist of the simultaneous surgical treatment of more than one site of upper airway obstruction in patients with obstructive sleep apnea.

Initially MLS included nasal, retropalatal and hypopharyngeal sites. Given the widespread adoption of drug-induced sleep endoscopy (DISE) and the VOTE classification, an updated definition might include the nose, palate, oropharyngeal lateral walls, tongue base, and epiglottis as potential subsites. For instance, genioglossus advancement (GGA) with hyoid suspension (HS) was previously categorized as



hypopharyngeal surgery only but this combination of surgeries has effects on the tongue base and epiglottis and therefore can be considered MLS. Maxillomandibular advancement (MMA) also meets the definition of MLS. Similarly, hypoglossal nerve stimulation (HNS) has the unique capability of treating palatal, tongue base and epiglottis levels of collapse through palatoglossal and glossopharyngeal coupling.

Surgery for OSA is not considered first line therapy of OSA in adults. Patients pursue MLS for salvage of untreated or incompletely treated OSA due to positive airway pressure therapy intolerance. Therefore, comparing response rates to PAP effectiveness rather than efficacy is more appropriate.<sup>1915</sup> Defining surgical success is most typically by polysomnographic (PSG) parameters but recognizing improvement in quality of life, bedpartner reports of snoring and ideally reduced long-term health risk are of importance as well.

When interpreting the results of various MLS protocols over the past 20 years, it is important to recognize that not only have the thresholds for defining surgical success evolved over time, the core definition of a hypopnea has changed and the apnea-hypopnea index (AHI) has replaced the respiratory disturbance index (RDI) as the outcome measure of choice.<sup>1916,1917</sup> Currently, the most accepted definition of surgical success are the Sher criteria: achieving a 50% decrease in AHI and to less than 20 events/hour. However, there is a movement towards using more objective outcomes (oxygen desaturation index, ODI, e.g.) and/or a 50% AHI decrease to under 15 events/hour into the mild OSA range, which correlates with long-term health risk and mortality.<sup>114,118,432,433,637,641,659,682</sup> The selection of patients has largely shifted from awake staging systems assigned by physical exam and awake flexible laryngoscopy (Friedman stage, Fujita classification, Muller maneuver) to dynamic assessment under drug-induced sedation (drug-induced sleep endoscopy, DISE).

Overall the literature on MLS is predominantly comprised of case series and lower quality prospective and retrospective cohort studies. Note that many smaller and lower quality studies are not included in the references due to citation limits. The exceptions are a randomized, sham-placebo controlled trial examining the effects of radiofrequency ablation and a randomized controlled trial examining medical management versus MLS.<sup>1496,1918</sup> The studies are heterogeneous in terms of patient selection, procedures and outcome reporting. Even in papers using the same general procedure, there remains significant variability between studies such as the palatopharyngoplasty technique used or number of radiofrequency ablation (RFA) sessions.

Overall, surgical success rates based on AHI/RDI improvements are in the 60-70% range.<sup>1810,1816,1829,1912,1919,1920</sup> Table XX describes specific and heterogeneous success rates with a given MLS protocol. Most typically, post-operative AHI/RDI is determined within the first 12 months following surgery, however a small number of studies have demonstrated longer-term efficacy.<sup>1921-1926</sup> Most studies additionally compare pre- and post-operative nocturnal oximetry data including average SpO<sub>2</sub>, O<sub>2</sub> nadir and time spent below 88% which similarly show significant improvements overall.

Snoring and quality of life measures, most commonly the Epworth Sleepiness Scale, demonstrate significant improvements after MLS. Most studies describe raw ESS score changes rather than improvement below established thresholds for defining pathologic sleepiness. Finally, a smaller number of studies report significant improvements in other metrics such as arousal index<sup>1496,1823,1927,1928</sup>, sleep architecture<sup>1797,1919,1928-1930</sup>, C-reactive protein<sup>1931</sup>, airway cross-sectional area<sup>1932-1935</sup> and volume changes<sup>1496,1936</sup>, reflux symptoms<sup>927</sup>, swallowing function<sup>1937</sup> and reaction time.<sup>1496,1925,1935</sup> Notably absent are cardiovascular outcomes measures.

A few studies attempted to compare the efficacy of single level and MLS surgery. None of these are randomized controlled trials and therefore are fundamentally flawed to answer this question. Most of these studies assign patients to single or multi-level surgery based on classification systems such as Fujita or Friedman, where inherently easier to treat patients may be more likely to receive single level surgery. Some studies show greater efficacy with multilevel surgery, while others showed superiority of single level surgery. This question is not as relevant at the present time given the trend towards individualization of treatment selection using strategies such as DISE and endotyping.

MLS for OSA is effective at reducing polysomnographic measures of OSA severity, bedpartner reports of snoring, and quality of life measures. Patients should be adequately counseled regarding success rates of specific MLS protocols. Procedure selection should be tailored to levels of upper airway collapse, patient goals and surgeon comfort/experience.

### **Safety of MLS**

All patients with OSA are at an increased risk of perioperative complications, and this is especially true for upper airway surgery such as MLS for OSA. Contributors to this increased risk include muscle relaxation from general anesthesia, respiratory suppression and heightened arousal threshold from narcotics, upper airway edema and difficulty tolerating PAP post-operatively. It therefore stands to reason that MLS may increase risk by extending general anesthesia time, increasing narcotic requirements and worsening upper airway edema. Patients requiring MLS likely also have more severe OSA.

Multiple studies have shown significantly increased complication rates and pain scores in MLS when compared to single level surgery, represented by UPPP alone.<sup>1938-1940</sup> However, in one large national database analysis, Baker and coauthors did not find increased complications between UPPP alone and UPPP combined with tongue base or nasal surgery but did identify differences in length of hospital stay.<sup>1941</sup> Another consideration is the risk-benefit of staged versus simultaneous upper airway surgery. One study found no difference in complications between staged and simultaneous MLS, but did find higher healthcare expenses in the staged group.<sup>1942</sup>

Concurrent nasal surgery may theoretically increase complication rates by temporarily promoting open-mouth breathing and abolishing the nasal-ventilatory reflex. BuSaba et al compared single stage UPPP with nasal surgery to staged UPPP and nasal surgery and found no difference in complication rates.<sup>1943</sup> Similarly Pang et al. reviewed MLS cases with and without nasal surgery and found no difference in complication rates.<sup>1944</sup>

Post-operative disposition is another peri-operative safety concern. Although the biggest risk following MLS may occur around post-operative day 3 coinciding with REM rebound, peaking edema and pain (and therefore narcotic use), most post-operative patients are admitted for overnight observation for one night only.<sup>1520</sup> Same-day discharge versus overnight admission for nasal surgery with UPPP showed no difference in complication rates.<sup>1945</sup> There are no studies reporting on the safety of same-day discharge following combined palate and hypopharyngeal surgery.

As mentioned, MLS is a heterogeneous collection of protocols, some of which are minimally invasive. For instance, RFA treatments of the palate and tongue base are routinely performed on an outpatient basis due to the limited risk profile. One study even reported performing GGA with hyoid myotomy and uvulopalatal flap under local anesthesia with no difference in complication rates compared to when performed in the OR.<sup>1549</sup>

Overall, complications- and especially major complications- are relatively uncommon as demonstrated in a large single series of MLS patients.<sup>1558</sup> Due to wide-ranging morbidity of various procedures, reporting a single, generalized complication rate is misleading. The reader is therefore encouraged to review specific protocols to evaluate common adverse events.

Guidelines for the perioperative care of OSA surgery patients are well summarized by Ravesloot et al. although these are largely based on low quality studies and expert opinion and specifically does not address MLS.<sup>1520</sup> Therefore, developing guidelines for perioperative care of patients undergoing MLS represents an opportunity for further work.

### Multilevel Airway Surgery for Treatment of OSA

**Aggregate Quality of Evidence:** B (Level 1b: 1 study, level 2b: 30 studies, level 3b: 2 studies, level 4: 81 studies)

**Benefit:** Effective at reducing OSA severity and improving quality of life in PAP-intolerant patients.

**Harm:** Increased pain and possibly increased complications compared to single level surgery and medical treatments for OSA.

**Cost:** Moderate to high costs associated with surgery and time off work for recovery.

**Benefits-Harm Assessment:** Slight preponderance of benefit over harm.

**Value Judgments:** Properly selected patients and procedure combinations can result in improved OSA severity and symptoms. Data on efficacy of MLS over single-level surgery is mixed.

**Recommendation Level:** Option.

**Intervention:** MLS may be considered in patients intolerant of PAP therapy. Patients should receive adequate counseling expectations regarding the published success rates and complications and shared-decision making to create a mutual treatment plan.

**Table IX.D.8: Evidence on the Efficacy of Multi-Level Surgery**

Study	Year	LOE (1a to 5)	Study Design	Study Group	Clinical End-point	Conclusion
Riley RW et al <sup>1796</sup>	1993	4	Retrospective case series	UPPP, GGA and HS (Phase I) (n=306)	RDI (<20/hr), normalized oxygenation	Phase 1 MLS is effective (76.5% success rate)
Elasfour A et al <sup>1946</sup>	1998	2b	Cohort study	1) UPPP (n=11) 2) UPPP with MLG (n=18) Groups assigned based levels of negative pressure (mesopharynx vs mesopharynx and esophagus)	AHI (50% reduction)	Group 1 success (72.7%) higher than group 2 (61.1%) but group assignment based on presence of multiple levels of negative pressure
Friedman M	200	2b	Retrospective	1) UPPP with tongue	AHI, AI,	The additional of

et al <sup>1785</sup>	3		ve cohort study	RFA (n=143) 2) UPPP alone (n=134)	O2 nadir, ESS, snoring	tongue RFA seems to benefit Friedman stage II and III patients
Woodson BT et al <sup>1496</sup>	2003	1b	RCT	1) Tongue and palate RFA (n=30) 2) CPAP (n=30) 3) Sham-placebo RFA (n=30)	ESS, FOSQ, SNORE25 median reaction time, AHI	RFA improved reaction time, QoL, ESS vs baseline. RFA improved QoL, airway volume, AI, Ari. No difference in QoL and ESS improvement in CPAP vs RFA. Mild side effects in RFA vs sham
Baisch A et al <sup>1927</sup>	2006	2b	Retrospective cohort study	Tongue RFA and/or modified UPF or palate RFA and/or tonsillectomy and/or septoplasty or septorhinoplasty and/or inferior turbinate RFA 1) with HS (n=67) 2) without HS (n=16)	AHI, Ari, SpO2	AHI, Ari, SpO2 and ESS all significantly improved overall. Inclusion of hyoid suspension improved AHI success rate
Verse T et al <sup>1823</sup>	2006	2b	Prospective cohort study	UPF, tonsillectomy, tongue RFA and nasal surgery if needed; 1) with HS (n=45) 2) without HS (n=15)	ESS and AHI; O2 nadir, mean SpO2, Ari	Group 1 showed improvements in all outcomes, group 2 showed improvements in arousal index and ESS only
Friedman et al <sup>1947</sup>	2007	4	Case series	Nasal surgery, Pillar implant, tongue RFA (n=145)	AHI, ESS, snoring VAS, pain levels, narcotic use, complications	All outcome measures significantly improved with 47.5% cure rate.
Lin HC et al <sup>1919</sup>	2008	4	SR and MA (predominantly level 4 studies)	Surgery for OSA at least two sites: nose, oropharynx, hypopharynx (n=1978)	AHI decrease of 50% and less than	Surgical success 66.4%, complication rate 14.6%. All outcome

					20/hr, complication rate, ESS, snoring VAS, AI, sleep architecture, O2 nadir	measures significantly improved.
Friedman M et al <sup>1787</sup>	2008	2b	Retrospective cohort study	UPPP or Pillar implants and/or nasal surgery with 1) Tongue RFA (n=48) 2) Submucosal minimally invasive lingual excision (n=48)	AHI, O2 nadir, AI, snoring, ESS, complications	Group 2 had higher success rate (64.6 vs 41.7%) but had higher complication rate and morbidity.
van den Broek E et al <sup>1786</sup>	2008	2b	Retrospective cohort study	1) UPPP (n=37) 2) UPPP with tongue RFA (n=38)	AHI (Sher criteria), subjective improvement, AI, ODI, mean SpO2), adverse events	Mild improvement in success rate in group 2 (49% vs 42%) without significant added morbidity
Eun YG et al <sup>1948</sup>	2009	2b	Cohort study	UPPP and tongue RFA in: 1) REM related OSA (n=28) 2) Non-REM related OSA (n=62)	AHI (Sher criteria)	Group1 had higher success rate (50% vs 35.5%), however there were significant baseline differences between groups
Fernandez E et al <sup>1790</sup>	2009	2b	Prospective cohort study, randomized	1) UPPP with TBS (n=29) 2) UPPP with tongue RFA (n=28)	AHI (>15 and 50% drop), ESS	Success rates comparable between groups (57.1% and 51.7%) but significantly worse in obese patients
Ceylan K et al <sup>1495</sup>	2009	2b	Prospective cohort study	1) Tongue and palate RFA (n=26) 2) Nasal CPAP (n=21)	ESS, AHI, T90, O2 nadir	No difference in treatment success between groups
Kezirian EJ et	201	2b	Prospectiv	UPPP, tonsillectomy,	AHI (50%	43% surgical

al <sup>1931</sup>	0		e cohort study	GGA ± HS (n=30)	decrease and to <15/hr), CRP, IL6, homocysteine, insulin resistance, leptin, FOSQ	response rate. Significantly improved mean AHI, FOSQ. Significant reduction in CRP in responders, otherwise no differences
Friedman Met al <sup>1826</sup>	2012	2b	Cohort study	1) TORS with ZPP (n=27) 2) Submucosal coblation of tongue base with ZPP (n=22) 3) Tongue RFA with ZPP (n=24)	Complications, pain, ESS, snoring, AHI, O2 nadir	Complications, pain and hospital LOS no different. ESS and snoring improved in all groups. Return to diet and activity longest in group 1. Success rate highest in group 1 (66.7% vs 45.5% vs 20.8%).
Van Maanen JP et al <sup>1949</sup>	2012	2b	Retrospective cohort series	Influence of positional OSA following: 1) UPPP or Z-PP with BOT surgery (n=94) 2) BOT surgery alone (n=36)	AHI, AI	Sleep position not correlated with outcomes
Li S et al <sup>1950</sup>	2013	2b	Cohort study	1) UPPP with TBS (n=45) 2) UPPP (n=33)	AHI, ESS, O2 nadir	Success rates significantly greater in group 1
Plzak J et al <sup>1951</sup>	2013	2b	Cohort study	1) UPPP (n=35) 2) UPPP with tongue RFA (n=79)	AHI, ESS, ODI, mean SpO2, snoring, adverse events	All measures significantly improved except mean SpO2. Success rate better in group 2 (51.7% vs 41.9%)
Van Maanen JP et al <sup>1952</sup>	2014	3b	Case control study	UPPP or ZPP ± tongue RFA in patients with: 1) Non-positional OSA (n=71) 2) Positional OSA (n=68)	AHI	Significant improvement is AHI though greater in non-positional OSA
Handler E et al <sup>1810</sup>	2014	4	SR of case series	1) TBS 2) TBS and UPPP	Surgical success	Group 1 success 36.6%, group 2

				3) GGA and UPPP 4) GGA, HS and UPPP	rate	62.3%, groups 3 and 4 61.1%. No significant difference between groups 2 and 3/4
Verse T et al <sup>1669</sup>	2015	2b	Prospective cohort study	1) UPPP and lingual tonsillectomy (n=58) 2) UPPP, tongue RFA and HS (n=50)	AHI	Greater reductions in AHI in Group 1
Bostanci A et al <sup>1816</sup>	2016	4	SR of case series and cohort studies	1) TBS (Repose) (n=62) 2) Modified TBS (n=51) 3) UPPP with TBS (Repose) (n=176) 4) UPPP with modified TBS (n=124)	AHI	Success rates higher in group 2 compared to group 1. Success higher and not different in groups 3 and 4.
Salapatas AM et al <sup>1953</sup>	2016	4	Retrospective case series	Various nasal procedures, palatal stiffening and tongue RFA (n=601)	AHI, ESS, snoring intensity	AHI: 19.8 +/- 5.9/hr to 12.7 +/- 7.6 /hr (P < .0001), 45.9% surgical success; ESS: 12.1 +/- 4.8 to 6.8 +/- 2.9 (P < .001); mean snoring intensity 8.8 +/- 0.8 to 4.0 +/- 2.1 (P < .001).
Li HY et al <sup>1954</sup>	2016	2b	Retrospective cohort study	1) Relocation pharyngoplasty ± coblation endoscopic lingual lightening (n=30) 2) Relocation pharyngoplasty (n=60)	AHI, complications	Surgical response rate greater in MLS group, no increase in complications
Brietzke SE et al <sup>1938</sup>	2017	2b	Retrospective cohort study, national database	1) UPPP alone (n=7559) 2) UPPP with nasal surgery (n=5219) 3) UPPP with hypopharyngeal surgery (n=1164) 4) UPPP with nasal surgery and hypopharyngeal surgery	Complications, post-operative CPAP orders (implying surgical failure)	MLS (groups 2-4) had higher rates of post-operative bleeding and post-operative CPAP orders

				(n=691)		
Song SA et al <sup>1793</sup>	2017	4	SR and MA of predominantly case series	1) Standard genioplasty (n=27) 2) Modified genioplasty (n=10) 3) GTA (n=24) 4) GTA + HS (n=50)	AHI, O2 nadir	Group 1 and 4 improved AHI and O2 nadir significantly, Groups 3 improved AHI significantly
Samutsakorn P et al <sup>1829</sup>	2018	4	SR and MA of case series	Lingual tonsillectomy with palate surgery (n=107)	AHI, ESS, O2 nadir	All outcome measures improved significantly
Mulholland GB et al <sup>1920</sup>	2019	4	SR and MA	Multilevel palate and tongue base surgery (n=1806)	AHI	MLS results in significant improvements in OSA severity
Missale F et al <sup>1955</sup>	2019	2b	Cohort study	ESP or barbed suspension/relocation pharyngoplasty ± nasal surgery (n=70)	AHI, ESS, intraoperative anteroposterior pharyngeal width	All measures significantly improved. Pharyngeal measurements correlated with success.
MacKay S et al MacKay, 2020 #2997}	2020	1b	RCT	mUPPP and tongue RFA (n=51) vs medical management (weight loss, positional) (n=51)	AHI, ESS	Surgery more effective than medical management in PAP failure

AHI = apnea hypopnea index, AI = apnea index, Ari = arousal index, RDI = respiratory disturbance index, T88 = time spent with SpO<sub>2</sub> <88%, T90 = time spent with SpO<sub>2</sub> <90%, UPPP = uvulopalatalpharyngoplasty, UPF = uvulopalatal flap, RFA = radiofrequency ablation, GGA = genioglossal advancement, GTA = genial tubercle advancement, HS = hyoid suspension, TORS = transoral robotic surgery, ESS = Epworth sleepiness scale, MLG = midline glossectomy, LT = lingual tonsillectomy, BTR = bilateral inferior turbinate reduction, TBS = tongue base suspension

#### IX.D.9 Durability of Surgery: Long Term Results

Evidence regarding the durability of response to surgical intervention for obstructive sleep apnea (OSA) is limited. While short-term effects of sleep surgery have been well-studied, there tends to be a lack of long-term follow up data in studies of this population. There are no systematic reviews that examine long-term efficacy of surgical interventions.

Outcomes that determine durability of treatment include symptoms, somnographic variables, and comorbidities. These parameters are not uniformly examined across the literature when assessing for long-term response.<sup>1685</sup> In addition, surgery can have a variable effects on the durability of different subjective outcomes within the same patient compared to its effect on objective polysomnographic



criteria.<sup>1664</sup> Surgical success is traditionally defined as >50% reduction in AHI to a level less than 20,<sup>1500,1506</sup> although this is not synonymous with complete resolution of disease.<sup>1956</sup> This definition of “success” has been met with criticism,<sup>1956</sup> citing possible sub-therapeutic responses.

One Cochrane review examined the efficacy of any surgical intervention for OSA compared to non-surgical or no intervention.<sup>1482</sup> Of the studies included in this review, duration of follow up for surgical patients was heterogeneous, with a mean duration of 11 months (range: 3 months -4 years). Few studies of surgical intervention for OSA include long-term data beyond 4 years, with longest follow up at 8 years.<sup>1957</sup>

Durability of response to pharyngeal and palatal surgeries has been shown to be variable. About half of patients who undergo such procedures are reported to have persistent improvement in clinical and polysomnographic OSA parameters at time of long-term follow up, which ranges from 3-8 years.<sup>811,1506,1957</sup> Maxillomandibular advancement, whether performed as an isolated procedure or as a secondary phased intervention in a multi-phase approach, has been associated with more consistent longstanding improvement of OSA parameters for 2-6 years after surgery in upwards of 90% of patients.<sup>1500,1958</sup> Data for hypoglossal nerve stimulation (HNS) has demonstrated up to a 75% surgical success rate at 5-year follow up.<sup>1889</sup>

Sleep surgeries targeting structures of the upper airway have been reported to show better long-term outcomes for patients with mild-to-moderate OSA,<sup>1957,1959</sup> especially in those with clearly identifiable obstructive anatomic variants.<sup>1960</sup> A >50% improvement of AHI in mild to moderate OSA is more likely to result in AHI reduction to levels closer to the normal range. The greater propensity for relapse in patients with severe OSA may be due to the higher preexisting burden of disease in this population, as well as presence of comorbid conditions, such as obesity.<sup>1961,1962</sup> Although a greater clinical effect of surgery on reduction of AHI has been noted for patients with more severe OSA,<sup>1500,1958</sup> somnographic parameters can still remain above the normal range, thus necessitating continued treatment. Surgeries targeting skeletal structures and hypoglossal nerve stimulation have demonstrated longer-lasting success rates in patients with moderate-to-severe OSA at 2-6 years.<sup>1889,1958</sup>

Response to surgery tends to degrade over time, and up to half of patients treated with surgery for OSA can eventually relapse.<sup>1506,1664,1957</sup> Relapse has been suggested to be related, in part, to weight gain, interval development of illness, or medication changes, although it can still occur without clear cause.<sup>1481,1961</sup> The majority of failures tend to be apparent between 6 to 12 months after surgery. Improved outcomes and longer persistence of response have been shown with multi-phase and multi-level surgeries that address multiple anatomic sites rather than single-site surgery.<sup>1664,1685,1920,1958</sup>

There is a paucity of data examining the long-term effects of sleep surgery on morbidity and mortality.<sup>1685</sup> Short-term improvements in symptoms, somnographic variables, and comorbid parameters<sup>1963,1964</sup> have been well-reported in these patients; however, the best way of measuring longstanding impact has yet to be determined. Surgical treatment of OSA has been suggested to have positive effects on cardiovascular outcomes and on mortality,<sup>1497,1963</sup> although the evidence is limited and should be interpreted cautiously.

The variety of surgical interventions available, along with the clinical and anatomic variability of patients undergoing these procedures, makes it difficult to generalize durability of response. Newer surgical techniques, such as hypoglossal nerve stimulator implantation, are also just beginning to amass

longitudinal evidence based on therapeutic AHI. Improvements in surgical techniques, such as expansion palatopharyngoplasty, have led to increased success of short-term surgical response rates,<sup>1965</sup> and long-term data will be needed for these updated techniques.

Surgery has the potential to provide long-lasting benefit, but long term follow up is required as OSA is a chronic disease. The variability of response and the risk of relapse noted in the current literature reinforce the necessity of evidence-driven patient selection and directed counseling about the expected goals and range of outcomes.

#### Long-term Response to Surgery for OSA

Aggregate Grade of Evidence: C (Level 1a: 1 study; Level 2a: 2 studies; Level 2b: 3 studies; Level 3b: 2 studies). Evidence grade is based on studies with mean follow up duration greater than 2 years.

**Table IX.D.9: Summary of Evidence for Durability of Response to Surgery**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
He et al. <sup>811</sup>	2019	2a	SR and meta-analysis (2 RCTs and 9 cohort studies).	Adults who underwent UPPP or its modification for OSA and had short-term (n=285) and/or long-term (n=368) follow-up (at least 34 months) with objective sleep study results	AHI	1) Despite surgical efficacy decreasing over time (67.3% short-term and 44.35% long-term), UPPP surgeries are effective. 2) BMI, lowest O2 sat, and proportion of sleep time with O2 sat <90% were potentially predictive of long-term response.
Costantino et al. <sup>1889</sup>	2019	2a	SR and meta-analysis of cohort studies	Adult patients (n=350) who underwent hypoglossal nerve stimulation (HNS) for treatment of moderate-to-severe OSA	AHI, ESS, adverse events	1) At 5 year follow up: surgical success rate was 75%, mean AHI reduction was 18.00, and ESS mean reduction was 5.27 (for Inspire HNS). 2) 6% of patients with serious

						device-related adverse events.
Janson et al. <sup>1957</sup>	1997	2b	Cohort study	Patients (n=34) with OSA who underwent UPPP with (n=25) or without (n=9) long-term follow-up	Symptoms, AHI (responders with >50% AHI reduction and AHI ≤10)	1) 48% were responders at long-term (4-8 year) follow up. 2) Responders had lower preoperative AHI. 3) Some initially successfully treated patients (n=4, 16%) relapsed in the long term.
Riley et al. <sup>1958</sup>	2000	2b	Cohort study	Patients (n=40) with severe OSA who underwent phase II (skeletal and soft tissue) surgical reconstruction for sleep apnea	PSG variables (RDI, LSAT), QoL, complications	90% of patients showed persistent clinical success (improved quality of life assessments and polysomnography equivalent to CPAP patients; or postoperative RDI<20 with at least 50% reduction and LSAT levels equivalent to nasal CPAP patients) at time of long-term follow up (mean follow-up 50.7 ± 31.9 months).
Boot et al. <sup>1664</sup>	2000	2b	Cohort study	Patients (n=58) with OSA who underwent UPPP with long-term follow up data (11-74 months, median 34 months)	Snoring, excessive daytime sleepiness, ODI	1) Response to UPPP for OSA decreases progressively over years after surgery. 2) UPPP in combination with tonsillectomy more effective than UPPP alone.

Lee et al. <sup>1963</sup>	2018	3b	Retrospective case-control study	1) Adults with OSA who underwent UPPP (n=22,213) 2) Adults with OSA who did not undergo surgical intervention (n=170,103) 3) Matched control group of adults without OSA (n=961,590)	Newly diagnosed MI, CHF, and AF	UPPP, regardless of its effects on AHI, can significantly reduce risk of CHF (hazard ratio [HR]: 1.17 [1.10–1.24] without surgery to 0.76 [0.60–0.96]) and AF (HR: 1.39 [1.32–1.46] without surgery to 1.12 [0.94–1.32]) in patients with OSA for up to 8 years after surgery.
Walker-Engström et al. <sup>1506</sup>	2002	1a	Randomized controlled trial	Patients with mild-to-moderate OSA treated with oral appliance (OA, n=45) vs. UPPP (n=43).	AI, AHI (success defined as >50% reduction of AI/AHI), symptoms, compliance, need for complementary treatment, adverse effects.	1) Success rate at 4 year follow up was higher in OA group vs. UPPP (81% vs. 53%), but effectiveness of OA partly invalidated by its long-term compliance of 62%. 2) Success rate of UPPP decreased from 1 to 4 year follow up: 70% to 53% (AI), and from 60% to 35% (AHI).

UPPP = uvulopalatopharyngoplasty, LAUP = laser-assisted uvulopalatoplasty, lateral PP = lateral pharyngoplasty, TA = tongue advancement (mandibular osteotomy), TS = tongue suspension, TCRTA = temperature-controlled radiofrequency tissue ablation, OA = oral appliance, ESS = Epworth Sleepiness Scale, RDI = respiratory disturbance index, LSAT = low oxyhemoglobin desaturation, ODI = nocturnal oxygen desaturation index

#### IX.D.10 Tracheotomy

Tracheostomy, a surgical procedure in which an opening is created in the trachea to bypass an upper airway obstruction, was described in 1969 for treatment of OSA. Until that time, there were no other

treatments for OSA or its medical sequelae of pulmonary and systemic hypertension, disabling daytime sleepiness, and decreased mental function.<sup>1966</sup>

During the 1970s, the medical management of OSA with continuous positive airway pressure was not widely used or available and many articles evaluated the efficacy of tracheostomy for OSA. Guilleminault et al.<sup>1967</sup> reported on 268 patients seen between 1972-1978 who were classified as “predominantly OSA” based on clinical symptoms and polysomnography. Of the 72 patients that underwent tracheostomies, there were 50 patients with follow up; these patients had a mean pre-operative apnea Index (AI) >60 events/hour and had post operative PSGs carried out 6 weeks to 3 months after surgery. For all patients, the AI decreased to below 5 events/hour and elimination of daytime sleepiness and fatigue. Patients, when asked, responded that they would opt for surgery again, based on their improvement in symptoms.

Simmons et al.<sup>1968</sup> reported on 14 patients (12 adults and 2 children) with OSA where no specific anatomical cause was found. Indications for surgery were hypertension, loss of livelihood and social contacts, and inability to drive due to disabling hypersomnolence for adults, and for children were emotional and learning problems and enuresis. Tracheostomy was successful in all 14 patients after medical management had failed. Several additional articles describe resolution of hypersomnolence, hemodynamic abnormalities, cardiac arrhythmias, sleep cycle disruptions, and arterial blood gas abnormalities associated with OSA, as well as resolution of obstructive events with tracheostomy.<sup>1969-1976</sup>

In 1980, continuous positive airway pressure (CPAP) was developed by Dr. Colin Sullivan which applied pressure through the nose to keep the upper airway open. As CPAP use has become more prevalent, it has evolved into the initial treatment for many patients with OSA. However, there are many patients who did not tolerate CPAP, while others who continued to have hypersomnolence, morning headaches, and cardiovascular disease secondary to OSA despite CPAP use.

To determine if tracheostomy results increased survival for patients with OSA, Partinen et al.<sup>1977</sup> evaluated the long-term outcome of 198 OSA patients undergoing tracheostomy compared to individuals treated with weight loss and better sleep hygiene. The patients were seen between 1972 and 1980 and received tracheostomy (n=71) or recommendations for weight loss (n=127). At 5-year follow up, all deaths (14) had occurred in the non-surgical group, and this group also had a higher 5-year crude vascular mortality rate. He et al.<sup>1978</sup> studied 385 male OSA patients for over a decade and found that those with an AI>20 events/hour had a greater mortality rate than those with an AI<20/hour. For patients with an AI>20/hour, none of the patients treated with tracheostomy (N=19) or nasal CPAP (4) died.

A systematic review of the literature by Camacho et al.<sup>1979</sup> identified 10 relevant studies that had reported outcomes for AI, apnea-hypopnea index (AHI), oxygen desaturation index (ODI), effect on daytime sleepiness, and mortality. Tracheostomy was found to significantly decrease AI, oxygen desaturation index, sleepiness, and cardiovascular mortality in both obese and non-obese patients with OSA.

Mild complications from tracheostomy include wound infections, necrosis of skin flaps after permanent tracheostomy, and an increase in pulmonary secretions resulting in pneumonia or bronchitis. Respiratory distress secondary to mucous plugging and presence of granulation tissue requiring operative or procedural intervention have been reported. There was one report of the severe complication of tracheal innominate fistula, which resulted in death.<sup>1967,1970,1973</sup>

Tracheostomy is difficult for some patients to adjust to and can result in depression and psychosocial problems.<sup>1967,1980</sup> To counter this, some patients may wear a scarf or high collared shirt to cover the

tracheostomy tube during the day while it is plugged. The tracheostomy can also restrict activities of daily living and social activities.

Tracheostomy has been shown to be an effective surgical procedure for patients with OSA and obesity hypoventilation syndrome. It can result in resolution of OSA-associated conditions such as sleep stage abnormalities, pulmonary and systemic hypertension, hypersomnolence and poor quality of life. Mortality has also been shown to decrease in OSA patients who have had tracheostomy versus those treated with medical therapies. Currently, tracheostomy is reserved for those patients who are unable to use CPAP, or have not benefited from CPAP and do not have addressable identifiable upper airway abnormalities but are amenable to surgery.

#### IX.D.11 Bariatric Surgery

Obesity, as defined by a BMI  $\geq 30\text{kg/m}^2$ , continues to be a worldwide epidemic. According to the most recent World Health Organization data, the prevalence of worldwide obesity has tripled since 1975. In 2016, more than 1.9 billion adults worldwide were overweight with 650 million categorized as obese.<sup>1981</sup> The prevalence of obstructive sleep apnea (OSA) amongst obese adults is high (55-90%), with a positive correlation between OSA and increasing BMI<sup>1982-1984</sup>. Of the various treatment options available for OSA in obese patients, bariatric surgery has been shown to improve various co-morbidities including OSA.<sup>193,194,1985</sup>

Several randomized control trials (RCT) have been completed evaluating the impacts of bariatric surgery on OSA.<sup>193,1986,1987</sup> Two of these primarily compare the results of diet, exercise, and intense nutritional care versus the results of bariatric surgery.<sup>193,1987</sup> These two studies revealed that the surgical group achieved significantly higher weight loss than the nutrition group, but there was no significant difference in their apnea hypopnea index (AHI) values. Furthermore, there was found to be no significant difference in their ability to be weaned from a positive airway pressure system.<sup>1987</sup> The RCTs listed may have been limited by their method of bariatric surgical intervention as both utilized gastric banding. However, systematic reviews show that procedures that are both restrictive as well as malabsorptive (such as roux-en-y surgery), where the stomach anatomy and transit time are altered, are more efficacious in reducing OSA when compared to purely restrictive procedures like gastric banding.<sup>1988,1989</sup>

More recent systematic reviews suggest that there is significant reduction in AHI levels following bariatric surgery. One systematic review compared intensive lifestyle interventions to bariatric surgery with regards to their effect on OSA. Those undergoing bariatric surgery had a two times greater reduction in AHI than those in the intensive lifestyle intervention group.<sup>1962</sup> Several of the studies included other OSA endpoints, specifically the Epworth Sleepiness Scale Scores (ESS) and nocturnal oxygen saturation nadir (SaO<sub>2</sub>).<sup>1962,1982,1986,1990,1991</sup> In a study comparing bariatric surgery with CPAP treatment, both groups had similar decreases in ESS.<sup>1986</sup> Two other studies, and one systematic review, noted a reduction in the ESS after bariatric surgery,<sup>1962,1982,1990</sup> while one study noted a decrease in the percent time with nocturnal SaO<sub>2</sub> below 90%.<sup>1982</sup> Additionally, a systematic review noted an increase in the nocturnal mean and nadir SaO<sub>2</sub> following bariatric surgery.<sup>1991</sup>

There are general trends noted amongst all these studies. The most important is that bariatric surgery often results in a significant reduction in AHI levels. However, OSA often persists following bariatric surgery. There is little data about the ability to discontinue positive airway pressure use once significant weight reduction has occurred.

**Bariatric Surgery to Improve OSA**

Aggregate Quality of Evidence: B (level 1: 5 studies ; level 2: 9 studies)

Benefit: OSA severity improves after bariatric surgery when there is significant weight reduction.

Harm: Bariatric surgery is an invasive procedure with potential risks. Residual sleep disordered breathing may persist following bariatric surgery.

Cost: High costs associated with surgery, hospitalization, and time off work for follow up visits and recovery.

Benefits-Harm Assessment: Benefits outweigh the harms.

Value Judgments: Bariatric surgery in obese patients with OSA can lead to a significant reduction in the OSA severity and other obesity-related comorbidities. Surgery is associated with improved OSA-related symptoms. Durability of OSA outcomes requires further investigation.

Recommendation Level: Recommendation

Intervention: Bariatric surgery is recommended to reduce OSA severity in obese patients with comorbid OSA

**Table IX.D.11: Evidence for Bariatric Surgery and OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Ashrafian H et al. <sup>194</sup>	2015	1c	Systematic Review	1. Bariatric Surgery 2. Non-surgical Weight Loss	AHI before and after intervention	1. Surgical intervention associated with significant reduction in post op AHI (but significant heterogeneity) 2. Non-surgical intervention also associated with significant post op reduction in AHI (but significant heterogeneity)
Bakker JP et al. <sup>1986</sup>	2018	2b	1 RCT, low quality, did not meet power	1. Laparoscopic gastric banding 2. CPAP	AHI at 9 months and 18 months after intervention	1. No difference in AHI off CPAP between groups at 9 or 18 months.
Buchwald H et al. <sup>1992</sup>	2004	1c	Systematic Review	Meta-analysis of improvement / resolution of OSA in patients undergoing bariatric surgery	Improvement/ resolution of OSA	83.6-85.7% resolution/ improvement in OSA among total patient population, but significant heterogeneity of studies, with inclusion of RCTs, non-randomized CTs, and uncontrolled case series. Also included all types of bariatric procedures.

Dixon JB et al. <sup>193</sup>	2012	1b	1 RCT	1. Diet, exercise, behavioral program 2. Laparoscopic adjustable gastric banding	1. Reduction in AHI at 2 years	Surgical group achieved significantly greater weight loss but no difference in AHI reduction. Patterns suggest that much of benefit to AHI is associated with mild to moderate weight loss with diminishing returns with further weight loss.
Feigel-Guiller, B. et al. <sup>1987</sup>	2015	1b	1 RCT	1. Intensive nutritional care 2. Laparoscopic adjustable gastric banding	1. Rate of PAP weaning (AHI < 20) at years 1 and 3	Surgical group achieved significantly greater weight loss at years 1 and 3, but no difference in ability to wean from PAP at years 1 and 3.
Greenburg DL et al. <sup>1993</sup>	2009	1c	Systematic Review	Meta-analysis of improvement /resolution of OSA in patients undergoing bariatric surgery	1. BMI reduction 2. AHI reduction	Significant heterogeneity between studies. Significant reduction in BMI and AHI seen, but AHI was still moderate. Bariatric surgery improves, but does not resolve OSA.
Haines KL et al. <sup>1990</sup>	2007	2c	Prospective uncontrolled trial	Patients with OSA undergoing bariatric surgery	1. BMI reduction 2. RDI reduction at 6-42 months after surgery	Significant reduction in BMI and RDI, but RDI remained moderate. Bariatric surgery improves, but does not resolve OSA.
Hariri K et al. <sup>1994</sup>	2018	2c	Retrospective review	1. Obesity Classes (I, II, III); 2. Sleeve Gastrectomy versus Roux-en-Y Bypass; 3. Pre-op AHI severity (mild, med, severe); All 3 evaluated at 6 months and 1 year	Subjective post op OSA remission (STOP-BANG <2 and discontinuation of CPAP)	No difference in subjective OSA remission between obesity class groups at 6 or 12 months. No difference in subjective OSA remission by type of surgery at 6 or 12 months. No difference in subjective OSA remission by pre-op AHI severity.



Lettieri CJ et al. <sup>1982</sup>	2008	2c	Prospective uncontrolled trial	Patients with OSA undergoing bariatric surgery	AHI severity (mild, mod, severe) at 1 year post bariatric surgery	Significant change in BMI, ESS score, and AHI post op at 1 year, but AHI remained moderate. Severity improved in 50%.
Miras AD et al. <sup>1995</sup>	2018	2c	Retrospective review	All patients in the National Bariatric Surgery Registry (NBRS) from 2000-2015 totaling 50,782 patients.	Prevalence of OSA before and after bariatric surgery recorded years 1-5 postoperatively	19.7% of patients had diagnosed sleep apnea prior to bariatric surgery (79.8% with no diagnosis or indication of OSA). Postoperatively, the prevalence dropped to 10%. However, there are no specific numbers listed for sleep apnea results post-procedure. In general, a decrease in the prevalence of OSA reported after bariatric surgery.
Quintas-Neves M et al. <sup>1988</sup>	2016	2a	Systematic Review	Review of 22 cohort studies involving pre- and postoperative OSA in the setting of bariatric surgery.	Improvement/resolution of OSA. Type of bariatric surgery and impacts on OSA.	Significant reduction in BMI and AHI values following bariatric surgery with short term follow up (1-2 years). Greater reduction in AHI values in those undergoing restrictive and malabsorptive procedures (roux-en-y) vs restrictive alone (gastric banding)
Sarkhosh K et al. <sup>1989</sup>	2013	2a	Systematic Review	69 studies reviewed: 3 RCTs, 11 controlled trials, 55 case series.	Type of bariatric surgery and impacts on OSA.	Significant improvement or resolution in OSA following bariatric surgery. Interventions with a malabsorptive mechanism, which alter the gut anatomy and transit time, are more efficacious in impacting in obstructive sleep apnea.
Wong AM et al. <sup>1962</sup>	2018	2a	Systematic Review	Meta-analysis of improvement/resolution of OSA in patients undergoing bariatric surgery. 15	Improvement and resolution of OSA following bariatric surgery. Secondary measures such as BMI, ESS, and	Significant reduction in AHI following bariatric surgery with greater reduction noted in those with higher presurgical AHI. Two times greater reduction in AHI in bariatric surgery group compared to intensive lifestyle interventions. 97.5% of

				studies included in analysis.	comparisons to intensive lifestyle interventions were performed.	bariatric patients still had residual OSA (AHI >5). Also noted no correlation between amount of weight lost and change in AHI.
Zhang, Y. et al. <sup>1991</sup>	2019	2a	Systematic Review	Systematic review of improvement /resolution of OSA in patients undergoing bariatric surgery. 15 studies included: 13 prospective, 1 RCT, and 1 retrospective	Improvement and resolution of OSA following bariatric surgery. Primary endpoints included AHI, Mean SaO <sub>2</sub> , and Nadir SaO <sub>2</sub> .	Improvement of mean and nadir SaO <sub>2</sub> following bariatric surgery. Significant reduction in AHI between pre and post surgical period. Significant heterogeneity noted.

## IX.E Surgical Efficacy for OSA Symptoms and Comorbidities

### IX.E.1 Surgery and Daytime Sleepiness and Quality of Life

Sleepiness is arguably the most common daytime complaint of OSA sufferers<sup>1996,1997</sup>. It is attributed to the recurrent arousals and desaturations that lead to sleep fragmentation and decreased slow wave sleep. Assessing sleepiness with patient-reported scales such as the Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ) and Calgary Sleep Apnea Quality of Life Index (SAQLI) are critical. Scores are often not associated with the apnea-hypopnea index (AHI)<sup>1998,1999</sup>.

Evidence supports that upper airway surgery reduces sleepiness. Palatal surgery outcomes are the most widely published. The traditional uvulopalatopharyngoplasty (UPPP) with and without tonsillectomy was found to be significantly more effective at reducing ESS compared to no treatment<sup>1687</sup>. Other palatal techniques and hypopharyngeal surgeries have also been effective at alleviating sleepiness<sup>1801,1803,1816,1919,1965,2000-2003</sup>. Studies on hypoglossal nerve stimulation and maxillomandibular advancement (MMA) report significant improvements lasting beyond five and eight years respectively, with normalization of ESS and sleep-related QOL scores (FOSQ and SAQLI)<sup>1867,1873,1889,2004-2006</sup>. Nasal surgery significantly improved ESS despite not having a large effect on AHI<sup>544,905,1659,1960,2007</sup>. Less invasive techniques such as radiofrequency and soft palate implants may have benefit on sleepiness<sup>1736,1745,1781,2008-2011</sup>. Tracheostomy resolves sleepiness in most, but not all, OSA patients<sup>1979</sup>. The only surgical technique that has been labelled ineffective in this regard is laser-assisted uvulopalatoplasty (LAUP)<sup>1482</sup>.

Certain factors appear to further improve the effect of surgery on sleepiness. Repeated treatments in cases of minimally invasive procedures can achieve longer-term results<sup>2012</sup>. Targeting multiple levels is more effective than single-site procedures, in the short-term<sup>2011,2013</sup>. Steward et al showed that ESS and

FOSQ significantly improved with five sessions of multilevel (tongue and soft palate) temperature-controlled radiofrequency tissue ablation (TCRFTA) compared to three single-level (tongue) sessions<sup>2014</sup>.

Surgery has been compared against non-surgical interventions in a few randomized controlled studies. Mackay et al. recently reported that surgery (combined modified uvulopalatopharyngoplasty and minimally invasive tongue volume reduction) was significantly more effective in lowering ESS (12.4 to 5.3) compared to ongoing medical management (11.1 to 10.5) over six months<sup>1918</sup>. The aim of this trial was to assess whether modified uvulopalatopharyngoplasty (UPPP) and minimally invasive tongue reduction was beneficial for those with moderate to severe OSA<sup>1918</sup>. This was a multicenter, open-label randomized controlled trial to assess the benefits of surgical intervention versus medical management (instruction on mitigating reversible causes of inspiratory flow resistance – weight loss, bed positioning, etc.). Symptomatic adults (age 18-70 years) with an apnea-hypopnea index (AHI) >15 were enrolled with 51 patients in each group (n=102). Primary outcomes were reduction in AHI and Epworth Sleepiness Score (ESS).

The mean AHI was reduced from 47.9 to 20.8/h at 6 months in the surgery cohort and decreased from 45.3 to 34.5/h for the medical management group. The mean ESS was 12.4 to 5.3 at 6 months in the surgery group and marginally decreased from 11.1 to 10.5 in the medical management group ( $P < .001$ ). Four percent in the surgery group had serious adverse events. Of note, only 7 of 51 medical management patients attempted CPAP during the trial, indicating that 44 patients in the control arm were not receiving active treatment, perhaps contributing to differences between groups.

Collectively however, the observed benefits from surgery are seen in both objective and subjective findings. However, it is unclear what truly is a significant reduction in AHI and thus such changes should be interpreted in the context of patient reports and/or hard outcomes.

Walker-Engstrom et al. found similar score improvements for sleep and vitality in both UPPP and oral appliance therapy groups with mild-moderate OSA after a year<sup>2015</sup>. Woodson et al conducted a trial of mild-moderate OSA patients who underwent multilevel TCRFTA (palate and tongue base) versus CPAP versus sham<sup>1496</sup>. ESS and FOSQ scores of both CPAP and TCRFTA treatment groups improved significantly compared to sham, although the confidence interval included zero<sup>1496,2016</sup>. Vicini et al. demonstrated that both MMA and autotitrating positive airway pressure (APAP) reduced ESS scores equally one year after commencing treatment, with no statistical difference between the groups<sup>1502</sup>.

### **Vigilance**

Vigilance, a surrogate marker for sleepiness, has been reported as an outcome measure in a few studies. Multilevel TCRFTA (palate and tongue base) significantly improved reaction time testing compared with baseline, while continuous positive airway pressure (CPAP) did not<sup>1496</sup>. Faster reaction time correlated with a greater number of levels and sessions of TCRFTA<sup>2014</sup>. Modified UPPP was shown to significantly improve alertness through better Oxford sleep resistance (OSLER) test scores compared to the untreated group<sup>2000</sup>. The proportion of patients who passed the 40-minute test after surgery rose from 41% to 91%<sup>2000</sup>. Boyd et al found that patients performed better in a psychomotor vigilance task that measures sustained attention over 10 minutes after MMA<sup>2004</sup>. MMA and CPAP improved vigilance to the same extent from baseline in 24 patients who had been treated with CPAP initially, and then underwent MMA<sup>2017</sup>.

### **Sexual function**

Two small prospective studies on UPPP have shown post-operative increase in testosterone levels and

normalization of decreased libido, as well as significant improvement in the International Index of Erectile Function<sup>2018,2019</sup>.

### Psychological symptoms

Prospective cohort studies and case series have shown improvement or resolution in anxiety, depression, hostility and daytime dysfunction after OSA surgery<sup>2013,2020-2023</sup>. Ishman et al found that the reduction in sleepiness scores, and not the OSA severity, is predictive of improvement in depressive scores using the Beck Depression Inventory-II<sup>2013</sup>. Li et al, however, did not find any correlation between mood improvement and changes in polysomnographic parameters or ESS scores<sup>2022</sup>. There is a possibility that psychological symptoms improve at least in part due to the patient's perception of his/her disease being treated, and not purely due to change in AHI<sup>2021</sup>.

### General quality of life

Holty and Guillemainault reported that MMA reduced symptoms such as irritability, morning headaches, memory loss and impaired concentration in most patients<sup>1866</sup>. Skeletal advancement surgery can improve 36-Item Short Form Health Survey (SF-36) scores, with 66.7% to 100% of patients returning to normal levels post-operatively<sup>2004,2005</sup>. SF-36 scores similarly improved in patients who underwent modified UPPP, and not in the untreated group<sup>2000</sup>.

The Cochrane review by Sundaram et al in 2005 concluded that symptoms and QOL were not significantly improved with surgery<sup>1482</sup>. The review however was not comprehensive and did not include all types of sleep surgery such as MMA and many newer surgical techniques.

### Surgery to Improve Sleep Related Quality of Life

**Aggregate Quality of Evidence:** B (Level 1a: 8 studies; Level 1b: 11 studies; Level 2a: 4 studies; Level 2b: 3 studies; Level 4: 20 studies).

**Benefit:** Improved sleepiness, reduced daytime symptoms, and improved quality of life.

**Harm:** Risks specific to surgery type and potential for complications.

**Cost:** Moderate to high costs related to surgery and hospital care. Indirect costs: Time off work after surgery.

**Benefits-Harm Assessment:** Preponderance of benefit over harm.

**Value Judgments:** Properly selected surgical interventions can lead to improvement in symptoms of SDB with low risk for harm.

**Recommendation Level:** Recommendation.

**Intervention:** OSA surgery may be offered to patients who cannot use CPAP. Surgery has the ability to improve sleep-related and general quality of life measures in properly selected patients.

**Table IX.D.12.a: Evidence for Surgery and Improved Daytime Sleepiness and Quality of Life**

STUDY	YEAR	LO E	STUDY DESIGN	STUDY GROUPS	CLINICAL END-POINT	CONCLUSION
Farrar et al <sup>2008</sup>	2008	1a	SR and MA	Isolated radiofrequency ablation of the palate, tongue base, or both	ESS, RDI, LSAT	Radiofrequency ablation reduces ESS and RDI levels. ESS decreased by 31%. RDI reduced by 31% in short-term and 45% in

						long-term.
Franklin et al <sup>2016</sup>	2009	1a	SR	1) Surgery 2) Sham or no treatment	ESS, AHI, QOL	Laser-assisted uvulopalatoplasty or radiofrequency ablation has no effect on daytime sleepiness, apnea reduction and QOL.
Gao et al <sup>2009</sup>	2019	1a	SR and network MA	1) Minimally invasive treatments including surgery	AHI, ESS	Simple surgical procedures improve AHI and ESS insignificantly.
Ishii et al <sup>544</sup>	2015	1a	SR and MA	Nasal surgery including endoscopic sinus surgery	AHI, RDI, ESS	Significant improvements in ESS and RDI after nasal surgery, but no significant improvements in AHI.
Kezirian and Goldberg <sup>1801</sup>	2006	1a	SR	Hypopharyngeal surgeries	PSG, ESS, QOL	Hypopharyngeal surgery has success rates of 35-62%. Improved ESS and FOSQ were seen.
Stuck et al <sup>1687</sup>	2018	1a	SR	UPPP ± tonsillectomy	PSG, ESS, sexual function, cardiac parameters morbidity and mortality	UPPP ± tonsillectomy reduced AHI and ESS, and improved sexual function. AHI change was 18.59. ESS change was 5.37.
Sundaram et al <sup>1482</sup>	2005	1a	SR	1) Surgical intervention for OSA 2) Other surgical or nonsurgical interventions, or no intervention	PSG, sleepiness, QOL	Surgery has inconsistent effects. There is no convincing evidence to support surgical treatment of OSA.
Zaghi et al <sup>2006</sup>	2016	1a	SR and MA	MMA	AHI, RDI, LSAT, ESS	MMA is an effective treatment for OSA. Success rate of 85.5%; cure rate of 38.5%. ESS decreased from 13.5 to 3.2.
Atef et al <sup>2012</sup>	2005	1b	RCT	1) Bipolar radiofrequency volumetric tissue reduction of the palate 2) LAUP	AHI	Bipolar radiofrequency volumetric tissue reduction of the palate required more sessions to achieve a favorable outcome, but benefit

						was also maintained for longer.
Baba et al <sup>1781</sup>	2015	1b	SR and MA	Isolated TCRFTA of the soft palate, base of tongue or both	ESS, RDI, LSAT, SF-36	TCRFTA can reduce RDI and sleepiness when directed at the base of tongue or as a multilevel procedure.
Browaldh et al <sup>2000</sup>	2016	1b	RCT	1) Modified UPPP including tonsillectomy 2) No treatment	ESS, SF-36, vigilance	ESS, SF-36, vigilance improved after surgery.
Holmlund et al <sup>1736</sup>	2014	1b	RCT	1) Radiofrequency of the soft palate 2) Sham surgery	AHI, ESS, snoring	Radiofrequency surgery of the soft palate has no effect on daytime sleepiness or apnea frequency.
Li et al <sup>905</sup>	2011	1b	SR and MA	Nasal surgery including endoscopic sinus surgery	AHI, ESS	Nasal surgery can effectively reduce daytime sleepiness, but is limited in reducing OSA severity.
Mackay et al <sup>1918</sup>	2020	1b	RCT	1) Combined modified UPPP and radiofrequency of the tongue 2) Ongoing medical management	ESS, PSG	Combined palatal and tongue surgery, compared with medical management, reduced AHI and ESS at 6 months. Mean AHI and ESS baseline-adjusted between-group difference was -17.6 and -6.7 respectively.
Sharma et al <sup>1960</sup>	2019	1b	SR and descriptive MA	1) Rhinological surgical intervention 2) Non-surgical and/or non-rhinological surgical intervention	AHI, RDI, ESS	Nasal surgery may have limited benefit on OSA, although improvements in sleep parameters and ESS are seen. ESS changed by 3.9.
Vicini et al <sup>1502</sup>	2010	1b	RCT	1) MMA 2) Auto-titrating positive airway pressure	AHI, ESS	Both groups had similar improvement of mean AHI and ESS.
Walker-Engstrom et al <sup>2015</sup>	2000	1b	RCT	1) UPPP 2) MAD	PSG, Minor Symptoms Evaluation-Profile (MSE-P)	QOL improved in both groups 1 year after intervention. The dental group had superior PSG values, but lower contentment.

Woodson et al <sup>1496</sup>	2003	1b	RCT	1) TCRFTA 2) CPAP 3) Sham-placebo	QOL, ESS, PSG, reaction time	TCRFTA improved reaction time, OSA-specific QOL and ESS compared to baseline. TCRFTA improved reaction time, while CPAP did not.
Wu et al <sup>1659</sup>	2017	1b	MA	Isolated nasal surgery	AHI, ESS	AHI and ESS improve significantly after isolated nasal surgery, but AHI demonstrated only slight improvement.
Bostanci and Turhan <sup>1816</sup>	2016	2a	SR	Tongue base suspension (TBS) techniques ± UPPP	AHI, LSAT, ESS	Tongue base suspension has some efficacy, with or without UPPP. ESS improved with tongue base suspension.
Choi et al <sup>1745</sup>	2013	2a	MA	Pillar implant for mild to moderate OSA	ESS, AHI, snoring	The Pillar implant reduced ESS and AHI significantly for mild to moderate OSA.
Holty and Guilleminault <sup>1866</sup>	2010	2a	SR and MA	MMA	PSG, ESS, QOL	MMA improved AHI, reduced daytime symptoms and improved QOL. Success and cure rates were 86.0% and 43.2% respectively.
Wang et al <sup>2007</sup>	2019	2a	SR and MA	Nasal surgery ± endoscopic sinus surgery	AHI, ODI, LSAT, ESS	Isolated nasal and sinus surgery can reduce daytime sleepiness in OSA. ESS change was 3.79. There was no significant improvement on objective parameters.
Conradt et al <sup>2017</sup>	1998	2b	Cohort	Patients were treated with CPAP before undergoing MMA	PSG, vigilance	MMA has positive effects on sleep, respiration and vigilance which are comparable to CPAP.
Klonoff et al <sup>2021</sup>	1987	2b	Cohort	1) UPPP 2) Coronary bypass surgery	Psychological assessment battery, PSG	Anxiety and depression are lower after both surgeries, possibly by virtue of the surgery resolving the disease.

Xiao et al <sup>2023</sup>	2016	2b	Cohort	1) Nasal surgery for patients with nasal obstruction 2) No surgery for patients without nasal obstruction	PSG, PSQI, Symptom Check List-90	Nasal surgery reduced daytime dysfunction scores on PSQI, anxiety and hostility scores.
Boyd et al <sup>2004</sup>	2019	4	Case series	MMA	ESS, QOL, AHI, psychomotor vigilance testing	MMA improved all measures. AHI decreased by 81.3%. ESS change was 8.5. 66.7% had normal FOSQ after surgery compared to 10% before surgery.
Camacho et al <sup>1979</sup>	2014	4	SR and MA	Tracheostomy	AI, AHI, ODI, sleepiness	Tracheostomy significantly decreases AI, AHI and sleepiness. AI change was 83.47. Mean AHI and ODI was in the moderate range post tracheostomy.
Camacho et al <sup>1867</sup>	2019	4	SR and MA	MMA	AHI, ESS, LSAT	Improvements in AHI, sleepiness, and lowest oxygen saturation were maintained in the long term (4 to <8 years). Mean AHI increased to moderate OSA in the very long term ( $\geq 8$ years).
Certal et al <sup>1873</sup>	2015	4	SR and MA	Hypoglossal nerve stimulation therapy	AHI, ODI, ESS, QOL	Hypoglossal nerve stimulation improves AHI, ODI and ESS fairly consistently over 12 months. There was improvement in QOL.
Costantino et al <sup>1889</sup>	2020	4	SR and MA	Hypoglossal nerve stimulation therapy	AHI, ESS, ODI	Hypoglossal nerve stimulation achieves high surgical success rates of up to 76.9% (ImThera) at 12 months, and 75% (Inspire) at 60 months. ESS improved with all devices.
Dahlof et al <sup>2020</sup>	2000	4	Case series	UPPP	Psychiatric symptoms,	Sleep disturbance and reduced daytime



					dexamethasone suppression test, PSG	alertness may be at least one of the factors behind depressive symptoms in OSA. Relapse occurred at 6 months, but symptoms were still less than baseline.
Ishman et al <sup>2013</sup>	2014	4	Case series	Any OSA surgery	ESS, Beck Depression Index, RDI	Surgery, especially multilevel surgery, significantly reduces depression and sleepiness scores. 77.3% and 75.0% had resolution of sleepiness and depression respectively.
Justin et al <sup>2001</sup>	2016	4	SR and MA	TORS	AHI, LSAT, ESS	TORS appears to be a promising procedure as part of multilevel surgery. AHI decreased by 24.0. Success achieved in 48.2%. ESS decreased by 7.2.
Li et al <sup>2022</sup>	2004	4	Case series	Extended uvulopalatal flap	RDI, LSAT, 5-Item Mental Health scale (MH-5), ESS	Extended uvulopalatal flap can mildly improve, but not normalize, mood. Success rate was 79.8%. The improvement is not purely due to changes in PSG or ESS.
Lin et al <sup>1919</sup>	2008	4	SR and MA	Multilevel surgery involving at least 2 levels (nose, oropharynx, hypopharynx)	PSG, ESS, QOL	Multilevel surgery can improve outcomes. Success rate was 66.4%. ESS improved in 23/26 groups and changed by 43.0%.
Llewellyn et al <sup>2010</sup>	2019	4	SR and MA	Cautery-assisted palatal stiffening operation	AHI, ODI, LSAT, ESS	Cautery-assisted palatal stiffening operation improved respiratory parameters. ESS improved from 11.8 to 5.1.
Meccarillo et al <sup>2002</sup>	2017	4	SR and MA	TORS	AHI, LSAT, ESS	TORS appears to be a promising procedure as part of multilevel

						surgery. Failure rate is 36.1%. ESS decreased significantly.
Murphey et al <sup>2003</sup>	2015	4	SR and MA	Glossectomy	AHI, LSAT, ESS	Glossectomy significantly improves sleep outcomes and ESS as part of multilevel surgery. AHI decreased by 27.81. Success achieved in 59.56%. ESS decreased by 5.49.
Pang et al <sup>1965</sup>	2018	4	MA	Palate surgeries	AHI, ESS, QOL	Palate surgery improved AHI and ESS. AHI change was 19.9. Success rate was 67.5%. ESS change was 5.8.
Santamaria et al <sup>2018</sup>	1988	4	Case series cross-sectional study, then prospective cohort study	UPPP	Serum testosterone, interview on sexual function	Increased testosterone, and return of libido and sexual functioning to normal range was seen after UPPP.
Shin et al <sup>2019</sup>	2013	4	Cohort	1) UPPP 2) CPAP 3) MAD	International Index of Erectile Function (KIIEF5), SAQLI, ESS, AHI, LSAT	Erectile dysfunction may improve after UPPP. ESS, AHI, LSAT improved significantly in the UPPP group.
Song et al <sup>1803</sup>	2016	4	SR and MA	Hyoid surgery	AHI, ESS	Isolated hyoid surgery reduced OSA severity and improved sleepiness. Hypothyroidopexy achieved the largest AHI reduction.
Steward et al <sup>2014</sup>	2004	4	Case series	TCRFTA of tongue and palate	ESS, FOSQ, reaction time	The addition of more sessions and levels of TCRFTA result in further improvement of ESS, QOL and reaction time.
Tsui et al <sup>2005</sup>	2020	4	Cohort	1) Surgery (sagittal split ramus osteotomy/mandibular dis-	ESS, QOL	ESS improved in the surgical arm. QOL scores in the

				traction osteogenesis) 2) Matched controls without OSA		surgical groups improved to the level of the control group. QOL was similar between the 2 surgical arms.
Veer et al <sup>2011</sup>	2014	4	SR	Radiofrequency ablation	AHI, ESS	Radiofrequency ablation can improve AHI and ESS. Absolute reduction could not be calculated due to paucity of available data.

Abbreviations: AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; ESS, Epworth sleepiness scale; FOSQ, Functional Outcomes of Sleep Questionnaire; LAUP, laser-assisted uvulopalatoplasty; LSAT, lowest oxygen saturation; MA, meta-analysis; MAD, mandibular advancement device; MMA, maxillomandibular advancement; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; QOL, quality of life; RCT, randomized controlled trial; RDI, respiratory disturbance index; SAQLI, Calgary Sleep Apnea Quality of Life Index; SF-36, 36-Item Short Form Survey; SR, systematic review; TCRFTA, temperature-controlled radiofrequency tissue ablation; UPPP, uvulopalatopharyngoplasty

### IX.E.2 Surgery to Improve OSA Severity

The apnea-hypopnea index (AHI) is the most popular parameter for measuring OSA severity and surgical outcomes. The definition of surgical success based on AHI change varies across studies, with the most common being Sher's criteria (a reduction in AHI of  $\geq 50\%$  and to a value of  $< 20$ ) which was used in most of the studies reviewed<sup>1633</sup>. However, newer metrics such as the sleep apnea-specific hypoxia and composite scores may better capture sleep apnea disease burden.<sup>2024,2025</sup>

Nasal surgery has a limited ability to improve respiratory parameters<sup>544,905,2007</sup>, although Ishii et al and Wu et al found small improvements in RDI (respiratory disturbance index) and AHI respectively<sup>544,1659</sup>. Palatal surgeries, one of the most commonly performed OSA surgeries, have a reputation for not consistently lowering AHI even in mild to moderate OSA<sup>1685</sup>. UPPP was cited as having a success rate of 40.7% in an unselected patient population; success rates reached 52.3% in cases with solely retropalatal obstruction<sup>1633</sup>. A recent meta-analysis in 2018 by Pang et al reported an overall pooled success rate of 67.5% for palate surgeries based on patients without hypopharyngeal collapse<sup>1965</sup>. New palatal techniques may further improve the success of procedures targeting retropalatal obstruction<sup>1689,1721,2026</sup>. However, even the simple tonsillectomy can achieve 100% success in a targeted population, i.e., mild-moderate OSA patients with enlarged tonsils<sup>334</sup>.

Hypopharyngeal techniques were developed to deal with retroglossal obstruction, but they have unpredictable success rates of between 35% and 62%, even when combined with UPPP<sup>1801,1810,1816</sup>. Transoral robotic surgery for tongue base resection and lingual tonsillectomy demonstrate improved lowest saturations and success rates between 48.2% to 68.4%<sup>1828,2001,2002</sup>. In general, tongue base resection and advancement techniques have better results than minimally invasive tongue base reduction with radiofrequency<sup>1789,1810,2003</sup>.

There is inconsistent evidence on minimally invasive procedures<sup>1735,1736,2009</sup>. Some studies report significant improvement in RDI and apnea index after both single and multilevel radiofrequency procedures<sup>1496,1781,2008</sup>. Multiple sessions may be required and data reports on short follow-up periods of six months<sup>1735,2012</sup>. Techniques such as cautery-assisted palatal stiffening operation (CAPSO) and the Pillar procedure have also been reported to reduce AHI and ODI<sup>1745,2010</sup>.

Hypoglossal nerve stimulation has shown statistically significant reductions of approximately 50% in both AHI and ODI at 12 months, with similar efficacy persisting to 60 months<sup>1873,1889</sup>. Its adherence data may be better than that of CPAP (median nightly usage of 5.8h, with self-reported nightly device use in 80% at five years)<sup>1889</sup>. A withdrawal study that showed return of OSA severity to baseline after the device was turned off for at least a week confirmed its efficacy<sup>1876</sup>.

MMA and tracheostomy have consistently high success rates<sup>1500,1685,2027</sup>. The cornerstone of skeletal surgery that expands pharyngeal dimensions at all levels, Holty and Guilleminault first reported a pooled success rate of 86.0% ( $p < 0.001$ ) after MMA, with mean AHI dropping from 63.9 to 9.5<sup>1866,2028</sup>. Cure (AHI  $< 5$ ) was achieved in 43.2%<sup>1866</sup>. MMA has classically been a second-line surgery in the older Stanford protocol. Elshaug et al reported that the pooled success rate of patients rose from 55% after phase I surgeries to 86% after phase II surgery<sup>1956</sup>. However, MMA can be highly effective as either primary or second-line surgery<sup>1685,2006</sup>. Limited data on other types of skeletal surgery suggests efficacy in selected patients too<sup>1793,1803,2029,2030</sup>. Bypassing the upper airway with a tracheostomy as a last resort can dramatically reduce the apnea index ( $73.0 \pm 27.1/h$  to  $0.2 \pm 1.2/h$ )<sup>1979</sup>.

Multilevel surgeries can achieve decent outcomes in OSA which is frequently a multilevel disease<sup>1829,1919,1920</sup>. Using Sher's criteria, the success rate of multilevel surgery was 66.4% (59.2% if MMA was excluded)<sup>1919</sup>. Certain techniques such as tongue base procedures may have better results as part of multilevel surgery<sup>1810</sup>. Mackay et al showed multilevel surgery reduced AHI (47.9 to 20.8) significantly more than ongoing medical management (45.3 to 34.5), with more patients (26% vs 8%) in the surgical arm achieving an AHI  $< 10$ <sup>1918</sup>. That said, additional levels of surgery do not always yield further AHI reductions<sup>2031</sup>.

It is prudent to be mindful that initial efficacy may decrease with time due to tissue laxity and non-anatomical factors. The surgical response of UPPP decreased from 67.3% in the short-term to 44.35% after at least 34 months<sup>811</sup>. The improvement in AHI post-MMA persists with 89% of patients maintaining surgical successes at a mean of 44 months, but mean AHI increased to the moderate range after eight years<sup>1866,1867</sup>.

The meta-analysis by Sundaram et al concluded that surgery was less successful than non-surgical interventions, stating that TCRFTA and UPPP had poorer AHI outcomes compared to CPAP and oral appliance therapy<sup>1482,1496,1506</sup>. However, Vicini et al compared the most consistently successful OSA surgery to date, MMA, against APAP and showed both groups had marked AHI reduction after a year, without a statistically significant difference between the groups<sup>1502</sup>.

It can be argued that CPAP adherence is highly variable, so surgery may have an overall better outcome in some patients<sup>1494</sup>. Surgery is an option to reduce OSA severity in CPAP-intolerant patients. When appropriately selected, some surgeries can have high success rates. Overall the literature is limited by lack of comparative analyses and long term outcomes.

## Surgery to Improve OSA Severity

**Aggregate Quality of Evidence:** B (Level 1a: 11 studies; Level 1b: 12 studies; Level 2a: 8 studies; Level 3a: 2 studies; Level 3b: 1 study; Level 4: 19 studies).

**Benefit:** Improved sleep parameters such as the apnea-hypopnea index, oxygen desaturation index, lowest oxygen saturation has been reported after surgery. Reduced OSA severity may improve risk for OSA-associated comorbidities.

**Harm:** Side effects depend on the site of surgery. Some of the more common risks include: bleeding, aspiration, airway edema, stenosis, velopharyngeal insufficiency, dysphagia, globus sensation, numbness, change in taste, numbness, damaged teeth, respiratory compromise, worsened OSA, death.

**Cost:** Moderate to high costs for surgery and postoperative care. Indirect cost of time off for recovery.

**Benefits-Harm Assessment:** Preponderance of benefit over harm.

**Value Judgments:** Properly selected surgical interventions for patients can lead to significant reductions in OSA severity with low risks for harm.

**Recommendation Level:** Recommendation.

**Intervention:** Assessment and discussion of surgical candidacy should be offered to patients who cannot use CPAP. Surgery has the ability to reduce OSA severity.

**Table IX.E.2: Evidence for Surgery to Improve OSA severity**

STUDY	YEAR	LOE	STUDY DESIGN	STUDY GROUPS	CLINICAL END-POINT	CONCLUSION
Back et al <sup>1735</sup>	2009	1a	SR	Radiofrequency ablation of the soft palate	PSG, snoring	Effectiveness of radiofrequency ablation of the soft palate is uncertain.
Camacho et al <sup>2032</sup>	2017	1a	SR and MA	LAUP	AHI, LSAT	AHI worsened in 44%. LAUP should be performed with caution or not performed at all given its unfavorable results.
Caples et al <sup>1685</sup>	2010	1a	SR and MA	Various surgeries (MMA, soft palate procedures, LAUP, radiofrequency ablation, soft palate implants, multi-level simultaneous and phased surgeries)	AHI	MMA results in substantial and consistent reductions in AHI. Pharyngeal surgeries are less consistent. Newer pharyngeal techniques and multilevel procedures appear promising.
Gao et al <sup>2009</sup>	2019	1a	SR and network MA	Minimally invasive treatments including surgery	AHI, ESS	Simple surgical procedures improve AHI and ESS insignificantly.
Farrar et al <sup>2008</sup>	2008	1a	SR and MA	Isolated radiofrequency ablation of the palate, tongue base, or both	ESS, RDI, LSAT	Radiofrequency ablation reduces ESS and RDI levels. ESS decreased by 31%. RDI reduced by 31% in short-term and 45% in long-term.
He et al <sup>811</sup>	2019	1a	SR and MA	UPPP and its modifications	AHI, ODI, LSAT, and CT90	Surgical response decreased from 67.3% to 44.35% from short to long-term ( $\geq 34$ months).

Ishii et al <sup>544</sup>	2015	1a	SR and MA	Nasal surgery including endoscopic sinus surgery	AHI, RDI, ESS	Significant improvements in ESS and RDI after nasal surgery, but no significant improvements in AHI.
Kezirian and Goldberg <sup>1801</sup>	2006	1a	SR	Hypopharyngeal surgeries	PSG, ESS, QOL	Hypopharyngeal surgery has success rates of 35-62%. Improved ESS and FOSQ were seen.
Rotenberg et al <sup>1494</sup>	2016	1a	SR	1) CPAP 2) Surgery	Adherence rates of CPAP	The majority of patients are not adherent to CPAP. Surgery may provide a better overall outcome.
Sundaram et al <sup>1482</sup>	2005	1a	SR	1) Surgical intervention for OSA 2) Other surgical or non-surgical interventions, or no intervention	PSG, sleepiness, QOL	Surgery has inconsistent effects. There is no convincing evidence to support surgical treatment of OSA.
Zaghi et al <sup>2006</sup>	2016	1a	SR and MA	MMA	AHI, RDI, LSAT, ESS	MMA is an effective treatment for OSA. Success rate of 85.5%; cure rate of 38.5%. ESS decreased from 13.5 to 3.2.
Atef et al <sup>2012</sup>	2005	1b	RCT	1) Bipolar radiofrequency volumetric tissue reduction of the palate 2) LAUP	AHI	Bipolar radiofrequency volumetric tissue reduction of the palate required more sessions to achieve a favorable outcome, but benefit was also maintained for longer.
Baba et al <sup>1781</sup>	2015	1b	SR and MA	Isolated TCRFTA of the soft palate, base of tongue or both	ESS, RDI, LSAT, SF-36	TCRFTA can reduce RDI and sleepiness when directed at the base of tongue or as a multilevel procedure.
Elshaug et al <sup>1956</sup>	2007	1b	MA	Phase I and II upper airway surgeries	AHI	Phase II surgeries have a higher success rate than Phase I (86% vs 55%).
Holmlund et al <sup>1736</sup>	2014	1b	RCT	1) Radiofrequency of the soft palate 2) Sham surgery	AHI, ESS, snoring	Radiofrequency surgery of the soft palate has no effect on daytime sleepiness or apnea frequency.
Li et al <sup>905</sup>	2011	1b	SR and MA	Nasal surgery including endoscopic sinus surgery	AHI, ESS	Nasal surgery can effectively reduce daytime sleepiness, but is limited in reducing OSA severity.
Mackay et al <sup>1918</sup>	2020	1b	RCT	1) Combined modified UPPP and radiofrequency of the tongue 2) Ongoing medical management	ESS, PSG	Combined palatal and tongue surgery, compared with medical management, reduced AHI and ESS at 6 months. Mean AHI and ESS baseline-adjusted between-group difference was -17.6 and -6.7 respectively.
Pirklbauer et al <sup>2027</sup>	2011	1b	SR	MMA	AHI, QOL	MMA can be a successful primary intervention for OSA.
Vicini et	2010	1b	RCT	1) MMA	AHI, ESS	Both groups had similar

al <sup>1502</sup>				2) Auto-titrating positive airway pressure		improvement of mean AHI and ESS.
Walker-Engstrom et al <sup>1506</sup>	2002	1b	RCT	1) UPPP 2) MAD	AHI, AI, ODI	Success rate with MAD (81%) was significantly higher than with UPPP (53%).
Woodson et al <sup>1496</sup>	2003	1b	RCT	1) TCRFTA 2) CPAP 3) Sham-placebo	QOL, ESS, PSG, reaction time	TCRFTA improved reaction time, OSA-specific QOL and ESS compared to baseline. TCRFTA improved reaction time, while CPAP did not.
Woodson et al <sup>1876</sup>	2014	1b	RCT	1) Hypoglossal nerve stimulation turned off 2) Hypoglossal nerve stimulation turned on	AHI, ODI, arousal index, ESS, FOSQ	OSA returned to baseline severity in the withdrawal arm. Improvement in OSA severity and QOL are due to electrical stimulation of the hypoglossal nerve.
Wu et al <sup>1659</sup>	2017	1b	MA	Isolated nasal surgery	AHI, ESS	AHI and ESS improve significantly after isolated nasal surgery, but AHI demonstrated only slight improvement.
Bostanci and Turhan <sup>1816</sup>	2016	2a	SR	Tongue base suspension (TBS) techniques ± UPPP	AHI, LSAT, ESS	Tongue base suspension has some efficacy, with or without UPPP. ESS improved with tongue base suspension.
Choi et al <sup>1745</sup>	2013	2a	MA	Pillar implant for mild to moderate OSA	ESS, AHI, snoring	The Pillar implant reduced ESS and AHI significantly for mild to moderate OSA.
John et al <sup>1500</sup>	2018	2a	SR and MA	MMA	AHI, RDI, ESS, LSAT	MMA achieved 100% surgical success.
Holty and Guillemina ult <sup>1866</sup>	2010	2a	SR and MA	MMA	PSG, ESS, QOL	MMA improved AHI, reduced daytime symptoms and improved QOL. Success and cure rates were 86.0% and 43.2% respectively.
Mulholland et al <sup>1920</sup>	2019	2a	SR and MA	Multilevel palate and tongue base surgery	AHI, LSAT	Multilevel (non-MMA) surgeries can significantly reduce AHI. Mean AHI change of 23.67.
Pang et al <sup>1689</sup>	2016	2a	SR and MA	1) Expansion sphincter pharyngoplasty 2) Other palate surgeries	AHI	The surgical success rate of expansion sphincter pharyngoplasty was 86.3%.
Sher et al <sup>1633</sup>	1996	2a	SR and MA	Various upper airway surgeries (nasal surgeries, UPPP, retrolingual operations, tracheostomy)	PSG	UPPP has at best <50% chance of success.
Wang et al <sup>2007</sup>	2019	2a	SR and MA	Nasal surgery ± endoscopic sinus surgery	AHI, ODI, LSAT, ESS	Isolated nasal and sinus surgery can reduce daytime sleepiness in OSA. ESS change was 3.79. There was no significant improvement on objective parameters.
Camacho	2016	3a	SR and	Tonsillectomy	PSG, ESS	Tonsillectomy can have high success

et al <sup>334</sup>			MA			(85.2%) and cure (57.4%) rates in patients with large tonsils.
Noller et al <sup>2029</sup>	2017	3a	SR and MA	Mandibular advancement surgeries	AHI, LSAT	Isolated mandibular advancement is efficacious for adult patients with mandibular insufficiency.
Volner et al <sup>1721</sup>	2017	3b	SR and MA	Transpalatal advancement pharyngoplasty	AHI, LSAT	Transpalatal advancement pharyngoplasty reduced AHI and LSAT significantly. AHI reduced by 64.8%. LSAT improved by 3.55 points.
Binar and Karakoc <sup>2026</sup>	2018	4	SR and MA	Anterior palatoplasty	AHI	The surgical success rate of anterior palatoplasty was 60.6%.
Camacho et al <sup>1979</sup>	2014	4	SR and MA	Tracheostomy	AI, AHI, ODI, sleepiness	Tracheostomy significantly decreases AI, AHI and sleepiness. AI change was 83.47. Mean AHI and ODI was in the moderate range post tracheostomy. Sleepiness decreased significantly.
Camacho et al <sup>1867</sup>	2019	4	SR and MA	MMA	AHI, ESS, LSAT	Improvements in AHI, sleepiness, and lowest oxygen saturation were maintained in the long term (4 to <8 years). Mean AHI increased to moderate OSA in the very long term ( $\geq 8$ years).
Certal et al <sup>1873</sup>	2015	4	SR and MA	Hypoglossal nerve stimulation therapy	AHI, ODI, ESS, QOL	Hypoglossal nerve stimulation improves AHI, ODI and ESS fairly consistently over 12 months. There was improvement in QOL.
Costantino et al <sup>1889</sup>	2020	4	SR and MA	Hypoglossal nerve stimulation therapy	AHI, ESS, ODI	Hypoglossal nerve stimulation achieves high surgical success rates of up to 76.9% (ImThera) at 12 months, and 75% (Inspire) at 60 months. ESS improved with all devices.
Handler et al <sup>1810</sup>	2014	4	SR	Tongue advancement surgeries $\pm$ UPPP	AHI	Tongue suspension is effective and safe as part of multilevel surgery. Success rate is 36.6% as a standalone procedure.
Justin et al <sup>2001</sup>	2016	4	SR and MA	TORS	AHI, LSAT, ESS	TORS appears to be a promising procedure as part of multilevel surgery. AHI decreased by 24.0. Success achieved in 48.2%. ESS decreased by 7.2.
Lin et al <sup>1919</sup>	2008	4	SR and MA	Multilevel surgery involving at least 2 levels (nose, oropharynx,	PSG, ESS, QOL	Multilevel surgery can improve outcomes. Success rate was 66.4%. ESS improved in 23/26 groups and



				hypopharynx)		changed by 43.0%.
Llewellyn et al <sup>2010</sup>	2019	4	SR and MA	Cautery-assisted palatal stiffening operation	AHI, ODI, LSAT, ESS	Cautery-assisted palatal stiffening operation improved respiratory parameters. ESS improved from 11.8 to 5.1.
Meccariello et al <sup>2002</sup>	2017	4	SR and MA	TORS	AHI, LSAT, ESS	TORS appears to be a promising procedure as part of multilevel surgery. Failure rate is 36.1%. ESS decreased significantly.
Miller et al <sup>1828</sup>	2017	4	SR and MA	TORS tongue base reduction	AHI, LSAT, ESS, snoring	The surgical success rate of TORS for tongue base reduction was 68.4%. Cure rate was 23.8%.
Minni et al <sup>2031</sup>	2020	4	Case series	UPPP and barbed reposition pharyngoplasty ± hyoid suspension	AHI, ODI, ESS	Barbed reposition pharyngoplasty was more effective than UPPP. Hyoid suspension added benefit when performed with UPPP, and not with barbed reposition pharyngoplasty.
Murphey et al <sup>2003</sup>	2015	4	SR and MA	Glossectomy	AHI, LSAT, ESS	Glossectomy significantly improves sleep outcomes and ESS as part of multilevel surgery. AHI decreased by 27.81. Success achieved in 59.56%. ESS decreased by 5.49.
Pang et al <sup>1965</sup>	2018	4	MA	Palate surgeries	AHI, ESS, QOL	Palate surgery improved AHI and ESS. AHI change was 19.9. Success rate was 67.5%. ESS change was 5.8.
Samutsakorn et al <sup>1829</sup>	2018	4	SR and MA	Lingual tonsillectomy with palatal surgery	AHI, LSAT, ESS	Lingual tonsillectomy and palatal surgery may benefit selected patients.
Song et al <sup>1803</sup>	2016	4	SR and MA	Hyoid surgery	AHI, ESS	Isolated hyoid surgery reduced OSA severity and improved sleepiness. Hyothyroidopexy achieved the largest AHI reduction.
Song et al <sup>1793</sup>	2017	4	SR and MA	Genial tubercle advancement and genioplasty	AHI, LSAT, ESS	Standard genioplasty, and genial tubercle advancement with and without hyoid suspension can improve AHI and LSAT.
Stuck et al <sup>1789</sup>	2002	4	Case series	Radiofrequency volumetric tissue reduction of the tongue base	RDI, ESS	33% were cured. 55.6% showed a reduction in RDI of >20%. ESS decreased from 7.9 to 4.9.
Tsui et al <sup>2030</sup>	2016	4	SR	Mandibular distraction osteogenesis	AHI, RDI	Mandibular distraction osteogenesis can achieve success in adults with retrognathic mandibles.

Abbreviations: AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; CT90, percentage of sleep time with oxyhemoglobin saturation <90%; ESS, Epworth sleepiness scale; FOSQ, Functional Outcomes of Sleep Questionnaire; LAUP, laser-assisted uvulopalatoplasty; LSAT, lowest oxygen saturation; MA, meta-analysis; MAD, mandibular advancement device; MMA, maxillomandibular advancement; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSG, polysomnography; QOL, quality of life; RCT, randomized controlled trial; RDI, respiratory disturbance index; SR, systematic review; TCRFTA, temperature-controlled radiofrequency tissue ablation; TORS, transoral robotic surgery; UPPP, uvulopalatopharyngoplasty

### IX.E.3 Surgery and Mortality Risk

Few studies to date have focused on the impact of surgical procedures for OSA on all-cause mortality and survival. A retrospective cohort study of OSAS patients including those treated with uvulopalatopharyngoplasty (UPPP), CPAP, or weight loss demonstrated a lower likelihood of all-cause death in UPPP patients when compared to untreated patients<sup>2033</sup>. After adjusting for age, sex, BMI, AHI, and select medical comorbidities, the adjusted hazard ratio for all-cause mortality in the UPPP group was 0.14 (95% confidence interval, 0.04-0.50)<sup>2033</sup>. The likelihood of OSA-related mortality was also lower in UPPP patients than in untreated patients (adjusted hazard ratio of 0).

A retrospective case-control study investigated mortality in heavy snorers including 256 with OSA who underwent UPPP compared to that of a control group of 744 patients without snoring or sleep-disordered breathing who underwent nasal surgery<sup>2034</sup>. During a follow-up period of 5-9 years, the long-term all-cause mortality rate was not different between the OSA patients treated with UPPP (3.9%) and the nasal surgery control group (3.9%,  $p = .99$ ). Given the increased mortality risk of OSA, the comparable mortality between the UPPP and the control groups may indicate that UPPP treatment of OSA conferred a survival benefit in OSA patients.

Few studies have compared OSA patient survival or mortality between surgically and medically treated patients. The largest retrospective cohort study on this topic studied survival in veterans with OSA treated with UPPP ( $n = 2,072$ ) or provision of CPAP ( $n = 18,754$ )<sup>1497</sup>. When comparing all-cause mortality rates between the two groups, the CPAP group had a statistically significantly higher mortality rate (7.1%) than did the UPPP group (3.4%). On average, the UPPP group had an overall survival of 22 days longer than did the CPAP group. After adjusting for known confounders of mortality, patients in the CPAP group had a 31% greater probability of mortality at any time during the study period than did patients in the UPPP group.

In another retrospective cohort study of OSA patients, 5-year survival and mortality were compared amongst 149 UPPP and 126 CPAP (confirmed active use) patients<sup>2035</sup>. The 5-year survival probability did not differ between the UPPP ( $0.94 \pm 0.24$ , mean  $\pm$  standard deviation) and CPAP ( $0.95 \pm 0.34$ ) groups. On subset analysis of patients with an apnea index  $> 20$ , there were similarly no difference in 5-year survival probability between the UPPP ( $0.92 \pm 0.17$ ) and CPAP groups ( $0.90 \pm 0.14$ ). There was also no statistically significant difference in all-cause mortality rates between the two groups at 4.0% for the UPPP patients and 2.4% for the CPAP patients.

Taken together, retrospective cohort studies indicate that sleep apnea surgery may confer a mortality and survival benefit.

## OSA Surgery for Mortality Risk Reduction

**Aggregate Quality of Evidence:** Grade C (Level 2b: 2 studies, Level 2c: 2 studies).

**Benefit:** Potential for reduced mortality when compared to no treatment. Mortality and survival may be equivalent to provision of CPAP.

**Harm:** Risks related to specific surgery types. Rare perioperative mortality risk. (see Table X).

**Cost:** Moderate costs related to surgery and recovery.

**Benefits-Harm Assessment:** Balance of benefit and harm.

**Value Judgments:** OSA surgery may improve mortality outcomes compared to no treatment based on retrospective cohort data.

**Recommendation Level:** Option.

**Intervention:** Consider surgical treatment in patients with moderate to severe OSA who cannot use CPAP to improve mortality risk.

**Table IX.E.3: Evidence for Surgery and Mortality Risk**

Study	Year	LOE	Study Design	Study Groups	Clinical End-Point	Conclusion
Marti <i>et al.</i> <sup>2033</sup>	2002	2c	Retrospective cohort (outcomes) study	OSA patients (N=475) who underwent UPPP, weight loss, CPAP, or no treatment	Mortality (all cause and OSA-related)	Surgery reduces all-cause and OSA-related mortality compared to no treatment.
Lysdahl and Haraldsson <sup>2034</sup>	2000	2b	Retrospective matched cohort	Heavy snorers including OSA (n=256) patients, non-heavy snorer nasal surgery patients (n=744)	Mortality (all cause)	Mortality was no different between OSA patients treated with UPPP and non-OSA nasal surgery.
Weaver <i>et al.</i> <sup>1497</sup>	2004	2b	Retrospective cohort database study	Veterans with OSA managed with UPPP (n = 2,072) or provision of CPAP (n = 18,754)	Mortality (all cause), survival	Survival and mortality were better for UPPP patients than for patients prescribed CPAP.
Keenan <i>et al.</i> <sup>2035</sup>	2002	2c	Retrospective cohort (outcomes) study	OSA patients (N=362), including those treated with UPPP (n=149) and nasal CPAP with active use	All-cause mortality, survival	All-cause mortality and 5-year survival were no different between UPPP and CPAP patients.

				(n=126)		
--	--	--	--	---------	--	--

#### IX.E.4 Surgery and Hypertension Improvement

A meta-analysis of thirty different randomized controlled studies demonstrated clinically relevant reductions in blood pressure for those patients treated with CPAP.<sup>1208</sup> Whether similar clinically relevant reductions in blood pressure can be achieved in patients who have undergone sleep apnea surgery will be addressed in this section.

There have been no Cochrane reviews of the effect of sleep apnea surgery on blood pressure. The data outlined include mostly case series with risks for bias and limitations from lack of control groups.<sup>2036</sup>

The most recent study by Chin et al. examined 89 patients who underwent multilevel soft tissue surgery of which 40 were identified as responders, as defined by a post-surgical AHI of less than 20 events/hour.<sup>2037</sup> In these responders, a statistically significant reduction in morning and nocturnal systolic blood pressure (SBP) was noted. Diastolic blood pressure (DBP) reduction was not statistically significant. In 2017, Fehrm et al. designed a randomized controlled trial to assess blood pressure changes in patients undergoing modified uvulopalatopharyngoplasty (UPPP) in comparison to a control group.<sup>2038</sup> The study included 65 patients of which 32 initially underwent the surgery and 33 remained in the control arm with use of CPAP therapy. Blood pressure measurements were taken after surgery and 6 months post-operatively. After 6 months, the control arm was also offered the modified UPPP, and both groups were followed for a total of 24 months. SBP and DBP measurements were significantly reduced in the surgical treatment arm at 6 months, with a -9.4 mmHg difference in SBP and -6.4 mmHg in DBP. This change in blood pressure was greater than in the initial CPAP control group, which demonstrated only a -2.6 mmHg and -2.0 mmHg drop in both SBP and DBP, respectively. After the CPAP control arm was offered surgery at 6 months, at the time of the 24 month follow up, there was persistent improvement in blood pressure in both groups that underwent surgery. In 2014, Rotenberg et al. published his experience with soft tissue palatal surgery ± nasal surgery in a cohort of 126 patients. In regards to blood pressure, a statistically significant reduction in SBP was seen ( $p < 0.001$ ) in the surgical group with a reduction noted from 143.2 mmHg to 134.5 mmHg.<sup>1498</sup> Finally, one study evaluated a cohort of 18 patients who underwent soft tissue surgery with the use of 24-hour ambulatory blood pressure monitoring—considered superior to in-office spot blood pressure monitoring.<sup>1713</sup> This study demonstrated statistically significant improvements in nocturnal SBP, DBP, and MAP measurements after surgery at 6 months.

A multicenter prospective cohort study on 30 patients undergoing maxillomandibular advancement (MMA) surgery demonstrated notable findings regarding quality of life measures and AHI reductions.<sup>2004</sup> In regards to blood pressure, a non-significant reduction in mean diastolic blood pressure and in systolic blood pressure were noted. Another study on patients undergoing MMA was completed in 2015 by Islam et al.<sup>2039</sup> This study looked at 45 patients that underwent the surgery, and in the 85% who were determined to have surgical success (AHI < 15 or 50% reduction from the index AHI), significant reductions in both SBP and DBP were seen, particularly in patients with previously diagnosed hypertension treated with medications. In the 10 patients with a history of hypertension treated with medications, the reductions in mean SBP, mean DBP, and mean arterial pressure (MAP), were -6 mmHg, -10 mmHg, and -9 mmHg, respectively. Those patients who did not meet the definition of surgical success had significant reductions in DBP alone. Regarding the long-term effect of blood pressure reduction in surgically managed patients, Boyd et al. studied 30 patients that underwent MMA surgery and determined that over a mean of 6.6 years of follow-up (range, 2.1-11.2 years), statistically

significant reductions were seen in DBP with non-statistically significant reductions in SBP.<sup>2040</sup> Notably the extent of blood pressure improvements seen in these small surgical studies are substantial, along the lines seen with effective blood pressure medications and larger than reported with CPAP.<sup>1208,2038</sup> More research is needed to understand the long-term pathophysiologic effects of sleep surgery on blood pressure control.

### Sleep Surgery for Hypertension Management

**Aggregate Quality of Evidence:** C (Level 1b: 1 study; Level 4: 6 studies).

**Benefit:** Reductions are seen in systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure in patients who have undergone successful sleep apnea surgery (soft tissue and MMA surgery).

**Harm:** Risks specific to surgery type, potential for surgical complications and ineffective post-surgical response.

**Cost:** Moderate costs associated with surgery and time for recovery.

**Benefits-Harm Assessment:** Balance of benefit and harm.

**Value Judgments:** OSA patients with treatment resistant hypertension and CPAP intolerance, may benefit from sleep apnea surgery to lower blood pressure. The durability and long-term effects are unknown.

**Recommendation Level:** Option.

**Intervention:** Current data suggests that if surgery is successful in treated OSA, then meaningful reductions in blood pressure may be seen. Surgery can be considered in CPAP-intolerant patients.

**Table IX.E.4: Evidence for Blood Pressure Change after Surgery for OSA.**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Fehm et al. <sup>2038</sup>	2017	1b	Randomized controlled trial	65 patients 1. UPPP (n=32) 2. CPAP (n=33) Crossover of CPAP group at 6 months.	SBP and DBP at 6 months to 24 months.	Larger SBP and DBP reductions seen in surgical group compared to CPAP group. (SBP difference -9.4 mmHg and DBP difference -6.4 mmHg post surgery vs. -2.6 mmHg SBP and -2.0 mmHg DBP with CPAP)
Chin et al. <sup>2037</sup>	2019	4	Case series	89 patients that underwent multilevel ST surgery	Serum leptin, cholesterol, SBP, DBP, and triglycerides	Morning SBP improvements in surgical responders (mean difference -7.2 mmHg after surgery). Nocturnal BP change was not significant.
De Paula Soares et al. <sup>1713</sup>	2014	4	Case series	18 patients underwent ST surgery	ABPM before and 6 months after surgery	SBP, DBP, and MAP during sleep were significantly decreased after surgery. (SBP: -7.4 mmHg, DBP: -4.2 mmHg, MAP: -5.3 mmHg)

Rotenberg et al. <sup>1498</sup>	2014	4	Case series	126 patients underwent ST surgery ± nasal surgery	AHI, ESS, SAQLI, SBP	SBP significantly reduced after surgery. (SBP difference -8.7 mmHg after surgery vs. no difference with CPAP)
Boyd et al. <sup>2004</sup>	2019	4	Case series	30 patients that underwent MMA	ESS, FOSQ, AHI, PVT, SBP, DBP, and CRP	Significant DBP reduction seen (mean difference -3.3 mmHg).
Islam et al. <sup>2039</sup>	2015	4	Case series	45 patients that underwent MMA	Pre and PO SBP and DBP measurements	SBP significantly reduced after surgery (mean difference -3.8 mmHg). DBP change was not significant.
Boyd et al. <sup>2040</sup>	2015	4	Case series	30 patients that underwent MMA followed for > 2 yrs (average 6 yrs)	AHI, ESS, FOSQ, SBP, and DBP	Reductions in DBP were seen in patients followed for at least > 2yrs (mean difference -4.7 mmHg).

LOE = level of evidence, ST = soft tissue, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, MMA = maxillomandibular advancement, ESS = epworth sleepiness scale, FOSQ = functional outcomes of sleep questionnaire, AHI = apnea/hypopnea index, PVT = psychomotor vigilance testing, CRP = c-reactive protein, PO = post-operative, SAQLI = sleep apnea quality of life index, ABPM = 24 hr ambulatory blood pressure monitoring

### IX.E.5 Surgery and Cardiovascular Outcomes

Patients with obstructive sleep apnea (OSA) have increased inflammatory, metabolic, hemodynamic, and autonomic dysfunction, which contribute to increased risk of cardiovascular disease.<sup>110</sup> The obstruction of the airway with resultant hypoxemia cause increased sympathetic activity, which leads to downstream effects to the cardiovascular system through heart rate and blood pressure elevations. These deleterious effects have been linked to increases in heart failure, coronary artery disease, and all-cause mortality.<sup>640,641</sup>

Treatment with continuous positive airway pressure (CPAP) has been evaluated in an attempt to discern its effect on the incidence of cardiovascular events such as myocardial infarction, acute coronary syndrome, and stroke. The results of these studies have been mixed, but overall, they do suggest cardiovascular benefits with CPAP treatment for OSA.<sup>38,118,1248</sup>

One systematic review analyzed a total of 33 articles on the effects of sleep surgery on cardiovascular outcomes.<sup>1686</sup> This study determined that the overall evidence regarding cardiovascular outcomes imply a benefit; however the studies were mostly case series, and larger randomized prospective trials were recommended to more definitively understand the role of sleep surgery in reducing long-term cardiovascular consequences associated with OSA.

A recent study in 2018 by Lee et al. examined the entire population of South Korea over a seven year time frame via their national healthcare database and found that 22,231 UPPP patients had a statistically significant reduction in rates of congestive heart failure (CHF) and atrial fibrillation (AF) in

comparison to untreated patients with OSA (n=170,085).<sup>1963</sup> Regarding myocardial infarction (MI), the incidence in the untreated OSA group was higher than in the UPPP group, but lacked statistical significance.

A variety of secondary markers of cardiovascular function and/or stress are associated with cardiovascular dysfunction. These markers include C-reactive protein (CRP), serum leptin, blood pressure, cholesterol, left and right ventricular function, nitric oxide levels, and heart rate variability. These surrogate markers of cardiovascular outcomes are used in lieu of long-term follow up, given the challenges with identifying differences in incidence of heart failure, myocardial infarction, or stroke, which can take large cohorts and several years of follow up not yet done in sleep surgery research.

Studies have examined the role of pharyngeal soft tissue surgery and the reduction of cardiovascular marker levels such as CRP and highly sensitive C-reactive protein (hs-CRP), serum leptin, triglycerides, cholesterol, nitric oxide, and carotid artery intima-media thickness. A case-control study done by Binar et al. demonstrated a significant difference in hs-CRP in patients undergoing pharyngeal surgery.<sup>1692</sup> A total of 23 patients were followed after surgery, and the reduction in hs-CRP, which was significant, was only seen in the post-surgical patients that were able to obtain an AHI <5/hr, which occurred in only 26%. Lee et al., in a study of 30 patients undergoing lateral expansion pharyngoplasty, found reductions in hs-CRP in patients irrespective of post-surgical AHI—however this only reached significance in the group of surgical patients with severe OSA prior to intervention.<sup>2041</sup>

Nocturnal heart rate variability (HRV) is a marker of autonomic dysfunction brought on by nightly hypoxemia from OSA and is considered a significant risk factor for cardiovascular dysfunction. Dehdia et al. evaluated upper airway stimulation therapy and its effect on nocturnal HRV in a cohort of 32 patients that underwent a repeat sleep study 12 months after their stimulation device was implanted, in addition to a withdrawal period.<sup>1897</sup> This study demonstrated that HRV was improved between the patient's baseline sleep study to the 12-month treatment study, and these effects did not change during the one-week therapy withdrawal period. Studies that examined HRV in patient's undergoing pharyngeal surgery showed that in patients with post-surgical AHI of less than 20/hr, significant reductions in HRV were seen.<sup>1704,2042</sup>

Carotid artery intima-media thickness (CIMT), assessed via ultrasound or MRI, has been used as a screening tool for arteriosclerosis and risk stratification for future cardiac events.<sup>2043</sup> CIMT, which is often used to monitor the effects of cardiac drugs such as lipid lowering agents and anti-hypertensive medications, has also been used as a surrogate cardiac marker. Peng et al. demonstrated in 52 patients that underwent UPPP and nasal surgery, that CIMT thickness, cholesterol, triglycerides, and BP were all significantly reduced.<sup>2044</sup> This effect was mirrored in a group of patients that elected to start CPAP, and furthermore, changes in CIMT were not seen in the group that did not pursue surgery or CPAP therapy. A similar study, published in 2019 by Zhan et al., demonstrated that in 53 patients undergoing UPPP surgery, a variety of cardiac markers, such as CIMT, arterial stiffness parameters, and echocardiography, improved after UPPP surgery.<sup>1964</sup> The surgical success rate in the group was 60.4%, and in this group, the reduction in the above mentioned parameters was demonstrated, including flow velocity reductions across the aortic and pulmonary valves on echocardiography.

In summary, cardiovascular events are a known risk factor of OSA, particularly for patients with moderate or severe disease. For OSA patients unable to tolerate CPAP therapy, one potential goal of surgical management is the reduction of cardiac risk factors in an effort to improve cardiac outcomes. Caution must be taken in reviewing the published literature regarding the reduction of cardiovascular

risk for this group given the lack of rigorous long term trials; however, the current research has demonstrated improvements in cardiac outcomes, and multiple surrogate markers of cardiac outcomes have been positively affected by adequate sleep surgery.

### Surgery for Improved Cardiovascular Outcomes and Markers of Disease

**Aggregate Quality of Evidence:** C (Level 2a: 1 study; Level 2b: 1 study; Level 3b: 5 studies; Level 4: 7 studies).

**Benefit:** Reductions in the incidence of heart failure and atrial fibrillation are seen after soft tissue surgery. Improvements in surrogate markers of cardiovascular dysfunction such as CRP, HRV, serum leptin, NOx, cholesterol, and arterial stiffness are seen after successful sleep surgery.

**Harm:** Potential for surgical complications and ineffective post-surgical response

**Cost:** Moderate costs related to surgery and time for recovery.

**Benefits-Harm Assessment:** Balanced benefit and harm.

**Value Judgments:** Evidence suggests successful surgery is associated with protective effects to the cardiovascular system. One large retrospective study demonstrated improvements in some cardiovascular outcomes. The durability and long-term effects are unknown.

**Recommendation Level:** Option.

**Intervention:** Sleep apnea surgery is an option to improve markers of cardiovascular disease in those who cannot use CPAP.

**Table IX.E.5 Evidence for Surgery and Cardiovascular Markers and Outcomes**

Study	Year	LOE	Study Design	Study Groups	Clinical End-point	Conclusion
Halle et al. <sup>1686</sup>	2017	2a	Systematic Review of cohort studies and case series	Multiple studies on different surgical interventions.	19 different cardiovascular endpoints assessed.	Data is limited secondary to weak study design (level 4 evidence) but surgery showed improvements in CV outcomes.
Lee et al. <sup>1963</sup>	2018	2b	Cohort study	170,103 patients with OSA (no surgery), 22, 213 with OSA and had UPPP; Propensity score matched controls: 961,590 no OSA.	Newly diagnosed MI, CHF, and AF	UPPP was associated with lower incidences of CHF and AF. MI incidence rate was not significant.



Zhan et al. <sup>1964</sup>	2019	4	Case series	53 patients that underwent UPPP surgery	CIMT, arterial stiffness, echocardiography, and PSG	ST surgery improves parameters associated with carotid arteriosclerosis .
Chin et al. <sup>2037</sup>	2019	4	Case series	89 patients that underwent multilevel ST surgery	Serum leptin, cholesterol, SBP, DBP, and triglycerides	Cardiovascular markers such as total cholesterol, triglycerides, and leptin improved with successful surgery.
Dedhia et al. <sup>1897</sup>	2019	4	Case series	32 patients with UAS device	Nocturnal heart rate variability	Pts with UAS had reduced nocturnal heart rate variability.
Suslu et al. <sup>1704</sup>	2017	4	Case series	28 patients that underwent lateral expansion pharyngoplasty	Nocturnal heart rate variability	Autonomic variables included HRV were decreased in the patients who achieved surgical success.
Binar et al. <sup>1692</sup>	2017	3b	Case - Control Study	23 patients that underwent lateral expansion pharyngoplasty vs 28 patient on CPAP	hs-CRP, AHI, ESS	Only surgical patients that had AHI <5 PO had significant hs-CRP reductions.
Peng et al. <sup>2044</sup>	2016	3b	Case- Control Study	52 patients underwent nasal surgery and UPPP, 12 had CPAP only	AHI, ESS, CIMT cholesterol	6 months after surgery significant changes in CIMT and with successful surgery.
Lin et al. <sup>2045</sup>	2014	3b	Case – Control study	15 healthy patients compared to 35 OSA pts undergoing UPPP	AHI, serum leptin, NOx	Patients with surgical success had normalization in leptin and NOx.
Choi et al. <sup>2042</sup>	2012	3b	Case – Control study	14 patient with unsuccessful ST surgery and 22 pts with successful ST surgery	BMI, PSG data, HRV	HRV significantly decreased in the successful surgical group.

Lee et al. <sup>2041</sup>	2011	4	Case series	30 patients underwent lateral expansion pharyngoplasty	BMI, ESS, AHI, and hs-CRP before and 6 months after surgery	Significant reductions in hs-CRP was noted regardless of AHI reduction.
Kinoshita et al. <sup>2046</sup>	2006	4	Case series	15 patients that underwent UPPP surgery	BMI, AHI, cholesterol, BP, and CRP	Significant reduction in CRP seen.
Zoha et al. <sup>2047</sup>	1992	4	Case series	19 patients undergoing UPPP surgery	AHI, left and right ventricular EF	91% of patient had global improvements in EF.
Partinen et al. <sup>2048</sup>	1990	3b	Case series – Control study	71 patients that underwent tracheostomy vs 127 recommended weight loss	Stroke, MI, CAD, Mortality, BP	Significant differences in mortality and cardiovascular events at 7 years of follow-up.

ST = soft tissue, CIMT = carotid intima-media thickness, PSG = polysomnography, MI = myocardial infarction, CHF = congestive heart failure, AF = atrial fibrillation, UAS = upper airway stimulator, HRV = heart rate variability, hs-CRP = high sensitive c-reactive protein, AHI = apnea/hypopnea index, ESS = Epworth sleepiness scale, NOx = nitric oxide derivative, BMI = body mass index, BP = blood pressure, CRP = c-reactive protein, EF = ejection fraction, CAD = coronary artery disease, UPPP = uvulopalatopharyngoplasty

### IX.E.6 Surgery and Cognitive Measures

It is well recognized that obstructive sleep apnea (OSA) is associated with neurocognitive impairment. Among the various cognitive functions, attention, memory, and executive function are most commonly affected by this chronic disorder.<sup>828,845,848,2049,2050</sup> There is compelling evidence that surgical treatment reduces OSA severity and daytime sleepiness.<sup>1685,1920,1965,2051</sup> Furthermore, in children, multiple studies have evaluated the efficacy of adenotonsillectomy for OSA on cognitive function.<sup>2052,2053</sup> This section will focus on the neurocognitive effects of sleep surgery in adults suffering from OSA (**Table X**).

*Klonoff et al.* were the first to assess neurocognitive function in adult patients undergoing surgery for OSA.<sup>2021</sup> Although notable improvements in cognitive function were found after uvulopalatopharyngoplasty (UPPP), similar results were observed in a control group of patients scheduled for cardiac surgery, suggesting that these changes were not disease-specific. Since then, two other studies have demonstrated improvements in cognitive function, albeit in different domains, after UPPP with or without tongue base surgery.<sup>2054,2055</sup> Additionally, a multicenter study on maxillomandibular advancement (MMA) has shown positive effects on neurocognitive performance by means of an attention test.<sup>2004</sup> Other cognitive domains were not examined. In general, the findings of these cohort studies are quite heterogeneous, showing improvements in different domains. Based on this limited evidence, surgical treatment might be effective to counteract some of the neurocognitive

deficits associated with OSA. This might be consistent with previous research on continuous positive airway pressure (CPAP) therapy.<sup>1280,2056</sup>

There is one randomized controlled trial (RCT) available on the neurocognitive effect of OSA surgery.<sup>2057</sup> In this study, 49 patients were offered CPAP or multilevel surgery based on clinical findings. Each group was subsequently randomized to active treatment or conservative measures consisting of weight reduction and alcohol avoidance. All patients were administered a neuropsychological test battery at baseline, and 3 and 12 months after treatment. The results revealed a significant improvement in visual memory among CPAP users; however, there were no differences in cognitive function between surgical patients and controls. Importantly, surgical patients did not achieve a satisfactory reduction in OSA severity and the study was limited by its small sample size and lack of executive function testing.

*Lin et al.* investigated morphologic brain changes in OSA patients following multilevel surgical treatment using volumetric magnetic resonance imaging.<sup>2055</sup> According to their results, surgery decreased aberrant gray matter volumes of the precuneus, insula, and cerebellum, but did not change the anterior cingulate gyrus, which is mainly involved in cardiovascular control. Notably, these changes were not associated with neurocognitive outcome after surgery.

Overall, the evidence supporting the efficacy of OSA surgery in terms of neurocognitive outcome is sparse and inconclusive with heterogeneous findings due to the use of diverse neuropsychological test batteries. Therefore, *Décary et al.* proposed a standardized neurocognitive assessment for patients with OSA, covering executive function, attention, memory, and general intelligence.<sup>2058</sup> Confounding factors, such as age, cognitive reserve, and surgical response, can complicate comparison between studies. Future research addressing these caveats is warranted to evaluate the efficacy of surgical treatment on neurocognitive function in OSA patients.

#### Surgery to Improve Cognitive Measures

Aggregate Grade of Evidence: C (level 2b: 1 study; level 3b: 1 study; level 4: 3 studies; conflicting evidence;).

Table IX.E.6 Evidence for Surgery and Cognitive Measures

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusion
Lojander et al. <sup>2057</sup>	1999	2b	RCT	OSA patients (n = 49) 1. UPPP ± MO with HS 2. CPAP 3. Conservative measures	Comprehensive NP battery (3 and 12 months FS)	No difference in cognitive function between UPPP and control group. Patients with CPAP showed a better visual memory than controls.
Klonoff et al. <sup>2021</sup>	1987	3b	Cohort	1. UPPP (n = 11) 2. Controls without OSA scheduled for cardiac surgery (n = 11)	Comprehensive NP battery (3 months FS)	UPPP improved memory, executive, and language functions, as well as IQ. Both groups

						experienced similar improvements.
Boyd et al. <sup>2004</sup>	2019	4	Cohort	MMA (n = 30)	Attention (6 months FS)	MMA improved response time and reduced errors.
Dahlof et al. <sup>2054</sup>	2002	4	Cohort	UPPP (n = 51)	1. General intelligence 2. Learning and memory 3. Executive function (6 months FS)	UPPP improved learning, visuospatial, and executive functions. No correlation between NP findings and surgical outcome.
Lin et al. <sup>2055</sup>	2016	4	Cohort	1. Multilevel surgery (n = 21) 2. Controls without OSA (n = 15)	1. Comprehensive NP battery (3 months FS) 2. Gray matter volume measured by volumetric MRI	Surgery improved attention, visuospatial, and executive domains. No correlation between NP findings and gray matter volume.

CPAP = continuous positive airway pressure; HS = hyoid suspension; FS = following surgery; IQ = intelligence quotient; LOE = level of evidence; MMA = maxillomandibular advancement; MRI = magnetic resonance imaging; MO = mandibular osteotomy; NP = neuropsychological; RCT = randomized controlled trial; UPPP = uvulopalatopharyngoplasty.

### IX.E.7 Surgery and Cerebrovascular Disease

If untreated, obstructive sleep apnea (OSA) can have grave medical consequences. These adverse effects are often more profound in the cerebrovascular than in the cardiovascular system.<sup>646</sup> Hence, ischemic stroke represents an important clinical endpoint for evaluating efficacy of OSA treatment.<sup>26,38</sup>

Several studies have demonstrated that surgical treatment for OSA can improve surrogate endpoints of stroke, including blood pressure,<sup>1713,1864,1876,2038,2040,2059</sup> lipid profile,<sup>2060,2061</sup> platelet volume,<sup>2062,2063</sup> C-reactive protein,<sup>2041,2064</sup> inflammatory cytokines,<sup>2065-2067</sup> matrix metalloproteinases,<sup>2068</sup> carotid artery intima-media thickness,<sup>2069</sup> heart rate variability,<sup>1897,2042</sup> and endothelial function.<sup>2070,2071</sup> However, few studies have examined the effect of OSA surgery on incident stroke (Table X).

*Partinen and Guilleminault* evaluated cardiovascular events in patients with OSA treated by tracheostomy or weight loss counseling.<sup>2072</sup> Despite an increased prevalence of cardiovascular disease in the tracheostomy group, these patients had significantly lower vascular mortality than the conservatively treated patients did after accounting for age, body mass index, and OSA severity. Furthermore, during the 7-year follow-up, the incidence of stroke was significantly lower in the tracheostomy than in the weight loss group. Using the Taiwan National Health Insurance database, *Chen et al.* explored the 1-year incidence of stroke among patients with OSA who underwent uvulopalatopharyngoplasty (UPPP) versus those who did not receive any treatment.<sup>2073</sup> As a result, the authors found an adjusted relative risk of 0.45 for stroke in the UPPP group compared with the

noninterventional group. Because some members of the latter group engaged in undocumented OSA treatment, this beneficial effect of surgery may have been underestimated. In another retrospective study comparing UPPP with continuous positive airway pressure (CPAP), weight reduction, and no treatment, patients receiving treatment had significantly lower cardiovascular mortality than patients without treatment.<sup>2033</sup> Statistical differences between treatment groups were not noted.

Besides this empirical research, cost-effectiveness models have indicated protective effects of hypoglossal nerve stimulation (HGNS) therapy on cardiovascular outcomes. Based on data of the STAR trial, *Pietzsch et al.* estimated a substantial risk reduction of stroke with HGNS (10-year relative risk 0.75).<sup>2074</sup> Another model based on real-world data revealed a similar benefit of HGNS over a 10-year period (relative risk 0.76; number needed to treat 55.6 for stroke).<sup>2075</sup>

In summary, there is limited evidence that surgical treatment for OSA reduces the risk of cerebrovascular accidents. Most research on this topic has been conducted with surrogate endpoints for stroke. Only one retrospective study was identified that evaluated the direct effect of conventional OSA surgery on incident stroke.<sup>2073</sup> Analogous to CPAP-therapy,<sup>26,38</sup> large randomized trials with rigorous study design are needed to delineate the effects of surgery on cerebrovascular morbidity and mortality in patients with OSA.

#### Surgery to Reduce Cerebrovascular Disease Risk

Aggregate Grade of Evidence: C (level 2b: 2 studies; level 4: 1 study).

**Table IX.E.7 Evidence for Surgery and Cerebrovascular Disease**

Study	Year	LOE	Study design	Study groups	Clinical endpoints	Conclusion
Partinen and Guilleminault <sup>2072</sup>	1990	4	Cohort (retrospective)	OSA patients 1. Tracheostomy (n = 71) 2. Weight loss recommendation (n = 127)	1. Stroke / TIA 2. Myocardial infarction 3. Mortality (7 years follow-up)	Lower mortality and CV morbidity in tracheostomy group
Marti et al. <sup>2033</sup>	2002	2b	Cohort (retrospective)	OSA patients 1. UPPP (n = 88) 2. CPAP (n = 124) 3. Successful weight loss (n = 134) 4. No intervention (n = 98)	Mortality (4 to 9 years follow-up)	Higher CV mortality in group without treatment. No significant differences between UPPP, CPAP and weight loss groups. No CV events in UPPP group.
Chen et al. <sup>2073</sup>	2015	2b	Cohort (retrospective)	OSA patients 1. UPPP (n = 5635) 2. No	Stroke / TIA (1 year follow-up)	Significantly lower incidence of stroke in UPPP group.

				intervention (n = 4704)		
--	--	--	--	-------------------------	--	--

CPAP = continuous positive airway pressure; CV = cardiovascular; LOE = level of evidence; OSA = obstructive sleep apnea; TIA = transient ischemic attack; UPPP = uvulopalatopharyngoplasty

### IX.E.8 Surgery and Work Productivity

Untreated OSA patients often have daytime symptoms that can affect work productivity. Ulfberg et al compared OSA patients with non-snorers and found that OSA patients had more difficulty doing their job because of tiredness/sleepiness (odds ratio, OR = 37), and had large or very large difficulties with concentrating on (OR = 7.5) and learning (OR = 9.1) new tasks<sup>2076</sup>. Mulgrew et al examined patients with suspected OSA and reported that excessively sleepy patients with an ESS  $\geq 18$  had significantly worse time management, mental-interpersonal relationships and work output than those whose ESS was  $\leq 5$ <sup>1321</sup>. Given that many OSA patients complain of excessive daytime sleepiness, poor work productivity is a highly probable consequence.

A negative impact on the economy may manifest in the form of the cost of days absent from work because of OSA and the cost of disability or work duty modifications<sup>1023,2077</sup>. In a large study of 19,438 OSA patients from the Danish National Patient Registry, Jennum et al showed that OSA patients have higher hospitalization rates than non-OSA controls<sup>133</sup>. OSA patients also have greater total direct (expenses for medical visits, hospitalizations and medication) and indirect (loss of income due to disease-related work disability) costs up to eight years prior to and after diagnosis<sup>133</sup>. The study reported that CPAP and surgery could reduce workplace costs, but not to the level two years prior to treatment initiation, and CPAP was comparatively more effective at doing so than surgery<sup>133</sup>. Adenotonsillectomy and UPPP were listed as examples of surgeries undergone by the population; no sub-analysis of specific surgeries was performed.

The handful of studies analyzing the impact of OSA treatment on work productivity are mostly focused on CPAP<sup>1023</sup>. Zhang et al is perhaps the only study that examined the impact of surgery on work ability using a work ability index questionnaire<sup>2078</sup>. Minimally invasive multilevel surgery was performed on the inferior nasal conchae, soft palate, tonsils and tongue base of 51 patients. Statistically significant improvements in polysomnogram parameters (e.g., AHI, lowest saturations, microarousal index), ESS, as well as better Work Ability Index (WAI) scores were noted one year after the surgery<sup>2078</sup>. WAI scores improved from  $37.76 \pm 4.46$  to  $40.00 \pm 4.53$  (maximum score being 49 points; a higher score indicating better work ability)<sup>2078</sup>. The study observed that the change in the WAI score was influenced by the change in ESS, and patients whose occupation was classified as “mental work” improved more than those who did “manual work”<sup>2078</sup>.

Extrapolation from improvements seen in sleepiness, vigilance, reaction time, perceived general well-being, and reduced errors or lapses<sup>2004</sup> after the majority of OSA surgeries suggests that surgery could lead to improved work productivity (refer to sub-section: Sleepiness/Daytime Symptoms). However, in the presence of scant hard evidence demonstrating this link, the efficacy of surgery on work productivity is not certain.

#### Surgery to Improve Work Productivity

Aggregate Quality of Evidence: D (Level 2b: 1 study; Level 4: 1 study)

**Benefit:** Reduced direct and indirect economic costs related to absenteeism, medical expenses and work duty modifications. Reduced sleepiness and improved alertness may translate to better work productivity.

**Harm:** Risks related to surgery and complications.

**Cost:** Direct costs: Moderate costs specific to surgery and hospitalization; Indirect costs: Time-off work after surgery.

**Benefits-Harm Assessment:** Balance of benefit and harm.

**Value Judgments:** Properly selected surgical interventions can be successful with low risk of harm. Evidence on direct relationship to workplace productivity is limited.

**Recommendation Level:** No Recommendation.

**Intervention:** Surgery may improve daytime sleepiness but the evidence demonstrating significant improvements in work productivity is limited.

**Table IX.E.8: Evidence for Surgery to Improve Work Productivity**

STUDY	YEAR	LOE	STUDY DESIGN	STUDY GROUPS	CLINICAL END-POINT	CONCLUSION
Jennum and Kjellberg <sup>133</sup>	2011	2b	Cross-sectional controlled study	1) Snoring 2) Sleep apnea 3) Obesity hypoventilation syndrome 4) Matched controls without sleep-disordered breathing	Direct and indirect economic costs, mortality	Sleep-disordered breathing has major socioeconomic consequences for the individual patient and society. Surgery can reduce workplace costs.
Zhang et al <sup>2078</sup>	2020	4	Case series	Minimally invasive surgery	PSG, ESS, Work Ability Index	PSG parameters and patients' perception of their ability to work improved significantly.

Abbreviations: ESS, Epworth sleepiness scale; PSG, polysomnography

## X. Pediatric OSA: Differences in Evaluation and Management

### X.A Evaluation for Pediatric OSA

Pediatric is distinct from adult OSA in epidemiology, pathophysiology, diagnosis, and treatment. Less common than in adults, OSA has an estimated prevalence of 1-3% in children.<sup>2079</sup> Untreated pediatric OSA is associated with hypertension,<sup>2080</sup> autonomic dysfunction,<sup>2081</sup> attention-deficit/hyperactivity disorder,<sup>2082</sup> neurobehavioral impairment,<sup>2083,2084</sup> and poor quality of life.<sup>2085</sup> Comorbidities in children that are associated with an increased risk of OSA include Down syndrome, craniofacial anomalies, neuromuscular disorders, mucopolysaccharidoses, and obesity.<sup>2079</sup>

### Diagnosis by History

Snoring, apneic pauses, and gasping or snorting during sleep are the cardinal features of OSA in children and routine screening for snoring is recommended by the American Academy of Pediatrics.<sup>2086,2087</sup> Though daytime sleepiness is also associated with childhood OSA, it is less common than in adults. Other symptoms common in children with OSA include nocturnal enuresis, daytime attention deficit or hyperactivity,<sup>2082,2088-2091</sup> learning difficulties and poor school performance.<sup>2079</sup> However, while these symptoms in combination with habitual snoring are suggestive of childhood OSA, clinical evaluation alone is inadequate in establishing a diagnosis of OSA. For this reason, attended overnight polysomnography (PSG) remains the gold standard and primary recommended method for diagnosis and severity grading of OSA in children.<sup>2087</sup> However, due to the limitations of attended polysomnography in children including lack of availability, high cost, and potential poor tolerance, a clinical diagnosis of obstructive sleep disordered breathing. (SDB) can be made by clinical history and physical exam.

### Sleep Disordered Breathing and Validated Subjective Measures

When a diagnosis of OSA based on PSG is not possible, a diagnosis of SDB is often made based on clinical evaluation alone. Symptom screening may be further supplemented with validated questionnaires for symptoms of SDB or to assess sleep-related quality of life.<sup>2092-2094</sup> Among these, the Sleep-Related Breathing Disorder scale of the Pediatric Sleep Questionnaire (SRBD-PSQ) and the OSA-18 are two of the most commonly used and cited questionnaires (Table I). A recent meta-analysis of the accuracy of the SRBD-PSQ in diagnosing OSA in children showed a sensitivity of 0.72 [95%CI 0.68, 0.77], specificity of 0.59 [95%CI 0.56, 0.63], and an overall fair diagnostic accuracy (area under the curve) of 0.73 [95%CI 0.63, 0.82].<sup>2095</sup> In general, questionnaires that have been validated against PSG have demonstrated variable sensitivities and specificities depending on the diagnostic cut-offs used, with frequently poor diagnostic accuracy.<sup>2093,2096</sup> However, these questionnaires do have clinical utility in measuring subjective disease burden and sleep-related quality of life. For example, the SRBD-PSQ score has been shown to correlate better than PSG with other measures of sleep-related morbidity (e.g. executive dysfunction, behavior, quality of life, sleepiness) as well as response to treatment.<sup>2097</sup>

### Physical Examination

As a standard part of the head and neck exam, tonsillar hypertrophy is described according to the Brodsky scale,<sup>1644</sup> though awake tonsil size assessment has not generally correlated well with either baseline OSA severity<sup>2098-2100</sup> or response to AT.<sup>2101</sup> Macroglossia should be noted and may be more significant in children with craniofacial syndromes. Other physical exam findings associated with OSA in children include adenoidal facies, nasal obstruction due to turbinate hypertrophy or septal deviation, mouth breathing, micrognathia, midface hypoplasia, and a narrow high-arched palate. General muscle tone and neurologic status should also be noted. Symptoms of stertor or stridor while awake may prompt flexible awake endoscopy during the clinic visit.

### Objective Testing

Unlike sleep testing in adults where home sleep testing is an accepted method of OSA diagnosis, no home sleep tests have been shown to be reliable or valid in children for routine clinical use. Therefore, attended overnight PSG remains the recommended method for diagnosis of OSA in children.<sup>2102</sup> The American Academy of Sleep Medicine (AASM) recommends the use of pediatric respiratory scoring rules for any children less than 18 years of age, but there is an option to use adult scoring rules for teenagers at least 13 years of age.<sup>12</sup> OSA is diagnosed when SDB is accompanied by an abnormal polysomnography (PSG) with an obstructive apnea-hypopnea index (AHI) >1. Although there is no universal consensus on cutoffs for OSA severity in children, several studies use an AHI of 1 to <5 for mild, 5 to <10 for moderate, and ≥10 for severe OSA.



According to the American Academy of Otolaryngology- Head and Neck Surgery Clinical Practice Guidelines for Tonsillectomy in Children, adenotonsillectomy may be recommended as treatment for SDB in the absence of polysomnography if clinical history and physical exam are congruent with the diagnosis.<sup>2103</sup> Further recommendations include obtaining polysomnography in children with SDB if they exhibit obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses.

### Drug-Induced Sleep Endoscopy in Children

First described and widely used in the evaluation of adults with OSA, drug-induced sleep endoscopy (DISE) is increasingly used in children with OSA. While the indications for DISE in adults are well established, the indications in children remain controversial.<sup>2104</sup> DISE has been described in the evaluation of surgically naïve children<sup>2105,2106</sup> as well as in those who have failed adenotonsillectomy<sup>2107</sup> to help guide surgical decision-making. Patterns of obstruction observed in children are not as well established as in adults and vary by age and comorbidity.<sup>2108</sup> While most adult rating scales like the VOTE scale focus primarily on dynamic obstruction at the soft palate, lateral oropharynx, base of tongue, and epiglottis, it is widely acknowledged that the nasal airway, adenoid hypertrophy, and arytenoid cartilages can also be important sources of obstruction in children.<sup>2109,2110</sup>

**Table X.A: Commonly Cited Surveys validated in children for assessment of obstructive sleep apnea or sleep-disordered breathing**

Name	Respondent	Age (years)	Items	Response type	Scoring	Purpose	Sensitivity/ Specificity against PSG
SRBD-PSQ <sup>2111</sup>	Caregiver	2-18	22	Yes/no/don't know	> 7 considered positive screen	Screening for symptoms of SDB	50-85%/ 13-72%
OSA-18 <sup>2112</sup>	Caregiver	0.5-12	18	7-pt Likert	Range 7-126 0-60 mild 60-80 moderate >80 severe	Sleep-related quality of life impact	55-93%/ 25-84%

SRBD-PSQ = Sleep related breathing disorder scale of the pediatric sleep questionnaire

### X.B Adenotonsillectomy as First-line Treatment for Pediatric OSA

The management of pediatric OSA depends on several factors including the severity of the sleep disorder, associated daytime and nighttime symptoms, and comorbidities. Adenotonsillar hypertrophy is the main contributor to OSA in the majority of healthy children.<sup>2103</sup> As such, adenotonsillectomy (T&A) is the first-line surgical treatment for OSA in children. This is the recommendation of guidelines published by the American Academy of Otolaryngology-Head and Neck Surgery (AAOHN)<sup>2103</sup>, the American Academy of Pediatrics (AAP)<sup>2087</sup> and the American Academy of Sleep Medicine (AASM).<sup>2113</sup> Evidence in randomized controlled trials and systematic reviews<sup>2052,2053,2114</sup> has shown that T&A results in improvements in PSG parameters as well as daytime and nighttime symptoms, quality of life (QoL), and behavior. While T&A should be recommended in children diagnosed with OSA by PSG, T&A is frequently

recommended for SDB based on clinical history and examination findings alone, and has been shown to result in significant improvements in neurocognitive and quality of life outcomes. However, there is increasing awareness that some children may see improvement and resolution of OSA without surgical intervention and may benefit from medical treatment or observation alone.

The most significant and widely referenced study on the management of OSA in children is the Childhood Adenotonsillectomy Trial (CHAT)<sup>2053</sup>. The CHAT study was a well-designed and rigorously conducted randomized controlled trial with wide geographic and racial representation for the United States, as well as high follow-up rates. It included 464 children (ages 5-9 years) with OSA randomized to T&A or watchful waiting with supportive care (observation). The study reported significantly greater improvements in the T&A versus observation groups in symptoms, behavior, QoL, and PSG outcomes. However, there was no difference in objective testing for attention and executive function between the groups. Normalization of PSG was much higher in the T&A versus the observation group 153/194 (79%) versus 93/203 (46%).<sup>2053</sup> At baseline, mean AHI scores were 6.9 (SD 5.7) in the T&A group and 6.6 (SD 5.6) in the observation group. At seven months, the mean AHI score in the T&A compared with the observation group was 1.6 (SD 3.0) versus 5.9 (SD 10.1) respectively. Children with more severe baseline OSA showed greater improvement after T&A compared to watchful waiting, but they were also less likely to show PSG normalization after T&A. Similarly, fewer African American children and those with obesity had normalization of AHI, irrespective of the assigned treatment.

Several observational cohort studies reported significant improvements after T&A for OSA in children.<sup>2115-2117</sup> A multicenter retrospective study of 578 children in 6 pediatric sleep centers in the United States and Europe was reported by Bhattacharjee et al.<sup>2115</sup> All children had a T&A for OSA with pre- and postoperative PSG and 50% were obese. T&A resulted in a significant reduction in AHI from a mean 18.2 to 6.4, but only 27% had complete resolution of OSA (AHI<1). Older age (>7 years), and those with chronic asthma or obesity were more likely to have persistent OSA. Most children had an improvement but not resolution in AHI after T&A. This study<sup>2115</sup> and several others, have reported persistent OSA after T&A in children with severe OSA, obesity, Down syndrome, craniofacial, genetic, and neuromuscular disorders.<sup>2116,2118</sup>

Two meta-analyses of outcomes of T&A for OSA were published in the last 5 years.<sup>2052,2114</sup> Both included data from the CHAT study and reported significant improvements in PSG parameters, symptoms, QoL and behavior in children with OSA undergoing T&A compared to observation. Chinnadurai et al,<sup>2052</sup> in a meta-analysis of 3 studies on outcomes of T&A for OSA, reported a significant 5-point difference in improvement in AHI after T&A versus observation. However, two studies included in this meta-analysis were small cohort trials.<sup>2052</sup> Venekamp et al<sup>2114</sup> reported on 3 studies with 562 children but were unable to combine the results because of substantial differences in the groups of children studied.<sup>2114</sup> They reported significant improvements following T&A versus observation but mostly in healthy, normal-weight children. They noted that these benefits were modified by comorbid conditions, such as craniofacial, neuromuscular, genetic, and metabolic disorders and that demographic characteristics, particularly obesity, can lead to more severe baseline OSA and a less significant response to T&A.<sup>2114</sup>

There is an ongoing debate about the efficacy and timing of T&A for mild OSA (AHI <5). Trosman et al studied children with mild OSA, including a variety of comorbidities such as obesity, craniofacial disorders, and hypotonia. Of 62 children, 19 had a T&A, and the rest were observed.<sup>2119</sup> T&A resulted in a significant improvement in AHI over observation in the non-syndromic, nonobese children that was not seen in the observation group. Indeed, several children in the observation group experienced

worsening AHI. Volsky et al<sup>2120</sup> studied 64 children with mild OSA and compared 30 who underwent T&A with 34 in the observation group. Outcomes were measured subjectively with QoL instruments. Baseline QoL measures improved significantly 4 and 8 months after T&A. There was no change in QoL measures for the observation group at 4 months but some improvement at 8-months. There is a paucity of outcomes data in children with significant comorbidities and mild OSA and it remains unknown if T&A should be a first-line treatment in these children. There is additional concern that T&A for mild OSA can lead to weight gain especially in obese children that can worsen the severity of the sleep disorder.<sup>2121</sup> Furthermore, the role of continuous positive airway pressure (CPAP) therapy as an alternative to T&A, especially in obese children, has not been studied extensively and better patient-focused outcome measures are needed.

As an alternative to adenotonsillectomy for treatment of pediatric OSA, medical treatment has been proposed including nasal steroids and oral montelukast.<sup>2122-2124</sup> A meta-analysis including 5 studies that evaluated montelukast as stand-alone treatment for pediatric OSA found a 55% improvement in AHI. A separate analysis of 2 studies found a 70% improvement in AHI when treatment with montelukast was combined with nasal steroid therapy.<sup>2125</sup> However, these studies did not compare medical treatment to standard surgical treatment and measured only short-term outcomes (typically 3-6 months). The long-term impact of these medical treatments and their potential side effects is unknown. In addition, montelukast now has a FDA black box warning due to risk of serious adverse mental health side effects.<sup>2126</sup>

In children with persistent obstructive sleep apnea symptoms after adenotonsillectomy, polysomnography is indicated. Options for treatment include non-invasive positive pressure therapy, medical therapy as described above, or further surgical treatment. Drug-induced sleep endoscopy (DISE) is being increasingly explored in the treatment of persistent OSA in children after T&A.<sup>2108</sup> Surgical therapy in these T&A failures can be dictated by findings on DISE and may commonly include revision adenotonsillectomy, lingual tonsillectomy, supraglottoplasty, or nasal surgery.<sup>2127</sup> Future directions include the increasing application of hypoglossal nerve stimulation in children who fail T&A. Initial studies in adolescents with Down Syndrome with persistent severe OSA after T&A showed median reduction of AHI by 85%.<sup>2128</sup>

In summary, there is strong evidence to support T&A as the first line treatment of OSA in children. However, in children with mild to moderate OSA and mild symptoms, a period of observation or medical therapy may be appropriate. There is a paucity of research on the best management of children with mild OSA or in children with significant comorbidities and OSA. Persistent OSA in children may be evaluated with DISE which can further dictate medical or surgical therapy.

#### Adenotonsillectomy as Treatment for Pediatric OSA

**Aggregate Quality of Evidence:** B (Level 1a: 2 study; Level 1b: 1 study; Level 2b: 2 study; Level 3a: 1 study; Level 3b: 2 studies)

**Benefit:** Improved postoperative sleep parameters, symptoms, quality-of-life and behavior.

**Harm:** Risk of bleeding, possible dehydration, parental days off work for postoperative care.

**Cost:** Moderate costs related to surgery and postoperative care.

**Benefits-Harm Assessment:** Preponderance of benefit over harm.

**Value Judgments:** Patients can experience improved sleep and symptoms related to OSA.

**Recommendation Level:** Recommendation.

**Intervention:** Tonsillectomy with or without adenoidectomy should be offered in children with OSA.

**Table X.B: Evidence on Adenotonsillectomy for Pediatric OSA**

Study	Year	LOE	Study Design	Study Groups	Clinical Endpoints	Conclusion
Marcus et al <sup>2053</sup>	2013	1b	RCT	Children with OSA followed up for 7-months: 1. T&A 2. Observation	PSG, behavior, quality of life, symptoms, neurobehavioral outcomes	Improvement in both groups. Significantly greater improvement in the surgical group. No improvement in neurobehavioral outcomes in either group
Bhattacharjee et al <sup>2115</sup>	2010	2b	Observational cohort	Children with OSA with before and after T&A PSG data	Resolution of OSA	Significant improvement in AHI but resolution in only 27%
Chinnadurai et al <sup>2052</sup>	2017	1a	SR of RCTs	Children with OSA with T&A versus observation	Improvement/Resolution of OSA	T&A compared to observation leads to short-term improvement in sleep outcomes in children with OSA
Venekamp et al <sup>2114</sup>	2015	1a	SR of RCTs	Children with OSA with T&A versus observation or CPAP	Improvement/Resolution of OSA	T&A compared to observation or CPAP leads to benefits in PSG parameters quality of life,

						symptoms and behavior
Trosman et al <sup>2119</sup>	2016	3a	Observational cohort	Children with mild OSA	PSG	T&A compared to observation leads to a significantly greater improvement in AHI especially in non-obese, non-syndromic children.
Volsky et al <sup>2120</sup>	2014	3b	Observational cohort	Children with mild OSA	OSA-18 quality of life scores	Quality of life significantly improves in children with mild OSA after T&A with less improvement with observation
Kheirandish-Gozal et al <sup>2122</sup>	2014	3b	Observational cohort	Children with mild OSA treated with intranasal corticosteroid and oral montelukast	PSG in subset; symptoms	Beneficial effects in >80% of children
Liming et al <sup>2124</sup>	2019	2b	SR of observational cohorts	Children with mild OSA treated with intranasal corticosteroid and oral montelukast	PSG	Treatment with montelukast and intranasal steroids or montelukast alone is beneficial for short-term management of mild pediatric OSA.

T&A= tonsillectomy with or without adenoidectomy; SR = Systematic Review

## XI. Knowledge Gaps and Research Opportunities

There continues to be rapid growth in knowledge and advancements within sleep disordered breathing with emerging areas for advanced understanding in the disease. Growing evidence demonstrates that OSA results from individualized features of physiology and symptomatology. The far-reaching independent effects of untreated OSA on cardiometabolic comorbidities, health outcomes, and mortality are unresolved. The next phase of investigation requires determining optimal paradigms for diagnosis and management of OSA by translating large-scale analyses into personalized care.

The ICS:OSA outlines areas where consistent evidence supports screening, diagnosis, and treatment for OSA while at the same time identifies important knowledge gaps. Specially, there is a need to demonstrate that the treatments for OSA have meaningful impact on outcomes other than sleep health and patient satisfaction.

### XI.A Phenotypes and Metrics of Disease

The contributors to adult OSA are multiple and complex. Integrated knowledge of sleep architecture, ventilatory control, upper airway anatomy, insomnia and neuromuscular control is necessary to appreciate the complexities of the disease and determine the best steps for management.

#### AHI and the need for alternative metrics of OSA

The ICS:OSA demonstrates a variability in OSA phenotypes and disease sequelae. Yet, the historical paradigm for stratification of OSA severity has centered primarily on the AHI as the outcome metric. Utility of a single outcome metric, whereas simple, does not adequately predict the multitude of clinical endpoints attributed to OSA. A recent publication from the Sleep Research Society summarizes the strengths and weaknesses of AHI as the main metric of OSA.<sup>2024</sup>

Traditionally, AHI is the summary metric that defines OSA presence and severity. It represents the focal measure of upper airway instability in a sleep study<sup>2129</sup> and of treatment efficacy. A 1999 consensus statement suggested that categories of mild (<5 events/hr), moderate (5-15 events/hr) and severe (>30 events/hr) for AHI were convenient and appropriate markers for clinical severity for the use of CPAP therapy<sup>2130</sup>. At the time, these experts-derived cutoffs were not determined based on strong evidence. While definitions and scoring of hypopneas have changed, these cutoff AHI values are still used for categorical severity and treatment goals.

Problems with AHI as the primary metric of OSA disease include its lack of correlation with symptoms and sleepiness severity and issues with consistency of reporting. AHI has been demonstrated to have poor correlation with sleepiness, neurocognitive function, and quality of life.<sup>420,953,2131-2134</sup> There are issues with consistency and reproducibility of the AHI metric. A night-to-night variability of AHI in the short term is related to variation in sleep stages, sleeping position, environment, and arousals.<sup>2135-2137</sup> Interscorer reliability of AHI when the scoring is tightly controlled within a sleep center is high.<sup>2138</sup> However, when applied to clinical practice, sleep laboratories may use a variety of AHI metrics depending on insurance payor edicts or updates in clinical scoring rules (i.e. hypopnea definitions). This leads to variability in interpretation of AHI.

While AHI was the starting point and is the best studied metric of OSA, it falls short as a unifying metric that captures both OSA severity and outcome prognostication. Alternative determinants of disease severity may involve combinations of other metrics. The ODI is defined by desaturations on pulse oximetry and is associated with the potential for more objective scoring.<sup>731</sup> Arousal index, area under the oxygen saturation curve to account for hypoxic exposure, apnea-hypopnea length, and inter-apneic interval are currently experimental but suggest associations with clinically-meaningful outcomes. Disease burden has been associated with metrics such as: hypoxic burden, which may contribute to cardiovascular mortality,<sup>2139</sup> arousal intensity, which has implications for memory disturbance,<sup>2140,2141</sup> and specific blood biomarkers, which may demonstrate inflammatory responses to chronic intermittent hypoxia.<sup>2142-2144</sup> Thus, the optimal metric to identify OSA severity may differ between individuals depending on time of onset and burden of disease, and may be outcome-specific. Further research is required to identify measures that capture potential heterogeneity in mechanisms underlying the origins of OSA and individual responses to hypoxia.<sup>2145-2147</sup>

Future definitions of OSA severity will likely merge the AHI with other quantitative and semi-quantitative dimensions linking OSA pathophysiology and symptomatology.<sup>2148,2149</sup> An integrative approach may better determine and stratify patients who will benefit from OSA treatment.

### Phenotypes of Disease

Initial clustering and multi-dimensional analyses of OSA demonstrate it is a heterogeneous disorder with three clinical “phenotypes” proposed: 1) Disturbed sleep, 2) Minimally symptomatic, and 3) Excessively sleepy.<sup>1997,2149-2151</sup> Other studies have identified additional phenotypic groups, but these three have been identified across multiple populations. Pien et al. studied changes in symptoms related to sleepiness and fatigue, insomnia, and apneic events in these groups and found that the effect of PAP treatment differed by phenotypic group.

OSA phenotypes may also be associated with different levels of cardiovascular risk. Analyses of OSA symptom subtypes and cardiovascular disease showed a higher risk of incident cardiovascular disease and cardiovascular mortality in the “excessively sleepy” when compared with other clusters.<sup>639,1204</sup>

Another proposed clinical phenotype is the distinction between positional patients who primarily manifest OSA when in the supine position compared to non-positional patients who demonstrate significant sleep disordered breathing in all positions.<sup>41</sup> Understanding the differences in OSA disease and treatment outcomes between positional and non-positional patients has important implications for multi-modal treatment discussions.

Physiologic phenotypes of disease describe the heterogeneity of anatomic and non-anatomic contributors to disease such as upper airway collapsibility (measured with Pcrit), airway dilator muscle tone changes in sleep (measured with EMG), respiratory triggers for awakening (arousal thresholds), and sensitivity of the ventilatory control system (loop gain). The PALM scale (Pcrit, arousal threshold, loop gain, muscle responsiveness) has been proposed to categorize OSA patients and target therapies to pathologic mechanism(s) of disease.<sup>36</sup>

Understanding the implications of these clustered traits and OSA phenotypes on treatment outcomes and other health risks will be an important area for individualized therapy.

Research Opportunities include:

This article is protected by copyright. All rights reserved.

- Determining which combination of PSG and symptom-based metrics capture OSA severity, inform prognosis and determine cardiovascular and mortality risks.
- Determine accessible biomarkers for OSA that can be used to determine treatment responses.
- Understand the differences between OSA patients who have significant daytime sleepiness compared to those without sleepiness.
- Predict risks and symptoms associated with REM-related OSA, especially in those with mild OSA (AHI 5-15 events/hr).
- Delineate the mechanisms behind how obesity relates to OSA and individual OSA severity prognosis with weight management.
- Determine the genetic associations of sleep disordered breathing.
- Examine utility of interventions to alter loop-gain and arousal thresholds as adjunctive treatments for OSA.
- Understand the role of sleep position and clinical outcomes.

### **XI.B OSA Screening and Diagnosis**

The impact of OSA screening in primary care settings is not settled in terms of cost, effectiveness, and outcomes at the population level. Support exists for the utility and performance of the STOP-BANG as a screening tool, but evidence on the long-term health impacts of screening is lacking. Understanding health risks or behaviors that can be modified for benefit will define the optimal screening and testing strategies.

Different testing modalities now exist and given the prevalence and concern for OSA diagnosis, improving testing access and convenience is an emerging market. Home sleep studies improve convenience. Understanding the limitations of home sleep testing interpretations compared to in-lab sleep studies or oximetry testing will allow practitioners to choose the optimal testing and management strategies. Additionally, there are various consumer sleep technologies including nearables, wearables used for sleep tracking with variable capabilities. Devices assessments for potential benefits, disadvantages, and needs for validation are currently ongoing.<sup>2152</sup>

Research opportunities include:

- Assess the cost-utility tradeoff for routine screening in primary care settings.
- Create programs for inclusive and equitable access to OSA testing and decision making.
- Understand the predictors for false-negative home sleep studies that warrant follow-up and repeat testing. Determine who requires in-lab testing for diagnosis.
- Analyze the financial tradeoffs of using home sleep study testing vs. in-lab sleep studies in specific high-risk populations.
- Optimize screening paradigms to determine those at highest risk for medical and behavioral consequences of untreated OSA.
- Systems to improve access to OSA testing.
- Understanding the role, utility and value of consumer sleep technologies for sleep tracking.

### **XI.C OSA Therapy**

#### **XI.C.1 Benefits of PAP**



In the face of conflicting data between cohort and RCT studies on the effect of PAP therapy on cardiometabolic health outcomes and mortality risk, it is difficult to interpret the overall benefits of PAP therapy. Pack et al. summarized the biases and limitations associated with the negative RCT studies on the effects of PAP therapy and cardiovascular events. Specifically, RCT studies were secondary prevention studies and all trials excluded OSA subjects with excessive sleepiness who are increased risk for cardiovascular events and most likely to benefit from treatment.<sup>1204</sup> RCTs also had inadequate adherence to PAP therapy and on secondary analysis of data in adherent patients, CPAP benefit was found to be consistent with prior epidemiological studies.<sup>1205</sup>

Research opportunities include:

- Incorporate real-world PAP usage patterns to better understand modifications to health risks and mortality risks.
- Identify the patient phenotypes that benefit most from PAP therapy.
- Understand the efficacy of mandibular advancement devices, weight reduction, and positional sleep on altering health risks.

### XI.C.2 PAP Adherence

PAP remains the first-line therapy for OSA treatment, but efficacy is limited by adherence. “Big data” analyses of CPAP telemonitoring data provide new opportunities to understand adherence and real-world use patterns. Yet, current dichotomization of PAP use into adherence vs. non-adherence based on pre-set thresholds, (i.e. > 4 hours per night on >70% of nights over a rolling 30-day period) ignores the potential for linear dose-dependent relationships between CPAP use and improved clinical outcomes and creates barriers to reimbursement in patients who may be receiving meaningful clinical benefit despite suboptimal use.<sup>1097</sup> Use of the 4-hour, 70% threshold may be contributing to reduced access to treatment by rendering users below this threshold ineligible for coverage. Thus, further work is required to identify clinically meaningful adherence thresholds for PAP use, which may be outcome-dependent and vary in the context of patient treatment goals.

Furthermore, identifying factors that influence PAP adherence can inform innovations for optimization of PAP use and motivate behavior change programs. Data suggests disparities exist with PAP adherence across socioeconomic and racial groups.<sup>1094-1096</sup> Predictors of adherence include sociodemographics, comorbid conditions, OSA severity and perceived benefit of treatment, and behavioral factors, which may explain up to 50% of variance in PAP adherence.<sup>1105,1116</sup> Interventions targeting modifiable predictors have informed protocols such as patient education and engagement programs, and optimization of device design. However, there remains an opportunity to identify predictors for non-adherence to improve patient expectation management and promote early consideration of alternative treatment options.

Research opportunities include:

- Reexamine current PAP use threshold definitions and identify clinically meaningful adherence thresholds.
- Determine predictors of PAP adherence and design protocols to automate and inform providers about patients at-risk for low adherence levels.
- Quality initiatives to utilize telehealth or EMR-integrated systems to provide feedback to patients about PAP use and importance of PAP adherence.

This article is protected by copyright. All rights reserved.

- Understand the relationship between rhinitis, and sinusitis with PAP adherence.
- Identify and disseminate the most common modifiable changes to influence PAP adherence such as nasal obstruction, humidification, insomnia, PAP desensitization.

### **XI.C.3 Surgery and Definitions of Success**

Based on the AASM clinical practice guideline by Kent et al., referral for sleep surgery evaluation should be strongly considered for adults with OSA and BMI < 40 who are intolerant or unaccepting of PAP, and referral for bariatric surgery evaluation for adults with obesity (BMI > 35) who are intolerant or unaccepting of PAP.<sup>1505</sup>

Classic definitions of surgical success are based on specific levels of AHI reduction (ie. Sher's criteria) are limiting and do not fully capture the benefits of surgery in patients who cannot use PAP. A refocus on measures of quality of life, symptoms, snoring sound reduction, and long-term health risk reduction that are important to patients<sup>2153</sup> will be vital to understanding the full effects of surgery. Standardized approaches for surgical outcome reporting will be important and should quantify AHI reduction with standard analyses<sup>2025</sup> along with considerations for T90, ODI, apnea index, and sleep related symptoms. Specifically, much of the surgical literature is based on small case series with short term outcomes instead of prospectively designed trials. Standardized methodology for outcomes reporting is critical to allow for meta-analyses and evaluation of combined data.

Further work is also required to better understand which PAP alternatives are best for individual patients. Traditionally, surgery is performed after PAP has been trialed, however, in candidates with amenable anatomy, primary surgery may have a high probability of success. Further work is needed to understand the best candidates for primary surgery and each surgery type.

### **XI.C.4 Surgical Outcomes**

Comparisons between surgical outcomes and PAP outcomes are lacking. Specifically, postsurgical AHI improvement has rarely been compared to real-world PAP outcomes. Results on a titration sleep study do not adequately reflect PAP adherence and effectiveness. Larger prospective studies are needed to compare long-term outcomes in patients who receive surgical therapy versus PAP therapy.

Limitations of literature on surgery includes variability in procedural choice and techniques, non-standardized reporting of outcomes, small and heterogeneous populations, and many uncontrolled cohort studies. Recent advances include the addition of surgical techniques that reduce long term risks for dysphagia and efforts to understand which anatomic and clinical features respond best to surgical interventions.

Anatomic surgery may not lead to OSA resolution in all patients in terms of achieving AHI < 5 events/hr. However, the reduction in obstructive events, improvement in hypoxic burden, improvements in quality of life, and potential for health risk reduction are factors essential to surgical counseling.

Research opportunities include:

- Examining the thresholds of BMI for surgical candidacy and understanding the relationship between BMI and surgical success.
- Determine predictors for surgical success for each surgical approach

- Determine candidates for surgery and candidates for surgery as first-line treatment for OSA.
- Protocols to determine how to use DISE and other diagnostic tools to improve surgical outcomes.
- Determine the best practices approach for surgical selection based on clinical exam, treatment goals, PSG results, anatomy, DISE, and other factors related to OSA.
- Understand surgical outcomes in terms of OSA reduction, daytime sleepiness, snoring, and sleep quality.
- Understand the long-term outcomes of surgery on hypertension, cardiovascular disease, neurocognitive function, and mortality.
- Determine the role of surgery as adjunctive therapy to medical treatments for OSA.
- Management of hypoglossal nerve stimulation therapy and determine how to resolve those with suboptimal response
- Determine best-practice approaches for hypoglossal nerve stimulation advanced titration, programming adjustments, and clinical follow-up. Determine which titration protocols improve outcomes and which approaches have the most meaningful effects.

#### XI.D Longitudinal OSA Care

Obstructive sleep apnea is a chronic disease that requires different modalities of therapy that may evolve over time. Long-term follow-up is necessary to assess for continued therapeutic response. As new medical and surgical treatment options for OSA are introduced, there is a need for large scale studies to identify long-term efficacy and determine who is at risk for disease recurrence. The optimal care models for long-term management of OSA are unknown. Frequency of sleep studies have not yet been well established. Furthermore, while changes in OSA severity have been demonstrated in different age, weight, and comorbidity groups, the longitudinal course of OSA in a single patient with variations in these factors over time is not fully known. Therefore, further collaboration is required to identify follow-up protocols that are sensitive to changes in OSA over the disease course.

Research opportunities include:

- Optimize paradigms for longitudinal testing that include risk factors for disease progression or recurrence.
- Validation and incorporation of consumer sleep technologies for tracking OSA as a chronic disease in a clinically meaningful manner.
- Understand the impact and roles of OSA treatment on cardiovascular and neurocognitive comorbidities. Specifically define OSA as a modifiable risk factor for each disease such as: diabetes, hypertension, coronary artery disease, atrial fibrillation, heart failure, stroke, memory loss, dementia and cancer.
- Examine the mechanisms that underly the association between OSA severity and cancer risk.
- Efficacy and candidacy for alternative therapies including myofunctional therapy, positional therapy, and oxygen therapy.

#### XI.E Patient-Centered Models of Care

It is evident from the data presented in the ICS:OSA that medical, and surgical therapy provide variable benefits. Identification of an optimal OSA treatment may prove challenging for patients given the multitude of therapeutic options and lack of clarity regarding optimal treatment paradigms. Improved

shared decision-making processes and decision tools will be important to help patients identify goals in OSA treatment and allow providers to recommend specific treatments that meet individual goals and values.<sup>2153</sup>

It is essential for providers to comprehensively counsel patients about options for OSA treatment. Shared-decision making is especially important with patients who have failed first-line PAP therapy, given the variety of alternative treatments and high levels of decisional conflict in considering alternatives.<sup>2154</sup> Prior studies have demonstrated that shared decision-making reduced decision delay, improved time to OSA therapy initiation, improved treatment compliance, and reduced decisional regret for parents of children with OSA.<sup>2155-2157</sup>

Multiple components of optimal OSA treatment require adherence to therapies such as PAP, HNS, MAD, weight management, and sleep hygiene. There is a need to understand patient-specific behaviors and influencers of behavioral change and motivation. Collaboration is key to furthering understanding, providing individualized care.

Research Opportunities include:

- Translating information from large datasets into personalized medicine.
- Improve the equity and access to knowledge about OSA and treatment options.
- Developing patient-facing decision support tools to navigate the options for OSA therapy and the risk and benefit tradeoffs.
- Align individual clinical factors and patient values with treatment options.

#### Acknowledgements:

We sincerely thank Ms. Julia Martinez and Ms. Ofeibia Laud-Darku for their efforts in the preparation of this manuscript. Mr. Christopher Stave for literature search assistance. We also thank Richard Orlandi, MD and Timothy Smith, MD for their encouragement, support and advice during development of this work.

1. Gastaut H, Tassinari CA, Duron B. [Polygraphic study of diurnal and nocturnal (hypnic and respiratory) episodal manifestations of Pickwick syndrome]. *Rev Neurol (Paris)*. 1965;112(6):568-579.
2. Jung R, Kuhlo W. Neurophysiological Studies of Abnormal Night Sleep and the Pickwickian Syndrome. *Prog Brain Res*. 1965;18:140-159.
3. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet*. 1981;1(8225):862-865.
4. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6 Suppl 1:S22-209.
5. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol*. 2011;1(6):431-437.
6. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. 2018;8(2):108-352.

7. Wang EW, Zanation AM, Gardner PA, et al. ICAR: endoscopic skull-base surgery. *Int Forum Allergy Rhinol.* 2019;9(S3):S145-S365.
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-34.
9. Oxford Centre for Evidence-Based Medicine (CEBM) – levels of evidence (March 2009). <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009>. Accessed.
10. American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics.* 114:874-877.
11. Berry RBea. *The AASM Manual for the Scoring of Sleep and Associated Events Version 2.6.* Vol Version 2.62020.
12. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2012;8(5):597-619.
13. Redline S, Kapur VK, Sanders MH, et al. Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. *Am J Resp Crit Care.* 2000;161(2):369-374.
14. Ho V, Crainiceanu CM, Punjabi NM, Redline S, Gottlieb DJ. Calibration Model for Apnea-Hypopnea Indices: Impact of Alternative Criteria for Hypopneas. *Sleep.* 2015;38(12):1887-1892.
15. Mansukhani MP, Kolla BP, Wang Z, Morgenthaler TI. Effect of Varying Definitions of Hypopnea on the Diagnosis and Clinical Outcomes of Sleep-Disordered Breathing: A Systematic Review and Meta-Analysis. *Journal of Clinical Sleep Medicine.* 2019;15(5):687-696.
16. Hirotsu C, Haba-Rubio J, Andries D, et al. Effect of Three Hypopnea Scoring Criteria on OSA Prevalence and Associated Comorbidities in the General Population. *Journal of Clinical Sleep Medicine.* 2019;15(2):183-194.
17. Budhiraja R, Javaheri S, Parthasarathy S, Berry RB, Quan SF. The Association Between Obstructive Sleep Apnea Characterized by a Minimum 3 Percent Oxygen Desaturation or Arousal Hypopnea Definition and Hypertension. *Journal of Clinical Sleep Medicine.* 2019;15(9):1261-1270.
18. Won CHJ, Reid M, Sofer T, et al. Sex differences in obstructive sleep apnea phenotypes, the multi-ethnic study of atherosclerosis. *Sleep.* 2020;43(5).
19. Roca GQ, Redline S, Claggett B, et al. Sex-Specific Association of Sleep Apnea Severity With Subclinical Myocardial Injury, Ventricular Hypertrophy, and Heart Failure Risk in a Community-Dwelling Cohort The Atherosclerosis Risk in Communities-Sleep Heart Health Study. *Circulation.* 2015;132(14):1329-1337.
20. Campos-Rodriguez F, Martinez-Garcia MA, Reyes-Nunez N, Selma-Ferrer MJ, Punjabi NM, Farre R. Impact of different hypopnea definitions on obstructive sleep apnea severity and cardiovascular mortality risk in women and elderly individuals. *Sleep Med.* 2016;27-28:54-58.
21. Brown LK. Use it or lose it: Medicare's new paradigm for durable medical equipment coverage? *Chest.* 2010;138(4):785-789.
22. Bliwise D, Bliwise NG, Kraemer HC, Dement W. Measurement Error in Visually Scored Electrophysiological Data - Respiration during Sleep. *J Neurosci Meth.* 1984;12(1):49-56.
23. Whitney CW, Gottlieb DJ, Redline S, et al. Reliability of scoring respiratory disturbance indices and sleep staging. *Sleep.* 1998;21(7):749-757.

24. Rashid NHA, Zaghi S, Scapuccin M, Camacho M, Certal V, Capasso R. The Value of Oxygen Desaturation Index for Diagnosing Obstructive Sleep Apnea: A Systematic Review. *Laryngoscope*. 2021;131(2):440-447.
25. Linz D, Kadhim K, Brooks AG, et al. Diagnostic accuracy of overnight oximetry for the diagnosis of sleep-disordered breathing in atrial fibrillation patients. *Int J Cardiol*. 2018;272:155-161.
26. McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *New Engl J Med*. 2016;375(10):919-931.
27. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-Disordered Breathing, Hypoxia, and Risk of Mild Cognitive Impairment and Dementia in Older Women. *Jama-J Am Med Assoc*. 2011;306(6):613-619.
28. Labarca G, Campos J, Thibaut K, Dreysse J, Jorquera J. Do T90 and SaO<sub>2</sub> nadir identify a different phenotype in obstructive sleep apnea? *Sleep Breath*. 2019;23(3):1007-1010.
29. Muraki I, Tanigawa T, Yamagishi K, et al. Nocturnal intermittent hypoxia and C reactive protein among middle-aged community residents: a cross-sectional survey. *Thorax*. 2010;65(6):523-527.
30. Yilmaz Avci A, Avci S, Lakadamyali H, Can U. Hypoxia and inflammation indicate significant differences in the severity of obstructive sleep apnea within similar apnea-hypopnea index groups. *Sleep Breath*. 2017;21(3):703-711.
31. Malhotra RK, Kirsch DB, Kristo DA, et al. Polysomnography for Obstructive Sleep Apnea Should Include Arousal-Based Scoring: An American Academy of Sleep Medicine Position Statement. *Journal of Clinical Sleep Medicine*. 2018;14(7):1245-1247.
32. Zinchuk AV, Gentry MJ, Concato J, Yaggi HK. Phenotypes in obstructive sleep apnea: A definition, examples and evolution of approaches. *Sleep Med Rev*. 2017;35:113-123.
33. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med*. 2010;182(2):269-277.
34. National Coverage Determination (NCD) for Continuous Positive Airway Pressure (CPAP) Therapy For Obstructive Sleep Apnea (OSA) (240.4). Centers for Medicare & Medicaid Services. <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=226&ncdver=3&SearchType=Advanced&CoverageSelection=Both&NCSelect ion=NCA%257CCAL%257CNCD%257CMEDCAC%257CTA%257CMCD&ArticleType=SAD%257CED &PolicyType=Both&s=-&AdvSearchName=3%257C>. Published 2008. Accessed 07/05/2020, 2020.
35. Ye LC, Plan GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J*. 2014;44(6):1600-1607.
36. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med*. 2013;188(8):996-1004.
37. Vavougiou GD, Natsios G, Pastaka C, Zarogiannis SG, Gourgoulis KI. Phenotypes of comorbidity in OSAS patients: combining categorical principal component analysis with cluster analysis. *J Sleep Res*. 2016;25(1):31-38.
38. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al. Effect of Continuous Positive Airway Pressure on the Incidence of Hypertension and Cardiovascular Events in Nonsleepy Patients With Obstructive Sleep Apnea A Randomized Controlled Trial. *Jama-J Am Med Assoc*. 2012;307(20):2161-2168.
39. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2019;15(2):335-343.
40. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7(2):110-114.
41. Ravesloot MJL, Vonk PE, Maurer JT, Oksenberg A, de Vries N. Standardized framework to report on the role of sleeping position in sleep apnea patients. *Sleep Breath*. 2021;25(4):1717-1728.

42. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients - Anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest*. 1997;112(3):629-639.
43. Sunnergren O, Brostrom A, Svanborg E. Positional sensitivity as a confounder in diagnosis of severity of obstructive sleep apnea. *Sleep Breath*. 2013;17(1):173-179.
44. Kim KT, Cho YW, Kim DE, Hwang SH, Song ML, Motamedi GK. Two subtypes of positional obstructive sleep apnea: Supine-predominant and supine-isolated. *Clin Neurophysiol*. 2016;127(1):565-570.
45. Heinzer R, Petitpierre NJ, Marti-Soler H, Haba-Rubio J. Prevalence and characteristics of positional sleep apnea in the HypnoLaus population-based cohort. *Sleep Med*. 2018;48:157-162.
46. Yingjuan M, Siang WH, Alvin TKL, Poh HP. Positional Therapy for Positional Obstructive Sleep Apnea. *Sleep Med Clin*. 2019;14(1):119-+.
47. McSharry DG, Saboisky JP, DeYoung P, et al. Physiological Mechanisms of Upper Airway Hypotonia during REM Sleep. *Sleep*. 2014;37(3):561-569.
48. Douglas NJ, White DP, Weil JV, Pickett CK, Zwillich CW. Hypercapnic Ventilatory Response in Sleeping Adults. *American Review of Respiratory Disease*. 1982;126(5):758-762.
49. Trinder J, Kleiman J, Carrington M, et al. Autonomic activity during human sleep as a function of time and sleep stage. *J Sleep Res*. 2001;10(4):253-264.
50. Conwell W, Patel B, Doeing D, et al. Prevalence, clinical features, and CPAP adherence in REM-related sleep-disordered breathing: a cross-sectional analysis of a large clinical population. *Sleep Breath*. 2012;16(2):519-526.
51. Haba-Rubio J, Janssens JP, Rochat T, Sforza E. Rapid eye movement-related disordered breathing - Clinical and polysomnographic features. *Chest*. 2005;128(5):3350-3357.
52. Koo BB, Patel SR, Strohl K, Hoffstein V. Rapid Eye Movement-Related Sleep-Disordered Breathing Influence of Age and Gender. *Chest*. 2008;134(6):1156-1161.
53. Koo BB, Dostal J, Ioachimescu O, Budur K. The effects of gender and age on REM-related sleep-disordered breathing. *Sleep Breath*. 2008;12(3):259-264.
54. Goh DYT, Galster P, Marcus CL. Sleep architecture and respiratory disturbances in children with obstructive sleep apnea. *Am J Resp Crit Care*. 2000;162(2):682-686.
55. O'Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. *Am J Resp Crit Care*. 2000;161(5):1465-1472.
56. Chervin RD, Aldrich MS. The relation between multiple sleep latency test findings and the frequency of apneic events in REM and Non-REM sleep. *Chest*. 1998;113(4):980-984.
57. Punjabi NM, Bandeen-Roche K, Marx JJ, Neubauer DN, Smith PL, Schwartz AR. The association between daytime sleepiness and sleep-disordered breathing in NREM and REM sleep. *Sleep*. 2002;25(3):307-314.
58. Lee SA, Paek JH, Han SH. REM-related sleep-disordered breathing is associated with depressive symptoms in men but not in women. *Sleep Breath*. 2016;20(3):995-1002.
59. Pamidi S, Knutson KL, Ghods F, Mokhlesi B. Depressive symptoms and obesity as predictors of sleepiness and quality of life in patients with REM-related obstructive sleep apnea: cross-sectional analysis of a large clinical population. *Sleep Med*. 2011;12(9):827-831.
60. Chami HA, Baldwin CM, Silverman A, et al. Sleepiness, quality of life, and sleep maintenance in REM versus non-REM sleep-disordered breathing. *Am J Respir Crit Care Med*. 2010;181(9):997-1002.
61. Khan A, Harrison SL, Kezirian EJ, et al. Obstructive sleep apnea during rapid eye movement sleep, daytime sleepiness, and quality of life in older men in Osteoporotic Fractures in Men (MrOS) Sleep Study. *J Clin Sleep Med*. 2013;9(3):191-198.

62. Su CS, Liu KT, Panjapornpon K, Andrews N, Foldvary-Schaefer N. Functional outcomes in patients with REM-related obstructive sleep apnea treated with positive airway pressure therapy. *J Clin Sleep Med*. 2012;8(3):243-247.
63. Gleadhill IC, Schwartz AR, Schubert N, Wise RA, Permutt S, Smith PL. Upper Airway Collapsibility in Snorers and in Patients with Obstructive Hypopnea and Apnea. *American Review of Respiratory Disease*. 1991;143(6):1300-1303.
64. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. *WMJ*. 2009;108(5):246-249.
65. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA*. 2004;291(16):2013-2016.
66. Cho N, Joo S, Kim J, et al. Relation of habitual snoring with components of metabolic syndrome in Korean adults. *Diabetes Res Clin Pract*. 2006;71(3):256-263.
67. Sogebi OA, Oyewole EA, Olusoga-Peters OO. Sleep disordered breathing (SDB) experiences associated with snoring in adult Nigerians. *Afr Health Sci*. 2011;11(3):309-314.
68. Wali SO, Abaalkhail BA. Prevalence and predictors of habitual snoring in a sample of Saudi middle-aged adults. *Saudi Med J*. 2015;36(8):920-927.
69. Young T, Finn L, Palta M. Chronic nasal congestion at night is a risk factor for snoring in a population-based cohort study. *Arch Intern Med*. 2001;161(12):1514-1519.
70. Medicine AaOs. AASM Manual for the Scoring of Sleep and Associated Events: Summary of Updates in Version 2.6. <https://j2vjt3dnbra3ps7ll1clb4q2-wpengine.netdna-ssl.com/wp-content/uploads/2020/01/Summary-of-Updates-in-v2.6-1.pdf>. Published 2020. Accessed.
71. Guilleminault C, Stoohs R, Shiomi T, Kushida C, Schnittger I. Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension. *Chest*. 1996;109(4):901-908.
72. Gold AR, Gold MS, Harris KW, Espeleta VJ, Amin MM, Broderick JE. Hypersomnolence, insomnia and the pathophysiology of upper airway resistance syndrome. *Sleep Med*. 2008;9(6):675-683.
73. Guilleminault C, Palombini L, Poyares D, Chowdhuri S. Chronic insomnia, postmenopausal women, and sleep disordered breathing: part 1. Frequency of sleep disordered breathing in a cohort. *J Psychosom Res*. 2002;53(1):611-615.
74. Stoohs RA, Knaack L, Blum HC, Janicki J, Hohenhorst W. Differences in clinical features of upper airway resistance syndrome, primary snoring, and obstructive sleep apnea/hypopnea syndrome. *Sleep Med*. 2008;9(2):121-128.
75. Kristo DA, Lettieri CJ, Andrada T, Taylor Y, Eliasson AH. Silent upper airway resistance syndrome: prevalence in a mixed military population. *Chest*. 2005;127(5):1654-1657.
76. de Godoy LB, Luz GP, Palombini LO, et al. Upper Airway Resistance Syndrome Patients Have Worse Sleep Quality Compared to Mild Obstructive Sleep Apnea. *PLoS one*. 2016;11(5):e0156244.
77. Douglas NJ. Upper airway resistance syndrome is not a distinct syndrome. *Am J Resp Crit Care*. 2000;161(5):1413-1415.
78. Gold AR, Dipalo F, Gold MS, O'Hearn D. The symptoms and signs of upper airway resistance syndrome: a link to the functional somatic syndromes. *Chest*. 2003;123(1):87-95.
79. So SJ, Lee HJ, Kang SG, Cho CH, Yoon HK, Kim L. A Comparison of Personality Characteristics and Psychiatric Symptomatology between Upper Airway Resistance Syndrome and Obstructive Sleep Apnea Syndrome. *Psychiatry Investig*. 2015;12(2):183-189.
80. Guilleminault C, Kirisoglu C, Poyares D, et al. Upper airway resistance syndrome: A long-term outcome study. *J Psychiatr Res*. 2006;40(3):273-279.
81. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014;146(5):1387-1394.



82. Littleton SW, Mokhlesi B. The pickwickian syndrome-obesity hypoventilation syndrome. *Clin Chest Med*. 2009;30(3):467-478, vii-viii.
83. Masa JF, Pepin JL, Borel JC, Mokhlesi B, Murphy PB, Sanchez-Quiroga MA. Obesity hypoventilation syndrome. *Eur Respir Rev*. 2019;28(151).
84. BaHammam AS. Prevalence, clinical characteristics, and predictors of obesity hypoventilation syndrome in a large sample of Saudi patients with obstructive sleep apnea. *Saudi Med J*. 2015;36(2):181-189.
85. Balachandran JS, Masa JF, Mokhlesi B. Obesity Hypoventilation Syndrome Epidemiology and Diagnosis. *Sleep Med Clin*. 2014;9(3):341-347.
86. Masa JF, Corral J, Alonso ML, et al. Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome. Pickwick Study. *Am J Respir Crit Care Med*. 2015;192(1):86-95.
87. Piper A. Obesity Hypoventilation Syndrome: Weighing in on Therapy Options. *Chest*. 2016;149(3):856-868.
88. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165(9):1217-1239.
89. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev*. 2017;34:70-81.
90. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328(17):1230-1235.
91. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep*. 1997;20(12):1077-1085.
92. Young T, Peppard P. Sleep-disordered breathing and cardiovascular disease: epidemiologic evidence for a relationship. *Sleep*. 2000;23 Suppl 4:S122-126.
93. Kim J, In K, Kim J, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. *Am J Respir Crit Care Med*. 2004;170(10):1108-1113.
94. Udawadia ZF, Doshi AV, Lonkar SG, Singh CI. Prevalence of sleep-disordered breathing and sleep apnea in middle-aged urban Indian men. *Am J Respir Crit Care Med*. 2004;169(2):168-173.
95. Peppard PE, Young T, Barnett JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177(9):1006-1014.
96. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Med*. 2010;11(5):441-446.
97. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med*. 2015;3(4):310-318.
98. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687-698.
99. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med*. 2003;167(9):1181-1185.
100. Basner M, Muller U, Elmenhorst EM. Single and combined effects of air, road, and rail traffic noise on sleep and recuperation. *Sleep*. 2011;34(1):11-23.
101. Redline S, Tishler PV. The genetics of sleep apnea. *Sleep Med Rev*. 2000;4(6):583-602.
102. Miles PG, Vig PS, Weyant RJ, Forrest TD, Rockette HE, Jr. Craniofacial structure and obstructive sleep apnea syndrome--a qualitative analysis and meta-analysis of the literature. *Am J Orthod Dentofacial Orthop*. 1996;109(2):163-172.
103. Redline S, Sotres-Alvarez D, Loreda J, et al. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds. The Hispanic Community Health Study/Study of Latinos. *Am J Respir Crit Care Med*. 2014;189(3):335-344.

104. Johnson DA, Guo N, Rueschman M, Wang R, Wilson JG, Redline S. Prevalence and correlates of obstructive sleep apnea among African Americans: the Jackson Heart Sleep Study. *Sleep*. 2018;41(10).
105. Chen X, Wang R, Zee P, et al. Racial/Ethnic Differences in Sleep Disturbances: The Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep*. 2015;38(6):877-888.
106. Lee RWW, Vasudavan S, Hui DS, et al. Differences in Craniofacial Structures and Obesity in Caucasian and Chinese Patients with Obstructive Sleep Apnea. *Sleep*. 2010;33(8):1075-1080.
107. Schwab RJ, Pasirstein M, Kaplan L, et al. Family aggregation of upper airway soft tissue structures in normal subjects and patients with sleep apnea. *Am J Respir Crit Care Med*. 2006;173(4):453-463.
108. Suen C, Wong J, Ryan CM, et al. Prevalence of Undiagnosed Obstructive Sleep Apnea Among Patients Hospitalized for Cardiovascular Disease and Associated In-Hospital Outcomes: A Scoping Review. *J Clin Med*. 2020;9(4).
109. Budhiraja R, Budhiraja P, Quan SF. Sleep-disordered breathing and cardiovascular disorders. *Respir Care*. 2010;55(10):1322-1332; discussion 1330-1322.
110. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet*. 2009;373(9657):82-93.
111. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S. Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science. *Circulation*. 2017;136(19):1840-1850.
112. Newman AB, Nieto FJ, Guidry U, et al. Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. *Am J Epidemiol*. 2001;154(1):50-59.
113. Khan A, Patel NK, O'Hearn DJ, Khan S. Resistant hypertension and obstructive sleep apnea. *Int J Hypertens*. 2013;2013:193010.
114. O'Connor GT, Caffo B, Newman AB, et al. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2009;179(12):1159-1164.
115. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *Jama-J Am Med Assoc*. 2000;283(14):1829-1836.
116. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med*. 2005;353(19):2034-2041.
117. Rice TB, Foster GD, Sanders MH, et al. The relationship between obstructive sleep apnea and self-reported stroke or coronary heart disease in overweight and obese adults with type 2 diabetes mellitus. *Sleep*. 2012;35(9):1293-1298.
118. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365(9464):1046-1053.
119. Drager LF, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: an emerging risk factor for atherosclerosis. *Chest*. 2011;140(2):534-542.
120. Bassetti CLA, Randerath W, Vignatelli L, et al. EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke. *Eur Respir J*. 2020;55(4).
121. Tasali E, Mokhlesi B, Van Cauter E. Obstructive sleep apnea and type 2 diabetes: interacting epidemics. *Chest*. 2008;133(2):496-506.
122. Foster GD, Borradaile KE, Sanders MH, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med*. 2009;169(17):1619-1626.

123. Kline CE, Reboussin DM, Foster GD, et al. The Effect of Changes in Cardiorespiratory Fitness and Weight on Obstructive Sleep Apnea Severity in Overweight Adults with Type 2 Diabetes. *Sleep*. 2016;39(2):317-325.
124. Billings ME, Johnson DA, Simonelli G, et al. Neighborhood Walking Environment and Activity Level Are Associated With OSA: The Multi-Ethnic Study of Atherosclerosis. *Chest*. 2016;150(5):1042-1049.
125. Brouillette RT, Horwood L, Constantin E, Brown K, Ross NA. Childhood sleep apnea and neighborhood disadvantage. *J Pediatr*. 2011;158(5):789-795.e781.
126. Wang R, Dong Y, Weng J, et al. Associations among Neighborhood, Race, and Sleep Apnea Severity in Children. A Six-City Analysis. *Ann Am Thorac Soc*. 2017;14(1):76-84.
127. Guglielmi O, Lanteri P, Garbarino S. Association between socioeconomic status, belonging to an ethnic minority and obstructive sleep apnea: a systematic review of the literature. *Sleep Med*. 2019;57:100-106.
128. Sharifi M, Sequist TD, Rifas-Shiman SL, et al. The role of neighborhood characteristics and the built environment in understanding racial/ethnic disparities in childhood obesity. *Preventive medicine*. 2016;91:103-109.
129. Hajat A, Hsia C, O'Neill MS. Socioeconomic Disparities and Air Pollution Exposure: a Global Review. *Current environmental health reports*. 2015;2(4):440-450.
130. Billings ME, Gold D, Szpiro A, et al. The Association of Ambient Air Pollution with Sleep Apnea: The Multi-Ethnic Study of Atherosclerosis. *Ann Am Thorac Soc*. 2018.
131. Shen YL, Liu WT, Lee KY, Chuang HC, Chen HW, Chuang KJ. Association of PM2.5 with sleep-disordered breathing from a population-based study in Northern Taiwan urban areas. *Environmental pollution (Barking, Essex : 1987)*. 2017;233:109-113.
132. Sullivan F. Hidden Health Crisis Costing America Billions: Underdiagnosing and Undertreating Obstructive Sleep Apnea Draining Healthcare System. American Academy of Sleep Medicine. <https://aasm.org/resources/pdf/sleep-apnea-economic-crisis.pdf>. Published 2016. Accessed.
133. Jennum P, Kjellberg J. Health, social and economical consequences of sleep-disordered breathing: a controlled national study. *Thorax*. 2011;66(7):560-566.
134. Kapur V, Blough DK, Sandblom RE, et al. The medical cost of undiagnosed sleep apnea. *Sleep*. 1999;22(6):749-755.
135. Kapur VK, Redline S, Nieto J, Young TB, Newman AB, Henderson JA. The relationship between chronically disrupted sleep and healthcare use. *Sleep*. 2002;25(3):289-296.
136. Vo TN, Kats AM, Langsetmo L, et al. Association of sleep-disordered breathing with total healthcare costs and utilization in older men: the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study. *Sleep*. 2020;43(1).
137. Sassani A, Findley LJ, Kryger M, Goldlust E, George C, Davidson TM. Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. *Sleep*. 2004;27(3):453-458.
138. Kim RD, Kapur VK, Redline-Bruch J, et al. An Economic Evaluation of Home Versus Laboratory-Based Diagnosis of Obstructive Sleep Apnea. *Sleep*. 2015;38(7):1027-1037.
139. Streatfeild J, Hillman D, Adams R, Mitchell S, Pezzullo L. Cost-effectiveness of continuous positive airway pressure therapy for obstructive sleep apnea: health care system and societal perspectives. *Sleep*. 2019;42(12).
140. Guest JF, Helter MT, Morga A, Stradling JR. Cost-effectiveness of using continuous positive airway pressure in the treatment of severe obstructive sleep apnoea/hypopnoea syndrome in the UK. *Thorax*. 2008;63(10):860-865.
141. Donovan LM, Kapur VK. Screening commercial drivers for sleep apnea: are profits and public safety aligned? *Sleep*. 2020;43(4).

142. Chhatre S, Chang YHA, Gooneratne NS, Kuna S, Strollo P, Jayadevappa R. Association between adherence to continuous positive airway pressure treatment and cost among medicare enrollees. *Sleep*. 2020;43(1).
143. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):608-613.
144. Durán J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):685-689.
145. Fietze I, Laharnar N, Obst A, et al. Prevalence and association analysis of obstructive sleep apnea with gender and age differences - Results of SHIP-Trend. *J Sleep Res*. 2019;28(5):e12770.
146. Huang TY, Lin BM, Redline S, Curhan GC, Hu FB, Tworoger SS. Type of Menopause, Age at Menopause, and Risk of Developing Obstructive Sleep Apnea in Postmenopausal Women. *American Journal of Epidemiology*. 2018;187(7):1370-1379.
147. Ip MS, Lam B, Lauder IJ, et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *Chest*. 2001;119(1):62-69.
148. Ip MS, Lam B, Tang LC, Lauder IJ, Ip TY, Lam WK. A community study of sleep-disordered breathing in middle-aged Chinese women in Hong Kong: prevalence and gender differences. *Chest*. 2004;125(1):127-134.
149. Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ. Prevalence of sleep-disordered breathing in ages 40-64 years: a population-based survey. *Sleep*. 1997;20(1):65-76.
150. Neruntarat C, Chantapant S. Prevalence of sleep apnea in HRH Princess Maha Chakri Srinthorn Medical Center, Thailand. *Sleep Breath*. 2011;15(4):641-648.
151. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):722-726.
152. Sforza E, Chouchou F, Collet P, Pichot V, Barthelemy JC, Roche F. Sex differences in obstructive sleep apnoea in an elderly French population. *Eur Respir J*. 2011;37(5):1137-1143.
153. Shahar E, Redline S, Young T, et al. Hormone replacement therapy and sleep-disordered breathing. *Am J Respir Crit Care Med*. 2003;167(9):1186-1192.
154. Subramanian S, Jayaraman G, Majid H, Aguilar R, Surani S. Influence of gender and anthropometric measures on severity of obstructive sleep apnea. *Sleep Breath*. 2012;16(4):1091-1095.
155. Tishler PV, Larkin EK, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. *JAMA*. 2003;289(17):2230-2237.
156. Bearpark H, Elliott L, Grunstein R, et al. Snoring and sleep apnea. A population study in Australian men. *Am J Respir Crit Care Med*. 1995;151(5):1459-1465.
157. Alotair H, Bahammam A. Gender differences in Saudi patients with obstructive sleep apnea. *Sleep Breath*. 2008;12(4):323-329.
158. Vagiakis E, Kapsimalis F, Lagogianni I, et al. Gender differences on polysomnographic findings in Greek subjects with obstructive sleep apnea syndrome. *Sleep Med*. 2006;7(5):424-430.
159. Yukawa K, Inoue Y, Yagyu H, et al. Gender differences in the clinical characteristics among Japanese patients with obstructive sleep apnea syndrome. *Chest*. 2009;135(2):337-343.
160. Gabbay IE, Lavie P. Age- and gender-related characteristics of obstructive sleep apnea. *Sleep Breath*. 2012;16(2):453-460.
161. Leppanen T, Kulkas A, Duce B, Mervaala E, Toyras J. Severity of individual obstruction events is gender dependent in sleep apnea. *Sleep Breath*. 2017;21(2):397-404.

162. Basoglu OK, Tasbakan MS. Gender differences in clinical and polysomnographic features of obstructive sleep apnea: a clinical study of 2827 patients. *Sleep Breath*. 2018;22(1):241-249.
163. Mano M, Hoshino T, Sasanabe R, et al. Impact of Gender and Age on Rapid Eye Movement-Related Obstructive Sleep Apnea: A Clinical Study of 3234 Japanese OSA Patients. *Int J Environ Res Public Health*. 2019;16(6).
164. Zhang Z, Cheng J, Yang W, Zou H, Su C, Miao J. Gender differences in clinical manifestations and polysomnographic findings in Chinese patients with obstructive sleep apnea. *Sleep Breath*. 2019.
165. Resta O, Carpagnano GE, Lacedonia D, et al. Gender difference in sleep profile of severely obese patients with obstructive sleep apnea (OSA). *Resp Med*. 2005;99(1):91-96.
166. Subramanian S, Hesselbacher S, Mattewal A, Surani S. Gender and age influence the effects of slow-wave sleep on respiration in patients with obstructive sleep apnea. *Sleep Breath*. 2013;17(1):51-56.
167. Cho SH, Jeon JY, Jang KS, et al. Gender-specific cephalometric features related to obesity in sleep apnea patients: trilogy of soft palate-mandible-hyoid bone. *Maxillofac Plast Reconstr Surg*. 2019;41(1):58.
168. Sutherland K, Lee RWW, Chan TO, Ng S, Hui DS, Cistulli PA. Craniofacial Phenotyping in Chinese and Caucasian Patients With Sleep Apnea: Influence of Ethnicity and Sex. *J Clin Sleep Med*. 2018;14(7):1143-1151.
169. Malhotra A, Huang Y, Fogel RB, et al. The male predisposition to pharyngeal collapse: importance of airway length. *Am J Respir Crit Care Med*. 2002;166(10):1388-1395.
170. Mohsenin V. Effects of gender on upper airway collapsibility and severity of obstructive sleep apnea. *Sleep Med*. 2003;4(6):523-529.
171. Segal Y, Malhotra A, Pillar G. Upper airway length may be associated with the severity of obstructive sleep apnea syndrome. *Sleep Breath*. 2008;12(4):311-316.
172. Brooks LJ, Strohl KP. Size and mechanical properties of the pharynx in healthy men and women. *Am Rev Respir Dis*. 1992;146(6):1394-1397.
173. Huang KT, Chin CH, Tseng CC, et al. The influence of obesity on different genders in patients with obstructive sleep apnea. *ScientificWorldJournal*. 2014;2014:487215.
174. Harada Y, Oga T, Chihara Y, et al. Differences in associations between visceral fat accumulation and obstructive sleep apnea by sex. *Ann Am Thorac Soc*. 2014;11(3):383-391.
175. Lim YH, Choi J, Kim KR, et al. Sex-specific characteristics of anthropometry in patients with obstructive sleep apnea: neck circumference and waist-hip ratio. *Ann Otol Rhinol Laryngol*. 2014;123(7):517-523.
176. Sin DD, Jones RL, Man GC. Hypercapnic ventilatory response in patients with and without obstructive sleep apnea: do age, gender, obesity, and daytime PaCO<sub>2</sub> matter? *Chest*. 2000;117(2):454-459.
177. Syed Z, Lin HS, Mateika JH. The impact of arousal state, sex, and sleep apnea on the magnitude of progressive augmentation and ventilatory long-term facilitation. *J Appl Physiol (1985)*. 2013;114(1):52-65.
178. Jordan AS, Catcheside PG, Orr RS, O'Donoghue FJ, Saunders NA, McEvoy RD. Ventilatory decline after hypoxia and hypercapnia is not different between healthy young men and women. *J Appl Physiol (1985)*. 2000;88(1):3-9.
179. Jordan AS, Wellman A, Edwards JK, et al. Respiratory control stability and upper airway collapsibility in men and women with obstructive sleep apnea. *J Appl Physiol (1985)*. 2005;99(5):2020-2027.
180. Pillar G, Malhotra A, Fogel R, Beauregard J, Schnall R, White DP. Airway mechanics and ventilation in response to resistive loading during sleep: influence of gender. *Am J Respir Crit Care Med*. 2000;162(5):1627-1632.

181. Zhou XS, Shahabuddin S, Zahn BR, Babcock MA, Badr MS. Effect of gender on the development of hypocapnic apnea/hypopnea during NREM sleep. *J Appl Physiol* (1985). 2000;89(1):192-199.
182. Quintana-Gallego E, Carmona-Bernal C, Capote F, et al. Gender differences in obstructive sleep apnea syndrome: a clinical study of 1166 patients. *Respir Med*. 2004;98(10):984-989.
183. Polesel DN, Nozoe KT, Tufik SB, et al. Gender differences in the application of anthropometric measures for evaluation of obstructive sleep apnea. *Sleep Sci*. 2019;12(1):2-9.
184. Perri RA, Kairaitis K, Wheatley JR, Amis TC. Anthropometric and craniofacial sexual dimorphism in obstructive sleep apnea patients: is there male-female phenotypical convergence? *J Sleep Res*. 2015;24(1):82-91.
185. Dancy DR, Hanly PJ, Soong C, Lee B, Shepard J, Jr., Hoffstein V. Gender differences in sleep apnea: the role of neck circumference. *Chest*. 2003;123(5):1544-1550.
186. Eckert DJ, Malhotra A, Lo YL, White DP, Jordan AS. The influence of obstructive sleep apnea and gender on genioglossus activity during rapid eye movement sleep. *Chest*. 2009;135(4):957-964.
187. Simpson L, Mukherjee S, Cooper MN, et al. Sex differences in the association of regional fat distribution with the severity of obstructive sleep apnea. *Sleep*. 2010;33(4):467-474.
188. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000;284(23):3015-3021.
189. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Arch Intern Med*. 2002;162(8):893-900.
190. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *Journal of Applied Physiology (Bethesda, Md: 1985)*. 2005;99(4):1592-1599.
191. Ashrafian H, Roux CWI, Rowland SP, et al. Metabolic surgery and obstructive sleep apnoea: the protective effects of bariatric procedures. *Thorax*. 2012;67(5):442-449.
192. Peromaa-Haavisto P, Tuomilehto H, Kössi J, et al. Obstructive sleep apnea: the effect of bariatric surgery after 12 months. A prospective multicenter trial. *Sleep Med*. 2017;35:85-90.
193. Dixon JB, Schachter LM, O'Brien PE, et al. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;308(11):1142-1149.
194. Ashrafian H, Toma T, Rowland SP, et al. Bariatric Surgery or Non-Surgical Weight Loss for Obstructive Sleep Apnoea? A Systematic Review and Comparison of Meta-analyses. *Obesity Surgery*. 2015;25(7):1239-1250.
195. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018. *NCHS Data Brief*. 2020(360):8.
196. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and Trends in Obesity Among US Adults, 1999–2008. *JAMA*. 2010;303(3):235-241.
197. Katz I, Stradling J, Slutsky AS, Zamel N, Hoffstein V. Do patients with obstructive sleep apnea have thick necks? *The American Review of Respiratory Disease*. 1990;141(5 Pt 1):1228-1231.
198. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and Obstructive Sleep Apnea. *Proceedings of the American Thoracic Society*. 2008;5(2):185-192.
199. Schwab RJ, Gupta KB, Geffter WB, Metzger LJ, Hoffman EA, Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med*. 1995;152(5 Pt 1):1673-1689.
200. Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). *Journal of Clinical Investigation*. 1992;89(5):1571-1579.
201. Li Y, Lin N, Ye J, Chang Q, Han D, Sperry A. Upper Airway Fat Tissue Distribution in Subjects With Obstructive Sleep Apnea and Its Effect on Retropalatal Mechanical Loads. *Resp Care*. 2012;57(7):1098-1105.

202. Stanchina ML, Malhotra A, Fogel RB, et al. Genioglossus Muscle Responsiveness to Chemical and Mechanical Stimuli during Non–Rapid Eye Movement Sleep. *Am J Resp Crit Care*. 2002;165(7):945-949.
203. Sands SA, Eckert DJ, Jordan AS, et al. Enhanced Upper-Airway Muscle Responsiveness Is a Distinct Feature of Overweight/Obese Individuals without Sleep Apnea. *Am J Resp Crit Care*. 2014;190(8):930-937.
204. Shelton KE, Woodson H, Gay S, Suratt PM. Pharyngeal fat in obstructive sleep apnea. *Am Rev Respir Dis*. 1993;148(2):462-466.
205. Pahkala R, Seppä J, Ikonen A, Smirnov G, Tuomilehto H. The impact of pharyngeal fat tissue on the pathogenesis of obstructive sleep apnea. *Sleep Breath*. 2014;18(2):275-282.
206. Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. *Am J Respir Crit Care Med*. 2003;168(5):522-530.
207. Kim AM, Keenan BT, Jackson N, et al. Tongue Fat and its Relationship to Obstructive Sleep Apnea. *Sleep*. 2014;37(10):1639-U1227.
208. Jang M-S, Kim HY, Dhong H-J, et al. Effect of Parapharyngeal Fat on Dynamic Obstruction of the Upper Airway in Patients with Obstructive Sleep Apnea. *Am J Resp Crit Care*. 2014;190(11):1318-1321.
209. Chen H-C, Wang C-J, Lo Y-L, et al. Parapharyngeal fat pad area at the subglosso-supraglottic level is associated with corresponding lateral wall collapse and apnea-hypopnea index in patients with obstructive sleep apnea: a pilot study. *Scientific Reports*. 2019;9(1):17722.
210. Kairaitis K, Byth K, Parikh R, Stavrinou R, Wheatley JR, Amis TC. Tracheal Traction Effects on Upper Airway Patency in Rabbits: The Role of Tissue Pressure. *Sleep*. 2007;30(2):179-186.
211. Hoffstein V, Zamel N, Phillipson EA. Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. *The American Review of Respiratory Disease*. 1984;130(2):175-178.
212. Shimura R, Tatsumi K, Nakamura A, et al. Fat Accumulation, Leptin, and Hypercapnia in Obstructive Sleep Apnea-Hypopnea Syndrome. *Chest*. 2005;127(2):543-549.
213. Ng SSS, Chan RSM, Woo J, et al. A Randomized Controlled Study to Examine the Effect of a Lifestyle Modification Program in OSA. *CHEST*. 2015;148(5):1193-1203.
214. Chirinos JA, Gurubhagavatula I, Teff K, et al. CPAP, weight loss, or both for obstructive sleep apnea. *New Engl J Med*. 2014;370(24):2265-2275.
215. Jamieson A, Guilleminault C, Partinen M, Quera-Salva MA. Obstructive sleep apneic patients have craniomandibular abnormalities. *Sleep*. 1986;9(4):469-477.
216. Hochban W, Brandenburg U. Morphology of the viscerocranium in obstructive sleep apnoea syndrome--cephalometric evaluation of 400 patients. *J Craniomaxillofac Surg*. 1994;22(4):205-213.
217. Froberg U, Naples RJ, Jones DL. Cephalometric comparison of characteristics in chronically snoring patients with and without sleep apnea syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;80(1):28-33.
218. Lowe AA, Fleetham JA, Adachi S, Ryan CF. Cephalometric and computed tomographic predictors of obstructive sleep apnea severity. *Am J Orthod Dentofacial Orthop*. 1995;107(6):589-595.
219. Battagel JM, L'Estrange PR. The cephalometric morphology of patients with obstructive sleep apnoea (OSA). *Eur J Orthod*. 1996;18(6):557-569.
220. Tsai HH, Ho CY, Lee PL, Tan CT. Cephalometric analysis of nonobese snorers either with or without obstructive sleep apnea syndrome. *Angle Orthod*. 2007;77(6):1054-1061.
221. Riha RL, Brander P, Vennelle M, Douglas NJ. A cephalometric comparison of patients with the sleep apnea/hypopnea syndrome and their siblings. *Sleep*. 2005;28(3):315-320.

222. Johal A, Patel SI, Battagel JM. The relationship between craniofacial anatomy and obstructive sleep apnoea: a case-controlled study. *J Sleep Res.* 2007;16(3):319-326.
223. Chi L, Comyn FL, Mitra N, et al. Identification of craniofacial risk factors for obstructive sleep apnoea using three-dimensional MRI. *Eur Respir J.* 2011;38(2):348-358.
224. Gungor AY, Turkkahraman H, Yilmaz HH, Yariktas M. Cephalometric comparison of obstructive sleep apnea patients and healthy controls. *Eur J Dent.* 2013;7(1):48-54.
225. Banhiran W, Wanichakorntrakul P, Methetrairut C, Chiewvit P, Planuphap W. Lateral cephalometric analysis and the risks of moderate to severe obstructive sleep-disordered breathing in Thai patients. *Sleep Breath.* 2013;17(4):1249-1255.
226. Costa ESRA, dos Santos Gil NA. Craniofacial skeletal architecture and obstructive sleep apnoea syndrome severity. *J Craniomaxillofac Surg.* 2013;41(8):740-746.
227. Sakat MS, Sütbeyaz Y, Yüceler Z, Kantarci M, Kilic K, Kurt S. Cephalometric Measurements With Multislice Computed Tomography in Patients With Obstructive Sleep Apnea Syndrome. *J Craniofac Surg.* 2016;27(1):82-86.
228. Neelapu BC, Kharbanda OP, Sardana HK, et al. Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: A systematic review and meta-analysis of cephalometric studies. *Sleep Med Rev.* 2017;31:79-90.
229. Seto BH, Gotsopoulos H, Sims MR, Cistulli PA. Maxillary morphology in obstructive sleep apnoea syndrome. *Eur J Orthod.* 2001;23(6):703-714.
230. Johal A, Conaghan C. Maxillary morphology in obstructive sleep apnea: a cephalometric and model study. *Angle Orthod.* 2004;74(5):648-656.
231. Kuzucu I, Parlak IS, Baklaci D, Guler I, Kum RO, Ozcan M. Morphometric evaluation of the pterygoid hamulus and upper airway in patients with obstructive sleep apnea syndrome. *Surg Radiol Anat.* 2020;42(5):489-496.
232. Conway WA, Bower GC, Barnes ME. Hypersomnolence and intermittent upper airway obstruction. Occurrence caused by micrognathia. *JAMA.* 1977;237(25):2740-2742.
233. Cistulli PA. Craniofacial abnormalities in obstructive sleep apnoea: implications for treatment. *Respirology.* 1996;1(3):167-174.
234. Tsai WH, Remmers JE, Brant R, Flemons WW, Davies J, Macarthur C. A decision rule for diagnostic testing in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2003;167(10):1427-1432.
235. Lam B, Ip MS, Tench E, Ryan CF. Craniofacial profile in Asian and white subjects with obstructive sleep apnoea. *Thorax.* 2005;60(6):504-510.
236. Miyao E, Noda A, Miyao M, Yasuma F, Inafuku S. The role of malocclusion in non-obese patients with obstructive sleep apnea syndrome. *Intern Med.* 2008;47(18):1573-1578.
237. Ferguson KA, Ono T, Lowe AA, Ryan CF, Fleetham JA. The relationship between obesity and craniofacial structure in obstructive sleep apnea. *Chest.* 1995;108(2):375-381.
238. Tangugsorn V, Krogstad O, Espeland L, Lyberg T. Obstructive sleep apnoea: multiple comparisons of cephalometric variables of obese and non-obese patients. *J Craniomaxillofac Surg.* 2000;28(4):204-212.
239. Paoli JR, Lauwers F, Lacassagne L, Tiberge M, Dodart L, Boutault F. Craniofacial differences according to the body mass index of patients with obstructive sleep apnoea syndrome: cephalometric study in 85 patients. *Br J Oral Maxillofac Surg.* 2001;39(1):40-45.
240. Yu X, Fujimoto K, Urushibata K, Matsuzawa Y, Kubo K. Cephalometric analysis in obese and nonobese patients with obstructive sleep apnea syndrome. *Chest.* 2003;124(1):212-218.
241. Xu L, Keenan BT, Wiemken AS, et al. Differences in three-dimensional upper airway anatomy between Asian and European patients with obstructive sleep apnea. *Sleep.* 2020;43(5).



242. Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. *Am J Respir Crit Care Med*. 1997;155(1):186-192.
243. Cakirer B, Hans MG, Graham G, Aylor J, Tishler PV, Redline S. The relationship between craniofacial morphology and obstructive sleep apnea in whites and in African-Americans. *Am J Respir Crit Care Med*. 2001;163(4):947-950.
244. Redline S, Tishler PV, Tosteson TD, et al. The familial aggregation of obstructive sleep apnea. *Am J Respir Crit Care Med*. 1995;151(3 Pt 1):682-687.
245. Mathur R, Douglas NJ. Family studies in patients with the sleep apnea-hypopnea syndrome. *Ann Intern Med*. 1995;122(3):174-178.
246. Douglas NJ, Luke M, Mathur R. Is the sleep apnoea/hypopnoea syndrome inherited? *Thorax*. 1993;48(7):719-721.
247. Gislason T, Johannsson JH, Haraldsson A, et al. Familial predisposition and cosegregation analysis of adult obstructive sleep apnea and the sudden infant death syndrome. *Am J Respir Crit Care Med*. 2002;166(6):833-838.
248. Pillar G, Lavie P. Assessment of the role of inheritance in sleep apnea syndrome. *Am J Respir Crit Care Med*. 1995;151(3 Pt 1):688-691.
249. Chi L, Comyn FL, Keenan BT, et al. Heritability of craniofacial structures in normal subjects and patients with sleep apnea. *Sleep*. 2014;37(10):1689-1698.
250. Johannsdottir B, Thorarinsson F, Thordarson A, Magnusson TE. Heritability of craniofacial characteristics between parents and offspring estimated from lateral cephalograms. *Am J Orthod Dentofacial Orthop*. 2005;127(2):200-207; quiz 260-201.
251. Liang J, Cade BE, Wang H, et al. Comparison of heritability estimation and linkage analysis for multiple traits using principal component analyses. *Genet Epidemiol*. 2016;40(3):222-232.
252. Gao X, Azarbarzin A, Keenan BT, et al. Heritability of heart rate response to arousals in twins. *Sleep*. 2017;40(6).
253. Ibrahim LH, Jacono FJ, Patel SR, et al. Heritability of abnormalities in cardiopulmonary coupling in sleep apnea: use of an electrocardiogram-based technique. *Sleep*. 2010;33(5):643-646.
254. Thomas RJ, Mietus JE, Peng CK, et al. Relationship between delta power and the electrocardiogram-derived cardiopulmonary spectrogram: possible implications for assessing the effectiveness of sleep. *Sleep Med*. 2014;15(1):125-131.
255. Rizzatti FG, Mazzotti DR, Mindel J, et al. Defining extreme phenotypes of obstructive sleep apnea across international sleep centers. *Chest*. 2020.
256. Wellman A, Edwards BA, Sands SA, et al. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. *J Appl Physiol (1985)*. 2013;114(7):911-922.
257. Wellman A, Eckert DJ, Jordan AS, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. *J Appl Physiol (1985)*. 2011;110(6):1627-1637.
258. Palmer LJ, Buxbaum SG, Larkin E, et al. A whole-genome scan for obstructive sleep apnea and obesity. *Am J Hum Genet*. 2003;72(2):340-350.
259. Palmer LJ, Buxbaum SG, Larkin EK, et al. Whole genome scan for obstructive sleep apnea and obesity in African-American families. *Am J Respir Crit Care Med*. 2004;169(12):1314-1321.
260. Liang J, Cade BE, He KY, et al. Sequencing Analysis at 8p23 Identifies Multiple Rare Variants in DLC1 Associated with Sleep-Related Oxyhemoglobin Saturation Level. *Am J Hum Genet*. 2019;105(5):1057-1068.
261. Varvarigou V, Dahabreh IJ, Malhotra A, Kales SN. A review of genetic association studies of obstructive sleep apnea: field synopsis and meta-analysis. *Sleep*. 2011;34(11):1461-1468.
262. Cade BE, Chen H, Stilp AM, et al. Genetic associations with obstructive sleep apnea traits in Hispanic/Latino Americans. *Am J Respir Crit Care Med*. 2016;194(7):886-897.

263. Cade BE, Lee J, Sofer T, et al. Whole-genome association analyses of sleep-disordered breathing phenotypes in the NHLBI TOPMed program. *bioRxiv*. 2019.
264. Chen H, Cade BE, Gleason KJ, et al. Multiethnic meta-analysis identifies RAI1 as a possible obstructive sleep apnea-related quantitative trait locus in men. *American journal of respiratory cell and molecular biology*. 2018;58(3):391-401.
265. Patel SR, Goodloe R, De G, et al. Association of genetic loci with sleep apnea in European Americans and African-Americans: the Candidate Gene Association Resource (CARE). *PLoS one*. 2012;7(11):e48836.
266. Elsea SH, Girirajan S. Smith-Magenis syndrome. *Eur J Hum Genet*. 2008;16(4):412-421.
267. Smith AC, Dykens E, Greenberg F. Sleep disturbance in Smith-Magenis syndrome (del 17 p11.2). *Am J Med Genet*. 1998;81(2):186-191.
268. Cade BE, Chen H, Stilp AM, et al. Associations of variants in the hexokinase 1 and interleukin 18 receptor regions with oxyhemoglobin saturation during sleep. *PLoS Genet*. 2019;15(4):e1007739.
269. Wang H, Cade BE, Sofer T, et al. Admixture mapping identifies novel loci for obstructive sleep apnea in Hispanic/Latino Americans. *Hum Mol Genet*. 2019;28(4):675-687.
270. Zhu X, Tang H, Risch N. Admixture mapping and the role of population structure for localizing disease genes. *Adv Genet*. 2008;60:547-569.
271. Veatch OJ, Bauer CR, Keenan BT, et al. Characterization of genetic and phenotypic heterogeneity of obstructive sleep apnea using electronic health records. *BMC Medical Genomics*. 2020 (in press).
272. Pendergrass SA, Brown-Gentry K, Dudek SM, et al. The use of phenome-wide association studies (PheWAS) for exploration of novel genotype-phenotype relationships and pleiotropy discovery. *Genet Epidemiol*. 2011;35(5):410-422.
273. Strausz S, Ruotsalainen S, Ollila HM, et al. Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health. *Eur Respir J*. 2021;57(5).
274. Ferris BG, Jr., Mead J, Opie LH. Partitioning of Respiratory Flow Resistance in Man. *J Appl Physiol*. 1964;19:653-658.
275. Magliulo G, Iannella G, Ciofalo A, et al. Nasal pathologies in patients with obstructive sleep apnoea. *Acta Otorhinolaryngol Ital*. 2019;39(4):250-256.
276. Georgalas C. The role of the nose in snoring and obstructive sleep apnoea: an update. *Eur Arch Otorhinolaryngol*. 2011;268(9):1365-1373.
277. Awad MI, Kacker A. Nasal Obstruction Considerations in Sleep Apnea. *Otolaryngol Clin North Am*. 2018;51(5):1003-1009.
278. Desfonds P, Planes C, Fuhrman C, Foucher A, Raffestin B. Nasal resistance in snorers with or without sleep apnea: effect of posture and nasal ventilation with continuous positive airway pressure. *Sleep*. 1998;21(6):625-632.
279. Craig TJ, Ferguson BJ, Krouse JH. Sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polyposis. *Am J Otolaryngol*. 2008;29(3):209-217.
280. Reinberg A, Gervais P, Levi F, Smolensky M, Del Cerro L, Ugolini C. Circadian and circannual rhythms of allergic rhinitis: an epidemiologic study involving chronobiologic methods. *J Allergy Clin Immunol*. 1988;81(1):51-62.
281. Rundcrantz H. Postural variations of nasal patency. *Acta Otolaryngol*. 1969;68(5):435-443.
282. Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S. Upper airway pressure-flow relationships in obstructive sleep apnea. *J Appl Physiol (1985)*. 1988;64(2):789-795.
283. Susarla SM, Thomas RJ, Abramson ZR, Kaban LB. Biomechanics of the upper airway: Changing concepts in the pathogenesis of obstructive sleep apnea. *Int J Oral Maxillofac Surg*. 2010;39(12):1149-1159.

284. Mickelson SA. Nasal Surgery for Obstructive Sleep Apnea Syndrome. *Otolaryngol Clin North Am*. 2016;49(6):1373-1381.
285. Meurice JC, Marc I, Carrier G, Series F. Effects of mouth opening on upper airway collapsibility in normal sleeping subjects. *Am J Respir Crit Care Med*. 1996;153(1):255-259.
286. Fitzpatrick MF, McLean H, Urton AM, Tan A, O'Donnell D, Driver HS. Effect of nasal or oral breathing route on upper airway resistance during sleep. *Eur Respir J*. 2003;22(5):827-832.
287. Hollowell DE, Suratt PM. Mandible position and activation of submental and masseter muscles during sleep. *J Appl Physiol (1985)*. 1991;71(6):2267-2273.
288. McNicholas WT, Coffey M, Boyle T. Effects of nasal airflow on breathing during sleep in normal humans. *Am Rev Respir Dis*. 1993;147(3):620-623.
289. Berry RB, Kouchi KG, Bower JL, Light RW. Effect of Upper Airway Anesthesia on Obstructive Sleep-Apnea. *Am J Resp Crit Care*. 1995;151(6):1857-1861.
290. Douglas NJ, White DP, Weil JV, Zwillich CW. Effect of breathing route on ventilation and ventilatory drive. *Respir Physiol*. 1983;51(2):209-218.
291. White DP, Cadieux RJ, Lombard RM, Bixler EO, Kales A, Zwillich CW. The effects of nasal anesthesia on breathing during sleep. *Am Rev Respir Dis*. 1985;132(5):972-975.
292. Lundberg J. Airborne nitric oxide: Inflammatory marker and aerocrine messenger in man. *Acta Physiol Scand*. 1996;157(S633):4-27.
293. Djupesland PG, Chatkin JM, Qian W, et al. Aerodynamic influences on nasal nitric oxide output measurements. *Acta Otolaryngol*. 1999;119(4):479-485.
294. Haight JS, Djupesland PG. Nitric oxide (NO) and obstructive sleep apnea (OSA). *Sleep Breath*. 2003;7(2):53-62.
295. Brander PE, Soirinsuo M, Lohela P. Nasopharyngeal symptoms in patients with obstructive sleep apnea syndrome. Effect of nasal CPAP treatment. *Respiration*. 1999;66(2):128-135.
296. Lofaso F, Coste A, d'Ortho MP, et al. Nasal obstruction as a risk factor for sleep apnoea syndrome. *Eur Respir J*. 2000;16(4):639-643.
297. Miljeteig H, Hoffstein V, Cole P. The effect of unilateral and bilateral nasal obstruction on snoring and sleep apnea. *Laryngoscope*. 1992;102(10):1150-1152.
298. Lavie P, Fischel N, Zomer J, Eliaschar I. The effects of partial and complete mechanical occlusion of the nasal passages on sleep structure and breathing in sleep. *Acta Otolaryngol*. 1983;95(1-2):161-166.
299. Wilhoit SC, Suratt PM. Effect of nasal obstruction on upper airway muscle activation in normal subjects. *Chest*. 1987;92(6):1053-1055.
300. Carskadon MA, Bearpark HM, Sharkey KM, et al. Effects of menopause and nasal occlusion on breathing during sleep. *Am J Respir Crit Care Med*. 1997;155(1):205-210.
301. Suratt PM, Turner BL, Wilhoit SC. Effect of intranasal obstruction on breathing during sleep. *Chest*. 1986;90(3):324-329.
302. Zwillich CW, Pickett C, Hanson FN, Weil JV. Disturbed sleep and prolonged apnea during nasal obstruction in normal men. *Am Rev Respir Dis*. 1981;124(2):158-160.
303. Olsen KD, Kern EB, Westbrook PR. Sleep and breathing disturbance secondary to nasal obstruction. *Otolaryngol Head Neck Surg*. 1981;89(5):804-810.
304. Cassisi NJ, Biller HF, Ogura JH. Changes in arterial oxygen tension and pulmonary mechanics with the use of posterior packing in epistaxis: a preliminary report. *Laryngoscope*. 1971;81(8):1261-1266.
305. Cole P, Haight JS. Mechanisms of nasal obstruction in sleep. *Laryngoscope*. 1984;94(12 Pt 1):1557-1559.
306. Slocum CW, Maisel RH, Cantrell RW. Arterial blood gas determination in patients with anterior packing. *Laryngoscope*. 1976;86(6):869-873.

307. Friedman M, Maley A, Kelley K, et al. Impact of nasal obstruction on obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2011;144(6):1000-1004.
308. Armengot M, Hernandez R, Miguel P, Navarro R, Basterra J. Effect of total nasal obstruction on nocturnal oxygen saturation. *Am J Rhinol.* 2008;22(3):325-328.
309. Turhan M, Bostanci A, Akdag M, Dinc O. A comparison of the effects of packing or transseptal suture on polysomnographic parameters in septoplasty. *Eur Arch Otorhinolaryngol.* 2013;270(4):1339-1344.
310. Ryan CM, Bradley TD. Pathogenesis of obstructive sleep apnea. *J Appl Physiol (1985).* 2005;99(6):2440-2450.
311. Katsantonis GP, Moss K, Miyazaki S, Walsh J. Determining the site of airway collapse in obstructive sleep apnea with airway pressure monitoring. *Laryngoscope.* 1993;103(10):1126-1131.
312. Bradley TD, Brown IG, Grossman RF, et al. Pharyngeal size in snorers, nonsnorers, and patients with obstructive sleep apnea. *N Engl J Med.* 1986;315(21):1327-1331.
313. Rodenstein DO, Doms G, Thomas Y, et al. Pharyngeal shape and dimensions in healthy subjects, snorers, and patients with obstructive sleep apnoea. *Thorax.* 1990;45(10):722-727.
314. Suratt PM, Dee P, Atkinson RL, Armstrong P, Wilhoit SC. Fluoroscopic and computed tomographic features of the pharyngeal airway in obstructive sleep apnea. *Am Rev Respir Dis.* 1983;127(4):487-492.
315. Pae EK, Lowe AA, Fleetham JA. A role of pharyngeal length in obstructive sleep apnea patients. *Am J Orthod Dentofacial Orthop.* 1997;111(1):12-17.
316. Malhotra A, Pillar G, Fogel RB, et al. Pharyngeal pressure and flow effects on genioglossus activation in normal subjects. *Am J Respir Crit Care Med.* 2002;165(1):71-77.
317. Schellenberg JB, Maislin G, Schwab RJ. Physical findings and the risk for obstructive sleep apnea. The importance of oropharyngeal structures. *Am J Respir Crit Care Med.* 2000;162(2 Pt 1):740-748.
318. Schwab RJ, Geftter WB, Hoffman EA, Gupta KB, Pack AI. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. *Am Rev Respir Dis.* 1993;148(5):1385-1400.
319. Anastassov GE, Trieger N. Edema in the upper airway in patients with obstructive sleep apnea syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;86(6):644-647.
320. Schwab RJ. Properties of tissues surrounding the upper airway. *Sleep.* 1996;19(10 Suppl):S170-174.
321. Horner RL, Mohiaddin RH, Lowell DG, et al. Sites and sizes of fat deposits around the pharynx in obese patients with obstructive sleep apnoea and weight matched controls. *Eur Respir J.* 1989;2(7):613-622.
322. Bradley TD, Rutherford R, Grossman RF, et al. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. *Am Rev Respir Dis.* 1985;131(6):835-839.
323. Ingman T, Nieminen T, Hurmerinta K. Cephalometric comparison of pharyngeal changes in subjects with upper airway resistance syndrome or obstructive sleep apnoea in upright and supine positions. *Eur J Orthod.* 2004;26(3):321-326.
324. Stauffer JL, Buick MK, Bixler EO, et al. Morphology of the uvula in obstructive sleep apnea. *Am Rev Respir Dis.* 1989;140(3):724-728.
325. Campana L, Eckert DJ, Patel SR, Malhotra A. Pathophysiology & genetics of obstructive sleep apnoea. *Indian J Med Res.* 2010;131:176-187.
326. Jara SM, Weaver EM. Association of palatine tonsil size and obstructive sleep apnea in adults. *Laryngoscope.* 2018;128(4):1002-1006.

327. Zonato AI, Bittencourt LR, Martinho FL, Junior JF, Gregorio LC, Tufik S. Association of systematic head and neck physical examination with severity of obstructive sleep apnea-hypopnea syndrome. *Laryngoscope*. 2003;113(6):973-980.
328. Friedman M, Tanyeri H, La Rosa M, et al. Clinical predictors of obstructive sleep apnea. *Laryngoscope*. 1999;109(12):1901-1907.
329. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64(21):2222-2231.
330. Cahali MB, Soares CF, Dantas DA, Formigoni GG. Tonsil volume, tonsil grade and obstructive sleep apnea: is there any meaningful correlation? *Clinics (Sao Paulo)*. 2011;66(8):1347-1352.
331. Yagi H, Nakata S, Tsuge H, et al. Morphological examination of upper airway in obstructive sleep apnea. *Auris Nasus Larynx*. 2009;36(4):444-449.
332. Dahlqvist J, Dahlqvist A, Marklund M, Berggren D, Stenlund H, Franklin KA. Physical findings in the upper airways related to obstructive sleep apnea in men and women. *Acta Otolaryngol*. 2007;127(6):623-630.
333. Thulesius HL, Thulesius HO, Jessen M. Pharyngometric correlations with obstructive sleep apnea syndrome. *Acta Otolaryngol*. 2004;124(10):1182-1186.
334. Camacho M, Li D, Kawai M, et al. Tonsillectomy for adult obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope*. 2016;126(9):2176-2186.
335. Woodson BT, Naganuma H. Comparison of methods of airway evaluation in obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg*. 1999;120(4):460-463.
336. Sforza E, Bacon W, Weiss T, Thibault A, Petiau C, Krieger J. Upper airway collapsibility and cephalometric variables in patients with obstructive sleep apnea. *Am J Respi Crit Care*. 2000;161(2):347-352.
337. Genta PR, Schorr F, Eckert DJ, et al. Upper Airway Collapsibility is Associated with Obesity and Hyoid Position. *Sleep*. 2014;37(10):1673-1678.
338. Verin E, Tardif C, Buffet X, et al. Comparison between anatomy and resistance of upper airway in normal subjects, snorers and OSAS patients. *Resp Physiol*. 2002;129(3):335-343.
339. Watanabe T, Isono S, Tanaka A, Tanzawa H, Nishino T. Contribution of body habitus and craniofacial characteristics to segmental closing pressures of the passive pharynx in patients with sleep-disordered breathing. *Am J Respi Crit Care*. 2002;165(2):260-265.
340. Schorr F, Kayamori F, Hirata RP, et al. Different Craniofacial Characteristics Predict Upper Airway Collapsibility in Japanese-Brazilian and White Men. *Chest*. 2016;149(3):737-746.
341. Brennick MJ, Delikatny J, Pack AI, et al. Tongue Fat Infiltration in Obese Versus Lean Zucker Rats. *Sleep*. 2014;37(6):1095-U1198.
342. Wang SH, Keenan BT, Wiemken A, et al. Effect of Weight Loss on Upper Airway Anatomy and the Apnea-Hypopnea Index The Importance of Tongue Fat. *Am J Respi Crit Care*. 2020;201(6):718-727.
343. Khoo M. Determinants of ventilatory instability and variability. *Respir Physiol*. 2000;122:167-182.
344. Hlastala MP, Berger AJ. Chemical Control of Breathing. In: *Physiology of Respiration*. Second ed. New York: Oxford University Press; 2001:151, 155.
345. Younes M, Ostrowski M, Thompson W, Leslie C, Shewchuk W. Chemical control stability in patients with obstructive sleep apnea. *Am J Respi Crit Care Med*. 2001;163(5):1181-1190.
346. Wellman A, Malhotra A, Jordan AS, Schory K, Gautam S, White DP. Chemical control stability in the elderly. *J Physiol*. 2007;581(Pt 1):291-298.
347. Malhotra A, Jordan AS. Did fat boy Joe need hormone replacement? *Sleep*. 2006;29(1):16-18.

348. Salloum A, Rowley JA, Mateika JH, Chowdhuri S, Omran Q, Badr MS. Increased propensity for central apnea in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure. *Am J Respir Crit Care Med*. 2010;181(2):189-193.
349. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiological reviews*. 2010;90(1):47-112.
350. Javaheri S. A mechanism of central sleep apnea in patients with heart failure. *N Engl J Med*. 1999;23:985-987.
351. Javaheri S, Smith J, Chung E. The prevalence and natural history of complex sleep apnea. *J Clin Sleep Med*. 2009;5(3):205-211.
352. Badr MS, Skatrud JB, Dempsey JA. Effect of Chemoreceptor Stimulation and Inhibition on Total Pulmonary Resistance in Humans during Nrem Sleep. *Journal of Applied Physiology*. 1994;76(4):1682-1692.
353. Badr MS. Pathophysiology of upper airway obstruction during sleep. *Clinics in Chest Medicine*. 1998;19(1):21-32.
354. Joosten SA, Landry SA, Sands SA, et al. Dynamic loop gain increases upon adopting the supine body position during sleep in patients with obstructive sleep apnoea. *Respirology*. 2017;22(8):1662-1669.
355. Younes M. Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. *Am J Respir Crit Care Med*. 2003;168(6):645-658.
356. Ainslie PN, Lucas SJ, Burgess KR. Breathing and sleep at high altitude. *Respiratory physiology & neurobiology*. 2013;188(3):233-256.
357. Bradley TD, Floras JS. Pathophysiologic and therapeutic implications of sleep apnea in congestive heart failure. [Review] [150 refs]. *Journal of Cardiac Failure*. 1996;2(3):223-240.
358. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *New Engl J Med*. 2005;353:2025-2033.
359. Hudgel DW, Devadatta P, Quadri M, Sioson ER, Hamilton H. Mechanism of sleep-induced periodic breathing in convalescing stroke patients and healthy elderly subjects. *Chest*. 1993;104(5):1503-1510.
360. Hudgel DW, Gordon EA, Thanakitcharu S, Bruce EN. Instability of ventilatory control in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 1998;158(4):1142-1149.
361. Deacon-Diaz N, Malhotra A. Inherent vs. Induced Loop Gain Abnormalities in Obstructive Sleep Apnea. *Front Neurol*. 2018;9:896.
362. Li Y, Ye J, Han D, et al. Physiology-Based Modeling May Predict Surgical Treatment Outcome for Obstructive Sleep Apnea. *J Clin Sleep Med*. 2017;13(9):1029-1037.
363. Li Y, Ye J, Han D, et al. The Effect of Upper Airway Surgery on Loop Gain in Obstructive Sleep Apnea. *J Clin Sleep Med*. 2019;15(6):907-913.
364. Joosten SA, Leong P, Landry SA, et al. Loop Gain Predicts the Response to Upper Airway Surgery in Patients With Obstructive Sleep Apnea. *Sleep*. 2017;40(7).
365. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: role of loop gain. *Respiratory physiology & neurobiology*. 2008;162(2):144-151.
366. Edwards BA, Sands SA, Eckert DJ, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. *J Physiol*. 2012;590(5):1199-1211.
367. Inoue Y, Takata K, Sakamoto I, Hazama H, Kawahara R. Clinical efficacy and indication of acetazolamide treatment on sleep apnea syndrome. *Psychiatry and clinical neurosciences*. 1999;53(2):321-322.
368. Orr JE, Sands SA, Edwards BA, et al. Measuring Loop Gain via Home Sleep Testing in Patients with Obstructive Sleep Apnea. *Am J Respir Crit Care Med*. 2018;197(10):1353-1355.

369. Sands SA, Edwards BA, Terrill PI, et al. Phenotyping Pharyngeal Pathophysiology Using Polysomnography in Patients with Obstructive Sleep Apnea. *Am J Respir Crit Care Med*. 2018.
370. Terrill PI, Edwards BA, Nemati S, et al. Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. *Eur Respir J*. 2015;45(2):408-418.
371. Haponik E, Smith P, Bohlman M, Allan R, Goldman S, Bleecker E. Computerized tomography in obstructive sleep apnea: correlation of airway size with physiology during sleep and wakefulness. *Am Rev Respir Dis*. 1983;127:221-226.
372. Tangel DJ, Mezzanotte WS, Sandberg EJ, White DP. Influences of NREM sleep on the activity of tonic vs. inspiratory phasic muscles in normal men. *J Appl Physiol*. 1992;73(3):1058-1066.
373. Horner RL. Motor control of the pharyngeal musculature and implications for the pathogenesis of obstructive sleep apnea. *Sleep*. 1996;19(10):827-853.
374. Horner RL, Hughes SW, Malhotra A. State-dependent and reflex drives to the upper airway: basic physiology with clinical implications. *J Appl Physiol (1985)*. 2014;116(3):325-336.
375. Badr MS. Effect of ventilatory drive on upper airway patency in humans during NREM sleep. *Respir Physiol*. 1996;103:1-10.
376. Saboisky JP, Jordan AS, Eckert DJ, et al. Recruitment and rate-coding strategies of the human genioglossus muscle. *J Appl Physiol*. 2010;109(6):1939-1949.
377. Saboisky JP, Stashuk DW, Hamilton-Wright A, et al. Neurogenic changes in the upper airway of patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2012;185(3):322-329.
378. Powell GL, Rice A, Bennett-Cross SJ, Fregosi RF. Respiration-related discharge of hyoglossus muscle motor units in the rat. *J Neurophysiol*. 2014;111(2):361-368.
379. Trinder J WFKAWP. Respiratory instability during sleep onset. *J Appl Physiol*. 1992;73(6):2462-2469.
380. Tangel D, Mezzanotte, WS, and White, DP. Influence of sleep on tensor palatini EMG and upper airway resistance in normal men. *J Appl Physiol*. 1991;70(6):2574-2581.
381. Strollo PJ, Jr., Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med*. 2014;370(2):139-149.
382. Woodson BT, Strohl KP, Soose RJ, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes. *Otolaryngol Head Neck Surg*. 2018;159(1):194-202.
383. Malhotra A. Hypoglossal-nerve stimulation for obstructive sleep apnea. *N Engl J Med*. 2014;370(2):170-171.
384. Mathew OP. Upper Airway Negative-Pressure Effects on Respiratory Activity of Upper Airway Muscles. *Journal of Applied Physiology*. 1984;56(2):500-505.
385. Mathew OP. Maintenance of Upper Airway Patency. *J Pediatr-Us*. 1985;106(6):863-869.
386. Mathew OP, Abuosba YK, Thach BT. Influence of Upper Airway Pressure Changes on Genioglossus Muscle Respiratory Activity. *Journal of Applied Physiology*. 1982;52(2):438-444.
387. Horner RL, Innes, JA, Murphy, K, and Guz, A. Evidence for reflex upper airway dilator muscle activation by sudden negative airway pressure in man. *J Physiol (Lond)*. 1991;436:15-29.
388. Wheatley JR, Mezzanotte WS, Tangel DJ, White DP. Influence of sleep on genioglossus muscle activation by negative pressure in normal men. *Am Rev Respir Dis*. 1993;148(3):597-605.
389. Berry RB, White DP, Roper J, et al. Awake negative pressure reflex response of the genioglossus in OSA patients and normal subjects. *J Appl Physiol*. 2003;94(5):1875-1882.
390. Chamberlin NL, Eikermann M, Fassbender P, White DP, Malhotra A. Genioglossus premotoneurons and the negative pressure reflex in rats. *J Physiol*. 2007;579(Pt 2):515-526.
391. Li Y, Owens RL, Sands S, et al. The Effect of Donepezil on Arousal Threshold and Apnea-Hypopnea Index. A Randomized, Double-Blind, Cross-Over Study. *Ann Am Thorac Soc*. 2016;13(11):2012-2018.

392. Taranto-Montemurro L, Messineo L, Sands SA, et al. The Combination of Atomoxetine and Oxybutynin Greatly Reduces Obstructive Sleep Apnea Severity. A Randomized, Placebo-controlled, Double-Blind Crossover Trial. *Am J Respir Crit Care Med*. 2019;199(10):1267-1276.
393. Pillar G, Malhotra A, Fogel R, et al. Upper airway muscle responsiveness to rising PCO<sub>2</sub> during NREM sleep. *J Appl Physiol*. 2000;89:1275-1282.
394. Malhotra A, Pillar G, Fogel R, Beauregard J, Edwards J, White DP. Upper-airway collapsibility: measurements and sleep effects. *Chest*. 2001;120(1):156-161.
395. Malhotra A, Fogel R, Edwards J, Shea S, White D. Local Mechanisms Drive Genioglossus Muscle Activation in Obstructive Sleep Apnea. *Am J Respir Crit Care Med*. 2000;161:1746-1749.
396. Berry RB, Gleeson K. Respiratory arousal from sleep: Mechanisms and significance. *Sleep*. 1997;20(8):654-675.
397. Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. *Am J Respir Crit Care Med*. 2004;169(5):623-633.
398. Heinzer RC, White DP, Jordan AS, et al. Trazodone increases arousal threshold in obstructive sleep apnoea. *Eur Respir J*. 2008;31(6):1308-1312.
399. Eckert DJ, Owens RL, Kehlmann GB, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. *Clin Sci (Lond)*. 2011;120(12):505-514.
400. Smales ET, Edwards BA, Deyoung PN, et al. Trazodone Effects on Obstructive Sleep Apnea and Non-REM Arousal Threshold. *Ann Am Thorac Soc*. 2015;12(5):758-764.
401. Ratnavadivel R, Stadler D, Windler S, et al. Upper airway function and arousability to ventilatory challenge in slow wave versus stage 2 sleep in obstructive sleep apnea. *Thorax*. 2010;65:107-112.
402. Horner RL. The neuropharmacology of upper airway motor control in the awake and asleep states: implications for obstructive sleep apnoea. *Respir Res*. 2001;2(5):286-294.
403. Horner RL. Pathophysiology of obstructive sleep apnea. *J Cardiopulm Rehabil Prev*. 2008;28(5):289-298.
404. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet*. 2014;383(9918):736-747.
405. Malhotra A, Pillar G, Fogel R, Beauregard J, White D. Genioglossal But Not Palatal Muscle Activity Relates Closely to Pharyngeal Pressure. *Am J Respir Crit Care Med*. 2000;162(3):1058-1062.
406. Schwarz PB, Peever JH. Noradrenergic control of trigeminal motoneurons in sleep: relevance to sleep apnea. *Adv Exp Med Biol*. 2010;669:281-284.
407. Schwarz PB, Peever JH. Dopamine triggers skeletal muscle tone by activating D1-like receptors on somatic motoneurons. *J Neurophysiol*. 2011;106(3):1299-1309.
408. Schwarz PB, Yee N, Mir S, Peever JH. Noradrenaline triggers muscle tone by amplifying glutamate-driven excitation of somatic motoneurons in anaesthetized rats. *J Physiol*. 2008;586(23):5787-5802.
409. Gleeson K, Zwillich CW, White DP. The influence of increasing ventilatory effort on arousal from sleep. *Am Rev Respir Dis*. 1990;142:295-300.
410. Edwards BA, Eckert DJ, McSharry DG, et al. Clinical Predictors of the Respiratory Arousal Threshold in Patients with Obstructive Sleep Apnea. *Am J Respir Crit Care Med*. 2014.
411. Younes M. Pharyngeal anatomy and severity of obstructive apnea. *Am J Respir Crit Care Med*. 2004;170(6):716.
412. Kobayashi I, et al. Inspiratory coactivation of the genioglossus enlarges retroglossal space in laryngectomized humans. *J Appl Physiol*. 1996;80(5):1595-1604.
413. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol*. 2007;49(5):565-571.



414. Edwards BA, Sands SA, Owens RL, et al. The Combination of Supplemental Oxygen and a Hypnotic Markedly Improves Obstructive Sleep Apnea in Patients with a Mild to Moderate Upper Airway Collapsibility. *Sleep*. 2016;39(11):1973-1983.
415. Li Y, Orr J, Jen R, et al. Is there a threshold that triggers cortical arousals in obstructive sleep apnea. *Sleep*. 2019;42(6).
416. Loewen A, Ostrowski M, Laprairie J, et al. Determinants of ventilatory instability in obstructive sleep apnea: inherent or acquired? *Sleep*. 2009;32(10):1355-1365.
417. Saboisky J, Eckert D, Malhotra A. Stable breathing through deeper sleeping. *Thorax*. 2010;65(2):95-96.
418. Lettieri CJ, Shah AA, Holley AB, Kelly WF, Chang AS, Roop SA. Effects of a short course of eszopiclone on continuous positive airway pressure adherence: a randomized trial. *Ann Intern Med*. 2009;151(10):696-702.
419. Zinchuk A, Yaggi HK. Phenotypic Subtypes of OSA: A Challenge and Opportunity for Precision Medicine. *Chest*. 2020;157(2):403-420.
420. Weaver EM, Woodson BT, Steward DL. Polysomnography indexes are discordant with quality of life, symptoms, and reaction times in sleep apnea patients. *Otolaryngol Head Neck Surg*. 2005;132(2):255-262.
421. Senaratna CV, Perret JL, Matheson MC, et al. Validity of the Berlin questionnaire in detecting obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Med Rev*. 2017;36:116-124.
422. Nagappa M, Liao P, Wong J, et al. Validation of the STOP-Bang Questionnaire as a Screening Tool for Obstructive Sleep Apnea among Different Populations: A Systematic Review and Meta-Analysis. *PLoS one*. 2015;10(12):e0143697.
423. Coutinho Costa J, Rebelo-Marques A, Machado JN, et al. Validation of NoSAS (Neck, Obesity, Snoring, Age, Sex) score as a screening tool for obstructive sleep apnea: Analysis in a sleep clinic. *Pulmonology*. 2019;25(5):263-270.
424. Hong C, Chen R, Qing S, et al. Validation of the NoSAS Score for the Screening of Sleep-Disordered Breathing: A Hospital-Based Retrospective Study in China. *J Clin Sleep Med*. 2018;14(2):191-197.
425. Marti-Soler H, Hirotsu C, Marques-Vidal P, et al. The NoSAS score for screening of sleep-disordered breathing: a derivation and validation study. *Lancet Respir Med*. 2016;4(9):742-748.
426. Peng M, Chen R, Cheng J, Li J, Liu W, Hong C. Application value of the NoSAS score for screening sleep-disordered breathing. *J Thorac Dis*. 2018;10(8):4774-4781.
427. Rong Y, Wang S, Wang H, et al. Validation of the NoSAS Score for the Screening of Sleep-Disordered Breathing in a Sleep Clinic. *Can Respir J*. 2020;2020:4936423.
428. Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. *Can J Anaesth*. 2010;57(5):423-438.
429. Amra B, Rahmati B, Soltaninejad F, Feizi A. Screening Questionnaires for Obstructive Sleep Apnea: An Updated Systematic Review. *Oman Med J*. 2018;33(3):184-192.
430. Chiu HY, Chen PY, Chuang LP, et al. Diagnostic accuracy of the Berlin questionnaire, STOP-BANG, STOP, and Epworth sleepiness scale in detecting obstructive sleep apnea: A bivariate meta-analysis. *Sleep Medicine Reviews*. 2017;36:57-70.
431. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol*. 2013;62(7):569-576.
432. Marshall NS, Wong KK, Liu PY, Cullen SR, Knudman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep*. 2008;31(8):1079-1085.

433. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: Eighteen-year follow-up of the Wisconsin Sleep Cohort. *Sleep*. 2008;31(8):1071-1078.
434. Moyer CA, Sonnad SS, Garetz SL, Helman JI, Chervin RD. Quality of life in obstructive sleep apnea: a systematic review of the literature. *Sleep Med*. 2001;2(6):477-491.
435. Kendzerska TB, Smith PM, Brignardello-Petersen R, Leung RS, Tomlinson GA. Evaluation of the measurement properties of the Epworth sleepiness scale: a systematic review. *Sleep Med Rev*. 2014;18(4):321-331.
436. Billings ME, Rosen CL, Auckley D, et al. Psychometric performance and responsiveness of the functional outcomes of sleep questionnaire and sleep apnea quality of life instrument in a randomized trial: the HomePAP study. *Sleep*. 2014;37(12):2017-2024.
437. Flemons WW, Reimer MA. Development of a disease-specific health-related quality of life questionnaire for sleep apnea. *Am J Respir Crit Care Med*. 1998;158(2):494-503.
438. Flemons WW, Reimer MA. Measurement properties of the calgary sleep apnea quality of life index. *Am J Respir Crit Care Med*. 2002;165(2):159-164.
439. Lacasse Y, Godbout C, Sériès F. Independent validation of the Sleep Apnoea Quality of Life Index. *Thorax*. 2002;57(6):483-488.
440. Silva GE, Goodwin JL, Vana KD, Quan SF. Obstructive Sleep Apnea and Quality of Life: Comparison of the SAQLI, FOSQ, and SF-36 Questionnaires. *Southwest J Pulm Crit Care*. 2016;13(3):137-149.
441. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20(10):835-843.
442. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep Med Rev*. 2016;25:52-73.
443. Abma IL, van der Wees PJ, Veer V, Westert GP, Rovers M. Measurement properties of patient-reported outcome measures (PROMs) in adults with obstructive sleep apnea (OSA): A systematic review. *Sleep Med Rev*. 2016;28:18-31.
444. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med*. 1999;131(7):485-491.
445. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire - A tool to screen patients for obstructive sleep apnea. *Anesthesiology*. 2008;108(5):812-821.
446. Chung F, Abdullah HR, Liao P. STOP-Bang Questionnaire A Practical Approach to Screen for Obstructive Sleep Apnea. *Chest*. 2016;149(3):631-638.
447. Rosenthal LD, Dolan DC. The Epworth sleepiness scale in the identification of obstructive sleep apnea. *J Nerv Ment Dis*. 2008;196(5):429-431.
448. Bohning N, Schultheiss B, Eilers S, Penzel T, Bohning W, Schmittendorf E. Comparability of pulse oximeters used in sleep medicine for the screening of OSA. *Physiological Measurement*. 2010;31(7):875-888.
449. de Vries CEE, de Raaff CAL, Ruys AT, de Vries N, Hilgevoord AAJ, van Wagenveld BA. Validity of a simple sleep monitor for diagnosing OSA in bariatric surgery patients. *Surg Obes Relat Dis*. 2018;14(7):1020-1025.
450. Dimitrov L, Macavei V. Can Screening Tools for Obstructive Sleep Apnea Predict Postoperative Complications? A Systematic Review of the Literature. *Journal of Clinical Sleep Medicine*. 2016;12(9):1293-1300.
451. Yaddanapudi SS, Pineda MC, Boorman DW, Bryne RE, Hing KL, Sharma S. High-Resolution Pulse Oximetry (HRPO): A Cost-Effective Tool in Screening for Obstructive Sleep Apnea (OSA) in Acute Stroke and Predicting Outcome. *J Stroke Cerebrovasc*. 2018;27(11):2986-2992.

452. Tan A, Yin JDC, Tan LWL, van Dam RM, Cheung YY, Lee CH. Predicting obstructive sleep apnea using the STOP-Bang questionnaire in the general population. *Sleep Med.* 2016;27-28:66-71.
453. Tan A, Yin JSDC, Tan LDWL, van Dam RM, Cheung YY, Lee CH. Using the Berlin Questionnaire to Predict Obstructive Sleep Apnea in the General Population. *Journal of Clinical Sleep Medicine.* 2017;13(3):427-432.
454. Kee K, Dixon J, Shaw J, et al. Comparison of Commonly Used Questionnaires to Identify Obstructive Sleep Apnea in a High-Risk Population. *Journal of Clinical Sleep Medicine.* 2018;14(12):2057-2064.
455. Silva GE, Vana KD, Goodwin JL, Sherrill DL, Quan SF. Identification of patients with sleep disordered breathing: comparing the four-variable screening tool, STOP, STOP-Bang, and Epworth Sleepiness Scales. *J Clin Sleep Med.* 2011;7(5):467-472.
456. Luo JM, Huang R, Zhong X, Xiao Y, Zhou J. STOP-Bang questionnaire is superior to Epworth sleepiness scales, Berlin questionnaire, and STOP questionnaire in screening obstructive sleep apnea hypopnea syndrome patients. *Chinese Med J-Peking.* 2014;127(17):3065-3070.
457. Jonas DE, Amick HR, Feltner C, et al. Screening for Obstructive Sleep Apnea in Adults Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama-J Am Med Assoc.* 2017;317(4):415-433.
458. Carlson LE, Waller A, Mitchell AJ. Screening for Distress and Unmet Needs in Patients With Cancer: Review and Recommendations. *J Clin Oncol.* 2012;30(11):1160-1177.
459. Hobbs FDR, Fitzmaurice DA, Mant J, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Asses.* 2005;9(40):1-+.
460. Valenstein M, Vijan S, Zeber JE, Boehm K, Buttar A. The cost-utility of screening for depression in primary care. *Annals of Internal Medicine.* 2001;134(5):345-360.
461. Lopez PP, Stefan B, Schulman CI, Byers PM. Prevalence of sleep apnea in morbidly obese patients who presented for weight loss surgery evaluation: more evidence for routine screening for obstructive sleep apnea before weight loss surgery. *Am Surg.* 2008;74(9):834-838.
462. O'Keeffe T, Patterson EJ. Evidence supporting routine polysomnography before bariatric surgery. *Obes Surg.* 2004;14(1):23-26.
463. Ramachandran SK, Kheterpal S, Consens F, et al. Derivation and validation of a simple perioperative sleep apnea prediction score. *Anesth Analg.* 2010;110(4):1007-1015.
464. Chan MTV, Chew YW, Seet E, et al. Association of Unrecognized Obstructive Sleep Apnea With Postoperative Cardiovascular Events in Patients Undergoing Major Noncardiac Surgery. *Jama-J Am Med Assoc.* 2019;321(18):1788-1798.
465. Hai F, Porhomayon J, Vermont L, Frydrych L, Jaoude P, El-Solh AA. Postoperative complications in patients with obstructive sleep apnea: a meta-analysis. *J Clin Anesth.* 2014;26(8):591-600.
466. Kaw R, Chung F, Pasupuleti V, Mehta J, Gay PC, Hernandez AV. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. *Br J Anaesth.* 2012;109(6):897-906.
467. Opperer M, Cozowicz C, Bugada D, et al. Does Obstructive Sleep Apnea Influence Perioperative Outcome? A Qualitative Systematic Review for the Society of Anesthesia and Sleep Medicine Task Force on Preoperative Preparation of Patients with Sleep-Disordered Breathing. *Anesth Analg.* 2016;122(5):1321-1334.
468. Chudeau N, Raveau T, Carlier L, et al. The STOP-BANG questionnaire and the risk of perioperative respiratory complications in urgent surgery patients: A prospective, observational study. *Anaesth Crit Care Pain Med.* 2016;35(5):347-353.

469. Chung F, Liao P, Farney R. Correlation between the STOP-Bang Score and the Severity of Obstructive Sleep Apnea. *Anesthesiology*. 2015;122(6):1436-1437.
470. Cote GA, Hovis CE, Hovis RM, et al. A screening instrument for sleep apnea predicts airway maneuvers in patients undergoing advanced endoscopic procedures. *Clin Gastroenterol Hepatol*. 2010;8(8):660-665 e661.
471. Fernandez-Bustamante A, Bartels K, Clavijo C, et al. Preoperatively Screened Obstructive Sleep Apnea Is Associated With Worse Postoperative Outcomes Than Previously Diagnosed Obstructive Sleep Apnea. *Anesth Analg*. 2017;125(2):593-602.
472. Gokay P, Tastan S, Orhan ME. Is there a difference between the STOP-BANG and the Berlin Obstructive Sleep Apnoea Syndrome questionnaires for determining respiratory complications during the perioperative period? *J Clin Nurs*. 2016;25(9-10):1238-1252.
473. Memtsoudis S, Liu SS, Ma Y, et al. Perioperative pulmonary outcomes in patients with sleep apnea after noncardiac surgery. *Anesth Analg*. 2011;112(1):113-121.
474. Pereira H, Xara D, Mendonca J, Santos A, Abelha FJ. Patients with a high risk for obstructive sleep apnea syndrome: postoperative respiratory complications. *Rev Port Pneumol*. 2013;19(4):144-151.
475. Seet E, Chua M, Liaw CM. High STOP-BANG questionnaire scores predict intraoperative and early postoperative adverse events. *Singapore Med J*. 2015;56(4):212-216.
476. Vasu TS, Doghrumji K, Cavallazzi R, et al. Obstructive sleep apnea syndrome and postoperative complications: clinical use of the STOP-BANG questionnaire. *Arch Otolaryngol Head Neck Surg*. 2010;136(10):1020-1024.
477. Fouladpour N, Jesudoss R, Bolden N, Shaman Z, Auckley D. Perioperative Complications in Obstructive Sleep Apnea Patients Undergoing Surgery: A Review of the Legal Literature. *Anesth Analg*. 2016;122(1):145-151.
478. Lee LA, Caplan RA, Stephens LS, et al. Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology*. 2015;122(3):659-665.
479. D'Apuzzo MR, Browne JA. Obstructive sleep apnea as a risk factor for postoperative complications after revision joint arthroplasty. *J Arthroplasty*. 2012;27(8 Suppl):95-98.
480. Lockhart EM, Willingham MD, Abdallah AB, et al. Obstructive sleep apnea screening and postoperative mortality in a large surgical cohort. *Sleep Med*. 2013;14(5):407-415.
481. Lyons PG, Zdravec FJ, Edelson DP, Mokhlesi B, Churpek MM. Obstructive sleep apnea and adverse outcomes in surgical and nonsurgical patients on the wards. *J Hosp Med*. 2015;10(9):592-598.
482. Mokhlesi B, Hovda MD, Vekhter B, Arora VM, Chung F, Meltzer DO. Sleep-disordered breathing and postoperative outcomes after elective surgery: analysis of the nationwide inpatient sample. *Chest*. 2013;144(3):903-914.
483. Mokhlesi B, Hovda MD, Vekhter B, Arora VM, Chung F, Meltzer DO. Sleep-disordered breathing and postoperative outcomes after bariatric surgery: analysis of the nationwide inpatient sample. *Obes Surg*. 2013;23(11):1842-1851.
484. Proczko MA, Stepaniak PS, de Quelerij M, et al. STOP-Bang and the effect on patient outcome and length of hospital stay when patients are not using continuous positive airway pressure. *J Anesth*. 2014;28(6):891-897.
485. Chung F, Memtsoudis SG, Ramachandran SK, et al. Society of Anesthesia and Sleep Medicine Guidelines on Preoperative Screening and Assessment of Adult Patients With Obstructive Sleep Apnea. *Anesth Analg*. 2016;123(2):452-473.
486. Abdelsattar ZM, Hendren S, Wong SL, Campbell DA, Jr., Ramachandran SK. The Impact of Untreated Obstructive Sleep Apnea on Cardiopulmonary Complications in General and Vascular Surgery: A Cohort Study. *Sleep*. 2015;38(8):1205-1210.

487. Sankar A, Dixon PR, Sivanathan L, Memtsoudis SG, de Almeida JR, Singh M. Cost-effectiveness Analysis of Preoperative Screening Strategies for Obstructive Sleep Apnea among Patients Undergoing Elective Inpatient Surgery. *Anesthesiology*. 2020;133(4):787-800.
488. Chung F, Yegneswaran B, Liao P, et al. Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. *Anesthesiology*. 2008;108(5):822-830.
489. Verbraecken J, Hedner J, Penzel T. Pre-operative screening for obstructive sleep apnoea. *Eur Respir Rev*. 2017;26(143).
490. Subramani Y, Wong J, Nagappa M, Chung F. The Benefits of Perioperative Screening for Sleep Apnea in Surgical Patients. *Sleep Med Clin*. 2017;12(1):123-135.
491. Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *Br J Anaesth*. 2012;108(5):768-775.
492. Farney RJ, Walker BS, Farney RM, Snow GL, Walker JM. The STOP-Bang equivalent model and prediction of severity of obstructive sleep apnea: relation to polysomnographic measurements of the apnea/hypopnea index. *J Clin Sleep Med*. 2011;7(5):459-465B.
493. Acar HV, Yarkan Uysal H, Kaya A, Ceyhan A, Dikmen B. Does the STOP-Bang, an obstructive sleep apnea screening tool, predict difficult intubation? *Eur Rev Med Pharmacol Sci*. 2014;18(13):1869-1874.
494. Chia P, Seet E, Macachor JD, Iyer US, Wu D. The association of pre-operative STOP-BANG scores with postoperative critical care admission. *Anaesthesia*. 2013;68(9):950-952.
495. Corso RM, Petrini F, Buccioli M, et al. Clinical utility of preoperative screening with STOP-Bang questionnaire in elective surgery. *Minerva Anestesiol*. 2014;80(8):877-884.
496. Gross JB, Bachenberg KL, Benumof JL, et al. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: a report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology*. 2006;104(5):1081-1093; quiz 1117-1088.
497. Deflandre E, Degey S, Brichant JF, Poirrier R, Bonhomme V. Development and Validation of a Morphologic Obstructive Sleep Apnea Prediction Score: The DES-OSA Score. *Anesth Analg*. 2016;122(2):363-372.
498. Chung F, Liao P, Elsaid H, Islam S, Shapiro CM, Sun YM. Oxygen Desaturation Index from Nocturnal Oximetry: A Sensitive and Specific Tool to Detect Sleep-Disordered Breathing in Surgical Patients. *Anesthesia and Analgesia*. 2012;114(5):993-1000.
499. Khiani VS, Salah W, Maimone S, Cummings L, Chak A. Sedation during endoscopy for patients at risk of obstructive sleep apnea. *Gastrointest Endosc*. 2009;70(6):1116-1120.
500. Mehta PP, Kochhar G, Kalra S, et al. Can a validated sleep apnea scoring system predict cardiopulmonary events using propofol sedation for routine EGD or colonoscopy? A prospective cohort study. *Gastrointest Endosc*. 2014;79(3):436-444.
501. Setaro J, Reinsel R, Brun D. Preoperative Screening for Obstructive Sleep Apnea and Outcomes in PACU. *J Perianesth Nurs*. 2019;34(1):66-73.
502. Lyons PG, Zdravec FJ, Edelson DP, Mokhlesi B, Churpek MM. In response to "Obstructive sleep apnea and adverse outcomes in surgical and nonsurgical patients on the wards". *J Hosp Med*. 2016;11(2):157.
503. Lechner M, Breeze CE, Ohayon MM, Kotecha B. Snoring and breathing pauses during sleep: interview survey of a United Kingdom population sample reveals a significant increase in the rates of sleep apnoea and obesity over the last 20 years - data from the UK sleep survey. *Sleep Med*. 2019;54:250-256.
504. Ustun B, Westover MB, Rudin C, Bianchi MT. Clinical Prediction Models for Sleep Apnea: The Importance of Medical History over Symptoms. *J Clin Sleep Med*. 2016;12(2):161-168.

505. Johnson DA, Sofer T, Guo N, Wilson J, Redline S. A Sleep Apnea Prediction Model Developed for African Americans, the Jackson Heart Sleep Study. *J Clin Sleep Med*. 2020.
506. Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnea?: The Rational Clinical Examination systematic review. *Jama*. 2013;310(7):731-741.
507. van der Spuy I, Zhao G, Karunanayake C, Pahwa P. Predictors of Sleep Apnea in the Canadian Population. *Can Respir J*. 2018;2018:6349790.
508. Senthilvel E, Auckley D, Dasarathy J. Evaluation of sleep disorders in the primary care setting: history taking compared to questionnaires. *J Clin Sleep Med*. 2011;7(1):41-48.
509. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. *Chest*. 1993;103(1):30-36.
510. Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. *Sleep*. 2005;28(3):309-314.
511. Li N, Wang J, Wang D, et al. Correlation of sleep microstructure with daytime sleepiness and cognitive function in young and middle-aged adults with obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2019;276(12):3525-3532.
512. Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5(3):263-276.
513. Van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardization of terminology in nocturia: report from the standardization subcommittee of the International Continence Society. *BJU Int*. 2002;90 Suppl 3:11-15.
514. Middelkoop HA, Smilde-van den Doel DA, Neven AK, Kamphuisen HA, Springer CP. Subjective sleep characteristics of 1,485 males and females aged 50-93: effects of sex and age, and factors related to self-evaluated quality of sleep. *J Gerontol A Biol Sci Med Sci*. 1996;51(3):M108-115.
515. Chung JH, Moon HS, Park SY, Kim KR, Cho SH, Kim YT. Effect of Nocturnal Hypoxia on Nocturia in Patients With Obstructive Sleep Apnea. *Int Neurourol J*. 2019;23(2):161-168.
516. Schatzl G, Temml C, Schmidbauer J, Dolezal B, Haidinger G, Madersbacher S. Cross-sectional study of nocturia in both sexes: analysis of a voluntary health screening project. *Urology*. 2000;56(1):71-75.
517. Zhou J, Xia S, Li T, Liu R. Association between obstructive sleep apnea syndrome and nocturia: a meta-analysis. *Sleep Breath*. 2020.
518. Finamore P, Scarlata S, Laudisio A, et al. Occurrence of nocturia is not mediated by nocturnal hypoxia length and severity in patients with sleep-disordered breathing. *Sleep Med*. 2018;45:69-73.
519. Umlauf MG, Chasens ER. Sleep disordered breathing and nocturnal polyuria: nocturia and enuresis. *Sleep Med Rev*. 2003;7(5):403-411.
520. Umlauf MG, Chasens ER, Greevy RA, Arnold J, Burgio KL, Pillion DJ. Obstructive sleep apnea, nocturia and polyuria in older adults. *Sleep*. 2004;27(1):139-144.
521. Wang T, Huang W, Zong H, Zhang Y. The Efficacy of Continuous Positive Airway Pressure Therapy on Nocturia in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis. *Int Neurourol J*. 2015;19(3):178-184.
522. Norman D, Bardwell WA, Loreda JS, Ancoli-Israel S, Heaton RK, Dimsdale JE. Caffeine intake is independently associated with neuropsychological performance in patients with obstructive sleep apnea. *Sleep Breath*. 2008;12(3):199-205.
523. Aurora RN, Crainiceanu C, Caffo B, Punjabi NM. Sleep-disordered breathing and caffeine consumption: results of a community-based study. *Chest*. 2012;142(3):631-638.
524. Bardwell WA, Ziegler MG, Ancoli-Israel S, et al. Does caffeine confound relationships among adrenergic tone, blood pressure and sleep apnoea? *J Sleep Res*. 2000;9(3):269-272.

525. Robinson GV, Pepperell JC, Davies RJ, Stradling JR. Caffeine levels following treatment of obstructive sleep apnoea. *Thorax*. 2003;58(9):801-802.
526. Shie DY, Tsou YA, Tai CJ, Tsai MH. Impact of obesity on uvulopalatopharyngoplasty success in patients with severe obstructive sleep apnea: a retrospective single-center study in Taiwan. *Acta Otolaryngol*. 2013;133(3):261-269.
527. Ahbab S, Ataoglu HE, Tuna M, et al. Neck circumference, metabolic syndrome and obstructive sleep apnea syndrome; evaluation of possible linkage. *Med Sci Monit*. 2013;19:111-117.
528. Chang ET, Yang MC, Wang HM, Lai HL. Snoring in a sitting position and neck circumference are predictors of sleep apnea in Chinese patients. *Sleep Breath*. 2014;18(1):133-136.
529. Davies RJ, Stradling JR. The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apnoea syndrome. *Eur Respir J*. 1990;3(5):509-514.
530. Mirrakhimov AE, Sooronbaev T, Mirrakhimov EM. Prevalence of obstructive sleep apnea in Asian adults: a systematic review of the literature. *Bmc Pulm Med*. 2013;13:10.
531. Park KM, Shin KJ, Ha SY, et al. Risk factors for obstructive sleep apnea in non-obese Korean patients: Significance of body weight. *Sleep Biol Rhythms*. 2014;12(3):162-168.
532. Stradling JR, Crosby JH. Predictors and Prevalence of Obstructive Sleep-Apnea and Snoring in 1001 Middle-Aged Men. *Thorax*. 1991;46(2):85-90.
533. Yildirim Y, Yilmaz S, Guven M, et al. Evaluation of Anthropometric and Metabolic Parameters in Obstructive Sleep Apnea. *Pulm Med*. 2015;2015:189761.
534. Agha B, Johal A. Facial phenotype in obstructive sleep apnea-hypopnea syndrome: a systematic review and meta-analysis. *J Sleep Res*. 2017;26(2):122-131.
535. Khoo SM, Tan WC, Ng TP, Ho CH. Risk factors associated with habitual snoring and sleep-disordered breathing in a multi-ethnic Asian population: a population-based study. *Respir Med*. 2004;98(6):557-566.
536. Kushida CA, Efron B, Guilleminault C. A predictive morphometric model for the obstructive sleep apnea syndrome. *Ann Intern Med*. 1997;127(8 Pt 1):581-587.
537. Yusoff MF, Baki MM, Mohamed N, et al. Obstructive sleep apnea among express bus drivers in Malaysia: important indicators for screening. *Traffic Inj Prev*. 2010;11(6):594-599.
538. Skomro RP, Kryger MH. Clinical presentations of obstructive sleep apnea syndrome. *Prog Cardiovasc Dis*. 1999;41(5):331-340.
539. Hoffstein V, Szalai JP. Predictive value of clinical features in diagnosing obstructive sleep apnea. *Sleep*. 1993;16(2):118-122.
540. Mihaicuta S, Topirceanu A, Udrescu L. Sas Score: An Innovative Prediction Model For Sleep Apnea Syndrome. *Am J Resp Crit Care*. 2015;191.
541. Santos RB, Silva WA, Parise BK, et al. Accuracy of global and/or regional anthropometric measurements of adiposity in screening sleep apnea: the ELSA-Brasil cohort. *Sleep Med*. 2019;63:115-121.
542. Fung E, Hong P, Moore C, Taylor SM. The effectiveness of modified cottle maneuver in predicting outcomes in functional rhinoplasty. *Plast Surg Int*. 2014;2014:618313.
543. Sugiura T, Noda A, Nakata S, Yasuda Y. Influence of nasal resistance on initial acceptance of continuous positive airway pressure in treatment for obstructive sleep apnea syndrome. *Respiration*. 2007;74(1):56-60.
544. Ishii L, Roxbury C, Godoy A, Ishman S, Ishii M. Does nasal surgery improve OSA in patients with nasal obstruction and OSA? A meta-analysis. *Otolaryng Head Neck*. 2015;153(3):478-478.
545. Brodsky L, Moore L, Stanievich JF. A comparison of tonsillar size and oropharyngeal dimensions in children with obstructive adenotonsillar hypertrophy. *Int J Pediatr Otorhinolaryngol*. 1987;13(2):149-156.

546. Friedman M, Hamilton C, Samuelson CG, Lundgren ME, Pott T. Diagnostic value of the Friedman tongue position and Mallampati classification for obstructive sleep apnea: a meta-analysis. *Otolaryngol Head Neck Surg.* 2013;148(4):540-547.
547. Yu JL, Rosen I. Utility of the modified Mallampati grade and Friedman tongue position in the assessment of obstructive sleep apnea. *J Clin Sleep Med.* 2020;16(2):303-308.
548. Bins S, Koster TD, de Heij AH, et al. No evidence for diagnostic value of Mallampati score in patients suspected of having obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2011;145(2):199-203.
549. Amra B, Pirpiran M, Soltaninejad F, Penzel T, Fietze I, Schoebel C. The prediction of obstructive sleep apnea severity based on anthropometric and Mallampati indices. *J Res Med Sci.* 2019;24:66.
550. Ruangsri S, Jorns TP, Puasiri S, Luecha T, Chaithap C, Sawanyawisuth K. Which oropharyngeal factors are significant risk factors for obstructive sleep apnea? An age-matched study and dentist perspectives. *Nat Sci Sleep.* 2016;8:215-219.
551. Lin HC, Lai CC, Lin PW, et al. Clinical Prediction Model for Obstructive Sleep Apnea among Adult Patients with Habitual Snoring. *Otolaryngol Head Neck Surg.* 2019;161(1):178-185.
552. Subramanian S, Hesselbacher SE, Aguilar R, Surani SR. The NAMES assessment: a novel combined-modality screening tool for obstructive sleep apnea. *Sleep Breath.* 2011;15(4):819-826.
553. Sundman J, Fehrm J, Friberg D. Low inter-examiner agreement of the Friedman staging system indicating limited value in patient selection. *Eur Arch Otorhinolaryngol.* 2018;275(6):1541-1545.
554. Banhiran W, Junlapan A, Assanasen P, Chongkolwatana C. Physical predictors for moderate to severe obstructive sleep apnea in snoring patients. *Sleep Breath.* 2014;18(1):151-158.
555. Friedman M, Yalamanchali S, Gorelick G, Joseph NJ, Hwang MS. A Standardized Lingual Tonsil Grading System: Interexaminer Agreement. *Otolaryng Head Neck.* 2015;152(4):667-672.
556. Tang JA, Friedman M. Incidence of Lingual Tonsil Hypertrophy in Adults with and without Obstructive Sleep Apnea. *Otolaryng Head Neck.* 2018;158(2):391-394.
557. Torre C, Zaghi S, Camacho M, Capasso R, Liu SY. Hypopharyngeal evaluation in obstructive sleep apnea with awake flexible laryngoscopy: Validation and updates to Cormack-Lehane and Modified Cormack-Lehane scoring systems. *Clin Otolaryngol.* 2018;43(3):823-827.
558. Riley R, Guilleminault C, Herran J, Powell N. Cephalometric analyses and flow-volume loops in obstructive sleep apnea patients. *Sleep.* 1983;6(4):303-311.
559. Armalaite J, Lopatiene K. Lateral teloradiography of the head as a diagnostic tool used to predict obstructive sleep apnea. *Dentomaxillofac Rad.* 2016;45(1).
560. Ramachandran SK, Josephs LA. A Meta-analysis of Clinical Screening Tests for Obstructive Sleep Apnea. *Anesthesiology.* 2009;110(4):928-939.
561. Guijarro-Martinez R, Swennen GR. Cone-beam computerized tomography imaging and analysis of the upper airway: a systematic review of the literature. *Int J Oral Maxillofac Surg.* 2011;40(11):1227-1237.
562. Hsu WE, Wu TY. Comparison of upper airway measurement by lateral cephalogram in upright position and CBCT in supine position. *J Dent Sci.* 2019;14(2):185-191.
563. Chen H, Aarab G, de Ruyter MH, de Lange J, Lobbezoo F, van der Stelt PF. Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review. *Sleep Med.* 2016;21:19-27.
564. Liu SY, Huon LK, Lo MT, et al. Static craniofacial measurements and dynamic airway collapse patterns associated with severe obstructive sleep apnoea: a sleep MRI study. *Clin Otolaryngol.* 2016;41(6):700-706.



565. Singh M, Tuteja A, Wong DT, et al. Point-of-Care Ultrasound for Obstructive Sleep Apnea Screening: Are We There Yet? A Systematic Review and Meta-analysis. *Anesthesia and Analgesia*. 2019;129(6):1673-1691.
566. Barrera JE, Pau CY, Forest VI, Holbrook AB, Popelka GR. Anatomic measures of upper airway structures in obstructive sleep apnea. *World J Otorhinolaryngol Head Neck Surg*. 2017;3(2):85-91.
567. Jafari B, Mohsenin V. Polysomnography. *Clinics in Chest Medicine*. 2010;31(2):287-+.
568. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The New Sleep Scoring Manual-The Evidence Behind The Rules. *Journal of Clinical Sleep Medicine*. 2007;3(2):107-107.
569. Corral-Penafiel J, Pepin JL, Barbe F. Ambulatory monitoring in the diagnosis and management of obstructive sleep apnoea syndrome. *European Respiratory Review*. 2013;22(129):312-324.
570. Claman D, Sunwoo B. Improving Accuracy of Home Sleep Apnea Testing. *Journal of Clinical Sleep Medicine*. 2017;13(1):9-10.
571. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2017;13(3):479-504.
572. Collop NA, Tracy SL, Kapur V, et al. Obstructive Sleep Apnea Devices for Out-Of-Center (OOC) Testing: Technology Evaluation. *Journal of Clinical Sleep Medicine*. 2011;7(5):531-548.
573. Pang KP, Gourin CG, Terris DJ. A comparison of polysomnography and the WatchPAT in the diagnosis of obstructive sleep apnea. *Otolaryng Head Neck*. 2007;137(4):665-668.
574. Ayas NT, Pittman S, MacDonald M, White DP. Assessment of a wrist-worn device in the detection of obstructive sleep apnea. *Sleep Med*. 2003;4(5):435-442.
575. Bar A, Pillar G, Dvir I, Sheffy J, Schnall RP, Lavie P. Evaluation of a portable device based on peripheral arterial tone for unattended home sleep studies. *Chest*. 2003;123(3):695-703.
576. O'Donnell CP, Allan L, Atkinson P, Schwartz AR. The effect of upper airway obstruction and arousal on peripheral arterial tonometry, in obstructive sleep apnea. *Am J Resp Crit Care*. 2002;166(7):965-971.
577. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep*. 2005;28(4):499-521.
578. Collop NA, Anderson WM, Boehlecke B, et al. Clinical Guidelines for the Use of Unattended Portable Monitors in the Diagnosis of Obstructive Sleep Apnea in Adult Patients. *Journal of Clinical Sleep Medicine*. 2007;3(7):737-+.
579. Masa JF, Corral J, Pereira R, et al. Effectiveness of home respiratory polygraphy for the diagnosis of sleep apnoea and hypopnoea syndrome. *Thorax*. 2011;66(7):567-573.
580. Garg N, Rolle AJ, Lee TA, Prasad B. Home-based Diagnosis of Obstructive Sleep Apnea in an Urban Population. *Journal of Clinical Sleep Medicine*. 2014;10(8):879-885.
581. Setty AR. Underestimation of Sleep Apnea With Home Sleep Apnea Testing Compared to In-Laboratory Sleep Testing. *Journal of Clinical Sleep Medicine*. 2017;13(4):531-532.
582. El Shayeb M, Topfer LA, Stafinski T, Pawluk L, Menon D. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: a systematic review and meta-analysis. *Can Med Assoc J*. 2014;186(1):E25-E51.
583. Abraham WT, Trupp RJ, Phillilps B, et al. Validation and clinical utility of a simple in-home testing tool for sleep-disordered breathing and arrhythmias in heart failure: results of the Sleep Events, Arrhythmias, and Respiratory Analysis in Congestive Heart Failure (SEARCH) study. *Congest Heart Fail*. 2006;12(5):241-247; quiz 248-249.
584. Abrahamyan L, Sahakyan Y, Chung S, et al. Diagnostic accuracy of level IV portable sleep monitors versus polysomnography for obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Breath*. 2018;22(3):593-611.

585. Kotzian ST, Schwarzing A, Haider S, Saletu B, Spatt J, Saletu MT. Home polygraphic recording with telemedicine monitoring for diagnosis and treatment of sleep apnoea in stroke (HOPES Study): study protocol for a single-blind, randomised controlled trial. *BMJ Open*. 2018;8(1):e018847.
586. Saletu MT, Kotzian ST, Schwarzing A, Haider S, Spatt J, Saletu B. Home Sleep Apnea Testing is a Feasible and Accurate Method to Diagnose Obstructive Sleep Apnea in Stroke Patients During In-Hospital Rehabilitation. *Journal of Clinical Sleep Medicine*. 2018;14(9):1495-1501.
587. Luyster FS, Buysse DJ, Strollo PJ, Jr. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *J Clin Sleep Med*. 2010;6(2):196-204.
588. Masa JF, Corral J, Pereira R, et al. Effectiveness of sequential automatic-manual home respiratory polygraphy scoring. *Eur Respir J*. 2013;41(4):879-887.
589. Corral J, Sanchez-Quiroga MA, Carmona-Bernal C, et al. Conventional Polysomnography Is Not Necessary for the Management of Most Patients with Suspected Obstructive Sleep Apnea. Noninferiority, Randomized Controlled Trial. *Am J Respir Crit Care Med*. 2017;196(9):1181-1190.
590. Douglas JA, Chai-Coetzer CL, McEvoy D, et al. Guidelines for sleep studies in adults - a position statement of the Australasian Sleep Association. *Sleep Med*. 2017;36:S2-S22.
591. Rosen CL, Auckley D, Benca R, et al. A Multisite Randomized Trial of Portable Sleep Studies and Positive Airway Pressure Autotitration Versus Laboratory-Based Polysomnography for the Diagnosis and Treatment of Obstructive Sleep Apnea: The HomePAP Study. *Sleep*. 2012;35(6):757-767.
592. Almeida G, Duran-Cantolla J, Guevara JC, et al. Automated analysis for the diagnosis of sleep apnoeas in patients with suspected disease. Validity of a new respiratory polygraphy system. *Eur Respir J*. 2019;54.
593. Flemons WW, Littner MR, Rowley JA, et al. Home diagnosis of sleep apnea: A systematic review of the literature - An evidence review cosponsored by the American academy of sleep medicine, the American College of Chest Physicians, and the American Thoracic Society. *Chest*. 2003;124(4):1543-1579.
594. Chesson AL, Ferber RA, Fry JM, et al. The indications for polysomnography and related procedures. *Sleep*. 1997;20(6):423-487.
595. Garcia-Diaz E, Quintana-Gallego E, Ruiz A, et al. Respiratory polygraphy with actigraphy in the diagnosis of sleep apnea-hypopnea syndrome. *Chest*. 2007;131(3):725-732.
596. Ayappa I, Norman RG, Seelall V, Rapoport DM. Validation of a Self-Applied Unattended Monitor for Sleep Disordered Breathing. *Journal of Clinical Sleep Medicine*. 2008;4(1):26-37.
597. Skomro RP, Cjevre J, Reid J, et al. Outcomes of Home-Based Diagnosis and Treatment of Obstructive Sleep Apnea. *Chest*. 2010;138(2):257-263.
598. Bravata DM, McClain V, Austin C, et al. Diagnosing and managing sleep apnea in patients with chronic cerebrovascular disease: a randomized trial of a home-based strategy. *Sleep Breath*. 2017;21(3):713-725.
599. Fitzpatrick M, Rac VE, Mitsakakis N, et al. SIESTA - Home sleep study with BresoDx for obstructive sleep apnea: a randomized controlled trial. *Sleep Med*. 2020;65:45-53.
600. Hui DS, Ng SS, To KW, et al. A randomized controlled trial of an ambulatory approach versus the hospital-based approach in managing suspected obstructive sleep apnea syndrome. *Scientific Reports*. 2017;7.
601. Mulgrew AT, Fox N, Ayas NT, Ryan CF. Diagnosis and initial management of obstructive sleep apnea without polysomnography - A randomized validation study. *Annals of Internal Medicine*. 2007;146(3):157-166.

602. Guerrero A, Embid C, Isetta V, et al. Management of Sleep Apnea without High Pretest Probability or with Comorbidities by Three Nights of Portable Sleep Monitoring. *Sleep*. 2014;37(8):1363-1373.
603. Ferber R, Millman R, Coppola M, et al. Portable Recording in the Assessment of Obstructive Sleep-Apnea. *Sleep*. 1994;17(4):378-392.
604. Morales CR, Hurley S, Wick LC, et al. In-Home, Self-Assembled Sleep Studies Are Useful in Diagnosing Sleep Apnea in the Elderly. *Sleep*. 2012;35(11):1491-1501.
605. Pietzsch JB, Garner A, Cipriano LE, Linehan JH. An Integrated Health-Economic Analysis of Diagnostic and Therapeutic Strategies in the Treatment of Moderate-to-Severe Obstructive Sleep Apnea. *Sleep*. 2011;34(6):695-709.
606. Araujo I, Marques F, Andre S, et al. Diagnosis of sleep apnea in patients with stable chronic heart failure using a portable sleep test diagnostic device. *Sleep Breath*. 2018;22(3):749-755.
607. Aurora RN, Patil SP, Punjabi NM. Portable Sleep Monitoring for Diagnosing Sleep Apnea in Hospitalized Patients With Heart Failure. *Chest*. 2018;154(1):91-98.
608. de Vries GE, van der Wal HH, Kerstjens HAM, et al. Validity and Predictive Value of a Portable Two-Channel Sleep-Screening Tool in the Identification of Sleep Apnea in Patients With Heart Failure. *Journal of Cardiac Failure*. 2015;21(10):848-855.
609. Savage HO, Khushaba RN, Zaffaroni A, et al. Development and validation of a novel non-contact monitor of nocturnal respiration for identifying sleep-disordered breathing in patients with heart failure. *ESC Heart Fail*. 2016;3(3):212-219.
610. Chang Y, Xu LY, Han F, et al. Validation of the Nox-T3 Portable Monitor for Diagnosis of Obstructive Sleep Apnea in Patients With Chronic Obstructive Pulmonary Disease. *Journal of Clinical Sleep Medicine*. 2019;15(4):587-596.
611. Jen R, Orr JE, Li Y, et al. Accuracy of WatchPAT for the Diagnosis of Obstructive Sleep Apnea in Patients with Chronic Obstructive Pulmonary Disease. *Copd*. 2020;17(1):34-39.
612. Johnson KG, Johnson DC. Frequency of Sleep Apnea in Stroke and TIA Patients: A Meta-analysis. *Journal of Clinical Sleep Medicine*. 2010;6(2):131-137.
613. Chernyshev OY, McCarty DE, Moul DE, et al. A pilot study: portable out-of-center sleep testing as an early sleep apnea screening tool in acute ischemic stroke. *Nat Sci Sleep*. 2015;7:127-138.
614. Zeidler MR, Santiago V, Dzierzewski JM, Mitchell MN, Santiago S, Martin JL. Predictors of Obstructive Sleep Apnea on Polysomnography after a Technically Inadequate or Normal Home Sleep Test. *Journal of Clinical Sleep Medicine*. 2015;11(11):1313-1318.
615. Pataka A, Kalamaras G, Vlachogianni E, Argyropoulou P. Combination of oximetry and sleep questionnaires as screening tools for CPAP initiation in patients with obstructive sleep apnea. *Pulmonology*. 2019;25(3):137-142.
616. Christensson E, Franklin KA, Sahlin C, et al. Can STOP-Bang and Pulse Oximetry Detect and Exclude Obstructive Sleep Apnea? *Anesthesia and Analgesia*. 2018;127(3):736-743.
617. Hang LW, Wang HL, Chen JH, et al. Validation of overnight oximetry to diagnose patients with moderate to severe obstructive sleep apnea. *Bmc Pulm Med*. 2015;15.
618. Sharma S, Mather PJ, Chowdhury A, et al. Sleep Overnight Monitoring for Apnea in Patients Hospitalized with Heart Failure (SOMA-HF Study). *Journal of Clinical Sleep Medicine*. 2017;13(10):1185-1190.
619. del Campo F, Hornero R, Zamarron C, Abasolo DE, Alvarez D. Oxygen saturation regularity analysis in the diagnosis of obstructive sleep apnea. *Artif Intell Med*. 2006;37(2):111-118.
620. Erdenebayar U, Park JU, Jeong P, Lee KJ. Obstructive Sleep Apnea Screening Using a Piezo-Electric Sensor. *J Korean Med Sci*. 2017;32(6):893-899.
621. Alakuijala A, Salmi T. Predicting Obstructive Sleep Apnea with Periodic Snoring Sound Recorded at Home. *Journal of Clinical Sleep Medicine*. 2016;12(7):953-958.

622. Ward NR, Cowie MR, Rosen SD, et al. Utility of overnight pulse oximetry and heart rate variability analysis to screen for sleep-disordered breathing in chronic heart failure. *Thorax*. 2012;67(11):1000-1005.
623. Sharma S, Mather P, Efirid JT, et al. Photoplethysmographic Signal to Screen Sleep-Disordered Breathing in Hospitalized Heart Failure Patients Feasibility of a Prospective Clinical Pathway. *Jacc-Heart Fail*. 2015;3(9):725-731.
624. Andres-Blanco AM, Alvarez D, Crespo A, et al. Assessment of automated analysis of portable oximetry as a screening test for moderate-to-severe sleep apnea in patients with chronic obstructive pulmonary disease. *PLoS one*. 2017;12(11).
625. Lajoie AC, Series F, Bernard S, et al. Reliability of Home Nocturnal Oximetry in the Diagnosis of Overlap Syndrome in COPD. *Respiration*. 2020;99(2):132-139.
626. Scott AS, Baltzan MA, Wolkove N. Examination of pulse oximetry tracings to detect obstructive sleep apnea in patients with advanced chronic obstructive pulmonary disease. *Canadian Respiratory Journal*. 2014;21(3):171-175.
627. Aaronson JA, van Bezeij T, van den Aardweg JG, van Bennekom CA, Hofman WF. Diagnostic accuracy of nocturnal oximetry for detection of sleep apnea syndrome in stroke rehabilitation. *Stroke*. 2012;43(9):2491-2493.
628. Lin SH, Branson C, Park L, Leung J, Doshi N, Auerbach SH. Oximetry as an Accurate Tool for Identifying Moderate to Severe Sleep Apnea in Patients With Acute Stroke. *Journal of Clinical Sleep Medicine*. 2018;14(12):2065-2073.
629. Ryan CM, Wilton K, Bradley TD, Alshaer H. In-hospital diagnosis of sleep apnea in stroke patients using a portable acoustic device. *Sleep Breath*. 2017;21(2):453-460.
630. Aarrestad S, Qvarfort M, Kleiven AL, Tollefsen E, Skjonsberg OH, Janssens JP. Diagnostic accuracy of simple tools in monitoring patients with chronic hypoventilation treated with non-invasive ventilation; a prospective cross-sectional study. *Resp Med*. 2018;144:30-35.
631. Bauters F, Rietzschel ER, Hertegonne KBC, Chirinos JA. The Link Between Obstructive Sleep Apnea and Cardiovascular Disease. *Curr Atheroscler Rep*. 2016;18(1).
632. Ge X, Han F, Huang Y, Zhang Y, Yang T. Is Obstructive Sleep Apnea Associated with Cardiovascular and All-Cause Mortality? (vol 8, e69432, 2013). *PLoS one*. 2014;9(4).
633. Javaheri S, Blackwell T, Ancoli-Israel S, et al. Sleep-disordered Breathing and Incident Heart Failure in Older Men. *Am J Respir Crit Care Med*. 2016;193(5):561-568.
634. Wang X, Zhang Y, Dong Z, Fan J, Nie S, Wei Y. Effect of continuous positive airway pressure on long-term cardiovascular outcomes in patients with coronary artery disease and obstructive sleep apnea: a systematic review and meta-analysis. *Respir Res*. 2018;19(1):61.
635. Drager LF, Polotsky VY, O'Donnell CP, Cravo SL, Lorenzi G, Machado BH. Translational approaches to understanding metabolic dysfunction and cardiovascular consequences of obstructive sleep apnea. *Am J Physiol-Heart C*. 2015;309(7):H1101-H1111.
636. Rosen D, Roux FJ, Shah N. Sleep and breathing in congestive heart failure. *Clin Chest Med*. 2014;35(3):521-534.
637. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2001;163(1):19-25.
638. Fu YQ, Xia YY, Yi HL, Xu HJ, Guan J, Yin SK. Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment. *Sleep Breath*. 2017;21(1):181-189.
639. Labarca G, Dreyse J, Salas C, Letelier F, Jorquera J. A Validation Study of Four Different Cluster Analyses of OSA and the Incidence of Cardiovascular Mortality in a Hispanic Population. *Chest*. 2021;160(6):2266-2274.

640. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective Study of Obstructive Sleep Apnea and Incident Coronary Heart Disease and Heart Failure The Sleep Heart Health Study. *Circulation*. 2010;122(4):352-360.
641. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med*. 2009;6(8):e1000132.
642. Bouzerda A. [Cardiovascular risk and obstructive sleep apnea]. *Pan Afr Med J*. 2018;29:47.
643. Nakashima H, Kurobe M, Minami K, et al. Effects of moderate-to-severe obstructive sleep apnea on the clinical manifestations of plaque vulnerability and the progression of coronary atherosclerosis in patients with acute coronary syndrome. *Eur Heart J-Acute Ca*. 2015;4(1):75-84.
644. Hla KM, Young T, Hagen EW, et al. Coronary heart disease incidence in sleep disordered breathing: the Wisconsin Sleep Cohort Study. *Sleep*. 2015;38(5):677-684.
645. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM. Cardiovascular Mortality in Women With Obstructive Sleep Apnea With or Without Continuous Positive Airway Pressure Treatment A Cohort Study. *Annals of Internal Medicine*. 2012;156(2):115-W122.
646. Catalan-Serra P, Campos-Rodriguez F, Reyes-Nunez N, et al. Increased Incidence of Stroke, but Not Coronary Heart Disease, in Elderly Patients With Sleep Apnea. *Stroke*. 2019;50(2):491-494.
647. Gonzaga C, Bertolami A, Bertolami M, Amodeo C, Calhoun D. Obstructive sleep apnea, hypertension and cardiovascular diseases. *J Hum Hypertens*. 2015;29(12):705-712.
648. Kasai T, Bradley TD. Obstructive sleep apnea and heart failure: pathophysiologic and therapeutic implications. *J Am Coll Cardiol*. 2011;57(2):119-127.
649. Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2012;5(5):720-728.
650. Martinez-Garcia MA, Campos-Rodriguez F, Catalan-Serra P, et al. Cardiovascular Mortality in Obstructive Sleep Apnea in the Elderly: Role of Long-Term Continuous Positive Airway Pressure Treatment A Prospective Observational Study. *Am J Resp Crit Care*. 2012;186(9):909-916.
651. Shah NA, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep Breath*. 2010;14(2):131-136.
652. Yeboah J, Redline S, Johnson C, et al. Association between sleep apnea, snoring, incident cardiovascular events and all-cause mortality in an adult population: MESA. *Atherosclerosis*. 2011;219(2):963-968.
653. Yu J, Zhou Z, McEvoy RD, et al. Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea: A Systematic Review and Meta-analysis. *Jama*. 2017;318(2):156-166.
654. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive Sleep Apnea as a Risk Factor for Type 2 Diabetes. *Am J Med*. 2009;122(12):1122-1127.
655. Iftikhar IH, Hoyos CM, Phillips CL, Magalang UJ. Meta-analyses of the Association of Sleep Apnea with Insulin Resistance, and the Effects of CPAP on HOMA-IR, Adiponectin, and Visceral Adipose Fat. *Journal of Clinical Sleep Medicine*. 2015;11(4):475-U482.
656. Ip MSM, Lam B, Ng MMT, Lam WK, Tsang KWT, Lam KSL. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Resp Crit Care*. 2002;165(5):670-676.
657. Milleron O, Pilliere R, Foucher A, et al. Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. *Eur Heart J*. 2004;25(9):728-734.
658. Patt BT, Jarjoura D, Haddad DN, et al. Endothelial Dysfunction in the Microcirculation of Patients with Obstructive Sleep Apnea. *Am J Resp Crit Care*. 2010;182(12):1540-1545.

659. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342(19):1378-1384.
660. Phillips CL, McEwen BJ, Morel-Kopp MC, et al. Effects of continuous positive airway pressure on coagulability in obstructive sleep apnoea: a randomised, placebo-controlled crossover study. *Thorax*. 2012;67(7):639-644.
661. Phillips SA, Olson EB, Morgan BJ, Lombard JH. Chronic intermittent hypoxia impairs endothelium-dependent dilation in rat cerebral and skeletal muscle resistance arteries. *Am J Physiol-Heart C*. 2004;286(1):H388-H393.
662. Schwarz EI, Puhan MA, Schlatzer C, Stradling JR, Kohler M. Effect of CPAP therapy on endothelial function in obstructive sleep apnoea: A systematic review and meta-analysis. *Respirology*. 2015;20(6):889-895.
663. Sorajja D, Gami AS, Somers VK, Behrenbeck TR, Garcia-Touchard A, Lopez-Jimenez F. Independent association between obstructive sleep apnea and subclinical coronary artery disease. *Chest*. 2008;133(4):927-933.
664. Konishi T, Kashiwagi Y, Funayama N, et al. Obstructive sleep apnea is associated with increased coronary plaque instability: an optical frequency domain imaging study. *Heart Vessels*. 2019;34(8):1266-1279.
665. Kuniyoshi FHS, Garcia-Touchard A, Gami AS, et al. Day-night variation of acute myocardial infarction in obstructive sleep apnea. *J Am Coll Cardiol*. 2008;52(5):343-346.
666. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic Neural Mechanisms in Obstructive Sleep-Apnea. *Journal of Clinical Investigation*. 1995;96(4):1897-1904.
667. Franklin KA, Nilsson JB, Sahlin C, Naslund U. Sleep-Apnea and Nocturnal Angina. *Lancet*. 1995;345(8957):1085-1087.
668. Moe T, Franklin KA, Wiklund U, Rabben T, Holmstrom K. Sleep-disordered breathing and myocardial ischemia in patients with coronary artery disease. *Chest*. 2000;117(6):1597-1602.
669. Lee CH, Khoo SM, Chan MY, et al. Severe Obstructive Sleep Apnea and Outcomes Following Myocardial Infarction. *Journal of Clinical Sleep Medicine*. 2011;7(6):616-621.
670. Lee CH, Sethi R, Li RG, et al. Obstructive Sleep Apnea and Cardiovascular Events After Percutaneous Coronary Intervention. *Circulation*. 2016;133(21):2008-2017.
671. Qu H, Guo M, Zhang Y, Shi DZ. Obstructive sleep apnea increases the risk of cardiac events after percutaneous coronary intervention: a meta-analysis of prospective cohort studies. *Sleep Breath*. 2018;22(1):33-40.
672. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstrom E. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. *Am J Respir Crit Care Med*. 2016;194(5):613-620.
673. Wu X, Lv S, Yu X, Yao L, Mokhlesi B, Wei Y. Treatment of OSA reduces the risk of repeat revascularization after percutaneous coronary intervention. *Chest*. 2015;147(3):708-718.
674. Xie J, Kuniyoshi FHS, Covassin N, et al. Nocturnal Hypoxemia Due to Obstructive Sleep Apnea Is an Independent Predictor of Poor Prognosis After Myocardial Infarction. *J Am Heart Assoc*. 2016;5(8).
675. Xie J, Kuniyoshi FHS, Covassin N, et al. Excessive Daytime Sleepiness Independently Predicts Increased Cardiovascular Risk After Myocardial Infarction. *J Am Heart Assoc*. 2018;7(2).
676. Yoon SS, Carroll MD, Fryar CD. Hypertension Prevalence and Control Among Adults: United States, 2011-2014. *NCHS Data Brief*. 2015(220):1-8.
677. Drager LF, Genta PR, Pedrosa RP, et al. Characteristics and predictors of obstructive sleep apnea in patients with systemic hypertension. *Am J Cardiol*. 2010;105(8):1135-1139.

678. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension*. 2011;58(5):811-817.
679. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. *J Am Coll Cardiol*. 2017;69(7):841-858.
680. Mansukhani MP, Covassin N, Somers VK. Apneic Sleep, Insufficient Sleep, and Hypertension. *Hypertension*. 2019;73(4):744-756.
681. Min HJ, Cho YJ, Kim CH, et al. Clinical Features of Obstructive Sleep Apnea That Determine Its High Prevalence in Resistant Hypertension. *Yonsei Med J*. 2015;56(5):1258-1265.
682. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *Jama*. 2012;307(20):2169-2176.
683. Xia W, Huang Y, Peng B, et al. Relationship between obstructive sleep apnoea syndrome and essential hypertension: a dose-response meta-analysis. *Sleep Med*. 2018;47:11-18.
684. Acosta-Castro P, Hirotsu C, Marti-Soler H, et al. REM-associated sleep apnoea: prevalence and clinical significance in the HypnoLaus cohort. *Eur Respir J*. 2018;52(2).
685. Kapur VK, Resnick HE, Gottlieb DJ. Sleep disordered breathing and hypertension: does self-reported sleepiness modify the association? *Sleep*. 2008;31(8):1127-1132.
686. Ren R, Li Y, Zhang J, et al. Obstructive Sleep Apnea With Objective Daytime Sleepiness Is Associated With Hypertension. *Hypertension*. 2016;68(5):1264-1270.
687. Wang Q, Zhang C, Jia P, et al. The association between the phenotype of excessive daytime sleepiness and blood pressure in patients with obstructive sleep apnea-hypopnea syndrome. *International journal of medical sciences*. 2014;11(7):713-720.
688. Nabe B, Lies A, Pankow W, Kohl FV, Lohmann FW. Determinants of circadian blood pressure rhythm and blood pressure variability in obstructive sleep apnoea. *J Sleep Res*. 1995;4(S1):97-101.
689. Wolf J, Hering D, Narkiewicz K. Non-dipping pattern of hypertension and obstructive sleep apnea syndrome. *Hypertens Res*. 2010;33(9):867-871.
690. Sasaki N, Ozono R, Yamauchi R, et al. Age-related differences in the mechanism of nondipping among patients with obstructive sleep apnea syndrome. *Clinical and experimental hypertension (New York, NY : 1993)*. 2012;34(4):270-277.
691. Dudenbostel T, Acelajado MC, Pisoni R, Li P, Oparil S, Calhoun DA. Refractory Hypertension: Evidence of Heightened Sympathetic Activity as a Cause of Antihypertensive Treatment Failure. *Hypertension*. 2015;66(1):126-133.
692. Dudenbostel T, Siddiqui M, Oparil S, Calhoun DA. Refractory Hypertension: A Novel Phenotype of Antihypertensive Treatment Failure. *Hypertension*. 2016;67(6):1085-1092.
693. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252.
694. Calhoun DA, Nishizaka MK, Zaman MA, Harding SM. Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea. *Chest*. 2004;125(1):112-117.
695. Martínez-García MA, Navarro-Soriano C, Torres G, et al. Beyond Resistant Hypertension. *Hypertension*. 2018;72(3):618-624.
696. Vongpatanasin W. Resistant hypertension: a review of diagnosis and management. *Jama*. 2014;311(21):2216-2224.
697. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens*. 2001;19(12):2271-2277.

698. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest*. 2007;131(2):453-459.
699. Sapiña-Beltrán E, Torres G, Benitez I, et al. Prevalence, Characteristics, and Association of Obstructive Sleep Apnea with Blood Pressure Control in Patients with Resistant Hypertension. *Ann Am Thorac Soc*. 2019;16(11):1414-1421.
700. Walia HK, Li H, Rueschman M, et al. Association of severe obstructive sleep apnea and elevated blood pressure despite antihypertensive medication use. *J Clin Sleep Med*. 2014;10(8):835-843.
701. Johnson DA, Thomas SJ, Abdalla M, et al. Association Between Sleep Apnea and Blood Pressure Control Among Blacks: Jackson Heart Sleep Study. *Circulation*. 2018.
702. Walia HK, Griffith SD, Foldvary-Schaefer N, et al. Longitudinal Effect of CPAP on BP in Resistant and Nonresistant Hypertension in a Large Clinic-Based Cohort. *Chest*. 2016;149(3):747-755.
703. Abumumar AM, Dorian P, Newman D, Shapiro CM. The prevalence of obstructive sleep apnea in patients with atrial fibrillation. *Clin Cardiol*. 2018;41(5):601-607.
704. Bazan V, Grau N, Valles E, et al. Obstructive Sleep Apnea in Patients With Typical Atrial Flutter Prevalence and Impact on Arrhythmia Control Outcome. *Chest*. 2013;143(5):1277-1283.
705. Bitter T, Langer C, Vogt J, Lange M, Horstkotte D, Oldenburg O. Sleep-disordered Breathing in Patients With Atrial Fibrillation and Normal Systolic Left Ventricular Function. *Dtsch Arztebl Int*. 2009;106(10):164-170.
706. Braga B, Poyares D, Cintra F, et al. Sleep-disordered breathing and chronic atrial fibrillation. *Sleep Med*. 2009;10(2):212-216.
707. Naruse Y, Tada H, Satoh M, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: Clinical impact of continuous positive airway pressure therapy. *Heart Rhythm*. 2013;10(3):331-337.
708. Szymanski FM, Filipiak KJ, Platek AE, et al. Presence and severity of obstructive sleep apnea and remote outcomes of atrial fibrillation ablations - a long-term prospective, cross-sectional cohort study. *Sleep Breath*. 2015;19(3):849-856.
709. Traaen GM, Overland B, Aakeroy L, et al. Prevalence, risk factors, and type of sleep apnea in patients with paroxysmal atrial fibrillation. *Ijc Heart Vasc*. 2020;26.
710. Bitter T, Nolker G, Vogt J, Prinz C, Horstkotte D, Oldenburg O. Predictors of Recurrence in Patients Undergoing Cryoballoon Ablation for Treatment of Atrial Fibrillation: The Independent Role of Sleep-Disordered Breathing. *J Cardiovasc Electr*. 2012;23(1):18-25.
711. Hojo R, Fukamizu S, Miyazawa S, Kawamura I, Sakurada H, Hiraoka M. The relationship between obstructive sleep apnea and recurrence of atrial fibrillation after pulmonary vein isolation using a contact force-sensing catheter. *J Interv Card Electr*. 2019;54(3):209-215.
712. Kawakami H, Nagai T, Fujii A, et al. Apnea-hypopnea index as a predictor of atrial fibrillation recurrence following initial pulmonary vein isolation: usefulness of type-3 portable monitor for sleep-disordered breathing. *J Interv Card Electr*. 2016;47(2):237-244.
713. Mazza A, Bendini MG, Cristofori M, et al. Baseline apnoea/hypopnoea index and high-sensitivity C-reactive protein for the risk of recurrence of atrial fibrillation after successful electrical cardioversion: a predictive model based upon the multiple effects of significant variables. *Europace*. 2009;11(7):902-909.
714. Stevenson IH, Teichtahl H, Cunnington D, Ciavarella S, Gordon I, Kalman JM. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. *Eur Heart J*. 2008;29(13):1662-1669.
715. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*. 2004;110(4):364-367.



716. Porthan KM, Melin JH, Kupila JT, Venho KKK, Partinen MM. Prevalence of sleep apnea syndrome in lone atrial fibrillation - A case-control study. *Chest*. 2004;125(3):879-885.
717. Kwon Y, Gharib SA, Biggs ML, et al. Association of sleep characteristics with atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Thorax*. 2015;70(9):873-879.
718. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing - The Sleep Heart Health Study. *Am J Resp Crit Care*. 2006;173(8):910-916.
719. Mehra R, Stone KL, Varosy PD, et al. Nocturnal Arrhythmias Across a Spectrum of Obstructive and Central Sleep-Disordered Breathing in Older Men Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study. *Archives of Internal Medicine*. 2009;169(12):1147-1155.
720. Chao TF, Liu CJ, Chen SJ, et al. Incidence and Risk of Atrial Fibrillation in Sleep-Disordered Breathing Without Coexistent Systemic Disease - Nationwide Longitudinal Cohort Study. *Circ J*. 2014;78(9):2182-U2280.
721. Lin GM, Colangelo LA, Lloyd-Jones DM, et al. Association of Sleep Apnea and Snoring With Incident Atrial Fibrillation in the Multi-Ethnic Study of Atherosclerosis. *American Journal of Epidemiology*. 2015;182(1):49-57.
722. Kendzerska T, Gershon AS, Atzema C, et al. Sleep Apnea Increases the Risk of New Hospitalized Atrial Fibrillation A Historical Cohort Study. *Chest*. 2018;154(6):1330-1339.
723. Cadby G, McArdle N, Briffa T, et al. Severity of OSA Is an Independent Predictor of Incident Atrial Fibrillation Hospitalization in a Large Sleep-Clinic Cohort. *Chest*. 2015;148(4):945-952.
724. May AM, Blackwell T, Stone PH, et al. Central Sleep-disordered Breathing Predicts Incident Atrial Fibrillation in Older Men. *Am J Resp Crit Care*. 2016;193(7):783-791.
725. Tung P, Levitzky YS, Wang R, et al. Obstructive and Central Sleep Apnea and the Risk of Incident Atrial Fibrillation in a Community Cohort of Men and Women. *J Am Heart Assoc*. 2017;6(7).
726. Matiello M, Nadal M, Tamborero D, et al. Low efficacy of atrial fibrillation ablation in severe obstructive sleep apnoea patients. *Europace*. 2010;12(8):1084-1089.
727. Jongnarangsin K, Chugh A, Good E, et al. Body mass index, obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation. *J Cardiovasc Electr*. 2008;19(7):668-672.
728. Neilan TG, Farhad H, Dodson JA, et al. Effect of Sleep Apnea and Continuous Positive Airway Pressure on Cardiac Structure and Recurrence of Atrial Fibrillation. *J Am Heart Assoc*. 2013;2(6).
729. Patel D, Mohanty P, Di Biase L, et al. Safety and Efficacy of Pulmonary Vein Antral Isolation in Patients With Obstructive Sleep Apnea The Impact of Continuous Positive Airway Pressure. *Circ-Arrhythmia Elec*. 2010;3(5):445-451.
730. Monahan K, Brewster J, Wang L, et al. Relation of the Severity of Obstructive Sleep Apnea in Response to Anti-Arrhythmic Drugs in Patients With Atrial Fibrillation or Atrial Flutter. *American Journal of Cardiology*. 2012;110(3):369-372.
731. Linz D, McEvoy RD, Cowie MR, et al. Associations of Obstructive Sleep Apnea With Atrial Fibrillation and Continuous Positive Airway Pressure Treatment. *Jama Cardiol*. 2018;3(6):532-540.
732. Monahan K, Storfer-Isser A, Mehra R, et al. Triggering of Nocturnal Arrhythmias by Sleep-Disordered Breathing Events. *J Am Coll Cardiol*. 2009;54(19):1797-1804.
733. Linz D, Brooks AG, Elliott AD, et al. Variability of Sleep Apnea Severity and Risk of Atrial Fibrillation The VARIOSAF Study. *Jacc-Clin Electrophy*. 2019;5(6):692-701.
734. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139(10):e56-e528.
735. Centers for Disease Control and Prevention NCFHS. Underlying Cause of Death, 1999–2017. Accessed January 7, 2019.

736. Brouwers FP, de Boer RA, van der Harst P, et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J*. 2013;34(19):1424-1431.
737. Khattak HK, Hayat F, Pamboukian SV, Hahn HS, Schwartz BP, Stein PK. Obstructive Sleep Apnea in Heart Failure: Review of Prevalence, Treatment with Continuous Positive Airway Pressure, and Prognosis. *Tex Heart Inst J*. 2018;45(3):151-161.
738. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail*. 2007;9(3):251-257.
739. Yumino D, Redolfi S, Ruttanaumpawan P, et al. Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. *Circulation*. 2010;121(14):1598-1605.
740. Khayat R, Jarjoura D, Porter K, et al. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. *Eur Heart J*. 2015;36(23):1463-1469.
741. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol*. 2007;49(15):1625-1631.
742. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med*. 2003;348(13):1233-1241.
743. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. *Thorax*. 2005;60(9):781-785.
744. Egea CJ, Aizpuru F, Pinto JA, et al. Cardiac function after CPAP therapy in patients with chronic heart failure and sleep apnea: a multicenter study. *Sleep Med*. 2008;9(6):660-666.
745. Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. *Am J Respir Crit Care Med*. 2004;169(3):361-366.
746. Sharma S, Fox H, Aguilar F, et al. Auto positive airway pressure therapy reduces pulmonary pressures in adults admitted for acute heart failure with pulmonary hypertension and obstructive sleep apnea. The ASAP-HF Pilot Trial. *Sleep*. 2019;42(7).
747. Arikawa T, Toyoda S, Haruyama A, et al. Impact of Obstructive Sleep Apnoea on Heart Failure with Preserved Ejection Fraction. *Heart Lung Circ*. 2016;25(5):435-441.
748. Wachter R, Luthje L, Klemmstein D, et al. Impact of obstructive sleep apnoea on diastolic function. *Eur Respir J*. 2013;41(2):376-383.
749. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Mediano O, Martinez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. *Circulation*. 2005;112(3):375-383.
750. Servantes DM, Javaheri S, Kravchychyn ACP, et al. Effects of Exercise Training and CPAP in Patients With Heart Failure and OSA: A Preliminary Study. *Chest*. 2018;154(4):808-817.
751. Labarca G, Dreyse J, Drake L, Jorquera J, Barbe F. Efficacy of continuous positive airway pressure (CPAP) in the prevention of cardiovascular events in patients with obstructive sleep apnea: Systematic review and meta-analysis. *Sleep Med Rev*. 2020;52:101312.
752. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017;70(6):776-803.
753. Kasai T, Narui K, Dohi T, et al. Prognosis of patients with heart failure and obstructive sleep apnea treated with continuous positive airway pressure. *Chest*. 2008;133(3):690-696.

754. Lyons OD, Ryan CM. Sleep Apnea and Stroke. *Canadian Journal of Cardiology*. 2015;31(7):918-927.
755. Mohammad Y, Almutlaq A, Al-Ruwaita A, Aldrees A, Alsubaie A, Al-Hussain F. Stroke during sleep and obstructive sleep apnea: there is a link. *Neurol Sci*. 2019;40(5):1001-1005.
756. Wang X, Ouyang YY, Wang Z, Zhao G, Liu LG, Bi YP. Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: A meta-analysis of prospective cohort studies. *Int J Cardiol*. 2013;169(3):207-214.
757. Wu ZS, Chen FH, Yu F, Wang Y, Guo ZD. A meta-analysis of obstructive sleep apnea in patients with cerebrovascular disease. *Sleep Breath*. 2018;22(3):729-742.
758. Mansukhani MP, Bellolio MF, Kolla BP, Enduri S, Somers VK, Stead LG. Worse Outcome after Stroke in Patients with Obstructive Sleep Apnea: An Observational Cohort Study. *J Stroke Cerebrovasc*. 2011;20(5):401-405.
759. Davis AP, Billings ME, Longstreth WT, Jr., Khot SP. Early diagnosis and treatment of obstructive sleep apnea after stroke: Are we neglecting a modifiable stroke risk factor? *Neurol Clin Pract*. 2013;3(3):192-201.
760. Khot SP, Davis AP, Crane DA, et al. Effect of Continuous Positive Airway Pressure on Stroke Rehabilitation: A Pilot Randomized Sham-Controlled Trial. *Journal of Clinical Sleep Medicine*. 2016;12(7):1019-1026.
761. Birbak J, Clark AJ, Hulvej N. The Effect of Sleep Disordered Breathing on the Outcome of Stroke and Transient Ischemic Attack: A Systematic Review. *Journal of Clinical Sleep Medicine*. 2014;10(1):103-108.
762. Culebras A, Anwar S. Sleep Apnea Is a Risk Factor for Stroke and Vascular Dementia. *Curr Neurol Neurosci*. 2018;18(8).
763. Dong RF, Dong ZL, Liu HM, Shi FK, Du JF. Prevalence, Risk Factors, Outcomes, and Treatment of Obstructive Sleep Apnea in Patients with Cerebrovascular Disease: A Systematic Review. *J Stroke Cerebrovasc*. 2018;27(6):1471-1480.
764. Li M, Hou WS, Zhang XW, Tang ZY. Obstructive sleep apnea and risk of stroke: A meta-analysis of prospective studies. *Int J Cardiol*. 2014;172(2):466-469.
765. McDermott M, Brown DL, Chervin RD. Sleep disorders and the risk of stroke. *Expert Rev Neurother*. 2018;18(7):523-531.
766. Seiler A, Camilo M, Korostovtseva L, et al. Prevalence of sleep-disordered breathing after stroke and TIA: A meta-analysis. *Neurology*. 2019;92(7):e648-e654.
767. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J*. 2015;46(4):903-975.
768. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1).
769. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC. Hemodynamics in sleep-induced apnea. Studies during wakefulness and sleep. *Ann Intern Med*. 1976;85(6):714-719.
770. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Martinez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. *Eur Heart J*. 2006;27(9):1106-1113.

771. Imran TF, Ghazipura M, Liu S, et al. Effect of continuous positive airway pressure treatment on pulmonary artery pressure in patients with isolated obstructive sleep apnea: a meta-analysis. *Heart Fail Rev.* 2016;21(5):591-598.
772. Javaheri S, Javaheri S, Javaheri A. Sleep apnea, heart failure, and pulmonary hypertension. *Curr Heart Fail Rep.* 2013;10(4):315-320.
773. Minai OA, Ricaurte B, Kaw R, et al. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am J Cardiol.* 2009;104(9):1300-1306.
774. Minic M, Granton JT, Ryan CM. Sleep disordered breathing in group 1 pulmonary arterial hypertension. *J Clin Sleep Med.* 2014;10(3):277-283.
775. Nagaoka M, Goda A, Takeuchi K, et al. Nocturnal Hypoxemia, But Not Sleep Apnea, Is Associated With a Poor Prognosis in Patients With Pulmonary Arterial Hypertension. *Circ J.* 2018;82(12):3076-3081.
776. Sun X, Luo J, Xiao Y. Continuous positive airway pressure is associated with a decrease in pulmonary artery pressure in patients with obstructive sleep apnoea: a meta-analysis. *Respirology.* 2014;19(5):670-674.
777. Flenley DC. Sleep in Chronic Obstructive Lung-Disease. *Clinics in Chest Medicine.* 1985;6(4):651-661.
778. Donovan LM, Feemster LC, Udriș EM, et al. Poor Outcomes Among Patients With Chronic Obstructive Pulmonary Disease With Higher Risk for Undiagnosed Obstructive Sleep Apnea in the LOTT Cohort. *Journal of Clinical Sleep Medicine.* 2019;15(1):71-77.
779. Du W, Liu J, Zhou J, Ye D, OuYang Y, Deng Q. Obstructive sleep apnea, COPD, the overlap syndrome, and mortality: results from the 2005-2008 National Health and Nutrition Examination Survey. *Int J Chron Obstruct Pulmon Dis.* 2018;13:665-674.
780. Sanders MH, Newman AB, Haggerty CL, et al. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. *Am J Resp Crit Care.* 2003;167(1):7-14.
781. Starr P, Agarwal A, Singh G, et al. Obstructive Sleep Apnea with Chronic Obstructive Pulmonary Disease among Medicare Beneficiaries. *Ann Am Thorac Soc.* 2019;16(1):153-156.
782. Shawon MSR, Perret JL, Senaratna CV, Lodge C, Hamilton GS, Dharmage SC. Current evidence on prevalence and clinical outcomes of co-morbid obstructive sleep apnea and chronic obstructive pulmonary disease: A systematic review. *Sleep Medicine Reviews.* 2017;32:58-68.
783. Tuomilehto H, Seppa J, Uusitupa M. Obesity and obstructive sleep apnea--clinical significance of weight loss. *Sleep Med Rev.* 2013;17(5):321-329.
784. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. *Arch Intern Med.* 2005;165(20):2408-2413.
785. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med.* 2004;141(11):846-850.
786. Phillips BG, Hisel TM, Kato M, et al. Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *J Hypertens.* 1999;17(9):1297-1300.
787. Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol.* 2000;279(1):H234-237.
788. Chin K, Shimizu K, Nakamura T, et al. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation.* 1999;100(7):706-712.
789. Collen J, Lettieri CJ, Eliasson A. Postoperative CPAP use impacts long-term weight loss following bariatric surgery. *J Clin Sleep Med.* 2015;11(3):213-217.

790. Basoglu OK, Zou D, Tasbakan MS, et al. Change in weight and central obesity by positive airway pressure treatment in obstructive sleep apnea patients: longitudinal data from the ESADA cohort. *J Sleep Res.* 2018;27(6):e12705.
791. Garcia JM, Sharafkhaneh H, Hirshkowitz M, Elkhatib R, Sharafkhaneh A. Weight and metabolic effects of CPAP in obstructive sleep apnea patients with obesity. *Respir Res.* 2011;12(1):80.
792. Myllyla M, Kurki S, Anttalainen U, Saaresranta T, Laitinen T. High Adherence to CPAP Treatment Does Not Prevent the Continuation of Weight Gain among Severely Obese OSAS Patients. *J Clin Sleep Med.* 2016;12(4):519-528.
793. Redenius R, Murphy C, O'Neill E, Al-Hamwi M, Zallek SN. Does CPAP lead to change in BMI? *J Clin Sleep Med.* 2008;4(3):205-209.
794. Tachikawa R, Ikeda K, Minami T, et al. Changes in Energy Metabolism after Continuous Positive Airway Pressure for Obstructive Sleep Apnea. *Am J Respir Crit Care Med.* 2016;194(6):729-738.
795. Stenlof K, Grunstein R, Hedner J, Sjostrom L. Energy expenditure in obstructive sleep apnea: effects of treatment with continuous positive airway pressure. *Am J Physiol.* 1996;271(6 Pt 1):E1036-1043.
796. Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Bensenor IM, Lotufo PA. Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax.* 2015;70(3):258-264.
797. West SD, Kohler M, Nicoll DJ, Stradling JR. The effect of continuous positive airway pressure treatment on physical activity in patients with obstructive sleep apnoea: A randomised controlled trial. *Sleep Med.* 2009;10(9):1056-1058.
798. Kanbay A, Demir NC, Tutar N, et al. The effect of CPAP therapy on insulin-like growth factor and cognitive functions in obstructive sleep apnea patients. *Clin Respir J.* 2017;11(4):506-513.
799. Palm A, Berne C, Igelstrom H, Asenlof P, Janson C, Lindberg E. The Impact of Continuous Positive Airway Pressure on Circulating IGF-1 in Patients With Obstructive Sleep Apnea. *J Clin Sleep Med.* 2018;14(3):385-391.
800. Shelton KE, Woodson H, Gay S, Suratt PM. Pharyngeal Fat in Obstructive Sleep-Apnea. *American Review of Respiratory Disease.* 1993;148(2):462-466.
801. Peppard PE, Ward NR, Morrell MJ. The impact of obesity on oxygen desaturation during sleep-disordered breathing. *Am J Respir Crit Care Med.* 2009;180(8):788-793.
802. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc.* 2008;5(2):185-192.
803. Heinzer RC, Stanchina ML, Malhotra A, et al. Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2005;172(1):114-117.
804. Lankford DA, Proctor CD, Richard R. Continuous positive airway pressure (CPAP) changes in bariatric surgery patients undergoing rapid weight loss. *Obes Surg.* 2005;15(3):336-341.
805. Kim H, Kim MS, Lee JE, et al. Treatment outcomes and compliance according to obesity in patients with obstructive sleep apnea. *Eur Arch Otorhinolaryngol.* 2013;270(11):2885-2890.
806. Chan AS, Cistulli PA. Oral appliance treatment of obstructive sleep apnea: an update. *Curr Opin Pulm Med.* 2009;15(6):591-596.
807. Holley AB, Lettieri CJ, Shah AA. Efficacy of an adjustable oral appliance and comparison with continuous positive airway pressure for the treatment of obstructive sleep apnea syndrome. *Chest.* 2011;140(6):1511-1516.
808. Ramar K, Dort LC, Katz SG, et al. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. *J Clin Sleep Med.* 2015;11(7):773-827.

809. Sutherland K, Vanderveken OM, Tsuda H, et al. Oral appliance treatment for obstructive sleep apnea: an update. *J Clin Sleep Med*. 2014;10(2):215-227.
810. Mayer G, Meier-Ewert K. Cephalometric predictors for orthopaedic mandibular advancement in obstructive sleep apnoea. *Eur J Orthod*. 1995;17(1):35-43.
811. He M, Yin GP, Zhan SY, et al. Long-term Efficacy of Uvulopalatopharyngoplasty among Adult Patients with Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Otolaryng Head Neck*. 2019;161(3):401-411.
812. Kandasamy T, Wright ED, Fuller J, Rotenberg BW. The incidence of early post-operative complications following uvulopalatopharyngoplasty: identification of predictive risk factors. *J Otolaryngol Head Neck Surg*. 2013;42(1):15.
813. Friedman M, Ibrahim H, Joseph NJ. Staging of obstructive sleep apnea/hypopnea syndrome: a guide to appropriate treatment. *Laryngoscope*. 2004;114(3):454-459.
814. Strollo PJ, Jr., Gillespie MB, Soose RJ, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18 Months. *Sleep*. 2015;38(10):1593-1598.
815. Almendros I, Garcia-Rio F. Sleep apnoea, insulin resistance and diabetes: the first step is in the fat. *Eur Respir J*. 2017;49(4).
816. Trinh MD, Plihalova A, Gojda J, et al. Obstructive sleep apnoea increases lipolysis and deteriorates glucose homeostasis in patients with type 2 diabetes mellitus. *Sci Rep*. 2021;11(1):3567.
817. Mesarwi O, Polak J, Jun J, Polotsky VY. Sleep disorders and the development of insulin resistance and obesity. *Endocrinol Metab Clin North Am*. 2013;42(3):617-634.
818. Punjabi NM, Shahar E, Redline S, et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol*. 2004;160(6):521-530.
819. Pamidi S, Tasali E. Obstructive sleep apnea and type 2 diabetes: is there a link? *Front Neurol*. 2012;3:126.
820. Azman M, Sani A, Kamaruddin NA. Insulin resistance using HOMA model in obstructive sleep apnea: a cross sectional study. *Ann Saudi Med*. 2014;34(6):476-481.
821. Kendzerska T, Gershon AS, Hawker G, Tomlinson G, Leung RS. Obstructive sleep apnea and incident diabetes. A historical cohort study. *Am J Respir Crit Care Med*. 2014;190(2):218-225.
822. Iiyori N, Alonso LC, Li J, et al. Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. *Am J Respir Crit Care Med*. 2007;175(8):851-857.
823. Lindberg E, Theorell-Haglow J, Svensson M, Gislason T, Berne C, Janson C. Sleep apnea and glucose metabolism: a long-term follow-up in a community-based sample. *Chest*. 2012;142(4):935-942.
824. Michalek-Zrabcowska M, Macek P, Martynowicz H, et al. Obstructive Sleep Apnea as a Risk Factor of Insulin Resistance in Nondiabetic Adults. *Life (Basel)*. 2021;11(1).
825. Murphy AM, Thomas A, Crinion SJ, et al. Intermittent hypoxia in obstructive sleep apnoea mediates insulin resistance through adipose tissue inflammation. *Eur Respir J*. 2017;49(4).
826. Liu Y ZJ, Li X, Zhao X, Zou J, Liu S, Meng L, Qian Y, Xu H, Yi H, Guan J. Effect of the interaction between obstructive sleep apnea and lipoprotein (a) on insulin resistance: a large-scale cross-sectional study. *Journal of diabetes research*. 2019 Apr 8.
827. Aurora RN, Punjabi NM. Obstructive Sleep Apnea, Sleepiness, and Glycemic Control in Type 2 Diabetes. *J Clin Sleep Med*. 2019;15(5):749-755.
828. Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. *Respirology*. 2013;18(1):61-70.
829. Olaithe M, Bucks RS, Hillman DR, Eastwood PR. Cognitive deficits in obstructive sleep apnea: Insights from a meta-review and comparison with deficits observed in COPD, insomnia, and sleep deprivation. *Sleep Med Rev*. 2018;38:39-49.

830. Zhu X, Zhao Y. Sleep-disordered breathing and the risk of cognitive decline: a meta-analysis of 19,940 participants. *Sleep Breath*. 2018;22(1):165-173.
831. Bubu OM, Andrade AG, Umasabor-Bubu OQ, et al. Obstructive sleep apnea, cognition and Alzheimer's disease: A systematic review integrating three decades of multidisciplinary research. *Sleep Med Rev*. 2020;50:101250.
832. Emamian F, Khazaie H, Tahmasian M, et al. The Association Between Obstructive Sleep Apnea and Alzheimer's Disease: A Meta-Analysis Perspective. *Front Aging Neurosci*. 2016;8:78.
833. Mubashir T, Abrahamyan L, Niazi A, et al. The prevalence of obstructive sleep apnea in mild cognitive impairment: a systematic review. *BMC Neurol*. 2019;19(1):195.
834. Gaeta AM, Benítez ID, Jorge C, et al. Prevalence of obstructive sleep apnea in Alzheimer's disease patients. *J Neurol*. 2020;267(4):1012-1022.
835. Gronewold J, Haensel R, Kleinschnitz C, Frohnhofen H, Hermann DM. Sleep-Disordered Breathing in Hospitalized Geriatric Patients with Mild Dementia and Its Association with Cognition, Emotion and Mobility. *Int J Environ Res Public Health*. 2019;16(5).
836. Lee JE, Yang SW, Ju YJ, Ki SK, Chun KH. Sleep-disordered breathing and Alzheimer's disease: A nationwide cohort study. *Psychiatry Res*. 2019;273:624-630.
837. Ju Y-e, Lopez O, Redline S, Stein P. Obstructive Sleep Apnea Increases Risk of Incident Dementia in Community-Dwelling Older Adults (P03.098). *Neurology*. 2013;80(7 Supplement):P03.098-P003.098.
838. Lutsey PL, Bengtson LG, Punjabi NM, et al. Obstructive Sleep Apnea and 15-Year Cognitive Decline: The Atherosclerosis Risk in Communities (ARIC) Study. *Sleep*. 2016;39(2):309-316.
839. Lutsey PL, Misialek JR, Mosley TH, et al. Sleep characteristics and risk of dementia and Alzheimer's disease: The Atherosclerosis Risk in Communities Study. *Alzheimers Dement*. 2018;14(2):157-166.
840. Wang G, Goebel JR, Li C, Hallman HG, Gilford TM, Li W. Therapeutic effects of CPAP on cognitive impairments associated with OSA. *J Neurol*. 2020;267(10):2823-2828.
841. Cross N, Lampit A, Pye J, Grunstein RR, Marshall N, Naismith SL. Is Obstructive Sleep Apnoea Related to Neuropsychological Function in Healthy Older Adults? A Systematic Review and Meta-Analysis. *Neuropsychol Rev*. 2017;27(4):389-402.
842. Stranks EK, Crowe SF. The Cognitive Effects of Obstructive Sleep Apnea: An Updated Meta-analysis. *Arch Clin Neuropsychol*. 2016;31(2):186-193.
843. Vaessen TJ, Overeem S, Sitskoorn MM. Cognitive complaints in obstructive sleep apnea. *Sleep Med Rev*. 2015;19:51-58.
844. Kilpinen R, Saunamäki T, Jehkonen M. Information processing speed in obstructive sleep apnea syndrome: a review. *Acta Neurol Scand*. 2014;129(4):209-218.
845. Wallace A, Bucks RS. Memory and obstructive sleep apnea: a meta-analysis. *Sleep*. 2013;36(2):203-220.
846. Saunamäki T, Jehkonen M. A review of executive functions in obstructive sleep apnea syndrome. *Acta Neurol Scand*. 2007;115(1):1-11.
847. Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. *J Int Neuropsychol Soc*. 2004;10(5):772-785.
848. Beebe DW, Groesz L, Wells C, Nichols A, McGee K. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. *Sleep*. 2003;26(3):298-307.
849. Fulda S, Schulz H. Cognitive dysfunction in sleep-related breathing disorders: A meta-analysis. *Sleep research online: SRO*. 2003;Sleep Research Online:19-51.

850. Marshall NS, Wong KK, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study cohort. *J Clin Sleep Med*. 2014;10(4):355-362.
851. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farre R. Sleep-disordered Breathing and Cancer Mortality: Results from the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med*. 2012;186(2):190-194.
852. Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, et al. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. *Am J Respir Crit Care Med*. 2013;187(1):99-105.
853. Martinez-Garcia MA, Campos-Rodriguez F, Duran-Cantolla J, et al. Obstructive sleep apnea is associated with cancer mortality in younger patients. *Sleep Med*. 2014;15(7):742-748.
854. Brenner R, Kivity S, Peker M, et al. Increased Risk for Cancer in Young Patients with Severe Obstructive Sleep Apnea. *Respiration*. 2019;97(1):15-23.
855. Pataka A, Bonsignore MR, Ryan S, et al. Cancer prevalence is increased in females with sleep apnoea: data from the ESADA study. *Eur Respir J*. 2019;53(6).
856. Jara SM, Phipps AI, Maynard C, Weaver EM. The Association of Sleep Apnea and Cancer in Veterans. *Otolaryngol Head Neck Surg*. 2020;162(4):581-588.
857. Chang WP, Liu ME, Chang WC, et al. Sleep apnea and the subsequent risk of breast cancer in women: a nationwide population-based cohort study. *Sleep Med*. 2014;15(9):1016-1020.
858. Kendzerska T, Leung RS, Hawker G, Tomlinson G, Gershon AS. Obstructive sleep apnea and the prevalence and incidence of cancer. *CMAJ*. 2014;186(13):985-992.
859. Chen JC, Hwang JH. Sleep apnea increased incidence of primary central nervous system cancers: a nationwide cohort study. *Sleep Med*. 2014;15(7):749-754.
860. Fang HF, Miao NF, Chen CD, Sithole T, Chung MH. Risk of Cancer in Patients with Insomnia, Parasomnia, and Obstructive Sleep Apnea: A Nationwide Nested Case-Control Study. *J Cancer*. 2015;6(11):1140-1147.
861. Chen CY, Hu JM, Shen CJ, et al. Increased incidence of colorectal cancer with obstructive sleep apnea: a nationwide population-based cohort study. *Sleep Med*. 2020;66:15-20.
862. Sillah A, Watson NF, Schwartz SM, Gozal D, Phipps AI. Sleep apnea and subsequent cancer incidence. *Cancer Causes Control*. 2018;29(10):987-994.
863. Faiz SA, Balachandran D, Hessel AC, et al. Sleep-related breathing disorders in patients with tumors in the head and neck region. *Oncologist*. 2014;19(11):1200-1206.
864. Saesen K, van der Veen J, Buyse B, Nuyts S. Obstructive sleep apnea in head and neck cancer survivors. *Support Care Cancer*. 2020.
865. Martinez-Garcia MA, Martorell-Calatayud A, Nagore E, et al. Association between sleep disordered breathing and aggressiveness markers of malignant cutaneous melanoma. *Eur Respir J*. 2014;43(6):1661-1668.
866. Dal Molin M, Brant A, Blackford AL, et al. Obstructive Sleep Apnea and Pathological Characteristics of Resected Pancreatic Ductal Adenocarcinoma. *PLoS one*. 2016;11(10):e0164195.
867. Huang HY, Lin SW, Chuang LP, et al. Severe Obstructive Sleep Apnea Associated With Higher Risk of Mortality in Stage III and IV Lung Cancer. *J Clin Sleep Med*. 2020.
868. Labarca G, Jorquera J, Dreyse J, Salas C, Letelier F. Hypoxemic features of obstructive sleep apnea and the risk of mortality: a cluster analysis. *Sleep Breath*. 2020.
869. Gaoatswe G, Kent BD, Corrigan MA, et al. Invariant Natural Killer T Cell Deficiency and Functional Impairment in Sleep Apnea: Links to Cancer Comorbidity. *Sleep*. 2015;38(10):1629-1634.



870. Freitas LS, Silveira AC, Martins FC, et al. Severe obstructive sleep apnea is associated with circulating microRNAs related to heart failure, myocardial ischemia, and cancer proliferation. *Sleep Breath*. 2020.
871. Liu Y, Lao M, Chen J, et al. Short-term prognostic effects of circulating regulatory T-Cell suppressive function and vascular endothelial growth factor level in patients with non-small cell lung cancer and obstructive sleep apnea. *Sleep Med*. 2020;70:88-96.
872. Jarrar Y, Zihlif M, Al Bawab AQ, Sharab A. Effects of Intermittent Hypoxia on Expression of Glucose Metabolism Genes in MCF7 Breast Cancer Cell Line. *Curr Cancer Drug Targets*. 2020;20(3):216-222.
873. Zhu H, Wang D, Zhang L, et al. Upregulation of autophagy by hypoxia-inducible factor-1alpha promotes EMT and metastatic ability of CD133+ pancreatic cancer stem-like cells during intermittent hypoxia. *Oncol Rep*. 2014;32(3):935-942.
874. Malec V, Gottschald OR, Li S, Rose F, Seeger W, Hanze J. HIF-1 alpha signaling is augmented during intermittent hypoxia by induction of the Nrf2 pathway in NOX1-expressing adenocarcinoma A549 cells. *Free Radic Biol Med*. 2010;48(12):1626-1635.
875. Cubillos-Zapata C, Hernandez-Jimenez E, Avendano-Ortiz J, et al. Obstructive Sleep Apnea Monocytes Exhibit High Levels of Vascular Endothelial Growth Factor Secretion, Augmenting Tumor Progression. *Mediators Inflamm*. 2018;2018:7373921.
876. Martinez CA, Kerr B, Jin C, Cistulli PA, Cook KM. Obstructive Sleep Apnea Activates HIF-1 in a Hypoxia Dose-Dependent Manner in HCT116 Colorectal Carcinoma Cells. *Int J Mol Sci*. 2019;20(2).
877. Kang Y, Greaves B, Perry RR. Effect of acute and chronic intermittent hypoxia on DNA topoisomerase II alpha expression and mitomycin C-induced DNA damage and cytotoxicity in human colon cancer cells. *Biochem Pharmacol*. 1996;52(4):669-676.
878. Cooper C, Liu GY, Niu YL, Santos S, Murphy LC, Watson PH. Intermittent hypoxia induces proteasome-dependent down-regulation of estrogen receptor alpha in human breast carcinoma. *Clin Cancer Res*. 2004;10(24):8720-8727.
879. Martinive P, Defresne F, Bouzin C, et al. Preconditioning of the tumor vasculature and tumor cells by intermittent hypoxia: implications for anticancer therapies. *Cancer Res*. 2006;66(24):11736-11744.
880. Chen A, Sceneay J, Godde N, et al. Intermittent hypoxia induces a metastatic phenotype in breast cancer. *Oncogene*. 2018;37(31):4214-4225.
881. Liu L, Liu W, Wang L, Zhu T, Zhong J, Xie N. Hypoxia-inducible factor 1 mediates intermittent hypoxia-induced migration of human breast cancer MDA-MB-231 cells. *Oncol Lett*. 2017;14(6):7715-7722.
882. Almendros I, Montserrat JM, Ramirez J, et al. Intermittent hypoxia enhances cancer progression in a mouse model of sleep apnoea. *Eur Respir J*. 2012;39(1):215-217.
883. Graves EE, Vilalta M, Cecic IK, et al. Hypoxia in models of lung cancer: implications for targeted therapeutics. *Clin Cancer Res*. 2010;16(19):4843-4852.
884. Guo X, Liu Y, Kim JL, et al. Effect of cyclical intermittent hypoxia on Ad5CMVCre induced solitary lung cancer progression and spontaneous metastases in the KrasG12D+; p53fl/fl; myristolated p110fl/fl ROSA-gfp mouse. *PLoS one*. 2019;14(2):e0212930.
885. Gaustad JV, Simonsen TG, Roa AMA, Rofstad EK. Tumors exposed to acute cyclic hypoxia show increased vessel density and delayed blood supply. *Microvasc Res*. 2013;85:10-15.
886. Almendros I, Montserrat JM, Torres M, et al. Intermittent hypoxia increases melanoma metastasis to the lung in a mouse model of sleep apnea. *Respiratory physiology & neurobiology*. 2013;186(3):303-307.

887. Cubillos-Zapata C, Avendano-Ortiz J, Hernandez-Jimenez E, et al. Hypoxia-induced PD-L1/PD-1 crosstalk impairs T-cell function in sleep apnoea. *Eur Respir J*. 2017;50(4).
888. Gallego-Martin T, Farre R, Almendros I, Gonzalez-Obeso E, Obeso A. Chronic intermittent hypoxia mimicking sleep apnoea increases spontaneous tumorigenesis in mice. *Eur Respir J*. 2017;49(2).
889. Huang MH, Zhang XB, Wang HL, et al. Intermittent hypoxia enhances the tumor programmed death ligand 1 expression in a mouse model of sleep apnea. *Ann Transl Med*. 2019;7(5):97.
890. Craig TJ, Hanks CD, Fisher LH. How do topical nasal corticosteroids improve sleep and daytime somnolence in allergic rhinitis? *J Allergy Clin Immunol*. 2005;116(6):1264-1266.
891. Stuck BA, Czajkowski J, Hagner AE, et al. Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: a controlled clinical trial. *J Allergy Clin Immunol*. 2004;113(4):663-668.
892. Young T, Finn L, Kim H, et al. Nasal obstruction as a risk factor for sleep-disordered breathing. *J Allergy Clin Immunol*. 1997;99(2):S757-S762.
893. Lavigne F, Petrof BJ, Johnson JR, et al. Effect of topical corticosteroids on allergic airway inflammation and disease severity in obstructive sleep apnoea. *Clin Exp Allergy*. 2013;43(10):1124-1133.
894. Kiely JL, Nolan P, McNicolas WT. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. *Thorax*. 2004;59(1):50-55.
895. Santos CB, Hanks C, McCann J, Lehman EB, Pratt E, Craig TJ. The role of montelukast on perennial allergic rhinitis and associated sleep disturbances and daytime somnolence. *Allergy Asthma Proc*. 2008;29(2):140-145.
896. Golden S, Teets SJ, Lehman EB, et al. Effect of topical nasal azelastine on the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. *Ann Allerg Asthma Im*. 2000;85(1):53-57.
897. Silvoniemi P, Suonpaa J, Sipila J, Grenman R, Erkinjuntti M. Sleep disorders in patients with severe nasal obstruction due to septal deviation. *Acta Oto-Laryngol*. 1997:199-201.
898. An YS, Li YR, Kang D, et al. The effects of nasal decongestion on obstructive sleep apnoea. *Am J Otolaryng*. 2019;40(1):52-56.
899. Clarenbach CF, Kohler M, Senn O, Thurnheer R, Bloch KE. Does nasal decongestion improve obstructive sleep apnea? *J Sleep Res*. 2008;17(4):444-449.
900. Djupesland PG, Skatvedt O, Borgersen AK. Dichotomous physiological effects of nocturnal external nasal dilation in heavy snorers: the answer to a rhinologic controversy? *Am J Rhinol*. 2001;15(2):95-103.
901. Kerr P, Millar T, Buckle P, Kryger M. The Importance of Nasal Resistance in Obstructive Sleep-Apnea Syndrome. *J Otolaryngol*. 1992;21(3):189-195.
902. McLean HA, Urton AM, Driver HS, et al. Effect of treating severe nasal obstruction on the severity of obstructive sleep apnoea. *Eur Respir J*. 2005;25(3):521-527.
903. Pevernagie D, Hamans E, Van Cauwenberge P, Pauwels R. External nasal dilation reduces snoring in chronic rhinitis patients: a randomized controlled trial. *Eur Respir J*. 2000;15(6):996-1000.
904. de Aguiar Vidigal T, Martinho Haddad FL, Gregorio LC, Poyares D, Tufik S, Azeredo Bittencourt LR. Subjective, anatomical, and functional nasal evaluation of patients with obstructive sleep apnea syndrome. *Sleep Breath*. 2013;17(1):427-433.
905. Li HY, Wang PC, Chen YP, Lee LA, Fang TJ, Lin HC. Critical appraisal and meta-analysis of nasal surgery for obstructive sleep apnea. *Am J Rhinol Allergy*. 2011;25(1):45-49.
906. Yamasaki A, Levesque PA, Lindsay RW. Improvement in Snoring-Related Quality-of-Life Outcomes After Functional Nasal Surgery. *Facial Plast Surg Ae*. 2020;22(1):25-35.

907. Bosco G, Perez-Martin N, Morato M, Racionero MA, Plaza G. Nasal Surgery May Improve Upper Airway Collapse in Patients With Obstructive Sleep Apnea: A Drug-Induced Sleep Endoscopy Study. *J Craniofac Surg*. 2020;31(1):68-71.
908. Li HY, Lee LA, Wang PC, Fang TJ, Chen NH. Can nasal surgery improve obstructive sleep apnea: Subjective or objective? *Am J Rhinol Allergy*. 2009;23(6):E51-E55.
909. Nakata S, Noda A, Yasuma F, et al. Effects of nasal surgery on sleep quality in obstructive sleep apnea syndrome with nasal obstruction. *American Journal of Rhinology*. 2008;22(1):59-63.
910. Shuaib SW, Undavia S, Lin J, Johnson CM, Stupak HD. Can Functional Septorhinoplasty Independently Treat Obstructive Sleep Apnea? *Plast Reconstr Surg*. 2015;135(6):1554-1565.
911. Hisamatsu K, Kudo I, Makiyama K. The effect of compound nasal surgery on obstructive sleep apnea syndrome. *Am J Rhinol Allergy*. 2015;29(6):e192-196.
912. Lenders H, Schaefer J, Pirsig W. Turbinate Hypertrophy in Habitual Snorers and Patients with Obstructive Sleep-Apnea - Findings of Acoustic Rhinometry. *Laryngoscope*. 1991;101(6):614-618.
913. Alt JA, DeConde AS, Mace JC, Steele TO, Orlandi RR, Smith TL. Quality of Life in Patients With Chronic Rhinosinusitis and Sleep Dysfunction Undergoing Endoscopic Sinus Surgery A Pilot Investigation of Comorbid Obstructive Sleep Apnea. *Jama Otolaryngol*. 2015;141(10):873-881.
914. Alt JA, Ramakrishnan VR, Platt MP, Schlosser RJ, Storck T, Soler ZM. Impact of chronic rhinosinusitis on sleep: a controlled clinical study. *Int Forum Allergy Rh*. 2019;9(1):16-22.
915. Orb Q, Orlandi RR, Alt JA. Sleep Dysfunction and its Association to Chronic Rhinosinusitis: Updated Review. *Laryngoscope Invest*. 2017;2(2):46-52.
916. Sunderram J, Weintraub M, Black K, et al. Chronic Rhinosinusitis Is an Independent Risk Factor for OSA in World Trade Center Responders. *Chest*. 2019;155(2):375-383.
917. Jiang RS, Liang KL, Hsin CH, Su MC. The impact of chronic rhinosinusitis on sleep-disordered breathing. *Rhinology*. 2016;54(1):75-79.
918. Rotenberg BW, Pang KP. The impact of sinus surgery on sleep outcomes. *Int Forum Allergy Rhinol*. 2015;5(4):329-332.
919. Tosun F, Kemikli K, Yetkin S, Ozgen F, Durmaz A, Gerek M. Impact of Endoscopic Sinus Surgery on Sleep Quality in Patients With Chronic Nasal Obstruction Due to Nasal Polyposis. *J Craniofac Surg*. 2009;20(2):446-449.
920. Yalamanchali S, Cipta S, Waxman J, Pott T, Joseph N, Friedman M. Effects of Endoscopic Sinus Surgery and Nasal Surgery in Patients with Obstructive Sleep Apnea. *Otolaryngol Head Neck Surg*. 2014;151(1):171-175.
921. Alt JA, Sautter NB, Mace JC, Detwiler KY, Smith TL. Antisomnogenic cytokines, quality of life, and chronic rhinosinusitis: a pilot study. *Laryngoscope*. 2014;124(4):E107-114.
922. Altintas A, Soylu A, Yegin Y, Celik M, Kaya KH. Impact of Laryngopharyngeal Reflux on the Levels of Depression and Anxiety in Patients With Obstructive Sleep Apnea Syndrome. *J Craniofac Surg*. 2017;28(2):E121-E124.
923. Caparroz F, Campanholo M, Stefanini R, et al. Laryngopharyngeal reflux and dysphagia in patients with obstructive sleep apnea: is there an association? *Sleep Breath*. 2019;23(2):619-626.
924. Chan KK, Ing AJ, Laks L, Cossa G, Rogers P, Birring SS. Chronic cough in patients with sleep-disordered breathing. *Eur Respir J*. 2010;35(2):368-372.
925. Elhennawi DM, Ahmed MR, Abou-Halawa AS. Correlation of obstructive sleep apnoea and laryngopharyngeal reflux: phmetry study. *Clin Otolaryngol*. 2016;41(6):758-761.
926. Eryilmaz A, Erisen L, Demir UL, et al. Management of patients with coexisting obstructive sleep apnea and laryngopharyngeal reflux disease. *Eur Arch Oto-Rhino-L*. 2012;269(12):2575-2580.
927. Kim SJ, Kim H, Jeong JI, Hong SD, Chung SK, Dhong HJ. Changes in the Reflux Symptom Index After Multilevel Surgery for Obstructive Sleep Apnea. *Clin Exp Otorhinolar*. 2017;10(3):259-264.

928. Lee JS, Heo SJ, Kim JS, Ahn D, Sohn JH, Kim H. Relationship between the severity of laryngopharyngeal reflux and sleep apnea: using drug-induced sleep endoscopy (DISE). *Eur Arch Oto-Rhino-L.* 2018;275(1):219-224.
929. Magliulo G, Iannella G, Polimeni A, et al. Laryngopharyngeal reflux in obstructive sleep apnoea patients: Literature review and meta-analysis. *Am J Otolaryng.* 2018;39(6):776-780.
930. Morse CA, Quan SF, Mays MZ, Green C, Stephen G, Fass R. Is There a Relationship Between Obstructive Sleep Apnea and Gastroesophageal Reflux Disease? *Clin Gastroenterol H.* 2004;2(9):761-768.
931. Qu Y, Ye JY, Han DM, et al. Esophageal Functional Changes in Obstructive Sleep Apnea/Hypopnea Syndrome and Their Impact on Laryngopharyngeal Reflux Disease. *Chinese Med J-Peking.* 2015;128(16):2162-2167.
932. Rodrigues MM, Dibbern RS, Santos VJB, Passeri LA. Influence of obesity on the correlation between laryngopharyngeal reflux and obstructive sleep apnea. *Braz J Otorhinolar.* 2014;80(1):5-10.
933. Sundar KM, Daly SE, Pearce MJ, Alward WT. Chronic cough and obstructive sleep apnea in a community-based pulmonary practice. *Cough.* 2010;6(1):2.
934. Teklu M, Gouveia CJ, Yalamanchili A, et al. Predicting Obstructive Sleep Apnea Status With the Reflux Symptom Index in a Sleep Study Population. *Laryngoscope.* 2020;130(12):E952-E957.
935. Xavier SD, Eckley CA, Duprat AC, et al. Temporal Association Between Respiratory Events and Reflux in Patients With Obstructive Sleep Apnea and Laryngopharyngeal Reflux. *Journal of Clinical Sleep Medicine.* 2019;15(10):1397-1402.
936. Caparroz FA, Campanholo MAT, Regina CG, et al. Clinical and polysomnographic predictors of laryngopharyngeal reflux in obstructive sleep apnea syndrome. *Braz J Otorhinolaryngol.* 2019;85(4):408-415.
937. Gilani S, Quan SF, Pynnonen MA, Shin JJ. Obstructive Sleep Apnea and Gastroesophageal Reflux: A Multivariate Population-Level Analysis. *Otolaryngol Head Neck Surg.* 2016;154(2):390-395.
938. Kim Y, Lee YJ, Park JS, et al. Associations between obstructive sleep apnea severity and endoscopically proven gastroesophageal reflux disease. *Sleep Breath.* 2018;22(1):85-90.
939. Rassameehiran S, Klomjit S, Hosiriluck N, Nugent K. Meta-analysis of the effect of proton pump inhibitors on obstructive sleep apnea symptoms and indices in patients with gastroesophageal reflux disease. *Proc (Bayl Univ Med Cent).* 2016;29(1):3-6.
940. Shepherd K, Orr W. Mechanism of Gastroesophageal Reflux in Obstructive Sleep Apnea: Airway Obstruction or Obesity? *J Clin Sleep Med.* 2016;12(1):87-94.
941. Xavier SD, Moraes JP, Eckley CA. Prevalence of signs and symptoms of laryngopharyngeal reflux in snorers with suspected obstructive sleep apnea. *Braz J Otorhinolaryngol.* 2013;79(5):589-593.
942. Bjornsdottir E, Janson C, Sigurdsson JF, et al. Symptoms of Insomnia among Patients with Obstructive Sleep Apnea Before and After Two Years of Positive Airway Pressure Treatment. *Sleep.* 2013;36(12):1901-1909.
943. Bjorvatn B, Pallesen S, Gronli J, Sivertsen B, Lehmann S. Prevalence and Correlates of Insomnia and Excessive Sleepiness in Adults with Obstructive Sleep Apnea Symptoms. *Percept Motor Skill.* 2014;118(2):571-586.
944. Cho YW, Kim KT, Moon HJ, Korostyshevskiy VR, Motamedi GK, Yang KI. Comorbid Insomnia With Obstructive Sleep Apnea: Clinical Characteristics and Risk Factors. *J Clin Sleep Med.* 2018;14(3):409-417.
945. Gupta MA, Knapp K. Cardiovascular and Psychiatric Morbidity in Obstructive Sleep Apnea (OSA) with Insomnia (Sleep Apnea Plus) versus Obstructive Sleep Apnea without Insomnia: A Case-Control Study from a Nationally Representative US Sample. *PloS one.* 2014;9(3).

946. Krakow B, Melendrez D, Ferreira E, et al. Prevalence of insomnia symptoms in patients with sleep-disordered breathing. *Chest*. 2001;120(6):1923-1929.
947. Lang CJ, Appleton SL, Vakulin A, et al. Co-morbid OSA and insomnia increases depression prevalence and severity in men. *Respirology*. 2017;22(7):1407-1415.
948. Mysliwiec V, Gill J, Lee H, et al. Sleep Disorders in US Military Personnel A High Rate of Comorbid Insomnia and Obstructive Sleep Apnea. *Chest*. 2013;144(2):549-557.
949. Nguyen XL, Chaskalovic J, Rakotonanahary D, Fleury B. Insomnia symptoms and CPAP compliance in OSAS patients: A descriptive study using Data Mining methods. *Sleep Med*. 2010;11(8):777-784.
950. Sivertsen B, Bjornsdottir E, Overland S, Bjorvatn B, Salo P. The joint contribution of insomnia and obstructive sleep apnoea on sickness absence. *J Sleep Res*. 2013;22(2):223-230.
951. Smith S, Sullivan K, Hopkins W, Douglas J. Frequency of insomnia report in patients with Obstructive Sleep Apnoea Hypopnea Syndrome (OSAHS). *Sleep Med*. 2004;5(5):449-456.
952. Stelzer FG, Garcia E, Schorr F, Barea LM, Barros HT. Prevalence of chronic insomnia in patients with obstructive sleep apnea. *Braz J Psychiatry*. 2020.
953. Tasbakan MS, Gunduz C, Pirildar S, Basoglu OK. Quality of life in obstructive sleep apnea is related to female gender and comorbid insomnia. *Sleep Breath*. 2018;22(4):1013-1020.
954. Wallace DM, Wohlgenuth WK. Predictors of Insomnia Severity Index Profiles in United States Veterans With Obstructive Sleep Apnea. *J Clin Sleep Med*. 2019;15(12):1827-1837.
955. Zhang Y, Ren R, Lei F, et al. Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Med Rev*. 2019;45:1-17.
956. Sweetman A, McEvoy RD, Smith S, et al. The effect of cognitive and behavioral therapy for insomnia on week-to-week changes in sleepiness and sleep parameters in patients with comorbid insomnia and sleep apnea: a randomized controlled trial. *Sleep*. 2020;43(7).
957. Sweetman A, Lack L, McEvoy RD, et al. Bi-directional relationships between co-morbid insomnia and sleep apnea (COMISA). *Sleep Med Rev*. 2021;60:101519.
958. Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain*. 2019;142:744-759.
959. Boeve BF, Dickson DW, Olson EJ, et al. Insights into REM sleep behavior disorder pathophysiology in brainstem-predominant Lewy body disease. *Sleep Med*. 2007;8(1):60-64.
960. Iranzo A, Santamaria J. Severe obstructive sleep apnea/hypopnea mimicking REM sleep behavior disorder. *Sleep*. 2005;28(2):203-206.
961. Li SX, Lam SP, Zhang JH, et al. A prospective, naturalistic follow-up study of treatment outcomes with clonazepam in rapid eye movement sleep behavior disorder. *Sleep Med*. 2016;21:114-120.
962. Gabryelska A, Roguski A, Simpson G, Maschauer EL, Morrison I, Riha RL. Prevalence of obstructive sleep apnoea in REM behaviour disorder: response to continuous positive airway pressure therapy. *Sleep Breath*. 2018;22(3):825-830.
963. Koo DL, Lee JY, Nam H. Difference in severity of sleep apnea in patients with rapid eye movement sleep behavior disorder with or without parkinsonism. *Sleep Med*. 2018;49:99-104.
964. Rodrigues RND, Rodrigues AADES, Pratesi R, Krieger J. Outcome of restless legs severity after continuous positive air pressure (CPAP) treatment in patients affected by the association of RLS and obstructive sleep apneas. *Sleep Med*. 2006;7(3):235-239.
965. Silva C, Peralta AR, Bentes C. The urge to move and breathe - the impact of obstructive sleep apnea syndrome treatment in patients with previously diagnosed, clinically significant restless legs syndrome. *Sleep Med*. 2017;38:17-20.

966. Aritake-Okada S, Namba K, Hidano N, et al. Change in frequency of periodic limb movements during sleep with usage of continuous positive airway pressure in obstructive sleep apnea syndrome. *J Neurol Sci.* 2012;317(1-2):13-16.
967. Ren R, Huang GP, Zhang JH, et al. Age and severity matched comparison of gender differences in the prevalence of periodic limb movements during sleep in patients with obstructive sleep apnea. *Sleep Breath.* 2016;20(2):821-827.
968. Iriarte J, Murie-Fernandez M, Toledo E, et al. Sleep Structure in Patients With Periodic Limb Movements and Obstructive Sleep Apnea Syndrome. *J Clin Neurophysiol.* 2009;26(4):267-271.
969. Al-Alawi A, Mulgrew A, Tench E, Ryan CF. Prevalence, Risk Factors and Impact on Daytime Sleepiness and Hypertension of Periodic Leg Movements With Arousals in Patients With Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine.* 2006;2(3):281-287.
970. Haba-Rubio J, Staner L, Krieger J, Macher JP. Periodic limb movements and sleepiness in obstructive sleep apnea patients. *Sleep Med.* 2005;6(3):225-229.
971. Drakatos P, Higgins S, Pengo MF, et al. Derived Arterial Stiffness is Increased in Patients with Obstructive Sleep Apnea and Periodic Limb Movements during Sleep. *Journal of Clinical Sleep Medicine.* 2016;12(2):195-202.
972. Murase K, Hitomi T, Hamada S, et al. The additive impact of periodic limb movements during sleep on inflammation in patients with obstructive sleep apnea. *Ann Am Thorac Soc.* 2014;11(3):375-382.
973. Wu MN, Lai CL, Liu CK, et al. Basal sympathetic predominance in periodic limb movements in sleep after continuous positive airway pressure. *Sleep Breath.* 2018;22(4):1005-1012.
974. Xie J, Chahal CAA, Covassin N, et al. Periodic limb movements of sleep are associated with an increased prevalence of atrial fibrillation in patients with mild sleep-disordered breathing. *Int J Cardiol.* 2017;241:200-204.
975. Jokubauskas L, Baltrusaityte A. Relationship between obstructive sleep apnoea syndrome and sleep bruxism: a systematic review. *J Oral Rehabil.* 2017;44(2):144-153.
976. Lopes AJD, Cunha TCA, Monteiro MCM, Serra-Negra JM, Cabral LC, Simamoto PC. Is there an association between sleep bruxism and obstructive sleep apnea syndrome? A systematic review. *Sleep Breath.* 2020;24(3):913-921.
977. Chiaro G, Maestri M, Riccardi S, et al. Sleep-Related Rhythmic Movement Disorder and Obstructive Sleep Apnea in Five Adult Patients. *Journal of Clinical Sleep Medicine.* 2017;13(10):1213-1217.
978. Bugalho P, Mendonca M, Barbosa R, Salavisa M. The influence of sleep disordered breathing in REM sleep behavior disorder. *Sleep Med.* 2017;37:210-215.
979. Lakshmanan S, Thompson NR, Pascoe M, et al. Impact of Positive Airway Pressure on International Restless Legs Syndrome Score in Sleep Disordered Breathing. *Journal of Clinical Medicine.* 2019;8(12).
980. Loewen A, Siemens A, Hanly P. Sleep Disruption in Patients with Sleep Apnea and End-Stage Renal Disease. *Journal of Clinical Sleep Medicine.* 2009;5(4):324-329.
981. Xie J, Covassin N, Chahal AA, et al. Effect of Adaptive Servo-Ventilation on Periodic Limb Movements in Sleep in Patients With Heart Failure. *American Journal of Cardiology.* 2019;123(4):632-637.
982. Longstreth WT, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. *Sleep.* 2007;30(1):13-26.
983. Mignot E, Lin L, Rogers W, et al. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. *American Journal of Human Genetics.* 2001;68(3):686-699.
984. Cohen A, Mandrekar J, St Louis EK, Silber MH, Kotagal S. Comorbidities in a community sample of narcolepsy. *Sleep Med.* 2018;43:14-18.

985. Frauscher B, Ehrmann L, Mitterling T, et al. Delayed Diagnosis, Range of Severity, and Multiple Sleep Comorbidities: A Clinical and Polysomnographic Analysis of 100 Patients of the Innsbruck Narcolepsy Cohort. *Journal of Clinical Sleep Medicine*. 2013;9(8):805-812.
986. Sansa G, Iranzo A, Santamaria J. Obstructive sleep apnea in narcolepsy. *Sleep Med*. 2010;11(1):93-95.
987. Black J, Reaven NL, Funk SE, et al. Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study. *Sleep Med*. 2017;33:13-18.
988. Jennum P, Thorstensen EW, Pickering L, Ibsen R, Kjellberg J. Morbidity and mortality of middle-aged and elderly narcoleptics. *Sleep Med*. 2017;36:23-28.
989. Sullivan SS. Narcolepsy in adolescents. *Adolesc Med State Art Rev*. 2010;21(3):542-555, x-xi.
990. Chervin RD, Aldrich MS. Sleep onset REM periods during multiple sleep latency tests in patients evaluated for sleep apnea. *Am J Respir Crit Care Med*. 2000;161(2 Pt 1):426-431.
991. George CF, Feldman N, Zheng Y, et al. A 2-week, polysomnographic, safety study of sodium oxybate in obstructive sleep apnea syndrome. *Sleep Breath*. 2011;15(1):13-20.
992. Poli F, Ricotta L, Vandi S, et al. Catathrenia under sodium oxybate in narcolepsy with cataplexy. *Sleep Breath*. 2012;16(2):427-434.
993. Seeck-Hirschner M, Baier PC, von Freier A, Aldenhoff J, Goder R. Increase in sleep-related breathing disturbances after treatment with sodium oxybate in patients with narcolepsy and mild obstructive sleep apnea syndrome: two case reports. *Sleep Med*. 2009;10(1):154-155.
994. Series F, Series I, Cormier Y. Effects of enhancing slow-wave sleep by gamma-hydroxybutyrate on obstructive sleep apnea. *Am Rev Respir Dis*. 1992;145(6):1378-1383.
995. Jennum P, Ibsen R, Knudsen S, Kjellberg J. Comorbidity and mortality of narcolepsy: a controlled retro- and prospective national study. *Sleep*. 2013;36(6):835-840.
996. Pizza F, Tartarotti S, Poryazova R, Baumann CR, Bassetti CL. Sleep-disordered breathing and periodic limb movements in narcolepsy with cataplexy: a systematic analysis of 35 consecutive patients. *Eur Neurol*. 2013;70(1-2):22-26.
997. Filardi M, Demir N, Pizza F, et al. Prevalence and neurophysiological correlates of sleep disordered breathing in pediatric type 1 narcolepsy. *Sleep Med*. 2020;65:8-12.
998. Settipane RA, Lieberman P. Update on nonallergic rhinitis. *Ann Allergy Asthma Immunol*. 2001;86(5):494-507; quiz 507-498.
999. Izci B, Vennelle M, Liston WA, Dundas KC, Calder AA, Douglas NJ. Sleep-disordered breathing and upper airway size in pregnancy and post-partum. *Eur Respir J*. 2006;27(2):321-327.
1000. Pamidi S, Kimoff RJ. Maternal Sleep-Disordered Breathing. *Chest*. 2018;153(4):1052-1066.
1001. Facco FL, Kramer J, Ho KH, Zee PC, Grobman WA. Sleep disturbances in pregnancy. *Obstet Gynecol*. 2010;115(1):77-83.
1002. Facco FL, Parker CB, Reddy UM, et al. Association Between Sleep-Disordered Breathing and Hypertensive Disorders of Pregnancy and Gestational Diabetes Mellitus. *Obstet Gynecol*. 2017;129(1):31-41.
1003. Pien GW, Fife D, Pack AI, Nkwuo JE, Schwab RJ. Changes in symptoms of sleep-disordered breathing during pregnancy. *Sleep*. 2005;28(10):1299-1305.
1004. Louis JM, Koch MA, Reddy UM, et al. Predictors of sleep-disordered breathing in pregnancy. *Am J Obstet Gynecol*. 2018;218(5):521 e521-521 e512.
1005. Pien GW, Pack AI, Jackson N, Maislin G, Macones GA, Schwab RJ. Risk factors for sleep-disordered breathing in pregnancy. *Thorax*. 2014;69(4):371-377.
1006. Lu Q, Zhang X, Wang Y, et al. Sleep disturbances during pregnancy and adverse maternal and fetal outcomes: A systematic review and meta-analysis. *Sleep Med Rev*. 2021;58:101436.
1007. Bourjeily G, Danilack VA, Bublitz MH, et al. Obstructive sleep apnea in pregnancy is associated with adverse maternal outcomes: a national cohort. *Sleep Med*. 2017;38:50-57.

1008. Louis JM, Mogos MF, Salemi JL, Redline S, Salihu HM. Obstructive sleep apnea and severe maternal-infant morbidity/mortality in the United States, 1998-2009. *Sleep*. 2014;37(5):843-849.
1009. Liu L, Su G, Wang S, Zhu B. The prevalence of obstructive sleep apnea and its association with pregnancy-related health outcomes: a systematic review and meta-analysis. *Sleep Breath*. 2019;23(2):399-412.
1010. Blyton DM, Skilton MR, Edwards N, Hennessy A, Celermajer DS, Sullivan CE. Treatment of sleep disordered breathing reverses low fetal activity levels in preeclampsia. *Sleep*. 2013;36(1):15-21.
1011. Stajic D, Ilic D, Vukovic J, Baturan B, Ilic A, Milovancev A. The effect of continuous positive airway pressure treatment on hypertensive disorder in pregnant women with obstructive sleep apnea. *Sleep Breath*. 2021.
1012. Facco FM. Sleep Disordered Breathing, Obesity and Pregnancy Study (SOAP). ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02086448>. Published 2022. Updated March 8, 2022. Accessed March 8, 2022, 2022.
1013. Humphries A, Mirjalili SA, Tarr GP, Thompson JMD, Stone P. The effect of supine positioning on maternal hemodynamics during late pregnancy. *J Matern-Fetal Neo M*. 2019;32(23):3923-3930.
1014. Dominguez JE, Street L, Louis J. Management of Obstructive Sleep Apnea in Pregnancy. *Obstet Gyn Clin N Am*. 2018;45(2):233-+.
1015. Tamisier R, Fabre F, O'Donoghue F, Levy P, Payen JF, Pepin JL. Anesthesia and sleep apnea. *Sleep Medicine Reviews*. 2018;40:79-92.
1016. Booth JM, Tonidandel AM. Peripartum Management of Obstructive Sleep Apnea. *Clin Obstet Gynecol*. 2017;60(2):405-417.
1017. Zaremba S, Mueller N, Heisig AM, et al. Elevated Upper Body Position Improves Pregnancy-Related OSA Without Impairing Sleep Quality or Sleep Architecture Early After Delivery. *Chest*. 2015;148(4):936-944.
1018. Amnakkittikul S, Chirakalwasan N, Wanitcharoenkul E, et al. Postpartum resolution of obstructive sleep apnea in women with gestational diabetes and the relationship with glucose metabolism. *Acta Diabetol*. 2018;55(7):751-754.
1019. Edwards N, Blyton DM, Hennessy A, Sullivan CE. Severity of sleep-disordered breathing improves following parturition. *Sleep*. 2005;28(6):737-741.
1020. Reid J, Glew RA, Skomro R, et al. Sleep Disordered Breathing and Gestational Hypertension: Postpartum Follow-up Study. *Sleep*. 2013;36(5):717-721.
1021. Ponce S, Pastor E, Orosa B, et al. The role of CPAP treatment in elderly patients with moderate obstructive sleep apnoea: a multicentre randomised controlled trial. *Eur Respir J*. 2019;54(2).
1022. Zhao YY, Wang R, Gleason KJ, et al. Effect of Continuous Positive Airway Pressure Treatment on Health-Related Quality of Life and Sleepiness in High Cardiovascular Risk Individuals With Sleep Apnea: Best Apnea Interventions for Research (BestAIR) Trial. *Sleep*. 2017;40(4).
1023. Wickwire EM, Albrecht JS, Towe MM, et al. The Impact of Treatments for OSA on Monetized Health Economic Outcomes: A Systematic Review. *Chest*. 2019;155(5):947-961.
1024. Zheng DN, Xu Y, You SJ, et al. Effects of continuous positive airway pressure on depression and anxiety symptoms in patients with obstructive sleep apnoea: results from the sleep apnoea cardiovascular Endpoint randomised trial and meta-analysis. *Eclinicalmedicine*. 2019;11:89-96.
1025. Ning Y, Zhang TS, Wen WW, et al. Effects of continuous positive airway pressure on cardiovascular biomarkers in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. *Sleep Breath*. 2019;23(1):77-86.
1026. Khan SU, Duran CA, Rahman H, Lekkala M, Saleem MA, Kaluski E. A meta-analysis of continuous positive airway pressure therapy in prevention of cardiovascular events in patients with obstructive sleep apnoea. *Eur Heart J*. 2018;39(24):2291-+.



1027. Labarca G, Reyes T, Jorquera J, Dreyse J, Drake L. CPAP in patients with obstructive sleep apnea and type 2 diabetes mellitus: Systematic review and meta-analysis. *Clin Respir J*. 2018;12(8):2361-2368.
1028. Gupta A, Shukla G, Afsar M, et al. Role of Positive Airway Pressure Therapy for Obstructive Sleep Apnea in Patients With Stroke: A Randomized Controlled Trial. *Journal of Clinical Sleep Medicine*. 2018;14(4):511-521.
1029. Congrete S, Thongprayoon C, Boonpheng B, et al. Effect of Obstructive Sleep Apnea and Its Treatment on Atrial Fibrillation Recurrence after Radiofrequency Catheter Ablation: A Meta-Analysis. *Am J Resp Crit Care*. 2018;197.
1030. Joyeux-Faure M, Baguet JP, Barone-Rochette G, et al. Continuous Positive Airway Pressure Reduces Night-Time Blood Pressure and Heart Rate in Patients With Obstructive Sleep Apnea and Resistant Hypertension: The RHOOSAS Randomized Controlled Trial. *Frontiers in Neurology*. 2018;9.
1031. Abuzaid AS, Al Ashry HS, Elbadawi A, et al. Meta-Analysis of Cardiovascular Outcomes With Continuous Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea. *Am J Cardiol*. 2017;120(4):693-699.
1032. Campos-Rodriguez F, Gonzalez-Martinez M, Sanchez-Armengol A, et al. Effect of continuous positive airway pressure on blood pressure and metabolic profile in women with sleep apnoea. *Eur Respir J*. 2017;50(2).
1033. Hoyos CM, Yee BJ, Wong KK, Grunstein RR, Phillips CL. Treatment of Sleep Apnea With CPAP Lowers Central and Peripheral Blood Pressure Independent of the Time-of-Day: A Randomized Controlled Study. *Am J Hypertens*. 2015;28(10):1222-1228.
1034. Ip S, D'Ambrosio C, Patel K, et al. Auto-titrating versus fixed continuous positive airway pressure for the treatment of obstructive sleep apnea: a systematic review with meta-analyses. *Syst Rev*. 2012;1.
1035. Bloch KE, Huber F, Furian M, et al. Autoadjusted versus fixed CPAP for obstructive sleep apnoea: a multicentre, randomised equivalence trial. *Thorax*. 2018;73(2):174-184.
1036. Lebret M, Rotty MC, Argento C, et al. Comparison of Auto- and Fixed-Continuous Positive Airway Pressure on Air Leak in Patients with Obstructive Sleep Apnea: Data from a Randomized Controlled Trial. *Canadian Respiratory Journal*. 2019;2019.
1037. Wimms AJ, Kelly JL, Turnbull CD, et al. Continuous positive airway pressure versus standard care for the treatment of people with mild obstructive sleep apnoea (MERGE): a multicentre, randomised controlled trial. *Lancet Resp Med*. 2020;8(4):349-358.
1038. Pepin JL, Tamisier R, Baguet JP, et al. Fixed-pressure CPAP versus auto-adjusting CPAP: comparison of efficacy on blood pressure in obstructive sleep apnoea, a randomised clinical trial. *Thorax*. 2016;71(8):726-733.
1039. Sarac S, Afsar GC, Oruc O, Topcuoglu OB, Salturk C, Peker Y. Impact of Patient Education on Compliance with Positive Airway Pressure Treatment in Obstructive Sleep Apnea. *Medical science monitor : international medical journal of experimental and clinical research*. 2017;23:1792-1799.
1040. Ballard RD, Gay PC, Strollo PJ. Interventions to improve compliance in sleep apnea patients previously non-compliant with continuous positive airway pressure. *J Clin Sleep Med*. 2007;3(7):706-712.
1041. Nigam G, Pathak C, Riaz M. A systematic review on prevalence and risk factors associated with treatment-emergent central sleep apnea. *Ann Thorac Med*. 2016;11(3):202-210.
1042. Selim B, Ramar K. Advanced positive airway pressure modes: adaptive servo ventilation and volume assured pressure support (vol 13, pg 839, 2016). *Expert Rev Med Devic*. 2016;13(9):878-878.

1043. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *New Engl J Med*. 2015;373(12):1095-1105.
1044. Knitter J, Bailey OF, Poongkunran C, et al. Comparison of Physiological Performance of Four Adaptive Servo Ventilation Devices in Patients with Complex Sleep Apnea. *Am J Resp Crit Care*. 2019;199(7):925-928.
1045. Kuzniar TJ, Patel S, Nierodzik CL, Smith LC. Comparison of two servo ventilator devices in the treatment of complex sleep apnea. *Sleep Med*. 2011;12(6):538-541.
1046. Allam JS, Olson EJ, Gay PC, Morgenthaler TI. Efficacy of adaptive servoventilation in treatment of complex and central sleep apnea syndromes. *Chest*. 2007;132(6):1839-1846.
1047. Brown SE, Mosko SS, Davis JA, Pierce RA, Godfrey-Pixton TV. A Retrospective Case Series of Adaptive Servoventilation for Complex Sleep Apnea. *Journal of Clinical Sleep Medicine*. 2011;7(2):187-195.
1048. Dellweg D, Kerl J, Hoehn E, Wenzel M, Koehler D. Randomized Controlled Trial of Noninvasive Positive Pressure Ventilation (NPPV) Versus Servoventilation in Patients with CPAP-Induced Central Sleep Apnea (Complex Sleep Apnea). *Sleep*. 2013;36(8):1163-1171.
1049. Huseini T, Mcardle N, Jasper E, et al. The Use and Efficacy of Adaptive Servo-Ventilation. *J Sleep Res*. 2017;26:69-69.
1050. Morgenthaler TI, Gay PC, Gordon N, Brown LK. Adaptive servoventilation versus noninvasive positive pressure ventilation for central, mixed, and complex sleep apnea syndromes. *Sleep*. 2007;30(4):468-475.
1051. Morgenthaler TI, Kuzniar TJ, Wolfe LF, Willes L, McLain WC, Goldberg R. The Complex Sleep Apnea Resolution Study: A Prospective Randomized Controlled Trial of Continuous Positive Airway Pressure Versus Adaptive Servoventilation Therapy. *Sleep*. 2014;37(5):927-U297.
1052. Pepin JLD, Woehrle H, Liu DQ, et al. Adherence to Positive Airway Therapy After Switching From CPAP to ASV: A Big Data Analysis. *Journal of Clinical Sleep Medicine*. 2018;14(1):57-63.
1053. Su M, Zhang X, Huang M, Ding N. Adaptive pressure support servoventilation: a novel treatment for residual sleepiness associated with central sleep apnea events. *Sleep Breath*. 2011;15(4):695-699.
1054. Yoshimura C, Toyoshima H, Matsumoto T, et al. Adaptive Servo-Ventilation (Asv) Therapy Improves Long-Term Prognosis in Patients with Complex Sleep Apnea Syndrome (Comp Sas) Better Than Cheyne-Stokes Respiration (Csr)-Central Sleep Apnea (Csa). *J Sleep Res*. 2017;26:71-71.
1055. Javaheri S, Harris N, Howard J, Chung E. Adaptive servoventilation for treatment of opioid-associated central sleep apnea. *J Clin Sleep Med*. 2014;10(6):637-643.
1056. Aurora RN, Bista SR, Casey KR, et al. Updated Adaptive Servo-Ventilation Recommendations for the 2012 AASM Guideline: "The Treatment of Central Sleep Apnea Syndromes in Adults: Practice Parameters with an Evidence-Based Literature Review and Meta-Analyses". *J Clin Sleep Med*. 2016;12(5):757-761.
1057. Bachour A, Vitikainen P, Maasilta P. Rates of initial acceptance of PAP masks and outcomes of mask switching. *Sleep Breath*. 2016;20(2):733-738.
1058. Chai CL, Pathinathan A, Smith B. Continuous positive airway pressure delivery interfaces for obstructive sleep apnoea. *Cochrane Db Syst Rev*. 2006(4).
1059. Andrade RGS, Viana FM, Nascimento JA, et al. Nasal vs Oronasal CPAP for OSA Treatment: A Meta-Analysis. *Chest*. 2018;153(3):665-674.
1060. Borel JC, Tamisier R, Dias-Domingos S, et al. Type of mask may impact on continuous positive airway pressure adherence in apneic patients. *PLoS one*. 2013;8(5):e64382.

1061. Anderson FE, Kingshott RN, Taylor DR, Jones DR, Kline LR, Whyte KF. A randomized crossover efficacy trial of oral CPAP (Oracle) compared with nasal CPAP in the management of obstructive sleep apnea. *Sleep*. 2003;26(6):721-726.
1062. Ebben MR, Narizhnaya M, Segal AZ, Barone D, Krieger AC. A randomised controlled trial on the effect of mask choice on residual respiratory events with continuous positive airway pressure treatment. *Sleep Med*. 2014;15(6):619-624.
1063. Ebben MR, Oyegbile T, Pollak CP. The efficacy of three different mask styles on a PAP titration night. *Sleep Med*. 2012;13(6):645-649.
1064. Goh KJ, Soh RY, Leow LC, et al. Choosing the right mask for your Asian patient with sleep apnoea: A randomized, crossover trial of CPAP interfaces. *Respirology*. 2019;24(3):278-285.
1065. Khanna R, Kline LR. A prospective 8 week trial of nasal interfaces vs. a novel oral interface (Oracle) for treatment of obstructive sleep apnea hypopnea syndrome. *Sleep Med*. 2003;4(4):333-338.
1066. Massie CA, Hart RW. Clinical outcomes related to interface type in patients with obstructive sleep apnea/hypopnea syndrome who are using continuous positive airway pressure. *Chest*. 2003;123(4):1112-1118.
1067. Mortimore IL, Whittle AT, Douglas NJ. Comparison of nose and face mask CPAP therapy for sleep apnoea. *Thorax*. 1998;53(4):290-292.
1068. Rowland S, Aiyappan V, Hennessy C, et al. Comparing the Efficacy, Mask Leak, Patient Adherence, and Patient Preference of Three Different CPAP Interfaces to Treat Moderate-Severe Obstructive Sleep Apnea. *J Clin Sleep Med*. 2018;14(1):101-108.
1069. Ryan S, Garvey JF, Swan V, Behan R, McNicholas WT. Nasal pillows as an alternative interface in patients with obstructive sleep apnoea syndrome initiating continuous positive airway pressure therapy. *J Sleep Res*. 2011;20(2):367-373.
1070. Teo M, Amis T, Lee S, Falland K, Lambert S, Wheatley J. Equivalence of nasal and oronasal masks during initial CPAP titration for obstructive sleep apnea syndrome. *Sleep*. 2011;34(7):951-955.
1071. Zhu X, Wimms AJ, Benjafield AV. Assessment of the performance of nasal pillows at high CPAP pressures. *J Clin Sleep Med*. 2013;9(9):873-877.
1072. Beecroft J, Zanon S, Lukic D, Hanly P. Oral continuous positive airway pressure for sleep apnea: effectiveness, patient preference, and adherence. *Chest*. 2003;124(6):2200-2208.
1073. Bettinzoli M, Taranto-Montemurro L, Messineo L, et al. Oronasal masks require higher levels of positive airway pressure than nasal masks to treat obstructive sleep apnea. *Sleep Breath*. 2014;18(4):845-849.
1074. Deshpande S, Joosten S, Turton A, et al. Oronasal masks require a higher pressure than nasal and nasal pillow masks for the treatment of obstructive sleep apnea. *Journal of Clinical Sleep Medicine*. 2016;12(9):1263-1268.
1075. Laaka A, Hollmen M, Bachour A. Evaluation of CPAP mask performance during 3 years of mask usage: time for reconsideration of renewal policies? *BMJ Open Respir Res*. 2021;8(1).
1076. Calero G, Farre R, Ballester E, Hernandez L, Daniel N, Canal JMM. Physiological consequences of prolonged periods of flow limitation in patients with sleep apnea hypopnea syndrome. *Resp Med*. 2006;100(5):813-817.
1077. Meurice J, Paquereau J, Denjean A, Patte F, Series F. Influence of correction of flow limitation on continuous positive airway pressure efficiency in sleep apnoea/hypopnoea syndrome. *Eur Respir J*. 1998;11(5):1121-1127.
1078. Kushida CA, Chediak A, Berry RB, et al. Clinical Guidelines for the Manual Titration of Positive Airway Pressure in Patients with Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine*. 2008;4(2):157-+.

1079. Morgenthaler TI, Aurora RN, Brown T, et al. Practice parameters for the use of autotitrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome: an update for 2007. An American Academy of Sleep Medicine report. *Sleep*. 2008;31(1):141-147.
1080. Bureau M, Series F. Comparison of two in-laboratory titration methods to determine effective pressure levels in patients with obstructive sleep apnoea. *Thorax*. 2000;55(9):741-745.
1081. Mc Ardle N, Grove A, Devereux G, Mackay-Brown L, Mackay T, Douglas N. Split-night versus full-night studies for sleep apnoea/hypopnoea syndrome. *Eur Respir J*. 2000;15(4):670-675.
1082. Sanders MH, Montserrat JM, Farre R, Givelber RJ. Positive pressure therapy: a perspective on evidence-based outcomes and methods of application. *Proceedings of the American Thoracic Society*. 2008;5(2):161-172.
1083. Patel NP, Ahmed M, Rosen I. Split-night polysomnography. *Chest*. 2007;132(5):1664-1671.
1084. Hoffstein V, Mateika S. Predicting nasal continuous positive airway pressure. *Am J Respir Crit Care Med*. 1994;150(2):486-488.
1085. Ebben MR, Narizhnaya M, Krieger AC. A new predictive model for continuous positive airway pressure in the treatment of obstructive sleep apnea. *Sleep Breath*. 2017;21(2):435-442.
1086. Rowley JA, Tarbichi AG, Badr MS. The use of a predicted CPAP equation improves CPAP titration success. *Sleep Breath*. 2005;9(1):26-32.
1087. Fitzpatrick MF, Alloway CE, Wakeford TM, MacLean AW, Munt PW, Day AG. Can patients with obstructive sleep apnea titrate their own continuous positive airway pressure? *Am J Respir Crit Care Med*. 2003;167(5):716-722.
1088. Lugo VM, Garmendia O, Suarez-Giron M, et al. Comprehensive management of obstructive sleep apnea by telemedicine: Clinical improvement and cost-effectiveness of a Virtual Sleep Unit. A randomized controlled trial. *PLoS one*. 2019;14(10):e0224069.
1089. Masa JF, Jimenez A, Duran J, et al. Alternative methods of titrating continuous positive airway pressure: a large multicenter study. *Am J Respir Crit Care Med*. 2004;170(11):1218-1224.
1090. Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1993;147(4):887-895.
1091. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Continuous Positive Airway Pressure (CPAP) Therapy For Obstructive Sleep Apnea (OSA) (240.4). 2008. <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?ncdid=226&ncdver=3&keyword=CPAP&keywordType=starts&areaid=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=AAAAAAQAAAAA&KeyWordLookUp=Doc&KeyWordSearchType=Exact>. Published March 13, 2008. Accessed April 1, 2021.
1092. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): Positive Airway Pressure (PAP) Devices for the Treatment of Obstructive Sleep Apnea (L33718). 2020. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33718>. Published January 1, 2020. Accessed April 1, 2021.
1093. Centers for Medicare & Medicaid Services. Local Coverage Article: Positive Airway Pressure (PAP) Devices for the Treatment of Obstructive Sleep Apnea - Policy Article (A52467). 2020. <https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleid=52467&ver=35&keyword=CPAP&keywordType=starts&areaid=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=AAAAAAQAAAAA&KeyWordLookUp=Doc&KeyWordSearchType=Exact>. Published April 3, 2020. Accessed April 1, 2021.
1094. Borker PV, Carmona E, Essien UR, et al. Neighborhoods with Greater Prevalence of Minority Residents Have Lower CPAP Adherence. *Am J Respir Crit Care Med*. 2021.

1095. Patel SR, Bakker JP, Stitt CJ, Aloia MS, Nourai SM. Age and Sex Disparities in Adherence to CPAP. *Chest*. 2021;159(1):382-389.
1096. Platt AB, Field SH, Asch DA, et al. Neighborhood of residence is associated with daily adherence to CPAP therapy. *Sleep*. 2009;32(6):799-806.
1097. Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep*. 2007;30(6):711-719.
1098. Rauscher H, Formanek D, Popp W, Zwick H. Self-reported vs measured compliance with nasal CPAP for obstructive sleep apnea. *Chest*. 1993;103(6):1675-1680.
1099. Meurice JC, Dore P, Paquereau J, et al. Predictive factors of long-term compliance with nasal continuous positive airway pressure treatment in sleep apnea syndrome. *Chest*. 1994;105(2):429-433.
1100. Pepin JL, Leger P, Veale D, Langevin B, Robert D, Levy P. Side effects of nasal continuous positive airway pressure in sleep apnea syndrome. Study of 193 patients in two French sleep centers. *Chest*. 1995;107(2):375-381.
1101. Engleman HM, Asgari-Jirhandeh N, McLeod AL, Ramsay CF, Deary IJ, Douglas NJ. Self-reported use of CPAP and benefits of CPAP therapy: a patient survey. *Chest*. 1996;109(6):1470-1476.
1102. Drake CL, Day R, Hudgel D, et al. Sleep during titration predicts continuous positive airway pressure compliance. *Sleep*. 2003;26(3):308-311.
1103. Means MK, Lichstein KL, Edinger JD, et al. Changes in depressive symptoms after continuous positive airway pressure treatment for obstructive sleep apnea. *Sleep Breath*. 2003;7(1):31-42.
1104. Engleman HM, Wild MR. Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHS). *Sleep Med Rev*. 2003;7(1):81-99.
1105. Aloia MS, Arnedt JT, Stepnowsky C, Hecht J, Borrelli B. Predicting treatment adherence in obstructive sleep apnea using principles of behavior change. *J Clin Sleep Med*. 2005;1(4):346-353.
1106. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev*. 2011;15(6):343-356.
1107. Bakker JP, O'Keefe KM, Neill AM, Campbell AJ. Ethnic disparities in CPAP adherence in New Zealand: effects of socioeconomic status, health literacy and self-efficacy. *Sleep*. 2011;34(11):1595-1603.
1108. Billings ME, Auckley D, Benca R, et al. Race and residential socioeconomic status as predictors of CPAP adherence. *Sleep*. 2011;34(12):1653-1658.
1109. Billings ME, Rosen CL, Wang R, et al. Is the relationship between race and continuous positive airway pressure adherence mediated by sleep duration? *Sleep*. 2013;36(2):221-227.
1110. Budhiraja R, Parthasarathy S, Drake CL, et al. Early CPAP use identifies subsequent adherence to CPAP therapy. *Sleep*. 2007;30(3):320-324.
1111. Schwartz SW, Sebastiao Y, Rosas J, Iannacone MR, Foulis PR, Anderson WM. Racial disparity in adherence to positive airway pressure among US veterans. *Sleep Breath*. 2016;20(3):947-955.
1112. Lewis KE, Seale L, Bartle IE, Watkins AJ, Ebdon P. Early predictors of CPAP use for the treatment of obstructive sleep apnea. *Sleep*. 2004;27(1):134-138.
1113. McArdle N, Devereux G, Heidarnjad H, Engleman HM, Mackay TW, Douglas NJ. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med*. 1999;159(4 Pt 1):1108-1114.
1114. Pelletier-Fleury N, Rakotonanahary D, Fleury B. The age and other factors in the evaluation of compliance with nasal continuous positive airway pressure for obstructive sleep apnea syndrome. A Cox's proportional hazard analysis. 2001;2(3):225-232.

1115. Sin DD, Mayers I, Man GC, Pawluk L. Long-term compliance rates to continuous positive airway pressure in obstructive sleep apnea: a population-based study. *Chest*. 2002;121(2):430-435.
1116. Stepnowsky CJ, Bardwell WA, Moore PJ, Ancoli-Israel S, Dimsdale JE. Psychologic correlates of compliance with continuous positive airway pressure. *Sleep*. 2002;25(7):758-762.
1117. Stepnowsky CJ, Marler MR, Ancoli-Israel S. Determinants of nasal CPAP compliance. *Sleep Med*. 2002;3(3):239-247.
1118. Lloberes P, Marti S, Sampol G, et al. Predictive factors of quality-of-life improvement and continuous positive airway pressure use in patients with sleep apnea-hypopnea syndrome: study at 1 year. *Chest*. 2004;126(4):1241-1247.
1119. Wild MR, Engleman HM, Douglas NJ, Espie CA. Can psychological factors help us to determine adherence to CPAP? A prospective study. *Eur Respir J*. 2004;24(3):461-465.
1120. Stepnowsky CJ, Marler MR, Palau J, Annette Brooks J. Social-cognitive correlates of CPAP adherence in experienced users. *Sleep Med*. 2006;7(4):350-356.
1121. Kohler M, Smith D, Tippett V, Stradling JR. Predictors of long-term compliance with continuous positive airway pressure. *Thorax*. 2010;65(9):829-832.
1122. Wallace DM, Shafazand S, Aloia MS, Wohlgemuth WK. The association of age, insomnia, and self-efficacy with continuous positive airway pressure adherence in black, white, and Hispanic U.S. Veterans. *J Clin Sleep Med*. 2013;9(9):885-895.
1123. Wallace DM, Sawyer AM, Shafazand S. Comorbid insomnia symptoms predict lower 6-month adherence to CPAP in US veterans with obstructive sleep apnea. *Sleep Breath*. 2018;22(1):5-15.
1124. Schoch OD, Baty F, Niedermann J, Rudiger JJ, Brutsche MH. Baseline predictors of adherence to positive airway pressure therapy for sleep apnea: a 10-year single-center observational cohort study. *Respiration*. 2014;87(2):121-128.
1125. Budhiraja R, Kushida CA, Nichols DA, et al. Impact of Randomization, Clinic Visits, and Medical and Psychiatric Comorbidities on Continuous Positive Airway Pressure Adherence in Obstructive Sleep Apnea. *J Clin Sleep Med*. 2016;12(3):333-341.
1126. Dzierzewski JM, Wallace DM, Wohlgemuth WK. Adherence to Continuous Positive Airway Pressure in Existing Users: Self-Efficacy Enhances the Association between Continuous Positive Airway Pressure and Adherence. *J Clin Sleep Med*. 2016;12(2):169-176.
1127. Jacobsen AR, Eriksen F, Hansen RW, et al. Determinants for adherence to continuous positive airway pressure therapy in obstructive sleep apnea. *PLoS one*. 2017;12(12):e0189614.
1128. Hoshino T, Sasanabe R, Tanigawa T, et al. Effect of rapid eye movement-related obstructive sleep apnea on adherence to continuous positive airway pressure. *J Int Med Res*. 2018;46(6):2238-2248.
1129. Liou HYS, Kapur VK, Consens F, Billings ME. The Effect of Sleeping Environment and Sleeping Location Change on Positive Airway Pressure Adherence. *J Clin Sleep Med*. 2018;14(10):1645-1652.
1130. Philip P, Bioulac S, Altena E, et al. Specific insomnia symptoms and self-efficacy explain CPAP compliance in a sample of OSAS patients. *PLoS one*. 2018;13(4):e0195343.
1131. Baron CE, Smith TW, Baucom BR, et al. Relationship partner social behavior and continuous positive airway pressure adherence: The role of autonomy support. *Health Psychol*. 2020;39(4):325-334.
1132. Richards D, Bartlett DJ, Wong K, Malouff J, Grunstein RR. Increased adherence to CPAP with a group cognitive behavioral treatment intervention: A randomized trial. *Sleep*. 2007;30(5):635-640.
1133. Wozniak DR, Lasserson TJ, Smith I. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Db Syst Rev*. 2014(1).

1134. Chervin RD, Theut S, Bassetti C, Aldrich MS. Compliance with nasal CPAP can be improved by simple interventions. *Sleep*. 1997;20(4):284-289.
1135. Falcone VA, Damiani MF, Quaranta VN, Capozzolo A, Resta O. Polysomnograph Chart View by Patients: A New Educational Strategy to Improve CPAP Adherence in Sleep Apnea Therapy. *Resp Care*. 2014;59(2):193-198.
1136. Hwang D, Chang JW, Benjafield AV, et al. Effect of Telemedicine Education and Telemonitoring on Continuous Positive Airway Pressure Adherence. The Tele-OSA Randomized Trial. *Am J Respir Crit Care Med*. 2018;197(1):117-126.
1137. Pengo MF, Czaban M, Berry MP, et al. The effect of positive and negative message framing on short term continuous positive airway pressure compliance in patients with obstructive sleep apnea. *Journal of Thoracic Disease*. 2018;10:S160-S169.
1138. Roecklein KA, Schumacher JA, Gabriele JM, Fagan C, Baran AS, Richert AC. Personalized Feedback to Improve CPAP Adherence in Obstructive Sleep Apnea. *Behav Sleep Med*. 2010;8(2):105-112.
1139. Fox N, Hirsch-Allen AJ, Goodfellow E, et al. The Impact of a Telemedicine Monitoring System on Positive Airway Pressure Adherence in Patients with Obstructive Sleep Apnea: A Randomized Controlled Trial. *Sleep*. 2012;35(4):477-481.
1140. Hoy CJ, Vennelle M, Kingshott RN, Engleman HM, Douglas NJ. Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome? *Am J Resp Crit Care*. 1999;159(4):1096-1100.
1141. Parthasarathy S, Wendel C, Haynes PL, Atwood C, Kuna S. A Pilot Study of CPAP Adherence Promotion by Peer Buddies with Sleep Apnea. *Journal of Clinical Sleep Medicine*. 2013;9(6):543-550.
1142. DeMolles DA, Sparrow D, Gottlieb DJ, Friedman R. A pilot trial of a telecommunications system in sleep apnea management. *Med Care*. 2004;42(8):764-769.
1143. Hoet F, Libert W, Sanida C, Van den Broecke S, Bruyneel AV, Bruyneel M. Telemonitoring in continuous positive airway pressure-treated patients improves delay to first intervention and early compliance: a randomized trial. *Sleep Med*. 2017;39:77-83.
1144. Mendelson M, Vivodtzev I, Tamisier R, et al. CPAP treatment supported by telemedicine does not improve blood pressure in high cardiovascular risk OSA patients: a randomized, controlled trial. *Sleep*. 2014;37(11):1863-1870.
1145. Munafo D, Hevener W, Crocker M, Willes L, Sridasome S, Muhsin M. A telehealth program for CPAP adherence reduces labor and yields similar adherence and efficacy when compared to standard of care. *Sleep Breath*. 2016;20(2):777-785.
1146. Pepin JL, Jullian-Desayes I, Sapene M, et al. Multimodal Remote Monitoring of High Cardiovascular Risk Patients With OSA Initiating CPAP A Randomized Trial. *Chest*. 2019;155(4):730-739.
1147. Stepnowsky CJ, Palau JJ, Marler MR, Gifford AL. Pilot randomized trial of the effect of wireless telemonitoring on compliance and treatment. *Journal of Medical Internet Research*. 2007;9(2).
1148. Stepnowsky C, Edwards C, Zamora T, Barker R, Agha Z. Patient Perspective on Use of an Interactive Website for Sleep Apnea. *Int J Telemed Appl*. 2013;2013.
1149. Turino C, de Batlle J, Woehrle H, et al. Management of continuous positive airway pressure treatment compliance using telemonitoring in obstructive sleep apnoea. *Eur Respir J*. 2017;49(2).
1150. Aloia MS, Di Dio L, Illiczky N, Perlis ML, Greenblatt DW, Giles DE. Improving compliance with nasal CPAP and vigilance in older adults with OAHs. *Sleep Breath*. 2001;5(1):13-21.
1151. Bakker JP, Wang R, Weng J, et al. Motivational Enhancement for Increasing Adherence to CPAP A Randomized Controlled Trial. *Chest*. 2016;150(2):337-345.

1152. Lai AYK, Fong DYT, Lam JCM, Weaver TE, Ip MSM. The Efficacy of a Brief Motivational Enhancement Education Program on CPAP Adherence in OSA A Randomized Controlled Trial. *Chest*. 2014;146(3):600-610.
1153. Dantas APT, Winck JC, Figueiredo-Braga M. Adherence to APAP in obstructive sleep apnea syndrome: effectiveness of a motivational intervention. *Sleep Breath*. 2015;19(1):327-334.
1154. Olsen S, Smith SS, Oei TPS, Douglas J. Motivational Interviewing (MINT) Improves Continuous Positive Airway Pressure (CPAP) Acceptance and Adherence: A Randomized Controlled Trial. *J Consult Clin Psych*. 2012;80(1):151-163.
1155. Wang WH, He GP, Wang MR, Liu LH, Tang HQ. Effects of patient education and progressive muscle relaxation alone or combined on adherence to continuous positive airway pressure treatment in obstructive sleep apnea patients. *Sleep Breath*. 2012;16(4):1049-1057.
1156. Watson NF, Mystkowski SK. Aerophagia and Gastroesophageal Reflux Disease in Patients using Continuous Positive Airway Pressure: A Preliminary Observation. *Journal of Clinical Sleep Medicine*. 2008;4(5):434-438.
1157. Shirlaw T, Hanssen K, Duce B, Hukins C. A Randomized Crossover Trial Comparing Autotitrating and Continuous Positive Airway Pressure in Subjects With Symptoms of Aerophagia: Effects on Compliance and Subjective Symptoms. *Journal of Clinical Sleep Medicine*. 2017;13(7):881-888.
1158. Weaver TE. Adherence to positive airway pressure therapy. *Current Opinion in Pulmonary Medicine*. 2006;12(6):409-413.
1159. Edmonds JC, Yang H, King TS, Sawyer DA, Rizzo A, Sawyer AM. Claustrophobic tendencies and continuous positive airway pressure therapy non-adherence in adults with obstructive sleep apnea. *Heart Lung*. 2015;44(2):100-106.
1160. Edinger JD, Radtke RA. Use of in vivo desensitization to treat a patient's claustrophobic response to nasal CPAP. *Sleep*. 1993;16(7):678-680.
1161. McCrae CS, Rowe MA, Dautovich ND, et al. Sleep hygiene practices in two community dwelling samples of older adults. *Sleep*. 2006;29(12):1551-1560.
1162. Means MK, Edinger JD. Graded exposure therapy for addressing claustrophobic reactions to continuous positive airway pressure: a case series report. *Behav Sleep Med*. 2007;5(2):105-116.
1163. Koutsourelakis I, Vagiakis E, Perraki E, et al. Nasal inflammation in sleep apnoea patients using CPAP and effect of heated humidification. *Eur Respir J*. 2011;37(3):587-594.
1164. Zhu D, Wu M, Cao Y, et al. Heated humidification did not improve compliance of positive airway pressure and subjective daytime sleepiness in obstructive sleep apnea syndrome: A meta-analysis. *PLoS one*. 2018;13(12):e0207994.
1165. Kennedy B, Lasserson TJ, Wozniak DR, Smith I. Pressure modification or humidification for improving usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Db Syst Rev*. 2019(12).
1166. Palm A, Midgren B, Theorell-Haglow J, et al. Factors influencing adherence to continuous positive airway pressure treatment in obstructive sleep apnea and mortality associated with treatment failure - a national registry-based cohort study. *Sleep Med*. 2018;51:85-91.
1167. Wiest GH, Harsch IA, Fuchs FS, et al. Initiation of CPAP therapy for OSA: Does prophylactic humidification during CPAP pressure titration improve initial patient acceptance and comfort? *Respiration*. 2002;69(5):406-412.
1168. Varendh M, Andersson M, Bjornsdottir E, et al. Nocturnal nasal obstruction is frequent and reduces sleep quality in patients with obstructive sleep apnea. *J Sleep Res*. 2018;27(4).
1169. Li HY, Engleman H, Hsu CY, et al. Acoustic reflection for nasal airway measurement in patients with obstructive sleep apnea-hypopnea syndrome. *Sleep*. 2005;28(12):1554-1559.
1170. Varendh M, Andersson M, Bjornsdottir E, et al. PAP treatment in patients with OSA does not induce long-term nasal obstruction. *J Sleep Res*. 2019;28(5):e12768.



1171. Mehrtash M, Bakker JP, Ayas N. Predictors of Continuous Positive Airway Pressure Adherence in Patients with Obstructive Sleep Apnea. *Lung*. 2019;197(2):115-121.
1172. Van Ryswyk E, Anderson CS, Antic NA, et al. Predictors of long-term adherence to continuous positive airway pressure in patients with obstructive sleep apnea and cardiovascular disease. *Sleep*. 2019;42(10).
1173. Skirko JR, James KT, Shusterman DJ, Weaver EM. Association of Allergic Rhinitis With Change in Nasal Congestion in New Continuous Positive Airway Pressure Users. *JAMA Otolaryngol Head Neck Surg*. 2020;146(6):523-529.
1174. Cisternas A, Aguilar F, Montserrat JM, et al. Effects of CPAP in patients with obstructive apnoea: is the presence of allergic rhinitis relevant? *Sleep Breath*. 2017;21(4):893-900.
1175. Balsalobre L, Pezato R, Mangussi-Gomes J, et al. What is the Impact of Positive Airway Pressure in Nasal Polyposis? An Experimental Study. *Int Arch Otorhinolar*. 2019;23(2):147-151.
1176. La Mantia I, Andaloro C. Effectiveness of intranasal sodium hyaluronate in mitigating adverse effects of nasal continuous positive airway pressure therapy. *Am J Rhinol Allergy*. 2017;31(6):364-369.
1177. Ryan S, Doherty LS, Nolan GM, McNicholas WT. Effects of Heated Humidification and Topical Steroids on Compliance, Nasal Symptoms, and Quality of Life in Patients with Obstructive Sleep Apnea Syndrome Using Nasal Continuous Positive Airway Pressure. *Journal of Clinical Sleep Medicine*. 2009;5(5):422-427.
1178. Charakorn N, Hirunwiwatkul P, Chirakalwasan N, Chaitusaney B, Prakassajjatham M. The effects of topical nasal steroids on continuous positive airway pressure compliance in patients with obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Breath*. 2017;21(1):3-8.
1179. Camacho M, Riaz M, Capasso R, et al. The Effect of Nasal Surgery on Continuous Positive Airway Pressure Device Use and Therapeutic Treatment Pressures: A Systematic Review and Meta-Analysis. *Sleep*. 2015;38(2):279-+.
1180. Kempfle JS, BuSaba NY, Dobrowski JM, Westover MB, Bianchi MT. A cost-effectiveness analysis of nasal surgery to increase continuous positive airway pressure adherence in sleep apnea patients with nasal obstruction. *Laryngoscope*. 2017;127(4):977-983.
1181. Nigam G, Riaz M, Chang ET, Camacho M. Natural history of treatment-emergent central sleep apnea on positive airway pressure: A systematic review. *Ann Thorac Med*. 2018;13(2):86-91.
1182. Javaheri S, Goetting MG, Khayat R, Wylie PE, Goodwin JL, Parthasarathy S. The Performance of Two Automatic Servo-Ventilation Devices in the Treatment of Central Sleep Apnea. *Sleep*. 2011;34(12):1693-1698.
1183. Heider K, Arzt M, Lerzer C, et al. Adaptive servo-ventilation and sleep quality in treatment emergent central sleep apnea and central sleep apnea in patients with heart disease and preserved ejection fraction. *Clin Res Cardiol*. 2018;107(5):421-429.
1184. Javaheri S, Winslow D, McCullough P, Wylie P, Kryger MH. The Use of a Fully Automated Automatic Adaptive Servoventilation Algorithm in the Acute and Long-term Treatment of Central Sleep Apnea. *Chest*. 2015;148(6):1454-1461.
1185. Neu D, Balkissou AD, Mairesse O, Pefura-Yone EW, Nosedá A. Complex sleep apnea at auto-titrating CPAP initiation: prevalence, significance and predictive factors. *Clinical Respiratory Journal*. 2017;11(2):200-209.
1186. Alessi CA, Fung CH, Dzierzewski JM, et al. Randomized controlled trial of an integrated approach to treating insomnia and improving the use of positive airway pressure therapy in veterans with comorbid insomnia disorder and obstructive sleep apnea. *Sleep*. 2021;44(4).
1187. Ong JC, Crawford MR, Dawson SC, et al. A randomized controlled trial of CBT-I and PAP for obstructive sleep apnea and comorbid insomnia: main outcomes from the MATRICS study. *Sleep*. 2020;43(9).

1188. Sweetman A, Lack L, Bastien C. Co-Morbid Insomnia and Sleep Apnea (COMISA): Prevalence, Consequences, Methodological Considerations, and Recent Randomized Controlled Trials. *Brain Sci.* 2019;9(12).
1189. Sweetman A, Lack L, Catcheside PG, et al. Cognitive and behavioral therapy for insomnia increases the use of continuous positive airway pressure therapy in obstructive sleep apnea participants with comorbid insomnia: a randomized clinical trial. *Sleep.* 2019;42(12).
1190. Sweetman A, Lack L, McEvoy RD, et al. Cognitive behavioural therapy for insomnia reduces sleep apnoea severity: a randomised controlled trial. *Erj Open Research.* 2020;6(2).
1191. Bjorvatn B, Berge T, Lehmann S, Pallesen S, Saxvig IW. No Effect of a Self-Help Book for Insomnia in Patients With Obstructive Sleep Apnea and Comorbid Chronic Insomnia - A Randomized Controlled Trial. *Front Psychol.* 2018;9.
1192. Zhang XJ, Li QY, Wang Y, Xu HJ, Lin YN. The effect of non-benzodiazepine hypnotics on sleep quality and severity in patients with OSA: a meta-analysis. *Sleep Breath.* 2014;18(4):781-789.
1193. Luyster FS, Strollo PJ, Thunstrom E, Peker Y. Long-term use of continuous positive airway pressure therapy in coronary artery disease patients with nonsleepy obstructive sleep apnea. *Clin Cardiol.* 2017;40(12):1297-1302.
1194. Weaver TE, Kribbs NB, Pack AI, et al. Night-to-night variability in CPAP use over the first three months of treatment. *Sleep.* 1997;20(4):278-283.
1195. Schwab RJ, Badr SM, Epstein LJ, et al. An official American Thoracic Society statement: continuous positive airway pressure adherence tracking systems. The optimal monitoring strategies and outcome measures in adults. *Am J Respir Crit Care Med.* 2013;188(5):613-620.
1196. Malhotra A, Crocker ME, Willes L, Kelly C, Lynch S, Benjafield AV. Patient Engagement Using New Technology to Improve Adherence to Positive Airway Pressure Therapy A Retrospective Analysis. *Chest.* 2018;153(4):843-850.
1197. Kuna ST, Shuttleworth D, Chi L, et al. Web-Based Access to Positive Airway Pressure Usage with or without an Initial Financial Incentive Improves Treatment Use in Patients with Obstructive Sleep Apnea. *Sleep.* 2015;38(8):1229-1236.
1198. Marshall NS, Barnes M, Travier N, et al. Continuous positive airway pressure reduces daytime sleepiness in mild to moderate obstructive sleep apnoea: a meta-analysis. *Thorax.* 2006;61(5):430-434.
1199. McDaid C, Duree KH, Griffin SC, et al. A systematic review of continuous positive airway pressure for obstructive sleep apnoea-hypopnoea syndrome. *Sleep Medicine Reviews.* 2009;13(6):427-436.
1200. Gay P, Weaver T, Loubé D, et al. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep.* 2006;29(3):381-401.
1201. Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev.* 2006(1):CD001106.
1202. Sanchez-de-la-Torre M, Sanchez-de-la-Torre A, Bertran S, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med.* 2020;8(4):359-367.
1203. Huang ZW, Liu ZH, Luo Q, et al. Long-Term Effects of Continuous Positive Airway Pressure on Blood Pressure and Prognosis in Hypertensive Patients with Coronary Heart Disease and Obstructive Sleep Apnea: A Randomized Controlled Trial. *Am J Hypertens.* 2015;28(3):300-306.
1204. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom Subtypes of Obstructive Sleep Apnea Predict Incidence of Cardiovascular Outcomes. *Am J Respir Crit Care Med.* 2019;200(4):493-506.

1205. Pack AI, Magalang UJ, Singh B, Kuna ST, Keenan BT, Maislin G. Randomized clinical trials of cardiovascular disease in obstructive sleep apnea: understanding and overcoming bias. *Sleep*. 2021;44(2).
1206. Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension*. 2007;50(2):417-423.
1207. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea A Systematic Review and Meta-analysis. *Jama-J Am Med Assoc*. 2015;314(21):2280-2293.
1208. Fava C, Dorigoni S, Dalle Vedove F, et al. Effect of CPAP on blood pressure in patients with OSA/hypopnea a systematic review and meta-analysis. *Chest*. 2014;145(4):762-771.
1209. Iftikhar IH, Valentine CW, Bittencourt LR, et al. Effects of continuous positive airway pressure on blood pressure in patients with resistant hypertension and obstructive sleep apnea: a meta-analysis. *J Hypertens*. 2014;32(12):2341-2350; discussion 2350.
1210. Liu L, Cao Q, Guo Z, Dai Q. Continuous Positive Airway Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension: A Meta-Analysis of Randomized Controlled Trials. *Journal of clinical hypertension (Greenwich, Conn)*. 2016;18(2):153-158.
1211. Mansukhani MP, Somers VK, Shafazand S. PAP and Cardiovascular Events in Adults With Sleep Apnea: Is PAP Useful? *J Clin Sleep Med*. 2017;13(12):1487-1489.
1212. Bakker JP, Edwards BA, Gautam SP, et al. Blood pressure improvement with continuous positive airway pressure is independent of obstructive sleep apnea severity (vol 10, pg 365, 2014). *Journal of Clinical Sleep Medicine*. 2014;10(6):711-711.
1213. Turnbull F, Blood Pressure Lowering Treatment Trialists C. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362(9395):1527-1535.
1214. Fein AS, Shvilkin A, Shah D, et al. Treatment of Obstructive Sleep Apnea Reduces the Risk of Atrial Fibrillation Recurrence After Catheter Ablation. *J Am Coll Cardiol*. 2013;62(4):300-305.
1215. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation*. 2003;107(20):2589-2594.
1216. Srivali N, Chahal AC, Mansukhani MP, Mandrekar J, Somers VK, Caples SM. The Effect of Positive Airway Pressure Treatment of Obstructive and Central Sleep Apnea on the Recurrence of Atrial Fibrillation/Flutter Postintervention. *Journal of Clinical Sleep Medicine*. 2019;15(10):1459-1468.
1217. Caples SM, Mansukhani MP, Friedman PA, Somers VK. The impact of continuous positive airway pressure treatment on the recurrence of atrial fibrillation post cardioversion: A randomized controlled trial. *Int J Cardiol*. 2019;278:133-136.
1218. McMillan A, Bratton DJ, Faria R, et al. Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (PREDICT): a 12-month, multicentre, randomised trial. *Lancet Resp Med*. 2014;2(10):804-812.
1219. Aaronson JA, Hofman WF, van Bennekom CAM, et al. Effects of Continuous Positive Airway Pressure on Cognitive and Functional Outcome of Stroke Patients with Obstructive Sleep Apnea: A Randomized Controlled Trial. *Journal of Clinical Sleep Medicine*. 2016;12(4):533-541.
1220. Bravata DM, Concato J, Fried T, et al. Auto-Titrating Continuous Positive Airway Pressure for Patients With Acute Transient Ischemic Attack A Randomized Feasibility Trial. *Stroke*. 2010;41(7):1464-1470.
1221. Kim Y, Koo YS, Lee HY, Lee SY. Can Continuous Positive Airway Pressure Reduce the Risk of Stroke in Obstructive Sleep Apnea Patients? A Systematic Review and Meta-Analysis. *PLoS one*. 2016;11(1).

1222. King S, Cuellar N. Obstructive Sleep Apnea as an Independent Stroke Risk Factor: A Review of the Evidence, Stroke Prevention Guidelines, and Implications for Neuroscience Nursing Practice. *J Neurosci Nurs*. 2016;48(3):133-142.
1223. McKee Z, Wilson RD, Auckley DH. Evaluation of an OSA risk stratifying and treatment protocol during inpatient rehabilitation of post-stroke patients. *Sleep Breath*. 2020;24(2):513-521.
1224. Parra O, Sanchez-Armengol A, Capote F, et al. Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial. *J Sleep Res*. 2015;24(1):47-53.
1225. Parra O, Sanchez-Armengol A, Bonnin M, et al. Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial. *Eur Respir J*. 2011;37(5):1128-1136.
1226. Ryan CM, Bayley M, Green R, Murray BJ, Bradley TD. Influence of Continuous Positive Airway Pressure on Outcomes of Rehabilitation in Stroke Patients With Obstructive Sleep Apnea. *Stroke*. 2011;42(4):1062-1067.
1227. Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation*. 1998;97(21):2154-2159.
1228. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med*. 1999;160(4):1101-1106.
1229. Tkacova R, Rankin F, Fitzgerald FS, Floras JS, Bradley TD. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. *Circulation*. 1998;98(21):2269-2275.
1230. Aggarwal S, Nadeem R, Loomba RS, Nida M, Vieira D. The effects of continuous positive airways pressure therapy on cardiovascular end points in patients with sleep-disordered breathing and heart failure: a meta-analysis of randomized controlled trials. *Clin Cardiol*. 2014;37(1):57-65.
1231. Usui K, Bradley TD, Spaak J, et al. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. *J Am Coll Cardiol*. 2005;45(12):2008-2011.
1232. Gilman MP, Floras JS, Usui K, Kaneko Y, Leung RS, Bradley TD. Continuous positive airway pressure increases heart rate variability in heart failure patients with obstructive sleep apnoea. *Clin Sci (Lond)*. 2008;114(3):243-249.
1233. Yoshinaga K, Burwash IG, Leech JA, et al. The effects of continuous positive airway pressure on myocardial energetics in patients with heart failure and obstructive sleep apnea. *J Am Coll Cardiol*. 2007;49(4):450-458.
1234. Hall AB, Ziadi MC, Leech JA, et al. Effects of short-term continuous positive airway pressure on myocardial sympathetic nerve function and energetics in patients with heart failure and obstructive sleep apnea: a randomized study. *Circulation*. 2014;130(11):892-901.
1235. Ferrier KA, Neill AM, O'Meeghan T, Richards M, Campbell AJ. Continuous positive airway pressure in heart failure patients with obstructive sleep apnoea. *Intern Med J*. 2008;38(11):829-836.
1236. Johnson CB, Beanlands RS, Yoshinaga K, et al. Acute and chronic effects of continuous positive airway pressure therapy on left ventricular systolic and diastolic function in patients with obstructive sleep apnea and congestive heart failure. *Can J Cardiol*. 2008;24(9):697-704.
1237. Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. *Lancet*. 1991;338(8781):1480-1484.

1238. Smith LA, Vennelle M, Gardner RS, et al. Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo-controlled trial. *Eur Heart J*. 2007;28(10):1221-1227.
1239. Lisi E, Faini A, Bilo G, et al. Diastolic dysfunction in controlled hypertensive patients with mild-moderate obstructive sleep apnea. *Int J Cardiol*. 2015;187:686-692.
1240. Cloward TV, Walker JM, Farney RJ, Anderson JL. Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. *Chest*. 2003;124(2):594-601.
1241. Akar Bayram N, Ciftci B, Durmaz T, et al. Effects of continuous positive airway pressure therapy on left ventricular function assessed by tissue Doppler imaging in patients with obstructive sleep apnoea syndrome. *Eur J Echocardiogr*. 2009;10(3):376-382.
1242. Alchanatis M, Paradellis G, Pini H, Tourkohoriti G, Jordanoglou J. Left ventricular function in patients with obstructive sleep apnoea syndrome before and after treatment with nasal continuous positive airway pressure. *Respiration*. 2000;67(4):367-371.
1243. Dursunoglu N, Dursunoglu D, Ozkurt S, et al. Effects of CPAP on left ventricular structure and myocardial performance index in male patients with obstructive sleep apnoea. *Sleep Med*. 2007;8(1):51-59.
1244. Glantz H, Johansson MC, Thunstrom E, et al. Effect of CPAP on diastolic function in coronary artery disease patients with nonsleepy obstructive sleep apnea: A randomized controlled trial. *Int J Cardiol*. 2017;241:12-18.
1245. Shivalkar B, Van de Heyning C, Kerremans M, et al. Obstructive sleep apnea syndrome: more insights on structural and functional cardiac alterations, and the effects of treatment with continuous positive airway pressure. *J Am Coll Cardiol*. 2006;47(7):1433-1439.
1246. Craig S, Kyliantreas I, Kohler M, et al. Effect of CPAP on Cardiac Function in Minimally Symptomatic Patients with OSA: Results from a Subset of the MOSAIC Randomized Trial. *J Clin Sleep Med*. 2015;11(9):967-973.
1247. Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. *Eur Respir J*. 2006;28(3):596-602.
1248. Buchner NJ, Sanner BM, Borgel J, Rump LC. Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. *Am J Resp Crit Care*. 2007;176(12):1274-1280.
1249. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. *Chest*. 2005;127(6):2076-2084.
1250. Cassar A, Morgenthaler TI, Lennon RJ, Rihal CS, Lerman A. Treatment of obstructive sleep apnea is associated with decreased cardiac death after percutaneous coronary intervention. *J Am Coll Cardiol*. 2007;50(14):1310-1314.
1251. da Silva Paulitsch F, Zhang L. Continuous positive airway pressure for adults with obstructive sleep apnea and cardiovascular disease: a meta-analysis of randomized trials. *Sleep Med*. 2019;54:28-34.
1252. Andrade AG, Bubu OM, Varga AW, Osorio RS. The Relationship between Obstructive Sleep Apnea and Alzheimer's Disease. *J Alzheimers Dis*. 2018;64:S255-S270.
1253. Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. *Lancet Neurol*. 2019;18(3):296-306.
1254. Perez-Cabezas V, Ruiz-Molinero C, Jimenez-Rejano JJ, Gonzalez-Medina G, Galan-Mercant A, Martin-Valero R. Continuous Positive Airway Pressure Treatment in Patients with Alzheimer's Disease: A Systematic Review. *J Clin Med*. 2020;9(1).

1255. Liguori C, Mercuri NB, Izzi F, et al. Obstructive Sleep Apnea is Associated With Early but Possibly Modifiable Alzheimer's Disease Biomarkers Changes. *Sleep*. 2017;40(5).
1256. Wang CN, Holtzman DM. Bidirectional relationship between sleep and Alzheimer's disease: role of amyloid, tau, and other factors. *Neuropsychopharmacol*. 2020;45(1):104-120.
1257. Lipford MC, Flemming KD, Calvin AD, et al. Associations between Cardioembolic Stroke and Obstructive Sleep Apnea. *Sleep*. 2015;38(11):1699-1705.
1258. Huang X, Tang S, Lyu XJ, Yang CQ, Chen XP. Structural and functional brain alterations in obstructive sleep apnea: a multimodal meta-analysis. *Sleep Med*. 2019;54:195-204.
1259. Mander BA, Winer JR, Jagust WJ, Walker MP. Sleep: A Novel Mechanistic Pathway, Biomarker, and Treatment Target in the Pathology of Alzheimer's Disease? *Trends Neurosci*. 2016;39(8):552-566.
1260. Lajoie AC, Lafontaine AL, Kimoff RJ, Kaminska M. Obstructive Sleep Apnea in Neurodegenerative Disorders: Current Evidence in Support of Benefit from Sleep Apnea Treatment. *Journal of Clinical Medicine*. 2020;9(2).
1261. Xie LL, Kang HY, Xu QW, et al. Sleep Drives Metabolite Clearance from the Adult Brain. *Science*. 2013;342(6156):373-377.
1262. O'Hara R, Luzon A, Hubbard J, Zeitzer JM. Sleep apnea, apolipoprotein epsilon 4 allele, and TBI: Mechanism for cognitive dysfunction and development of dementia. *J Rehabil Res Dev*. 2009;46(6):837-850.
1263. Polsek D, Gildeh N, Cash D, et al. Obstructive sleep apnoea and Alzheimer's disease: In search of shared pathomechanisms. *Neurosci Biobehav R*. 2018;86:142-149.
1264. Bellingham MC, Ireland MF. Contribution of cholinergic systems to state-dependent modulation of respiratory control. *Respiratory physiology & neurobiology*. 2002;131(1-2):135-144.
1265. Kylstra WA, Aaronson JA, Hofman WF, Schmand BA. Neuropsychological functioning after CPAP treatment in obstructive sleep apnea: a meta-analysis. *Sleep Med Rev*. 2013;17(5):341-347.
1266. Labarca G, Saavedra D, Dreyse J, Jorquera J, Barbe F. Efficacy of CPAP for Improvements in Sleepiness, Cognition, Mood, and Quality of Life in Elderly Patients With OSA: Systematic Review and Meta-analysis of Randomized Controlled Trials. *Chest*. 2020;158(2):751-764.
1267. Pan YY, Deng Y, Xu X, Liu YP, Liu HG. Effects of Continuous Positive Airway Pressure on Cognitive Deficits in Middle-aged Patients with Obstructive Sleep Apnea Syndrome: A Meta-analysis of Randomized Controlled Trials. *Chin Med J (Engl)*. 2015;128(17):2365-2373.
1268. Yan B, Jin Y, Hu Y, Li S. Effects of continuous positive airway pressure on elderly patients with obstructive sleep apnea: a meta-analysis. *Med Sci (Paris)*. 2018;34 Focus issue F1:66-73.
1269. Pan WH, Kastin AJ. Can sleep apnea cause Alzheimer's disease? *Neurosci Biobehav R*. 2014;47:656-669.
1270. Richards KC, Gooneratne N, Dicicco B, et al. CPAP Adherence May Slow 1-Year Cognitive Decline in Older Adults with Mild Cognitive Impairment and Apnea. *Journal of the American Geriatrics Society*. 2019;67(3):558-564.
1271. Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep*. 2012;35(12):1593-1602.
1272. Berlowitz DJ, Shafazand S. CPAP and Cognition in OSA (APPLES) Commentary on Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *SLEEP* 2012; 35:1593-1602. *Journal of Clinical Sleep Medicine*. 2013;9(5):516-517.
1273. Wang ML, Wang C, Tuo M, et al. Cognitive Effects of Treating Obstructive Sleep Apnea: A Meta-Analysis of Randomized Controlled Trials. *J Alzheimers Dis*. 2020;75(3):705-715.

1274. Ancoli-Israel S, Palmer BW, Cooke JR, et al. Cognitive Effects of Treating Obstructive Sleep Apnea in Alzheimer's Disease: A Randomized Controlled Study. *Journal of the American Geriatrics Society*. 2008;56(11):2076-2081.
1275. Cooke JR, Ayalon L, Palmer BW, et al. Sustained Use of CPAP Slows Deterioration of Cognition, Sleep, and Mood in Patients with Alzheimer's Disease and Obstructive Sleep Apnea: A Preliminary Study. *Journal of Clinical Sleep Medicine*. 2009;5(4):305-309.
1276. Wang Y, Cheng C, Moelter S, et al. One Year of Continuous Positive Airway Pressure Adherence Improves Cognition in Older Adults With Mild Apnea and Mild Cognitive Impairment. *Nurs Res*. 2020;69(2):157-164.
1277. Osorio RS, Gumb T, Pirraglia E, et al. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology*. 2015;84(19):1964-1971.
1278. Skiba V, Novikova M, Suneja A, McLellan B, Schultz L. Use of positive airway pressure in mild cognitive impairment to delay progression to dementia. *J Clin Sleep Med*. 2020;16(6):863-870.
1279. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers & Dementia*. 2018;14(4):535-562.
1280. Dalmasas M, Solé-Padullés C, Torres M, et al. Effect of CPAP on Cognition, Brain Function, and Structure Among Elderly Patients With OSA: A Randomized Pilot Study. *Chest*. 2015;148(5):1214-1223.
1281. McMillan A, Bratton DJ, Faria R, et al. A multicentre randomised controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people: PREDICT. *Health Technol Asses*. 2015;19(40):1-+.
1282. Martinez-Garcia MA, Chiner E, Hernandez L, et al. Obstructive sleep apnoea in the elderly: role of continuous positive airway pressure treatment. *Eur Respir J*. 2015;46(1):142-151.
1283. Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Arch Intern Med*. 2005;165(4):447-452.
1284. Hassaballa HA, Tulaimat A, Herdegen JJ, Mokhlesi B. The effect of continuous positive airway pressure on glucose control in diabetic patients with severe obstructive sleep apnea. *Sleep Breath*. 2005;9(4):176-180.
1285. Myhill PC, Davis WA, Peters KE, Chubb SA, Hillman D, Davis TM. Effect of continuous positive airway pressure therapy on cardiovascular risk factors in patients with type 2 diabetes and obstructive sleep apnea. *J Clin Endocrinol Metab*. 2012;97(11):4212-4218.
1286. Comondore VR, Cheema R, Fox J, et al. The impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with obstructive sleep apnea: a pilot feasibility randomized crossover trial. *Lung*. 2009;187(1):17-22.
1287. West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax*. 2007;62(11):969-974.
1288. Martinez-Ceron E, Barquiel B, Bezos AM, et al. Effect of Continuous Positive Airway Pressure on Glycemic Control in Patients with Obstructive Sleep Apnea and Type 2 Diabetes. A Randomized Clinical Trial. *Am J Respir Crit Care Med*. 2016;194(4):476-485.
1289. Abud R, Salgueiro M, Drake L, Reyes T, Jorquera J, Labarca G. Efficacy of continuous positive airway pressure (CPAP) preventing type 2 diabetes mellitus in patients with obstructive sleep apnea hypopnea syndrome (OSAHS) and insulin resistance: a systematic review and meta-analysis. *Sleep Med*. 2019;62:14-21.
1290. Martinez-Ceron E, Fernandez-Navarro I, Garcia-Rio F. Effects of continuous positive airway pressure treatment on glucose metabolism in patients with obstructive sleep apnea. *Sleep Med Rev*. 2016;25:121-130.

1291. Burks SV, Anderson JE, Bombyk M, et al. Nonadherence with Employer-Mandated Sleep Apnea Treatment and Increased Risk of Serious Truck Crashes. *Sleep*. 2016;39(5):967-975.
1292. Antonopoulos CN, Sergentanis TN, Daskalopoulou SS, Petridou ET. Nasal continuous positive airway pressure (nCPAP) treatment for obstructive sleep apnea, road traffic accidents and driving simulator performance: A meta-analysis. *Sleep Medicine Reviews*. 2011;15(5):301-310.
1293. Tregear S, Reston J, Schoelles K, Phillips B. Continuous Positive Airway Pressure Reduces Risk of Motor Vehicle Crash among Drivers with Obstructive Sleep Apnea: Systematic Review and Meta-analysis. *Sleep*. 2010;33(10):1373-1380.
1294. Barbé F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial. *Ann Intern Med*. 2001;134(11):1015-1023.
1295. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep Apnea/Hypopnea syndrome. *Am J Respir Crit Care Med*. 1999;159(2):461-467.
1296. Engleman HM, Martin SE, Kingshott RN, Mackay TW, Deary IJ, Douglas NJ. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax*. 1998;53(5):341-345.
1297. Monasterio C, Vidal S, Duran J, et al. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med*. 2001;164(6):939-943.
1298. Barbe F, Sunyer J, de la Pena A, et al. Effect of continuous positive airway pressure on the risk of road accidents in sleep apnea patients. *Respiration*. 2007;74(1):44-49.
1299. Cassel W, Ploch T, Becker C, Dugnus D, Peter JH, vonWichert P. Risk of traffic accidents in patients with sleep-disordered breathing: Reduction with nasal CPAP. *Eur Respir J*. 1996;9(12):2606-2611.
1300. Engleman HM, Gough K, Martin SE, Kingshott RN, Padfield PL, Douglas NJ. Ambulatory blood pressure on and off continuous positive airway pressure therapy for the sleep apnea/hypopnea syndrome: Effects in "non-dippers". *Sleep*. 1996;19(5):378-381.
1301. Findley L, Smith C, Hooper J, Dineen M, Suratt PM. Treatment with nasal CPAP decreases automobile accidents in patients with sleep apnea. *Am J Resp Crit Care*. 2000;161(3):857-859.
1302. George CFP. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax*. 2001;56(7):508-512.
1303. Horstmann S, Hess CW, Bassetti C, Gugger M, Mathis J. Sleepiness-related accidents in sleep apnea patients. *Sleep*. 2000;23(3):383-389.
1304. Karimi M, Hedner J, Habel H, Nerman O, Grote L. Sleep Apnea Related Risk of Motor Vehicle Accidents is Reduced by Continuous Positive Airway Pressure: Swedish Traffic Accident Registry Data. *Sleep*. 2015;38(3):341-+.
1305. Komada Y, Nishida Y, Namba K, Abe T, Tsuiki S, Inoue Y. Elevated Risk of Motor Vehicle Accident for Male Drivers with Obstructive Sleep Apnea Syndrome in the Tokyo Metropolitan Area. *Tohoku J Exp Med*. 2009;219(1):11-16.
1306. Krieger J, Meslier N, Lebrun T, et al. Accidents in obstructive sleep apnea patients treated with nasal continuous positive airway pressure - A prospective study. *Chest*. 1997;112(6):1561-1566.
1307. Yamamoto H, Akashiba T, Kosaka N, Ito D, Horie T. Long-term effects nasal continuous positive airway pressure on daytime sleepiness, mood and traffic accidents in patients with obstructive sleep apnoea. *Resp Med*. 2000;94(1):87-90.
1308. Barnes M, Houston D, Worsnop CJ, et al. A Randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *Am J Resp Crit Care*. 2002;165(6):773-780.



1309. Redline S, Adams N, Strauss ME, Roebuck T, Winters M, Rosenberg C. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. *Am J Resp Crit Care*. 1998;157(3):858-865.
1310. Scharf MB, Stover R, McDannold MD, Spinner O, Berkowitz DV, Conrad C. Outcome evaluation of long-term nasal continuous positive airway pressure therapy in obstructive sleep apnea. *Am J Ther*. 1999;6(6):293-297.
1311. Findley LJ, Fabrizio MJ, Knight H, Norcross BB, Laforte AJ, Suratt PM. Driving Simulator Performance in Patients with Sleep-Apnea. *American Review of Respiratory Disease*. 1989;140(2):529-530.
1312. George CFP, Boudreau AC, Smiley A. Effects of nasal CPAP on simulated driving performance in patients with obstructive sleep apnoea. *Thorax*. 1997;52(7):648-653.
1313. Hack M, Davies RJO, Mullins R, et al. Randomised prospective parallel trial of therapeutic versus subtherapeutic nasal continuous positive airway pressure on simulated steering performance in patients with obstructive sleep apnoea. *Thorax*. 2000;55(3):224-231.
1314. Orth M, Duchna HW, Leidag M, et al. Driving simulator and neuropsychological testing in OSAS before and under CPAP therapy (vol 26, pg 898, 2005). *Eur Respir J*. 2006;27(1):242-242.
1315. Suratt P, Findley, L. Effect of nasal CPAP treatment on automobile driving simulator performance and on self reported automobile accidents in subjects with sleep apnea (abstract). *Am Rev Respir Dis*. 1992;145(A169).
1316. Turkington PM, Sircar M, Saralaya D, Elliott MW. Time course of changes in driving simulator performance with and without treatment in patients with sleep apnoea hypopnoea syndrome. *Thorax*. 2004;59(1):56-59.
1317. Minemura H, Akashiba T, Yamamoto H, et al. [Traffic accidents in obstructive sleep apnea patients and effect of nasal CPAP treatment]. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1993;31(9):1103-1108.
1318. Botokeky E, Freymond N, Gormand F, et al. Benefit of continuous positive airway pressure on work quality in patients with severe obstructive sleep apnea. *Sleep Breath*. 2019;23(3):753-759.
1319. Jurado-Gamez B, Guglielmi O, Gude-Sampedro F, Buela-Casal G. Effect of CPAP therapy on job productivity and psychosocial occupational health in patients with moderate to severe sleep apnea. *Sleep Breath*. 2015;19(4):1293-1299.
1320. Ulfberg J, Jonsson R, Edling C. Improvement of subjective work performance among obstructive sleep apnea patients after treatment with continuous positive airway pressure. *Psychiatry and clinical neurosciences*. 1999;53(6):677-679.
1321. Mulgrew AT, Ryan CF, Fleetham JA, et al. The impact of obstructive sleep apnea and daytime sleepiness on work limitation. *Sleep Med*. 2007;9(1):42-53.
1322. Glidewell RN, Renn BN, Roby E, Orr WC. Predictors and patterns of insomnia symptoms in OSA before and after PAP therapy. *Sleep Med*. 2014;15(8):899-905.
1323. Alawami M, Mustafa A, Whyte K, Alkhater M, Bhikoo Z, Pemberton J. Echocardiographic and electrocardiographic findings in patients with obesity hypoventilation syndrome. *Intern Med J*. 2015;45(1):68-73.
1324. Kessler R, Chaouat A, Schinkewitch P, et al. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. *Chest*. 2001;120(2):369-376.
1325. Kreivi HR, Italuoma T, Bachour A. Effect of ventilation therapy on mortality rate among obesity hypoventilation syndrome and obstructive sleep apnoea patients. *ERJ Open Res*. 2020;6(2).
1326. Berg G, Delaive K, Manfreda J, Walld R, Kryger MH. The use of health-care resources in obesity-hypoventilation syndrome. *Chest*. 2001;120(2):377-383.
1327. Jennum P, Ibsen R, Kjellberg J. Social consequences of sleep disordered breathing on patients and their partners: a controlled national study. *Eur Respir J*. 2014;43(1):134-144.

1328. Castro-Anon O, de Llano LAP, Sanchez SD, et al. Obesity-Hypoventilation Syndrome: Increased Risk of Death over Sleep Apnea Syndrome. *PloS one*. 2015;10(2).
1329. Murphy PB, Davidson C, Hind MD, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. *Thorax*. 2012;67(8):727-734.
1330. Patout M, Gagnadoux F, Rabec C, et al. AVAPS-AE versus ST mode: A randomized controlled trial in patients with obesity hypoventilation syndrome. *Respirology*. 2020;25(10):1073-1081.
1331. Storre JH, Seuthe B, Fiechter R, et al. Average volume-assured pressure support in obesity hypoventilation - A randomized crossover trial. *Chest*. 2006;130(3):815-821.
1332. Steier J, Jolley CJ, Seymour J, Roughton M, Polkey MI, Moxham J. Neural respiratory drive in obesity. *Thorax*. 2009;64(8):719-725.
1333. Howard ME, Piper AJ, Stevens B, et al. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. *Thorax*. 2017;72(5):437-444.
1334. Piper AJ, Wang D, Yee BJ, Barnes DJ, Grunstein RR. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. *Thorax*. 2008;63(5):395-401.
1335. Royer CP, Schweiger C, Manica D, Rabaioli L, Guerra V, Sbruzzi G. Efficacy of bilevel ventilatory support in the treatment of stable patients with obesity hypoventilation syndrome: systematic review and meta-analysis. *Sleep Med*. 2019;53:153-164.
1336. Soghier I, Brozek JL, Afshar M, et al. Noninvasive Ventilation versus CPAP as Initial Treatment of Obesity Hypoventilation Syndrome. *Ann Am Thorac Soc*. 2019;16(10):1295-1303.
1337. Bouloukaki I, Mermigkis C, Michelakis S, et al. The Association Between Adherence to Positive Airway Pressure Therapy and Long-Term Outcomes in Patients With Obesity Hypoventilation Syndrome: A Prospective Observational Study. *Journal of Clinical Sleep Medicine*. 2018;14(9):1539-1550.
1338. Masa JF, Mokhlesi B, Benitez I, et al. Long-term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomised controlled trial. *Lancet*. 2019;393(10182):1721-1732.
1339. Corral J, Mogollon MV, Sanchez-Quiroga MA, et al. Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome. *Thorax*. 2018;73(4):361-368.
1340. Masa JF, Mokhlesi B, Benitez I, et al. Cost-effectiveness of positive airway pressure modalities in obesity hypoventilation syndrome with severe obstructive sleep apnoea. *Thorax*. 2020;75(6):459-467.
1341. Masa JF, Benitez I, Sanchez-Quiroga MA, et al. Long-term Noninvasive Ventilation in Obesity Hypoventilation Syndrome Without Severe OSA The Pickwick Randomized Controlled Trial. *Chest*. 2020;158(3):1176-1186.
1342. Mokhlesi B, Masa JF, Brozek JL, et al. Evaluation and Management of Obesity Hypoventilation Syndrome. An Official American Thoracic Society Clinical Practice Guideline (vol 200, pg e6, 2009). *Am J Resp Crit Care*. 2019;200(10):1325-1326.
1343. de Llano LAP, Golpe R, Piquer MO, et al. Clinical heterogeneity among patients with obesity hypoventilation syndrome: Therapeutic implications. *Respiration*. 2008;75(1):34-39.
1344. Masa JF, Corral J, Caballero C, et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea. *Thorax*. 2016;71(10):899-906.
1345. Carrillo A, Ferrer M, Gonzalez-Diaz G, et al. Noninvasive Ventilation in Acute Hypercapnic Respiratory Failure Caused by Obesity Hypoventilation Syndrome and Chronic Obstructive Pulmonary Disease. *Am J Resp Crit Care*. 2012;186(12):1279-1285.

1346. Chebib N, Nesme P, Freymond N, et al. Acute Respiratory Failure in Obesity-Hypoventilation Syndrome Managed in the ICU. *Resp Care*. 2019;64(12):1545-1554.
1347. Arellano-Maric MP, Hamm C, Duiverman ML, et al. Obesity hypoventilation syndrome treated with non-invasive ventilation: Is a switch to CPAP therapy feasible? *Respirology*. 2020;25(4):435-442.
1348. Orfanos S, Jaffuel D, Perrin C, Molinari N, Chanez P, Palot A. Switch of noninvasive ventilation (NIV) to continuous positive airway pressure (CPAP) in patients with obesity hypoventilation syndrome: a pilot study. *Bmc Pulm Med*. 2017;17.
1349. Priou P, Hamel JF, Person C, et al. Long-Term Outcome of Noninvasive Positive Pressure Ventilation for Obesity Hypoventilation Syndrome. *Chest*. 2010;138(1):84-90.
1350. Kakazu MT, Soghier I, Afshar M, et al. Weight Loss Interventions as Treatment of Obesity Hypoventilation Syndrome A Systematic Review. *Ann Am Thorac Soc*. 2020;17(4):492-502.
1351. Mandal S, Suh ES, Harding R, et al. Nutrition and Exercise Rehabilitation in Obesity hypoventilation syndrome (NERO): a pilot randomised controlled trial. *Thorax*. 2018;73(1):62-69.
1352. Mansfield D, Naughton MT. Effects of continuous positive airway pressure on lung function in patients with chronic obstructive pulmonary disease and sleep disordered breathing. *Respirology*. 1999;4(4):365-370.
1353. Mezzanotte WS, Tangel DJ, Fox AM, Ballard RD, White DP. Nocturnal Nasal Continuous Positive Airway Pressure in Patients with Chronic Obstructive Pulmonary-Disease - Influence on Waking Respiratory Muscle Function. *Chest*. 1994;106(4):1100-1108.
1354. Machado MC, Vollmer WM, Togeiro SM, et al. CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxaemic COPD. *Eur Respir J*. 2010;35(1):132-137.
1355. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med*. 2010;182(3):325-331.
1356. Stanchina ML, Welicky LM, Donat W, Lee D, Corrao W, Malhotra A. Impact of CPAP Use and Age on Mortality in Patients with Combined COPD and Obstructive Sleep Apnea: The Overlap Syndrome. *Journal of Clinical Sleep Medicine*. 2013;9(8):767-772.
1357. Singh G, Agarwal A, Zhang W, Kuo YF, Sultana R, Sharma G. Impact of PAP therapy on hospitalization rates in Medicare beneficiaries with COPD and coexisting OSA. *Sleep Breath*. 2019;23(1):193-200.
1358. Mapel DW, Dutro MP, Marton JP, Woodruff K, Make B. Identifying and characterizing COPD patients in US managed care. A retrospective, cross-sectional analysis of administrative claims data. *Bmc Health Serv Res*. 2011;11.
1359. Duiverman ML. Noninvasive ventilation in stable hypercapnic COPD: what is the evidence? *Erj Open Research*. 2018;4(2).
1360. Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation A Randomized Clinical Trial. *Jama-J Am Med Assoc*. 2017;317(21):2177-2186.
1361. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Db Syst Rev*. 2017(7).
1362. Kuklisova Z, Tkacova R, Joppa P, Wouters E, Sastry M. Severity of nocturnal hypoxia and daytime hypercapnia predicts CPAP failure in patients with COPD and obstructive sleep apnea overlap syndrome. *Sleep Med*. 2017;30:139-145.
1363. Dort L, Remmers J. A combination appliance for obstructive sleep apnea: the effectiveness of mandibular advancement and tongue retention. *J Clin Sleep Med*. 2012;8(3):265-269.

1364. Chang ET, Fernandez-Salvador C, Giambo J, et al. Tongue retaining devices for obstructive sleep apnea: A systematic review and meta-analysis. *Am J Otolaryngol*. 2017;38(3):272-278.
1365. Deane SA, Cistulli PA, Ng AT, Zeng B, Petocz P, Darendeliler MA. Comparison of mandibular advancement splint and tongue stabilizing device in obstructive sleep apnea: a randomized controlled trial. *Sleep*. 2009;32(5):648-653.
1366. Cartwright R, Ristanovic R, Diaz F, Caldarelli D, Alder G. A comparative study of treatments for positional sleep apnea. *Sleep*. 1991;14(6):546-552.
1367. Cartwright RD. Predicting response to the tongue retaining device for sleep apnea syndrome. *Arch Otolaryngol*. 1985;111(6):385-388.
1368. Banhiran W, Durongphan A, Keskoool P, Chongkolwatana C, Metheetrairut C. Randomized crossover study of tongue-retaining device and positive airway pressure for obstructive sleep apnea. *Sleep Breath*. 2019.
1369. Lazard DS, Blumen M, Levy P, et al. The tongue-retaining device: efficacy and side effects in obstructive sleep apnea syndrome. *J Clin Sleep Med*. 2009;5(5):431-438.
1370. Johal A, Agha B. Ready-made versus custom-made mandibular advancement appliances in obstructive sleep apnea: A systematic review and meta-analysis. *J Sleep Res*. 2018;27(6):e12660.
1371. Petit FX, Pepin JL, Bettega G, Sadek H, Raphael B, Levy P. Mandibular advancement devices: rate of contraindications in 100 consecutive obstructive sleep apnea patients. *Am J Respir Crit Care Med*. 2002;166(3):274-278.
1372. Ngiam J, Balasubramaniam R, Darendeliler MA, Cheng AT, Waters K, Sullivan CE. Clinical guidelines for oral appliance therapy in the treatment of snoring and obstructive sleep apnoea. *Aust Dent J*. 2013;58(4):408-419.
1373. Heidsieck DS, de Ruiter MH, de Lange J. Management of obstructive sleep apnea in edentulous patients: an overview of the literature. *Sleep Breath*. 2016;20(1):395-404.
1374. Cunali PA, Almeida FR, Santos CD, et al. Prevalence of temporomandibular disorders in obstructive sleep apnea patients referred for oral appliance therapy. *J Orofac Pain*. 2009;23(4):339-344.
1375. Smith MT, Wickwire EM, Grace EG, et al. Sleep disorders and their association with laboratory pain sensitivity in temporomandibular joint disorder. *Sleep*. 2009;32(6):779-790.
1376. Gao X, Otsuka R, Ono T, Honda E, Sasaki T, Kuroda T. Effect of titrated mandibular advancement and jaw opening on the upper airway in nonapneic men: a magnetic resonance imaging and cephalometric study. *Am J Orthod Dentofacial Orthop*. 2004;125(2):191-199.
1377. Ishiyama H, Inukai S, Nishiyama A, et al. Effect of jaw-opening exercise on prevention of temporomandibular disorders pain associated with oral appliance therapy in obstructive sleep apnea patients: A randomized, double-blind, placebo-controlled trial. *J Prosthodont Res*. 2017;61(3):259-267.
1378. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2006(1):CD004435.
1379. Bratton DJ, Gaisl T, Schlatzer C, Kohler M. Comparison of the effects of continuous positive airway pressure and mandibular advancement devices on sleepiness in patients with obstructive sleep apnoea: a network meta-analysis. *Lancet Respir Med*. 2015;3(11):869-878.
1380. Kuhn E, Schwarz EI, Bratton DJ, Rossi VA, Kohler M. Effects of CPAP and Mandibular Advancement Devices on Health-Related Quality of Life in OSA: A Systematic Review and Meta-analysis. *Chest*. 2017;151(4):786-794.
1381. Araie T, Okuno K, Ono Minagi H, Sakai T. Dental and skeletal changes associated with long-term oral appliance use for obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Med Rev*. 2018;41:161-172.

1382. Chen H, Eckert DJ, van der Stelt PF, et al. Phenotypes of responders to mandibular advancement device therapy in obstructive sleep apnea patients: A systematic review and meta-analysis. *Sleep Med Rev.* 2020;49:101229.
1383. Vanderveken OM, Dieltjens M, Wouters K, De Backer WA, Van de Heyning PH, Braem MJ. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. *Thorax.* 2013;68(1):91-96.
1384. Schwartz M, Acosta L, Hung YL, Padilla M, Enciso R. Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis. *Sleep Breath.* 2018;22(3):555-568.
1385. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJB. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest.* 2005;128(4):2130-2137.
1386. Bignold JJ, Deans-Costi G, Goldsworthy MR, et al. Poor Long-Term Patient Compliance with the Tennis Ball Technique for Treating Positional Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine.* 2009;5(5):428-430.
1387. Oksenberg A, Silverberg D, Offenbach D, Arons E. Positional therapy for obstructive sleep apnea patients: A 6-month follow-up study. *Laryngoscope.* 2006;116(11):1995-2000.
1388. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate Position Monitoring and Improved Supine-Dependent Obstructive Sleep Apnea with a New Position Recording and Supine Avoidance Device. *Journal of Clinical Sleep Medicine.* 2011;7(4):376-383.
1389. Permut I, Diaz-Abad M, Chatila W, et al. Comparison of Positional Therapy to CPAP in Patients with Positional Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine.* 2010;6(3):238-243.
1390. Ravesloot MJL, White D, Heinzer R, Oksenberg A, Pepin JL. Efficacy of the New Generation of Devices for Positional Therapy for Patients With Positional Obstructive Sleep Apnea: A Systematic Review of the Literature and Meta-Analysis. *Journal of Clinical Sleep Medicine.* 2017;13(6):813-824.
1391. Benoist L, de Ruiter M, de Lange J, de Vries N. A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. *Sleep Med.* 2017;34:109-117.
1392. Berry RB, Uhles ML, Abaluck BK, et al. NightBalance Sleep Position Treatment Device Versus Auto-Adjusting Positive Airway Pressure for Treatment of Positional Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine.* 2019;15(7):947-956.
1393. Beyers J, Vanderveken OM, Kastoer C, et al. Treatment of sleep-disordered breathing with positional therapy: long-term results. *Sleep Breath.* 2019;23(4):1141-1149.
1394. de Ruiter MHT, Benoist LBL, de Vries N, de Lange J. Durability of treatment effects of the sleep position trainer versus oral appliance therapy in positional OSA: 12-month follow-up of a randomized controlled trial (vol 22, pg 441, 2017). *Sleep Breath.* 2018;22(2):451-451.
1395. Eijsvogel MM, Ubbink R, Dekker J, et al. Sleep Position Trainer versus Tennis Ball Technique in Positional Obstructive Sleep Apnea Syndrome. *Journal of Clinical Sleep Medicine.* 2015;11(2):139-147.
1396. Laub RR, Tonnesen P, Jennum PJ. A Sleep Position Trainer for positional sleep apnea: a randomized, controlled trial. *J Sleep Res.* 2017;26(5):641-650.
1397. Levendowski DJ, Seagraves S, Popovic D, Westbrook PR. Assessment of a Neck-Based Treatment and Monitoring Device for Positional Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine.* 2014;10(8):863-871.
1398. Ravesloot MJL, Benoist L, van Maanen P, de Vries N. Novel Positional Devices for the Treatment of Positional Obstructive Sleep Apnea, and How This Relates to Sleep Surgery. *Adv Otorhinolaryngol.* 2017;80:28-36.

1399. van Maanen JP, de Vries N. Long-Term Effectiveness and Compliance of Positional Therapy with the Sleep Position Trainer in the Treatment of Positional Obstructive Sleep Apnea Syndrome. *Sleep*. 2014;37(7):1209-1215.
1400. van Maanen JP, Meester KAW, Dun LN, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep Breath*. 2013;17(2):771-779.
1401. Van Maanen JP, Richard W, Van Kesteren ER, et al. Evaluation of a new simple treatment for positional sleep apnoea patients. *J Sleep Res*. 2012;21(3):322-329.
1402. Mok Y, Tan A, Hsu PP, et al. Comparing treatment effects of a convenient vibratory positional device to CPAP in positional OSA: a crossover randomised controlled trial. *Thorax*. 2020;75(4):331-337.
1403. Dieltjens M, Vroegop AV, Verbruggen AE, et al. A promising concept of combination therapy for positional obstructive sleep apnea. *Sleep Breath*. 2015;19(2):637-644.
1404. Srijithesh PR, Aghoram R, Goel A, Dhanya J. Positional therapy for obstructive sleep apnoea. *Cochrane Db Syst Rev*. 2019(5).
1405. Desplan M, Mercier J, Sabate M, Ninot G, Prefaut C, Dauvilliers Y. A comprehensive rehabilitation program improves disease severity in patients with obstructive sleep apnea syndrome: a pilot randomized controlled study. *Sleep Med*. 2014;15(8):906-912.
1406. Fernandes JF, Araujo Lda S, Kaiser SE, Sanjuliani AF, Klein MR. The effects of moderate energy restriction on apnoea severity and CVD risk factors in obese patients with obstructive sleep apnoea. *Br J Nutr*. 2015;114(12):2022-2031.
1407. Johansson K, Neovius M, Lagerros YT, et al. Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial. *BMJ*. 2009;339:b4609.
1408. Maki-Nunes C, Toschi-Dias E, Cepeda FX, et al. Diet and exercise improve chemoreflex sensitivity in patients with metabolic syndrome and obstructive sleep apnea. *Obesity (Silver Spring)*. 2015;23(8):1582-1590.
1409. Ng SSS, Chan RSM, Woo J, et al. A Randomized Controlled Study to Examine the Effect of a Lifestyle Modification Program in OSA. *Chest*. 2015;148(5):1193-1203.
1410. Tuomilehto HP, Seppa JM, Partinen MM, et al. Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. *Am J Respir Crit Care Med*. 2009;179(4):320-327.
1411. Lopez-Padros C, Salord N, Alves C, et al. Effectiveness of an intensive weight-loss program for severe OSA in patients undergoing CPAP treatment: a randomized controlled trial. *J Clin Sleep Med*. 2020;16(4):503-514.
1412. Nerfeldt P, Nilsson BY, Udden J, Rossner S, Friberg D. Weight reduction improves nocturnal respiration in obese sleep apnoea patients-A randomized controlled pilot study. *Obes Res Clin Pract*. 2008;2(2):71-142.
1413. Papandreou C, Schiza SE, Bouloukaki I, et al. Effect of Mediterranean diet versus prudent diet combined with physical activity on OSAS: a randomised trial. *Eur Respir J*. 2012;39(6):1398-1404.
1414. Hudgel DW, Patel SR, Ahasic AM, et al. The Role of Weight Management in the Treatment of Adult Obstructive Sleep Apnea. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(6):e70-e87.
1415. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362.
1416. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes (Lond)*. 2016;40(8):1310-1319.

1417. Winslow DH, Bowden CH, DiDonato KP, McCullough PA. A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. *Sleep*. 2012;35(11):1529-1539.
1418. Christou GA, Katsiki N, Blundell J, Fruhbeck G, Kiortsis DN. Semaglutide as a promising antiobesity drug. *Obes Rev*. 2019;20(6):805-815.
1419. Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. *JAMA*. 2021;325(14):1403-1413.
1420. SEDATIVE | Definition of SEDATIVE by Oxford Dictionary on Lexico.com also meaning of SEDATIVE. <https://www.lexico.com/en/definition/sedative>. Published 2021. Accessed 4/28/2020, 2020.
1421. Cummiskey J, Guilleminault C, Delrio G, Silvestri R. The Effects of Flurazepam on Sleep Studies in Patients with Chronic Obstructive Pulmonary-Disease. *Chest*. 1983;84(2):143-147.
1422. Mendelson WB, Garnett D, Gillin JC. Flurazepam-Induced Sleep-Apnea Syndrome in a Patient with Insomnia and Mild Sleep-Related Respiratory Changes. *J Nerv Ment Dis*. 1981;169(4):261-264.
1423. Seda G, Tsai S, Lee-Chiong T. Medication Effects on Sleep and Breathing. *Clinics in Chest Medicine*. 2014;35(3):557-+.
1424. Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. *Cochrane Db Syst Rev*. 2015(7).
1425. Issa FG, Sullivan CE. Alcohol, Snoring and Sleep-Apnea. *J Neurol Neurosur Ps*. 1982;45(4):353-359.
1426. Kolla BP, Foroughi M, Saeidifard F, Chakravorty S, Wang Z, Mansukhani MP. The impact of alcohol on breathing parameters during sleep: A systematic review and meta-analysis. *Sleep Medicine Reviews*. 2018;42:59-67.
1427. Jordan AS, O'Donoghue FJ, Cori JM, Trinder J. Physiology of Arousal in Obstructive Sleep Apnea and Potential Impacts for Sedative Treatment. *Am J Resp Crit Care*. 2017;196(7):814-821.
1428. Sun H, Palcza J, Card D, et al. Effects of Suvorexant, an Orexin Receptor Antagonist, on Respiration during Sleep In Patients with Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine*. 2016;12(1):9-17.
1429. Wilhelm CP, deShazo RD, Tamanna S, Ullah MI, Skipworth LB. The nose, upper airway, and obstructive sleep apnea. *Ann Allergy Asthma Immunol*. 2015;115(2):96-102.
1430. Schönhofer B, Franklin KA, Brünig H, Wehde H, Köhler D. Effect of nasal-valve dilation on obstructive sleep apnea. *Chest*. 2000;118(3):587-590.
1431. Liu HT, Lin YC, Kuan YC, et al. Intranasal corticosteroid therapy in the treatment of obstructive sleep apnea: A meta-analysis of randomized controlled trials. *Am J Rhinol Allergy*. 2016;30(3):215-221.
1432. Smith DF, Sarber KM, Spiceland CP, Ishman SL, Augelli DM, Romaker AM. Effects of Medical Therapy on Mild Obstructive Sleep Apnea in Adult Patients. *J Clin Sleep Med*. 2019;15(7):979-983.
1433. Alt JA, Ramakrishnan VR, Platt MP, et al. Sleep quality outcomes after medical and surgical management of chronic rhinosinusitis. *Int Forum Allergy Rh*. 2017;7(2):113-118.
1434. Acar M, Cingi C, Sakallioglu O, San T, Fatih Yimenicioglu M, Bal C. The effects of mometasone furoate and desloratadine in obstructive sleep apnea syndrome patients with allergic rhinitis. *Am J Rhinol Allergy*. 2013;27(4):e113-116.
1435. Tam YY, Shao IH, Wu CC, Hsieh ML. The impact of intranasal fluticasone on patients with obstructive sleep apnea: a prospective study. *Braz J Otorhinolaryngol*. 2019.

1436. Meltzer EO, Munafo DA, Chung W, Gopalan G, Varghese ST. Intranasal mometasone furoate therapy for allergic rhinitis symptoms and rhinitis-disturbed sleep. *Ann Allergy Asthma Immunol*. 2010;105(1):65-74.
1437. Koutsourelakis I, Minaritzoglou A, Zakyntinos G, Vagiakis E, Zakyntinos S. The effect of nasal tramazoline with dexamethasone in obstructive sleep apnoea patients. *Eur Respir J*. 2013;42(4):1055-1063.
1438. Bahammam AS, Tate R, Manfreda J, Kryger MH. Upper airway resistance syndrome: Effect of nasal dilation, sleep stage, and sleep position. *Sleep*. 1999;22(5):592-598.
1439. Wenzel M, Schönhofer B, Siemon K, Köhler D. [Nasal strips without effect on obstructive sleep apnea and snoring]. *Pneumologie*. 1997;51(12):1108-1110.
1440. Yagihara F, Lorenzi G, Santos-Silva R. Nasal Dilator Strip is an Effective Placebo Intervention for Severe Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine*. 2017;13(2):215-221.
1441. Camacho M, Malu OO, Kram YA, et al. Nasal Dilators (Breathe Right Strips and NoZovent) for Snoring and OSA: A Systematic Review and Meta-Analysis. *Pulm Med*. 2016;2016.
1442. Hoijer U, Ejnell H, Hedner J, Petruson B, Eng LB. The Effects of Nasal Dilation on Snoring and Obstructive Sleep-Apnea. *Arch Otolaryngol*. 1992;118(3):281-284.
1443. Gosepath J, Amedee RG, Romantschuck S, Mann WJ. Breathe right nasal strips and the respiratory disturbance index in sleep related breathing disorders. *American Journal of Rhinology*. 1999;13(5):385-389.
1444. Metes A, Cole P, Hoffstein V, Miljeteig H. Nasal Airway Dilation and Obstructed Breathing in Sleep. *Laryngoscope*. 1992;102(9):1053-1055.
1445. Schonhofer B, Kerl J, Suchi S, Kohler D, Franklin KA. Effect of nasal valve dilation on effective CPAP level in obstructive sleep apnea. *Resp Med*. 2003;97(9):1001-1005.
1446. Amaro ACS, Duarte FHG, Jallad RS, Bronstein MD, Redline S, Lorenzi G. The use of nasal dilator strips as a placebo for trials evaluating continuous positive airway pressure. *Clinics*. 2012;67(5):469-474.
1447. Hoffstein V, Mateika S, Metes A. Effect of Nasal Dilation on Snoring and Apneas during Different Stages of Sleep. *Sleep*. 1993;16(4):360-365.
1448. VanderTouw T, Crawford ABH, Wheatley JR. Effects of a synthetic lung surfactant on pharyngeal patency in awake human subjects. *Journal of Applied Physiology*. 1997;82(1):78-85.
1449. Jokic R, Klimaszewski A, Mink J, Fitzpatrick MF. Surface tension forces in sleep apnea: The role of a soft tissue lubricant - A randomized double-blind, placebo-controlled trial. *Am J Resp Crit Care*. 1998;157(5):1522-1525.
1450. Kirkness JP, Madronio M, Stavrinou R, Wheatley JR, Amis TC. Relationship between surface tension of upper airway lining liquid and upper airway collapsibility during sleep in obstructive sleep apnea hypopnea syndrome. *Journal of Applied Physiology*. 2003;95(5):1761-1766.
1451. Morrell MJ, Arabi Y, Zahn BR, Meyer KC, Skatrud JB, Badr MS. Effect of surfactant on pharyngeal mechanics in sleeping humans: implications for sleep apnoea. *Eur Respir J*. 2002;20(2):451-457.
1452. Zozula R, Rosen R. Compliance with continuous positive airway pressure therapy: assessing and improving treatment outcomes. *Curr Opin Pulm Med*. 2001;7(6):391-398.
1453. Mehta V, Vasu TS, Phillips B, Chung F. Obstructive sleep apnea and oxygen therapy: a systematic review of the literature and meta-analysis. *J Clin Sleep Med*. 2013;9(3):271-279.
1454. Block AJ, Hellard DW, Cicale MJ. Snoring, nocturnal hypoxemia, and the effect of oxygen inhalation. *Chest*. 1987;92(3):411-417.
1455. Loreda JS, Ancoli-Israel S, Kim EJ, Lim WJ, Dimsdale JE. Effect of continuous positive airway pressure versus supplemental oxygen on sleep quality in obstructive sleep apnea: a placebo-CPAP-controlled study. *Sleep*. 2006;29(4):564-571.



1456. Phillips BA, Schmitt FA, Berry DT, Lamb DG, Amin M, Cook YR. Treatment of obstructive sleep apnea. A preliminary report comparing nasal CPAP to nasal oxygen in patients with mild OSA. *Chest*. 1990;98(2):325-330.
1457. Liao P, Wong J, Singh M, et al. Postoperative Oxygen Therapy in Patients With OSA: A Randomized Controlled Trial. *Chest*. 2017;151(3):597-611.
1458. Gottlieb DJ, Punjabi NM, Mehra R, et al. CPAP versus oxygen in obstructive sleep apnea. *N Engl J Med*. 2014;370(24):2276-2285.
1459. Norman D, Loredó JS, Nelesen RA, et al. Effects of continuous positive airway pressure versus supplemental oxygen on 24-hour ambulatory blood pressure. *Hypertension*. 2006;47(5):840-845.
1460. Turnbull CD, Sen D, Kohler M, Petousi N, Stradling JR. Effect of Supplemental Oxygen on Blood Pressure in Obstructive Sleep Apnea (SOX). A Randomized Continuous Positive Airway Pressure Withdrawal Trial. *Am J Respir Crit Care Med*. 2019;199(2):211-219.
1461. Sands SA, Edwards BA, Terrill PI, et al. Identifying obstructive sleep apnoea patients responsive to supplemental oxygen therapy. *Eur Respir J*. 2018;52(3).
1462. Wang D, Wong KK, Rowsell L, Don GW, Yee BJ, Grunstein RR. Predicting response to oxygen therapy in obstructive sleep apnoea patients using a 10-minute daytime test. *Eur Respir J*. 2018;51(1).
1463. Guimaraes KC, Drager LF, Genta PR, Marcondes BF, Lorenzi G. Effects of Oropharyngeal Exercises on Patients with Moderate Obstructive Sleep Apnea Syndrome. *Am J Resp Crit Care*. 2009;179(10):962-966.
1464. Camacho M, Certal V, Abdullatif J, et al. Myofunctional Therapy to Treat Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Sleep*. 2015;38(5):669-+.
1465. Verma RK, Johnson JJR, Goyal M, Banumathy N, Goswami U, Panda NK. Oropharyngeal exercises in the treatment of obstructive sleep apnoea: our experience. *Sleep Breath*. 2016;20(4):1193-1201.
1466. Ieto V, Kayamori F, Montes MI, et al. Effects of Oropharyngeal Exercises on Snoring A Randomized Trial. *Chest*. 2015;148(3):683-691.
1467. Diaferia G, Santos-Silva R, Truksinas E, et al. Myofunctional therapy improves adherence to continuous positive airway pressure treatment. *Sleep Breath*. 2017;21(2):387-395.
1468. Diaferia G, Badke L, Santos-Silva R, Bommarito S, Tufik S, Bittencourt L. Effect of speech therapy as adjunct treatment to continuous positive airway pressure on the quality of life of patients with obstructive sleep apnea. *Sleep Med*. 2013;14(7):628-635.
1469. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc*. 2008;5(2):173-178.
1470. Phurrough S, Jacques L, Spencer F, Stiller J, Brechner R. Decision Memo for Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA) (CAG-00093R2). 2008.
1471. Engleman HM, Martin SE, Douglas NJ. Compliance with CPAP therapy in patients with the sleep apnoea/hypopnoea syndrome. *Thorax*. 1994;49(3):263-266.
1472. Reeves-Hoche MK, Meck R, Zwillich CW. Nasal CPAP: an objective evaluation of patient compliance. *Am J Respir Crit Care Med*. 1994;149(1):149-154.
1473. Stradling JR, Davies RJ. Is more NCPAP better? *Sleep*. 2000;23 Suppl 4:S150-153.
1474. Campos-Rodriguez F, Pena-Grinan N, Reyes-Nunez N, et al. Mortality in obstructive sleep apnea-hypopnea patients treated with positive airway pressure. *Chest*. 2005;128(2):624-633.
1475. Antic NA, Catcheside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. *Sleep*. 2011;34(1):111-119.

1476. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med*. 2001;163(2):344-348.
1477. Zimmerman ME, Arnedt JT, Stanchina M, Millman RP, Aloia MS. Normalization of memory performance and positive airway pressure adherence in memory-impaired patients with obstructive sleep apnea. *Chest*. 2006;130(6):1772-1778.
1478. Aloia MS, Knoepke CE, Lee-Chiong T. The new local coverage determination criteria for adherence to positive airway pressure treatment: testing the limits? *Chest*. 2010;138(4):875-879.
1479. Krakow B, Ulibarri VA, Foley-Shea MR, Tidler A, McIver ND. Adherence and Subthreshold Adherence in Sleep Apnea Subjects Receiving Positive Airway Pressure Therapy: A Retrospective Study Evaluating Differences in Adherence Versus Use. *Respir Care*. 2016;61(8):1023-1032.
1480. Ravesloot MJ, de Vries N. Reliable calculation of the efficacy of non-surgical and surgical treatment of obstructive sleep apnea revisited. *Sleep*. 2011;34(1):105-110.
1481. Aurora RN, Casey KR, Kristo D, et al. Practice Parameters for the Surgical Modifications of the Upper Airway for Obstructive Sleep Apnea in Adults. *Sleep*. 2010;33(10):1408-1413.
1482. Sundaram S, Bridgman SA, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2005(4):CD001004.
1483. Rotenberg BW, Murariu D, Pang KP. Trends in CPAP adherence over twenty years of data collection: a flattened curve. *J Otolaryngol Head Neck Surg*. 2016;45(1):43.
1484. Friedman M, Ibrahim H, Bass L. Clinical staging for sleep-disordered breathing. *Otolaryngol Head Neck Surg*. 2002;127(1):13-21.
1485. Choi JH, Cho SH, Kim SN, Suh JD, Cho JH. Predicting Outcomes after Uvulopalatopharyngoplasty for Adult Obstructive Sleep Apnea: A Meta-analysis. *Otolaryng Head Neck*. 2016;155(6):904-913.
1486. Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. *Thorax*. 2013;68(9):846-853.
1487. Heiser C, Steffen A, Boon M, et al. Post-approval upper airway stimulation predictors of treatment effectiveness in the ADHERE registry. *Eur Respir J*. 2019;53(1).
1488. Huntley C, Steffen A, Doghramji K, Hofauer B, Heiser C, Boon M. Upper Airway Stimulation in Patients With Obstructive Sleep Apnea and an Elevated Body Mass Index: A Multi-institutional Review. *Laryngoscope*. 2018;128(10):2425-2428.
1489. Camacho M, Teixeira J, Abdullatif J, et al. Maxillomandibular advancement and tracheostomy for morbidly obese obstructive sleep apnea: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2015;152(4):619-630.
1490. Li HY, Wang PC, Lee LA, Chen NH, Fang TJ. Prediction of uvulopalatopharyngoplasty outcome: anatomy-based staging system versus severity-based staging system. *Sleep*. 2006;29(12):1537-1541.
1491. Martinho FL, Zonato AI, Bittencourt LR, et al. Obese obstructive sleep apnea patients with tonsil hypertrophy submitted to tonsillectomy. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas*. 2006;39(8):1137-1142.
1492. Vicente E, Marin JM, Carrizo S, Naya MJ. Tongue-base suspension in conjunction with uvulopalatopharyngoplasty for treatment of severe obstructive sleep apnea: long-term follow-up results. *Laryngoscope*. 2006;116(7):1223-1227.
1493. Chandrashekariah R, Shaman Z, Auckley D. Impact of upper airway surgery on CPAP compliance in difficult-to-manage obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2008;134(9):926-930.

1494. Rotenberg BW, Vicini C, Pang EB, Pang KP. Reconsidering first-line treatment for obstructive sleep apnea: a systematic review of the literature. *J Otolaryngol Head Neck Surg.* 2016;45:23.
1495. Ceylan K, Emir H, Kizilkaya Z, et al. First-choice treatment in mild to moderate obstructive sleep apnea: single-stage, multilevel, temperature-controlled radiofrequency tissue volume reduction or nasal continuous positive airway pressure. *Arch Otolaryngol Head Neck Surg.* 2009;135(9):915-919.
1496. Woodson BT, Steward DL, Weaver EM, Javaheri S. A randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2003;128(6):848-861.
1497. Weaver EM, Maynard C, Yueh B. Survival of veterans with sleep apnea: Continuous positive airway pressure versus surgery. *Otolaryngol Head Neck.* 2004;130(6):659-665.
1498. Rotenberg BW, Theriault J, Gottesman S. Redefining the timing of surgery for obstructive sleep apnea in anatomically favorable patients. *Laryngoscope.* 2014;124 Suppl 4:S1-9.
1499. Senchak AJ, McKinlay AJ, Acevedo J, et al. The effect of tonsillectomy alone in adult obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2015;152(5):969-973.
1500. John CR, Gandhi S, Sakharia AR, James TT. Maxillomandibular advancement is a successful treatment for obstructive sleep apnoea: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg.* 2018;47(12):1561-1571.
1501. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: a surgical protocol for dynamic upper airway reconstruction. *J Oral Maxillofac Surg.* 1993;51(7):742-747; discussion 748-749.
1502. Vicini C, Dallan I, Campanini A, et al. Surgery vs ventilation in adult severe obstructive sleep apnea syndrome. *Am J Otolaryngol.* 2010;31(1):14-20.
1503. Liu SY, Huon LK, Powell NB, et al. Lateral Pharyngeal Wall Tension After Maxillomandibular Advancement for Obstructive Sleep Apnea Is a Marker for Surgical Success: Observations From Drug-Induced Sleep Endoscopy. *J Oral Maxillofac Surg.* 2015;73(8):1575-1582.
1504. Yu MS, Ibrahim B, Riley RW, Liu SY. Maxillomandibular Advancement and Upper Airway Stimulation: Extrapharyngeal Surgery for Obstructive Sleep Apnea. *Clin Exp Otorhinolaryngol.* 2020;13(3):225-233.
1505. Kent D, Stanley J, Aurora RN, et al. Referral of adults with obstructive sleep apnea for surgical consultation: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med.* 2021;17(12):2507-2531.
1506. Walker-Engstrom ML, Tegelberg A, Wilhelmsson B, Ringqvist I. 4-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: a randomized study. *Chest.* 2002;121(3):739-746.
1507. Lojander J, Maasilta P, Partinen M, Brander PE, Salmi T, Lehtonen H. Nasal-CPAP, surgery, and conservative management for treatment of obstructive sleep apnea syndrome. A randomized study. *Chest.* 1996;110(1):114-119.
1508. Corso R, Russotto V, Gregoretti C, Cattano D. Perioperative management of obstructive sleep apnea: a systematic review. *Minerva Anestesiologica.* 2018;84(1):81-93.
1509. Leong SM, Tiwari A, Chung F, Wong DT. Obstructive sleep apnea as a risk factor associated with difficult airway management - A narrative review. *Journal of Clinical Anesthesia.* 2018;45:63-68.
1510. Vasu TS, Grewal R, Doghramji K. Obstructive sleep apnea syndrome and perioperative complications: a systematic review of the literature. *J Clin Sleep Med.* 2012;8(2):199-207.
1511. Kheterpal S, Healy D, Aziz MF, et al. Incidence, Predictors, and Outcome of Difficult Mask Ventilation Combined with Difficult Laryngoscopy A Report from the Multicenter Perioperative Outcomes Group. *Anesthesiology.* 2013;119(6):1360-1369.

1512. Neligan PJ, Porter S, Max B, Malhotra G, Greenblatt EP, Ochroch EA. Obstructive sleep apnea is not a risk factor for difficult intubation in morbidly obese patients. *Anesth Analg*. 2009;109(4):1182-1186.
1513. Vest D, Lee D, Newcome K, Stamper H. A Retrospective Review of Difficult Intubations Is Obstructive Sleep Apnea a Predictor? *Clin Nurse Spec*. 2013;27(3):128-131.
1514. Corso RM, Piraccini E, Calli M, et al. Obstructive sleep apnea is a risk factor for difficult endotracheal intubation. *Minerva Anestesiologica*. 2011;77(1):99-100.
1515. Kim JA, Lee JJ. Preoperative predictors of difficult intubation in patients with obstructive sleep apnea syndrome. *Canadian Journal of Anaesthesia-Journal Canadien D Anesthesie*. 2006;53(4):393-397.
1516. Riley RW, Powell NB, Guilleminault C, Pelayo R, Troell RJ, Li KK. Obstructive sleep apnea surgery: Risk management and complications. *Otolaryng Head Neck*. 1997;117(6):648-652.
1517. Siyam MA, Benhamou D. Difficult endotracheal intubation in patients with sleep apnea syndrome. *Anesthesia and Analgesia*. 2002;95(4):1098-1102.
1518. American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep a. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology*. 2014;120(2):268-286.
1519. Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2013;118(2):251-270.
1520. Ravesloot MJL, de Raaff CAL, van de Beek MJ, et al. Perioperative Care of Patients With Obstructive Sleep Apnea Undergoing Upper Airway Surgery: A Review and Consensus Recommendations. *JAMA Otolaryngol Head Neck Surg*. 2019.
1521. Connolly LA. Anesthetic management of obstructive sleep apnea patients. *Journal of Clinical Anesthesia*. 1991;3(6):461-469.
1522. Keamy MF, Cadieux RJ, Kofke WA, Kales A. The Occurrence of Obstructive Sleep-Apnea in a Recovery Room Patient. *Anesthesiology*. 1987;66(2):232-234.
1523. Rafferty TD, Ruskis A, Sasaki C, Gee JB. Perioperative Considerations in the Management of Tracheotomy for the Obstructive Sleep-Apnea Patient - 3 Illustrative Case-Reports. *Brit J Anaesth*. 1980;52(6):619-622.
1524. Kim JA, Lee JJ, Jung HH. Predictive factors of immediate postoperative complications after uvulopalatopharyngoplasty. *Laryngoscope*. 2005;115(10):1837-1840.
1525. Esclamado RM, Glenn MG, McCulloch TM, Cummings CW. Perioperative Complications and Risk-Factors in the Surgical-Treatment of Obstructive Sleep-Apnea Syndrome. *Laryngoscope*. 1989;99(11):1125-1129.
1526. Terris DJ, Clerk AA, Norbash AM, Troell RJ. Characterization of postoperative edema following laser-assisted uvulopalatoplasty using MRI and polysomnography: Implications for the outpatient treatment of obstructive sleep apnea syndrome. *Laryngoscope*. 1996;106(2):124-128.
1527. Li KK, Riley RW, Powell NB, Zonato A, Troell R, Guilleminault C. Postoperative airway findings after maxillomandibular advancement for obstructive sleep apnea syndrome. *Laryngoscope*. 2000;110(2):325-327.
1528. Mickelson SA. Preoperative and postoperative management of obstructive sleep apnea patients. *Otolaryng Clin N Am*. 2007;40(4):877-+.
1529. Iyer US, Koh KF, Chia NCH, Macachor J, Cheng A. Perioperative risk factors in obese patients for bariatric surgery: a Singapore experience. *Singap Med J*. 2011;52(2):94-99.

1530. Kheterpal S, Martin L, Shanks AM, Tremper KK. Prediction and Outcomes of Impossible Mask Ventilation A Review of 50,000 Anesthetics. *Anesthesiology*. 2009;110(4):891-897.
1531. Ulnick KM, Debo RF. Postoperative treatment of the patient with obstructive sleep apnea. *Otolaryng Head Neck*. 2000;122(2):233-236.
1532. Talei B, Cossu AL, Slepian R, Kacker A. Immediate Complications Related to Anesthesia in Patients Undergoing Uvulopalatopharyngoplasty for Obstructive Sleep Apnea. *Laryngoscope*. 2013;123(11):2892-2895.
1533. Meoli AL, Rosen CL, Kristo D, et al. Upper airway management of the adult patient with obstructive sleep apnea in the perioperative period - Avoiding complications. *Sleep*. 2003;26(8):1060-1065.
1534. Nagappa M, Mokhlesi B, Wong J, Wong DT, Kaw R, Chung F. The Effects of Continuous Positive Airway Pressure on Postoperative Outcomes in Obstructive Sleep Apnea Patients Undergoing Surgery: A Systematic Review and Meta-Analysis. *Anesthesia and Analgesia*. 2015;120(5):1013-1023.
1535. Gupta RM, Parvizi J, Hanssen AD, Gay PC. Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: A case-control study. *Mayo Clin Proc*. 2001;76(9):897-905.
1536. Corso RM, Gregoretti C, Braghiroli A, Fanfulla F, Insalaco G. Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea: Navigating through Uncertainty. *Anesthesiology*. 2014;121(3):664-665.
1537. Liao P, Luo QW, Elsaid H, Kang WM, Shapiro CM, Chung F. Perioperative Auto-titrated Continuous Positive Airway Pressure Treatment in Surgical Patients with Obstructive Sleep Apnea A Randomized Controlled Trial. *Anesthesiology*. 2013;119(4):837-847.
1538. Mutter TC, Chateau D, Moffatt M, Ramsey C, Roos LL, Kryger M. A matched cohort study of postoperative outcomes in obstructive sleep apnea: could preoperative diagnosis and treatment prevent complications? *Anesthesiology*. 2014;121(4):707-718.
1539. Rennotte MT, Baele P, Aubert G, Rodenstein DO. Nasal continuous positive airway pressure in the perioperative management of patients with obstructive sleep apnea submitted to surgery. *Chest*. 1995;107(2):367-374.
1540. de Araujo MTM, Bissoli NS, Gouvea SA, et al. CPAP therapy prevents increase in blood pressure after upper airway surgery for obstructive sleep apnoea. *Sleep Breath*. 2013;17(4):1289-1299.
1541. Goldet G, Howick J. Understanding GRADE: an introduction. *J Evid Based Med*. 2013;6(1):50-54.
1542. Choi DL, Reddy K, Weitzel EK, et al. Postoperative Continuous Positive Airway Pressure Use and Nasal Saline Rinses After Endonasal Endoscopic Skull Base Surgery in Patients With Obstructive Sleep Apnea: A Practice Pattern Survey. *Am J Rhinol Allergy*. 2019;33(1):51-55.
1543. Kezirian EJ, Weaver EM, Yueh B, Khuri SF, Daley J, Henderson WG. Risk factors for serious complication after uvulopalatopharyngoplasty. *Arch Otolaryngol*. 2006;132(10):1091-1098.
1544. Rocke D, Sharp S, Wiener D, Puscas L, Lee WT. Effectiveness of a postoperative disposition protocol for sleep apnea surgery. *Am J Otolaryng*. 2013;34(4):273-277.
1545. Kent DT, Lee JJ, Strollo PJ, Jr., Soose RJ. Upper Airway Stimulation for OSA: Early Adherence and Outcome Results of One Center. *Otolaryngol Head Neck Surg*. 2016;155(1):188-193.
1546. Soose RJ, Woodson BT, Gillespie MB, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Self-Reported Outcomes at 24 Months. *Journal of Clinical Sleep Medicine*. 2016;12(1):43-48.
1547. Steffen A, Sommer JU, Hofauer B, Maurer JT, Hasselbacher K, Heiser C. Outcome After One Year of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Post-Market Study. *Laryngoscope*. 2018;128(2):509-515.

1548. Huang HC, Lee LA, Fang TJ, Li HY, Lo CC, Wu JH. Transnasal butorphanol for pain relief after uvulopalatopharyngoplasty - a hospital-based, randomized study. *Chang Gung Med J*. 2009;32(4):390-399.
1549. Neruntarat C. Genioglossus advancement and hyoid myotomy under local anesthesia. *Otolaryngol Head Neck Surg*. 2003;129(1):85-91.
1550. Neruntarat C. Hyoid myotomy with suspension under local anesthesia for obstructive sleep apnea syndrome. *Eur Arch Oto-Rhino-L*. 2003;260(5):286-290.
1551. Walker RP, Garrity T, Gopalsami C. Early polysomnographic findings and long-term subjective results in sleep apnea patients treated with laser-assisted uvulopalatoplasty. *Laryngoscope*. 1999;109(9):1438-1441.
1552. Walker RP, Griggdamberger MM, Gopalsami C, Totten MC. Laser-Assisted Uvulopalatoplasty for Snoring and Obstructive Sleep-Apnea - Results in 170 Patients. *Laryngoscope*. 1995;105(9):938-943.
1553. Wassmuth Z, Mair E, Loube D, Leonard D. Cautery-assisted palatal stiffening operation for the treatment of obstructive sleep apnea syndrome. *Otolaryng Head Neck*. 2000;123(1):55-60.
1554. Cillo JE, Dattilo DJ. Early Major Medical Complications After Surgical Management of Obstructive Sleep Apnea: A Retrospective Cohort Analysis and Case Series. *J Oral Maxil Surg*. 2015;73(1):123-128.
1555. Gessler EM, Bondy PC. Respiratory complications following tonsillectomy/UPPP: is step-down monitoring necessary? *Ear Nose Throat J*. 2003;82(8):628-632.
1556. Hathaway B, Johnson JT. Safety of uvulopalatopharyngoplasty as outpatient surgery. *Otolaryng Head Neck*. 2006;134(4):542-544.
1557. Mickelson SA, Hakim I. Is postoperative intensive care monitoring necessary after uvulopalatopharyngoplasty? *Otolaryng Head Neck*. 1998;119(4):352-356.
1558. Pang KP, Siow JK, Tseng P. Safety of multilevel surgery in obstructive sleep apnea: a review of 487 cases. *Arch Otolaryngol Head Neck Surg*. 2012;138(4):353-357.
1559. Rotenberg B, Hu A, Fuller J, Bureau Y, Arra I, Sen M. The Early Postoperative Course of Surgical Sleep Apnea Patients. *Laryngoscope*. 2010;120(5):1063-1068.
1560. Spiegel JH, Raval TH. Overnight hospital stay is not always necessary after uvulopalatopharyngoplasty. *Laryngoscope*. 2005;115(1):167-171.
1561. Strocker AM, Cohen AN, Wang MB. The safety of outpatient UPPP for obstructive sleep apnea: a retrospective review of 40 cases. *Ear Nose Throat J*. 2008;87(8):466-468.
1562. Terris DJ, Fincher EF, Hanasono MM, Fee WE, Jr., Adachi K. Conservation of resources: indications for intensive care monitoring after upper airway surgery on patients with obstructive sleep apnea. *Laryngoscope*. 1998;108(6):784-788.
1563. Vicini C, Dallan I, Canzi P, Frassinetti S, La Pietra MG, Montevecchi F. Transoral robotic tongue base resection in obstructive sleep apnoea-hypopnoea syndrome: a preliminary report. *ORL J Otorhinolaryngol Relat Spec*. 2010;72(1):22-27.
1564. Nelson RE, Carter J, Anand AG. Hypopharyngeal Airway Surgery for Obstructive Sleep Apnea: Morbidity in the Early Postoperative Period. *J La State Med Soc*. 2015;167(1):11-16.
1565. Zaghi S, Holty JE, Certal V, et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2016;142(1):58-66.
1566. Glazer TA, Hoff PT, Spector ME. Transoral Robotic Surgery for Obstructive Sleep Apnea Perioperative Management and Postoperative Complications. *Jama Otolaryngol*. 2014;140(12):1207-1212.
1567. Macaluso RA, Reams C, Gibson WS, Vrabec DP, Matragrano A. Uvulopalatopharyngoplasty - Postoperative Management and Evaluation of Results. *Ann Oto Rhinol Laryn*. 1989;98(7):502-507.

1568. Yang L, Sun DF, Wu Y, Han J, Liu RC, Wang LJ. Intranasal administration of butorphanol benefits old patients undergoing H-uvulopalatopharyngoplasty: a randomized trial. *Bmc Anesthesiol.* 2015;15.
1569. Lee LA, Wang PC, Chen NH, et al. Alleviation of wound pain after surgeries for obstructive sleep apnea. *Laryngoscope.* 2007;117(9):1689-1694.
1570. Li L, Feng J, Xie SH, Geng LC. Preemptive Submucosal Infiltration with Ropivacaine for Uvulopalatopharyngoplasty. *Otolaryng Head Neck.* 2014;151(5):874-879.
1571. Xie GL, Chu QJ, Liu CL. Application of parecoxib in post-uvulopalatopharyngoplasty analgesia. *Journal of International Medical Research.* 2013;41(5):1699-1704.
1572. Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Dexmedetomidine Infusion for Maintenance of Anesthesia in Patients Undergoing Abdominal Hysterectomy. *Anesthesia and Analgesia.* 1992;75(6):940-946.
1573. Arain SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. *Anesthesia and Analgesia.* 2002;95(2):461-466.
1574. Venn RM, Bradshaw CJ, Spencer R, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia.* 1999;54(12):1136-1142.
1575. Chawla S, Robinson S, Norton A, Esterman A, Taneerananon T. Peri-operative use of dexmedetomidine in airway reconstruction surgery for obstructive sleep apnoea. *Journal of Laryngology and Otology.* 2010;124(1):67-72.
1576. Diakos EA, Gallos ID, El-Shunnar S, Clarke M, Kazi R, Mehanna H. Dexamethasone reduces pain, vomiting and overall complications following tonsillectomy in adults: a systematic review and meta-analysis of randomised controlled trials. *Clin Otolaryngol.* 2011;36(6):531-542.
1577. Titirunguang C, Seresirikachorn K, Kasemsuwan P, Hirunwiwatkul P. The use of steroids to reduce complications after tonsillectomy: a systematic review and meta-analysis of randomized controlled studies. *Eur Arch Oto-Rhino-L.* 2019;276(2):585-604.
1578. Brinck ECV, Tiippana E, Heesen M, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Db Syst Rev.* 2018(12).
1579. Chan AKM, Cheung CW, Chong YK. Alpha-2 agonists in acute pain management. *Expert Opin Pharmacol.* 2010;11(17):2849-2868.
1580. De Oliveira GS, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative Systemic Magnesium to Minimize Postoperative Pain: A Meta-analysis of Randomized Controlled Trials. *Anesthesiology.* 2013;119(1):178-190.
1581. Weibel S, Jelting Y, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. *Cochrane Db Syst Rev.* 2018(6).
1582. Tolska H, Hamunen, K, Takala, A, Kontinen, VK. Systemic review of analgesics and dexamethasone for post-tonsillectomy pain in adults. *Br J Anaesth.* 2019.
1583. Vroegop AV, Vanderveken OM, Boudewyns AN, et al. Drug-induced sleep endoscopy in sleep-disordered breathing: report on 1,249 cases. *Laryngoscope.* 2014;124(3):797-802.
1584. Denolf PL, Vanderveken OM, Marklund ME, Braem MJ. The status of cephalometry in the prediction of non-CPAP treatment outcome in obstructive sleep apnea patients. *Sleep Medicine Reviews.* 2016;27:56-73.
1585. Hong S-N, Won T-B, Kim J-W, Lee CH, Rhee C-S. Upper Airway Evaluation in Patients with Obstructive Sleep Apnea. *Sleep Med Res.* 2016;7(1):1-9.
1586. Kim ST, Choi JH, Jeon HG, Cha HE, Kim DY, Chung YS. Polysomnographic effects of nasal surgery for snoring and obstructive sleep apnea. *Acta Oto-Laryngol.* 2004;124(3):297-300.
1587. Osborn JL, Sacks R. Nasal obstruction. *Am J Rhinol Allergy.* 2013;27:S7-S8.

1588. Holmlund T, Franklin KA, Jaghagen EL, et al. Tonsillectomy in adults with obstructive sleep apnea. *Laryngoscope*. 2016;126(12):2859-2862.
1589. Nuckton TJ, Glidden DV, Browner WS, Claman DM. Physical examination: Mallampati score as an independent predictor of obstructive sleep apnea. *Sleep*. 2006;29(7):903-908.
1590. Min YG, Jang YJ, Rhee CK, Kim CN, Hong SK. Correlation between anthropometric measurements of the oropharyngeal area and severity of apnea in patients with snoring and obstructive sleep apnea. *Auris Nasus Larynx*. 1997;24(4):399-403.
1591. Olszewska E, Woodson BT. Palatal anatomy for sleep apnea surgery. *Laryngoscope Invest*. 2019;4(1):181-187.
1592. Dundar A, Ozunlu A, Sahan M, Ozgen F. Lingual tonsil hypertrophy producing obstructive sleep apnea. *Laryngoscope*. 1996;106(9):1167-1169.
1593. Friedman M, Salapatras AM, Bonzelaar LB. Updated Friedman Staging System for Obstructive Sleep Apnea. *Adv Otorhinolaryngol*. 2017;80:41-48.
1594. Delakorda M, Ovsenik N. Epiglottis shape as a predictor of obstruction level in patients with sleep apnea. *Sleep Breath*. 2019;23(1):311-317.
1595. Hormann KV, Thomas. Laryngeal Obstructive Sleep Apnea. In: Marion Philipp H, ed. *Surgery for Sleep Disordered Breathing*. Germany: Springer Berlin Heidelberg New York; 2005:107-114.
1596. Hsu PP, Tan BYB, Chan YH, Tay HN, Lu PKS, Blair RL. Clinical predictors in obstructive sleep apnea patients with computer-assisted quantitative videoendoscopic upper airway analysis. *Laryngoscope*. 2004;114(5):791-799.
1597. Fernandez-Julian E, Garcia-Perez MA, Garcia-Callejo J, Ferrer F, Marti F, Marco J. Surgical planning after sleep versus awake techniques in patients with obstructive sleep apnea. *Laryngoscope*. 2014;124(8):1970-1974.
1598. Soares D, Folbe AJ, Yoo G, Badr MS, Rowley JA, Lin HS. Drug-Induced Sleep Endoscopy vs Awake Muller's Maneuver in the Diagnosis of Severe Upper Airway Obstruction. *Otolaryng Head Neck*. 2013;148(1):151-156.
1599. Yegin Y, Celik M, Kaya KH, Koc AK, Kayhan FT. Comparison of drug-induced sleep endoscopy and Muller's maneuver in diagnosing obstructive sleep apnea using the VOTE classification system. *Braz J Otorhinolar*. 2017;83(4):445-450.
1600. Borowiecki B, Pollak CP, Weitzman ED, Rakoff S, Imperato J. Fibro-optic study of pharyngeal airway during sleep in patients with hypersomnia obstructive sleep-apnea syndrome. *Laryngoscope*. 1978;88(8 Pt 1):1310-1313.
1601. Genta PR, Sands SA, Butler JP, et al. Airflow Shape Is Associated With the Pharyngeal Structure Causing OSA. *Chest*. 2017;152(3):537-546.
1602. Park D, Kim JS, Heo SJ. Obstruction Patterns During Drug-Induced Sleep Endoscopy vs Natural Sleep Endoscopy in Patients With Obstructive Sleep Apnea. *JAMA Otolaryngol Head Neck Surg*. 2019.
1603. Rojewski TE, Schuller DE, Clark RW, Schmidt HS, Potts RE. Synchronous video recording of the pharyngeal airway and polysomnograph in patients with obstructive sleep apnea. *Laryngoscope*. 1982;92(3):246-250.
1604. Croft CB, Pringle M. Sleep nasendoscopy: a technique of assessment in snoring and obstructive sleep apnoea. *Clin Otolaryngol Allied Sci*. 1991;16(5):504-509.
1605. Kezirian EJ. Drug-induced sleep endoscopy. *Op Tech Otolaryngol*. 2006;17:230-232.
1606. De Vito A, Carrasco Llatas M, Ravesloot MJ, et al. European position paper on drug-induced sleep endoscopy: 2017 Update. *Clin Otolaryngol*. 2018;43(6):1541-1552.
1607. White DP. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med*. 2005;172(11):1363-1370.



1608. Fogel RB, Trinder J, Malhotra A, et al. Within-breath control of genioglossal muscle activation in humans: effect of sleep-wake state. *J Physiol*. 2003;550(Pt 3):899-910.
1609. Fogel RB, Trinder J, White DP, et al. The effect of sleep onset on upper airway muscle activity in patients with sleep apnoea versus controls. *J Physiol*. 2005;564(Pt 2):549-562.
1610. Horner RL, Innes JA, Morrell MJ, Shea SA, Guz A. The effect of sleep on reflex genioglossus muscle activation by stimuli of negative airway pressure in humans. *J Physiol*. 1994;476(1):141-151.
1611. Shea SA, Edwards JK, White DP. Effects of sleep-wake transitions and REM sleep on genioglossal response to upper airway negative pressure. *Am J Respir Crit Care Med*. 1998;157:A653.
1612. Wheatley JR, Tangel DJ, Mezzanotte WS, White DP. Influence of sleep on response to negative airway pressure of tensor palatini muscle and retropalatal airway. *J Appl Physiol*. 1993;75(5):2117-2124.
1613. Wheatley JR, White DP. The influence of sleep on pharyngeal reflexes. *Sleep*. 1993;16(8 Suppl):S87-89.
1614. Shteamer JW, Dedhia RC. Sedative choice in drug-induced sleep endoscopy: A neuropharmacology-based review. *Laryngoscope*. 2017;127(1):273-279.
1615. Alkire MT, Haier RJ, Fallon JH. Toward a unified theory of narcosis: brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anesthetic-induced unconsciousness. *Conscious Cogn*. 2000;9(3):370-386.
1616. Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci*. 2001;24(12):726-731.
1617. Hillman DR, Walsh JH, Maddison KJ, et al. Evolution of changes in upper airway collapsibility during slow induction of anesthesia with propofol. *Anesthesiology*. 2009;111(1):63-71.
1618. Eastwood PR, Platt PR, Shepherd K, Maddison K, Hillman DR. Collapsibility of the upper airway at different concentrations of propofol anesthesia. *Anesthesiology*. 2005;103(3):470-477.
1619. Rabelo FA, Braga A, Kupper DS, et al. Propofol-induced sleep: polysomnographic evaluation of patients with obstructive sleep apnea and controls. *Otolaryngol Head Neck Surg*. 2010;142(2):218-224.
1620. Berry S, Roblin G, Williams A, Watkins A, Whittet HB. Validity of sleep nasendoscopy in the investigation of sleep related breathing disorders. *Laryngoscope*. 2005;115(3):538-540.
1621. Murphy M, Bruno MA, Riedner BA, et al. Propofol anesthesia and sleep: a high-density EEG study. *Sleep*. 2011;34(3):283-291a.
1622. Abdullah VJ, Lee DL, Ha SC, van Hasselt CA. Sleep endoscopy with midazolam: sedation level evaluation with bispectral analysis. *Otolaryngol Head Neck Surg*. 2013;148(2):331-337.
1623. Genta PR, Eckert DJ, Gregorio MG, et al. Critical closing pressure during midazolam-induced sleep. *J Appl Physiol (1985)*. 2011;111(5):1315-1322.
1624. Huupponen E, Maksimow A, Lapinlampi P, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiol Scand*. 2008;52(2):289-294.
1625. Hsu YW, Cortinez LI, Robertson KM, et al. Dexmedetomidine pharmacodynamics: part I: crossover comparison of the respiratory effects of dexmedetomidine and remifentanyl in healthy volunteers. *Anesthesiology*. 2004;101(5):1066-1076.
1626. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. *Eur Arch Otorhinolaryngol*. 2011;268:1233-1236.
1627. Yoon BW, Hong JM, Hong SL, Koo SK, Roh HJ, Cho KS. A comparison of dexmedetomidine versus propofol during drug-induced sleep endoscopy in sleep apnea patients. *Laryngoscope*. 2016;126(3):763-767.

1628. Viana A, Zhao C, Rosa T, et al. The Effect of Sedating Agents on Drug-Induced Sleep Endoscopy Findings. *Laryngoscope*. 2019;129(2):506-513.
1629. Steinhart H, Kuhn-Lohmann J, Gewalt K, Constantinidis J, Mertzlufft F, Iro H. Upper airway collapsibility in habitual snorers and sleep apneics: evaluation with drug-induced sleep endoscopy. *Acta Otolaryngol*. 2000;120(8):990-994.
1630. Kezirian EJ, White DP, Malhotra A, Ma W, McCulloch CE, Goldberg AN. Interrater reliability of drug-induced sleep endoscopy. *Arch Otolaryngol Head Neck Surg*. 2010;136(4):393-397.
1631. Rodriguez-Bruno K, Goldberg AN, McCulloch CE, Kezirian EJ. Test-retest reliability of drug-induced sleep endoscopy. *Otolaryngol Head Neck Surg*. 2009;140(5):646-651.
1632. Vroegop AV, Vanderveken OM, Wouters K, et al. Observer variation in drug-induced sleep endoscopy: experienced versus nonexperienced ear, nose, and throat surgeons. *Sleep*. 2013;36(6):947-953.
1633. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep*. 1996;19(2):156-177.
1634. Abdullah VJ, Wing YK, van Hasselt CA. Video sleep nasendoscopy: the Hong Kong experience. *Otolaryngol Clin North Am*. 2003;36(3):461-471, vi.
1635. Iwanaga K, Hasegawa K, Shibata N, et al. Endoscopic examination of obstructive sleep apnea syndrome patients during drug-induced sleep. *Acta Otolaryngol Suppl*. 2003(550):36-40.
1636. Vicini C, De Vito A, Benazzo M, et al. The nose oropharynx hypopharynx and larynx (NOHL) classification: a new system of diagnostic standardized examination for OSAHS patients. *Eur Arch Otorhinolaryngol*. 2012;269(4):1297-1300.
1637. Nashi N, Kang S, Barkdull GC, Lucas J, Davidson TM. Lingual fat at autopsy. *Laryngoscope*. 2007;117(8):1467-1473.
1638. Blumen MB, Latournerie V, Bequignon E, Guillere L, Chabolle F. Are the obstruction sites visualized on drug-induced sleep endoscopy reliable? *Sleep Breath*. 2015;19(3):1021-1026.
1639. Hessel NS, Vries N. Increase of the apnoea-hypopnoea index after uvulopalatopharyngoplasty: analysis of failure. *Clin Otolaryngol Allied Sci*. 2004;29(6):682-685.
1640. Hsu YS, Jacobowitz O. Does Sleep Endoscopy Staging Pattern Correlate With Outcome of Advanced Palatopharyngoplasty for Moderate to Severe Obstructive Sleep Apnea? *J Clin Sleep Med*. 2017;13(10):1137-1144.
1641. Koutsourelakis I, Safiruddin F, Ravesloot M, Zakyntinos S, de Vries N. Surgery for obstructive sleep apnea: sleep endoscopy determinants of outcome. *Laryngoscope*. 2012;122(11):2587-2591.
1642. Soares D, Sinawe H, Folbe AJ, et al. Lateral oropharyngeal wall and supraglottic airway collapse associated with failure in sleep apnea surgery. *Laryngoscope*. 2012;122(2):473-479.
1643. Zhang P, Ye J, Pan C, Sun N, Kang D. The Role of Obstruction Length and Height in Predicting Outcome of Velopharyngeal Surgery. *Otolaryngol Head Neck Surg*. 2015;153(1):144-149.
1644. Brodsky L. Modern Assessment of Tonsils and Adenoids. *Pediatr Clin N Am*. 1989;36(6):1551-1569.
1645. Green KK, Kent DT, D'Agostino MA, et al. Drug-Induced Sleep Endoscopy and Surgical Outcomes: A Multicenter Cohort Study. *Laryngoscope*. 2019;129(3):761-770.
1646. Huyett P, Kent DT, D'Agostino MA, et al. Drug-Induced Sleep Endoscopy and Hypoglossal Nerve Stimulation Outcomes: A Multicenter Cohort Study. *Laryngoscope*. 2021;131(7):1676-1682.
1647. Eichler C, Sommer JU, Stuck BA, Hormann K, Maurer JT. Does drug-induced sleep endoscopy change the treatment concept of patients with snoring and obstructive sleep apnea? *Sleep Breath*. 2013;17(1):63-68.

1648. Gillespie MB, Reddy RP, White DR, Discolo CM, Overdyk FJ, Nguyen SA. A trial of drug-induced sleep endoscopy in the surgical management of sleep-disordered breathing. *Laryngoscope*. 2016;126(1):277-282.
1649. Golbin D, Musgrave B, Succar E, Yaremchuk K. Clinical analysis of drug-induced sleep endoscopy for the OSA patient. *Laryngoscope*. 2016;126(1):249-253.
1650. Pang KP, Baptista PM, Olszewska E, et al. Does drug-induced sleep endoscopy affect surgical outcome? A multicenter study of 326 obstructive sleep apnea patients. *Laryngoscope*. 2020;130(2):551-555.
1651. Sukato DC, Abramowitz JM, Boruk M, Goldstein NA, Rosenfeld RM. Endoscopic Sinus Surgery Improves Sleep Quality in Chronic Rhinosinusitis: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. 2018;158(2):249-256.
1652. Gunhan K, Zeren F, Uz U, Gumus B, Unlu H. Impact of nasal polyposis on erectile dysfunction. *Am J Rhinol Allergy*. 2011;25(2):112-115.
1653. Jiang R-S, Liang K-L. The Influence of Functional Endoscopic Sinus Surgery on Sleep Related Outcomes in Patients with Chronic Rhinosinusitis. *Int J Otolaryngol*. 2019;2019:7951045-7951045.
1654. Uz U, Günhan K, Yılmaz H, Ünlü H. The evaluation of pattern and quality of sleep in patients with chronic rhinosinusitis with nasal polyps. *Auris Nasus Larynx*. 2017;44(6):708-712.
1655. Alt JA, Smith TL, Schlosser RJ, Mace JC, Soler ZM. Sleep and quality of life improvements after endoscopic sinus surgery in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2014;4(9):693-701.
1656. Little RE, Alt JA, Ramakrishnan VR, et al. Objective sleep measures after endoscopic sinus surgery in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2020.
1657. Sériès F, St Pierre S, Carrier G. Surgical correction of nasal obstruction in the treatment of mild sleep apnoea: importance of cephalometry in predicting outcome. *Thorax*. 1993;48(4):360-363.
1658. Park CY, Hong JH, Lee JH, et al. Clinical effect of surgical correction for nasal pathology on the treatment of obstructive sleep apnea syndrome. *PLoS one*. 2014;9(6):e98765.
1659. Wu J, Zhao G, Li Y, et al. Apnea-hypopnea index decreased significantly after nasal surgery for obstructive sleep apnea: A meta-analysis. *Medicine (Baltimore)*. 2017;96(5):e6008.
1660. Koutsourelakis I, Georgouloupoulos G, Perraki E, Vagiakis E, Roussos C, Zakyntinos SG. Randomised trial of nasal surgery for fixed nasal obstruction in obstructive sleep apnoea. *Eur Respir J*. 2008;31(1):110-117.
1661. Cai Y, Goldberg AN, Chang JL. The Nose and Nasal Breathing in Sleep Apnea. *Otolaryngol Clin North Am*. 2020;53(3):385-395.
1662. Moxness MH, Nordgard S. An observational cohort study of the effects of septoplasty with or without inferior turbinate reduction in patients with obstructive sleep apnea. *BMC Ear Nose Throat Disord*. 2014;14:11.
1663. Hu B, Han D, Li Y, Ye J, Zang H, Wang T. Polysomnographic effect of nasal surgery on positional and non-positional obstructive sleep apnea/hypopnea patients. *Acta Otolaryngol*. 2013;133(8):858-865.
1664. Boot H, van Wegen R, Poublon RML, Bogaard JM, Schmitz PIM, van der Meche FGA. Long-term results of uvulopalatopharyngoplasty for obstructive sleep apnea syndrome. *Laryngoscope*. 2000;110(3):469-475.
1665. Sommer JU, Heiser C, Gahleitner C, et al. Tonsillectomy with Uvulopalatopharyngoplasty in Obstructive Sleep Apnea A Two-center Randomized Controlled Trial. *Dtsch Arztebl Int*. 2016;113(1-2):1-+.
1666. Stevenson EW, Turner GT, Sutton FD, Doekel RC, Pegram V, Hernandez J. Prognostic-Significance of Age and Tonsillectomy in Uvulopalatopharyngoplasty. *Laryngoscope*. 1990;100(8):820-823.

1667. Tetter N, Tschopp K. Contribution of Hyoid and Tonsillar Procedures to Outcome in Multilevel Surgery for Obstructive Sleep Apnea Syndrome. *ORL J Otorhinolaryngol Relat Spec*. 2016;78(6):353-360.
1668. Tschopp S, Tschopp K. Tonsil size and outcome of uvulopalatopharyngoplasty with tonsillectomy in obstructive sleep apnea. *Laryngoscope*. 2019;129(12):E449-E454.
1669. Verse T, Wenzel S, Brus J. Multi-level surgery for obstructive sleep apnea. Lingual tonsillectomy vs. hyoid suspension in combination with radiofrequency of the tongue base. *Sleep Breath*. 2015;19(4):1361-1366.
1670. Vidigal TA, Haddad FL, Cabral RF, et al. New clinical staging for pharyngeal surgery in obstructive sleep apnea patients. *Braz J Otorhinolaryngol*. 2014;80(6):490-496.
1671. Orr WC, Martin RJ. Obstructive sleep apnea associated with tonsillar hypertrophy in adults. *Arch Intern Med*. 1981;141(8):990-992.
1672. Cahali MB SC, Dantas ASD, Formigoni GGS. Objective and subjective tonsil volume and severity of obstructive sleep apnea: Is there a correlation in adults. *Sleep Med*. 2009;10:S65-S66.
1673. Tan LTH, Tan AKL, Hsu PP, et al. Effects of tonsillectomy on sleep study parameters in adult patients with obstructive sleep apnea—a prospective study. *Sleep Breath*. 2014;18(2):265-268.
1674. Nakata S, Noda A, Yanagi E, Suzuki K, Yamamoto H, Nakashima T. Tonsil size and body mass index are important factors for efficacy of simple tonsillectomy in obstructive sleep apnoea syndrome. *Clin Otolaryngol*. 2006;31(1):41-45.
1675. Nakata S, Miyazaki S, Ohki M, et al. Reduced nasal resistance after simple tonsillectomy in patients with obstructive sleep apnea. *American Journal of Rhinology*. 2007;21(2):192-195.
1676. Verse T, Kroker BA, Pirsig W, Brosch S. Tonsillectomy as a treatment of obstructive sleep apnea in adults with tonsillar hypertrophy. *Laryngoscope*. 2000;110(9):1556-1559.
1677. Smith MM, Peterson E, Yaremchuk KL. The Role of Tonsillectomy in Adults with Tonsillar Hypertrophy and Obstructive Sleep Apnea. *Otolaryng Head Neck*. 2017;157(2):331-335.
1678. Stow NW, Sale PJP, Lee D, Joffe D, Gallagher RM. Simultaneous Tonsillectomy and Nasal Surgery in Adult Obstructive Sleep Apnea: A Pilot Study. *Otolaryng Head Neck*. 2012;147(2):387-391.
1679. Miyazaki S, Itasaka Y, Tada H, Ishikawa K, Togawa K. Effectiveness of tonsillectomy in adult sleep apnea syndrome. *Psychiatry and clinical neurosciences*. 1998;52(2):222-223.
1680. Houghton DJ, Camilleri AE, Stone P. Adult obstructive sleep apnoea syndrome and tonsillectomy. *Journal of Laryngology and Otolaryngology*. 1997;111(9):829-832.
1681. Cheong TH, Wang YT, Poh SC. Sleep apnoea syndrome—a report of 14 cases. *Singapore Med J*. 1990;31(4):350-354.
1682. Aubert-Tulkens G, Hamoir M, Van den Eeckhaut J, Rodenstein DO. Failure of tonsil and nose surgery in adults with long-standing severe sleep apnea syndrome. *Arch Intern Med*. 1989;149(9):2118-2121.
1683. Moser RJ, Rajagopal KR. Obstructive Sleep-Apnea in Adults with Tonsillar Hypertrophy. *Archives of Internal Medicine*. 1987;147(7):1265-1267.
1684. Rubin AHE, Eliaschar I, Joachim Z, Alroy G, Lavie P. Effects of Nasal Surgery and Tonsillectomy on Sleep-Apnea. *B Eur Physiopath Res*. 1983;19(6):612-615.
1685. Caples SM, Rowley JA, Prinsell JR, et al. Surgical Modifications of the Upper Airway for Obstructive Sleep Apnea in Adults: A Systematic Review and Meta-Analysis. *Sleep*. 2010;33(10):1396-1407.
1686. Halle TR, Oh MS, Collop NA, Quyyumi AA, Bliwise DL, Dedhia RC. Surgical Treatment of OSA on Cardiovascular Outcomes: A Systematic Review. *Chest*. 2017;152(6):1214-1229.
1687. Stuck BA, Ravesloot MJL, Eschenhagen T, de Vet HCW, Sommer JU. Uvulopalatopharyngoplasty with or without tonsillectomy in the treatment of adult obstructive sleep apnea - A systematic review. *Sleep Med*. 2018;50:152-165.

1688. Pang KP, Woodson BT. Expansion sphincter pharyngoplasty: A new technique for the treatment of obstructive sleep apnea. *Otolaryng Head Neck*. 2007;137(1):110-114.
1689. Pang KP, Pang EB, Win MT, Pang KA, Woodson BT. Expansion sphincter pharyngoplasty for the treatment of OSA: a systemic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2016;273(9):2329-2333.
1690. Rashwan MS, Montevecchi F, Cammaroto G, et al. Evolution of soft palate surgery techniques for obstructive sleep apnea patients: A comparative study for single-level palatal surgeries. *Clin Otolaryngol*. 2018;43(2):584-590.
1691. Babademez MA, Gul F, Teleke YC. Barbed palatoplasty vs. expansion sphincter pharyngoplasty with anterior palatoplasty. *Laryngoscope*. 2020;130(4):E275-E279.
1692. Binar M, Akcam T, Karakoc O, Sagkan RI, Musabak U, Gerek M. A new surgical technique versus an old marker: can expansion sphincter pharyngoplasty reduce C-reactive protein levels in patients with obstructive sleep apnea? *Eur Arch Otorhinolaryngol*. 2017;274(2):829-836.
1693. Guler I, Kuzucu I, Baklaci D, Kum RO, Kum NY, Ozcan M. Efficiency of Expansion Sphincter Pharyngoplasty in the Treatment of Obstructive Sleep Apnea Syndrome. *Turk Arch Otorhinol*. 2018;56(4):206-209.
1694. Hong SN, Kim HG, Han SY, et al. Indications for and Outcomes of Expansion Sphincter Pharyngoplasty to Treat Lateral Pharyngeal Collapse in Patients With Obstructive Sleep Apnea. *Jama Otolaryngol*. 2019;145(5):405-412.
1695. Huntley C, Chou DW, Doghramji K, Boon M. Comparing Upper Airway Stimulation to Expansion Sphincter Pharyngoplasty: A Single University Experience. *Ann Oto Rhinol Laryn*. 2018;127(6):379-383.
1696. Karakoc O, Binar M, Aydin U, Genc H, Akcam T, Gerek M. A tertiary center experience with velopharyngeal surgical techniques for treatment of snoring and obstructive sleep apnea. *Auris Nasus Larynx*. 2018;45(3):492-498.
1697. Lorusso F, Dispenza F, Modica DM, Gallina S. The Role of Modified Expansion Sphincter Pharyngoplasty in Multilevel Obstructive Sleep Apnea Syndrome Surgery. *Int Arch Otorhinolar*. 2018;22(4):432-436.
1698. Pang KP, Piccin O, Pang EB, Pang KA, Chan YH, Rotenberg BW. Combined Expansion Pharyngoplasty and Anterior Palatoplasty for the Treatment of OSA. *Indian J Otolaryngol*. 2016;68(4):528-533.
1699. Despeghel AS, Mus L, Dick C, et al. Long-term results of a modified expansion sphincter pharyngoplasty for sleep-disordered breathing. *Eur Arch Oto-Rhino-L*. 2017;274(3):1665-1670.
1700. Plaza G, Baptista P, O'Connor-Reina C, Bosco G, Perez-Martin N, Pang KP. Prospective multi-center study on expansion sphincter pharyngoplasty. *Acta Oto-Laryngol*. 2019;139(2):219-222.
1701. Pang KP, Vicini C, Montevecchi F, et al. Long-term complications of palate surgery: A multicenter study of 217 patients. *Laryngoscope*. 2020;130(9):2281-2284.
1702. Liu SY, Hutz MJ, Poomkonsarn S, Chang CP, Awad M, Capasso R. Palatopharyngoplasty Resolves Concentric Collapse in Patients Ineligible for Upper Airway Stimulation. *Laryngoscope*. 2020;130(12):E958-E962.
1703. Bosco G, Perez-Martin N, Racionero MA, Plaza G. Expansion sphincter pharyngoplasty: Usefulness of DISE. *Acta Otorrinolaringol Esp (Engl Ed)*. 2019;70(4):215-221.
1704. Suslu AE, Pamuk G, Pamuk AE, Ozer S, Jafarov S, Onerci TM. Effects of Expansion Sphincter Pharyngoplasty on the Apnea-Hypopnea Index and Heart Rate Variability. *J Oral Maxillofac Surg*. 2017;75(12):2650-2657.
1705. Cahali MB. Lateral pharyngoplasty: A new treatment for obstructive sleep apnea hypopnea syndrome. *Laryngoscope*. 2003;113(11):1961-1968.

1706. Cahali MB, Formigoni GGS, Gebrim EMMS, Miziara ID. Lateral pharyngoplasty versus uvulopalatopharyngoplasty: a clinical, polysomnographic and computed tomography measurement comparison. *Sleep*. 2004;27(5):942-950.
1707. Cahali MB. Revaluing the role of the tongue in obstructive sleep apnea. *J Bras Pneumol*. 2019;45(4).
1708. Passos UL, Genta PR, Marcondes BF, Lorenzi G, Gebrim EMMS. State-dependent changes in the upper airway assessed by multidetector CT in healthy individuals and during obstructive events in patients with sleep apnea. *J Bras Pneumol*. 2019;45(4).
1709. Huon LK, Liu SYC, Shih TTF, Chen YJ, Lo MT, Wang PC. Dynamic upper airway collapse observed from sleep MRI: BMI-matched severe and mild OSA patients. *Eur Arch Oto-Rhino-L*. 2016;273(11):4021-4026.
1710. Chi JC, Chiang RP, Chou TY, Shu CH, Shiao AS, Lin CM. The role of lateral pharyngoplasty in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2015;272(2):489-496.
1711. Dizdar D, Civelek S, Calis ZA, Dizdar SK, Coskun BU, Vural A. Comparative Analysis of Lateral Pharyngoplasty and Uvulopalatopharyngoplasty Techniques With Polisomnography and Epworth Sleepiness Scales. *J Craniofac Surg*. 2015;26(7):e647-651.
1712. Carrasco-Llatas M, Marcano-Acuna M, Zerpa-Zerpa V, Dalmau-Galofre J. Surgical results of different palate techniques to treat oropharyngeal collapse. *Eur Arch Oto-Rhino-L*. 2015;272(9):2535-2540.
1713. de Paula Soares CF, Cavichio L, Cahali MB. Lateral pharyngoplasty reduces nocturnal blood pressure in patients with obstructive sleep apnea. *Laryngoscope*. 2014;124(1):311-316.
1714. Elzayat S, El-Sobki A, El-Deeb ME, Moussa HH. Managing obstructive sleep apnea patients with CPAP failure with a novel Lateral Pharyngoplasty as a stand-alone procedure. *Am J Otolaryng*. 2020;41(4).
1715. Tuncel U, Inancli HM, Kurkcuglu SS, Enoz M. A comparison of unilevel and multilevel surgery in obstructive sleep apnea syndrome. *Ear Nose Throat J*. 2012;91(8):E13-18.
1716. Woodson BT, Toohill RJ. Transpalatal Advancement Pharyngoplasty for Obstructive Sleep-Apnea. *Laryngoscope*. 1993;103(3):269-276.
1717. Woodson BT. Changes in airway characteristics after transpalatal advancement pharyngoplasty compared to uvulopalatopharyngoplasty (UPPP). *Sleep*. 1996;19(10):S291-S293.
1718. Woodson BT, Robinson S, Lim HJ. Transpalatal advancement pharyngoplasty outcomes compared with uvulopalatopharyngoplasty. *Otolaryng Head Neck*. 2005;133(2):211-217.
1719. Shine NP, Lewis RH. The "Propeller" incision for transpalatal advancement pharyngoplasty: A new approach to reduce post-operative oronasal fistulae. *Auris Nasus Larynx*. 2008;35(3):397-400.
1720. Chan L, Kitpornchai L, Mackay S. Causative Factors for Complications in Transpalatal Advancement. *Ann Oto Rhinol Larynx*. 2020;129(1):18-22.
1721. Volner K, Dunn B, Chang ET, et al. Transpalatal advancement pharyngoplasty for obstructive sleep apnea: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2017;274(3):1197-1203.
1722. Powell NB, Riley RW, Troell RJ, Li K, Blumen MB, Guilleminault C. Radiofrequency volumetric tissue reduction of the palate in subjects with sleep-disordered breathing. *Chest*. 1998;113(5):1163-1174.
1723. Back L, Palomaki M, Piilonen A, Ylikoski J. Sleep-disordered breathing: radiofrequency thermal ablation is a promising new treatment possibility. *Laryngoscope*. 2001;111(3):464-471.
1724. Back LJ, Tervahartiala PO, Piilonen AK, Partinen MM, Ylikoski JS. Bipolar radiofrequency thermal ablation of the soft palate in habitual snorers without significant desaturations assessed by magnetic resonance imaging. *Am J Respir Crit Care Med*. 2002;166(6):865-871.

1725. Blumen MB, Dahan S, Wagner I, De Dieuleveult T, Chabolle F. Radiofrequency versus LAUP for the treatment of snoring. *Otolaryngol Head Neck Surg.* 2002;126(1):67-73.
1726. Emery BE, Flexon PB. Radiofrequency volumetric tissue reduction of the soft palate: a new treatment for snoring. *Laryngoscope.* 2000;110(7):1092-1098.
1727. Blumen MB, Vezina JP, Bequignon E, Chabolle F. Snoring intensity after a first session of soft palate radiofrequency: predictive value of the final result. *Laryngoscope.* 2013;123(6):1556-1559.
1728. Boudewyns A, Van De Heyning P. Temperature-controlled radiofrequency tissue volume reduction of the soft palate (somnoplasty) in the treatment of habitual snoring: results of a European multicenter trial. *Acta Otolaryngol.* 2000;120(8):981-985.
1729. Hukins CA, Mitchell IC, Hillman DR. Radiofrequency tissue volume reduction of the soft palate in simple snoring. *Arch Otolaryngol Head Neck Surg.* 2000;126(5):602-606.
1730. Hultcrantz E, Harder L, Loord H, et al. Long-term effects of radiofrequency ablation of the soft palate on snoring. *Eur Arch Otorhinolaryngol.* 2010;267(1):137-142.
1731. Sher AE, Flexon PB, Hillman D, et al. Temperature-controlled radiofrequency tissue volume reduction in the human soft palate. *Otolaryngol Head Neck Surg.* 2001;125(4):312-318.
1732. Stuck BA, Maurer JT, Hein G, Hormann K, Verse T. Radiofrequency surgery of the soft palate in the treatment of snoring: a review of the literature. *Sleep.* 2004;27(3):551-555.
1733. Stuck BA, Sauter A, Hormann K, Verse T, Maurer JT. Radiofrequency surgery of the soft palate in the treatment of snoring. A placebo-controlled trial. *Sleep.* 2005;28(7):847-850.
1734. Tatla T, Sandhu G, Croft CB, Kotecha B. Celon radiofrequency thermo-ablative palatoplasty for snoring - a pilot study. *J Laryngol Otol.* 2003;117(10):801-806.
1735. Back LJ, Hytonen ML, Roine RP, Malmivaara AO. Radiofrequency ablation treatment of soft palate for patients with snoring: a systematic review of effectiveness and adverse effects. *Laryngoscope.* 2009;119(6):1241-1250.
1736. Holmlund T, Levring-Jaghagen E, Franklin KA, Lindkvist M, Berggren D. Effects of Radiofrequency versus sham surgery of the soft palate on daytime sleepiness. *Laryngoscope.* 2014;124(10):2422-2426.
1737. Ferguson M, Smith TL, Zanation AM, Yarbrough WG. Radiofrequency tissue volume reduction: multilesion vs single-lesion treatments for snoring. *Arch Otolaryngol Head Neck Surg.* 2001;127(9):1113-1118.
1738. Back LJ, Liukko T, Rantanen I, et al. Radiofrequency surgery of the soft palate in the treatment of mild obstructive sleep apnea is not effective as a single-stage procedure: A randomized single-blinded placebo-controlled trial. *Laryngoscope.* 2009;119(8):1621-1627.
1739. De Kermadec H, Blumen MB, Engalenc D, Vezina JP, Chabolle F. Radiofrequency of the soft palate for sleep-disordered breathing: a 6-year follow-up study. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2014;131(1):27-31.
1740. Hofmann T, Schwantzer G, Reckenzaun E, Koch H, Wolf G. Radiofrequency tissue volume reduction of the soft palate and UPPP in the treatment of snoring. *Eur Arch Otorhinolaryngol.* 2006;263(2):164-170.
1741. Stuck BA. Radiofrequency-Assisted Uvulopalatoplasty for Snoring: Long-Term Follow-up. *Laryngoscope.* 2009;119(8):1617-1620.
1742. Balsevicius T, Uloza V, Sakalauskas R, Miliauskas S, Jarutiene I. Efficacy of radiofrequency treatment of the soft palate for patients with mild to moderate obstructive sleep apnea hypopnea syndrome: treatment protocol with nine lesions to the soft palate. *Sleep Breath.* 2015;19(3):1003-1009.
1743. Birkent H, Soken H, Akcam T, Karahatay S, Gerek M. The effect of radiofrequency volumetric tissue reduction of soft palate on voice. *Eur Arch Otorhinolaryngol.* 2008;265(2):195-198.

1744. Haraldsson PO, Karling J, Lysdahl M, Svanborg E. Voice quality after radiofrequency volumetric tissue reduction of the soft palate in habitual snorers. *Laryngoscope*. 2002;112(7 Pt 1):1260-1263.
1745. Choi JH, Kim SN, Cho JH. Efficacy of the Pillar implant in the treatment of snoring and mild-to-moderate obstructive sleep apnea: a meta-analysis. *Laryngoscope*. 2013;123(1):269-276.
1746. Friedman M, Schalch P, Joseph NJ. Palatal stiffening after failed uvulopalatopharyngoplasty with the Pillar Implant System. *Laryngoscope*. 2006;116(11):1956-1961.
1747. Friedman M, Schalch P, Lin HC, Kakodkar KA, Joseph NJ, Mazloom N. Palatal implants for the treatment of snoring and obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2008;138(2):209-216.
1748. Goessler UR, Hein G, Verse T, Stuck BA, Hormann K, Maurer JT. Soft palate implants as a minimally invasive treatment for mild to moderate obstructive sleep apnea. *Acta Otolaryngol*. 2007;127(5):527-531.
1749. Maurer JT, Sommer JU, Hein G, Hormann K, Heiser C, Stuck BA. Palatal implants in the treatment of obstructive sleep apnea: a randomised, placebo-controlled single-centre trial. *Eur Arch Otorhinolaryngol*. 2012;269(7):1851-1856.
1750. Nordgard S, Stene BK, Skjostad KW. Soft palate implants for the treatment of mild to moderate obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2006;134(4):565-570.
1751. Steward DL, Huntley TC, Woodson BT, Surdulescu V. Palate implants for obstructive sleep apnea: multi-institution, randomized, placebo-controlled study. *Otolaryngol Head Neck Surg*. 2008;139(4):506-510.
1752. Walker RP, Levine HL, Hopp ML, Greene D, Pang K. Palatal implants: a new approach for the treatment of obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2006;135(4):549-554.
1753. Nordgard S, Hein G, Stene BK, Skjostad KW, Maurer JT. One-year results: palatal implants for the treatment of obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2007;136(5):818-822.
1754. Walker RP, Levine HL, Hopp ML, Greene D. Extended follow-up of palatal implants for OSA treatment. *Otolaryngol Head Neck Surg*. 2007;137(5):822-827.
1755. Neruntarat C. Long-term results of palatal implants for obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2011;268(7):1077-1080.
1756. Choi JH, Cho JH, Chung YS, Kim JW, Kim SW. Effect of the Pillar implant on snoring and mild obstructive sleep apnea: A multicenter study in Korea. *Laryngoscope*. 2015;125(5):1239-1243.
1757. Server EA, Alkan Z, Yigit O, Yasak AG. Long-term results of pillar implant procedure. *Kulak Burun Bogaz Ihtis Derg*. 2016;26(5):258-264.
1758. Bertoletti F, Indelicato A, Banfi P, Capolunghi B. Sleep apnoea/hypopnoea syndrome: combination therapy with the Pillar palatal implant technique and continuous positive airway pressure (CPAP). A preliminary report. *B-ENT*. 2009;5(4):251-257.
1759. Hu HC, Kuo CL, Tung TH, Chen SC, Li LP. Long-term results of palatal implantation for severe obstructive sleep apnea patients with prominent retropalatal collapse. *J Chin Med Assoc*. 2018;81(9):837-841.
1760. Gillespie MB, Wylie PE, Lee-Chiong T, Rapoport DM. Effect of palatal implants on continuous positive airway pressure and compliance. *Otolaryngol Head Neck Surg*. 2011;144(2):230-236.
1761. Friedman M, Vidyasagar R, Bliznikas D, Joseph NJ. Patient selection and efficacy of pillar implant technique for treatment of snoring and obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2006;134(2):187-196.
1762. Cammaroto G, Montevicchi F, D'Agostino G, et al. Palatal surgery in a transoral robotic setting (TORS): preliminary results of a retrospective comparison between uvulopalatopharyngoplasty (UPPP), expansion sphincter pharyngoplasty (ESP) and barbed repositioning pharyngoplasty (BRP). *Acta Otorhinolaryngo*. 2017;37(5):406-409.



1763. Vicini C, Meccariello G, Montevecchi F, et al. Effectiveness of barbed repositioning pharyngoplasty for the treatment of obstructive sleep apnea (OSA): a prospective randomized trial. *Sleep Breath*. 2020;24(2):687-694.
1764. Barbieri M, Missale F, Incandela F, et al. Barbed suspension pharyngoplasty for treatment of lateral pharyngeal wall and palatal collapse in patients affected by OSAHS. *Eur Arch Oto-Rhino-L*. 2019;276(6):1829-1835.
1765. Mantovani M, Rinaldi V, Torretta S, Carioli D, Salamanca F, Pignataro L. Barbed Roman blinds technique for the treatment of obstructive sleep apnea: how we do it? *Eur Arch Oto-Rhino-L*. 2016;273(2):517-523.
1766. Mantovani M, Carioli D, Torretta S, Rinaldi V, Ibba T, Pignataro L. Barbed snore surgery for concentric collapse at the velum: The Alianza technique. *J Cranio Maxill Surg*. 2017;45(11):1794-1800.
1767. Salamanca F, Costantini F, Mantovani M, et al. Barbed anterior pharyngoplasty: an evolution of anterior palatoplasty. *Acta Otorhinolaryngo*. 2014;34(6):434-438.
1768. Pianta L, Bertazzoni G, Morello R, Perotti P, Nicolai P. Barbed expansion sphincter pharyngoplasty for the treatment of oropharyngeal collapse in obstructive sleep apnoea syndrome: A retrospective study on 17 patients. *Clin Otolaryngol*. 2018;43(2):696-700.
1769. El-Ahl MAS, El-Anwar MW. Expansion Pharyngoplasty by New Simple Suspension Sutures without Tonsillectomy. *Otolaryng Head Neck*. 2016;155(6):1065-1068.
1770. Elbassiouny AMME. Modified barbed soft palatal posterior pillar webbing flap palatopharyngoplasty. *Sleep Breath*. 2016;20(2):829-836.
1771. Modica DM, Lorusso F, Presti G, Fasola S, Gallina S. Our Assessment Using Palate Postoperative Problems Score (PPOPS): Tool for the Evaluation of Results in Palatal Surgery Techniques. *Indian J Otolaryngol*. 2019;71:766-770.
1772. Rashwan MS, Montevecchi F, Firinua E, et al. Let's know from our patients: PPOPS score for palate surgery evaluation/a pilot study. *Eur Arch Oto-Rhino-L*. 2018;275(1):287-291.
1773. Rinaldi V, Costantino A, Moffa A, et al. Postoperative Pain and Wound Healing After Coblation-Assisted Barbed Anterior Pharyngoplasty (CABAPh): An Observational Study. *Indian J Otolaryngol*. 2019;71(Suppl 2):1157-1162.
1774. Askar SM, El-Anwar MW, Awad A. Modified anterior palatoplasty and double suspension sutures (with or without tonsillectomy) in selected patients with obstructive sleep apnea: a preliminary report. *Sleep Breath*. 2018;22(3):789-795.
1775. Askar SM, El-Anwar MW. Double suspension sutures: A simple surgical technique for selected cases of obstructive sleep apnoea: Our experience with twenty-two patients. *Clin Otolaryngol*. 2018;43(2):753-757.
1776. Babademez MA, Gul F, Kale H, Sancak M. Technical update of barbed pharyngoplasty for retropalatal obstruction in obstructive sleep apnoea. *Journal of Laryngology and Otology*. 2019;133(7):622-626.
1777. Powell NB, Riley RW, Guilleminault C. Radiofrequency tongue base reduction in sleep-disordered breathing: A pilot study. *Otolaryng Head Neck*. 1999;120(5):656-664.
1778. Stuck BA, Kopke J, Hormann K, et al. Volumetric tissue reduction in radiofrequency surgery of the tongue base. *Otolaryng Head Neck*. 2005;132(1):132-135.
1779. Blumen MB, Coquille F, Rocchiccioli C, Mellot F, Chabolle F. Radiofrequency tongue reduction through a cervical approach: A pilot study. *Laryngoscope*. 2006;116(10):1887-1893.
1780. den Herder C, Kox D, van Tinteren H, de Vries N. Bipolar radiofrequency induced thermotherapy of the tongue base: its complications, acceptance and effectiveness under local anesthesia. *Eur Arch Oto-Rhino-L*. 2006;263(11):1031-1040.

1781. Baba RY, Mohan A, Metta VV, Mador MJ. Temperature controlled radiofrequency ablation at different sites for treatment of obstructive sleep apnea syndrome: a systematic review and meta-analysis. *Sleep Breath*. 2015;19(3):891-910.
1782. Fibbi A, Ameli F, Brocchetti F, Mignosi S, Cabano ME, Semino L. Tongue base suspension and radiofrequency volume reduction: a comparison between 2 techniques for the treatment of sleep-disordered breathing. *Am J Otolaryng*. 2009;30(6):401-406.
1783. Li KK, Powell NB, Riley RW, Guilleminault C. Temperature-controlled radiofrequency tongue base reduction for sleep-disordered breathing: Long-term outcomes. *Otolaryng Head Neck*. 2002;127(3):230-234.
1784. Woodson BT, Nelson L, Mickelson S, Huntley T, Sher A. A multi-institutional study of radiofrequency volumetric tissue reduction for OSAS. *Otolaryng Head Neck*. 2001;125(4):303-311.
1785. Friedman M, Ibrahim H, Lee G, Joseph NJ. Combined uvulopalatopharyngoplasty and radiofrequency tongue base reduction for treatment of obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2003;129(6):611-621.
1786. van den Broek E, Richard W, van Tinteren H, de Vries N. UPPP combined with radiofrequency thermotherapy of the tongue base for the treatment of obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2008;265(11):1361-1365.
1787. Friedman M, Soans R, Gurpinar B, Lin HC, Joseph N. Evaluation of submucosal minimally invasive lingual excision technique for treatment of obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2008;139(3):378-384; discussion 385.
1788. Riley RW, Powell NB, Li KK, Weaver EM, Guilleminault C. An adjunctive method of radiofrequency volumetric tissue reduction of the tongue for OSAS. *Otolaryng Head Neck*. 2003;129(1):37-42.
1789. Stuck BA, Maurer JT, Verse T, Hormann K. Tongue base reduction with temperature-controlled radiofrequency volumetric tissue reduction for treatment of obstructive sleep apnea syndrome. *Acta Otolaryngol*. 2002;122(5):531-536.
1790. Fernández-Julián E, Muñoz N, Achiques MT, García-Pérez MA, Orts M, Marco J. Randomized study comparing two tongue base surgeries for moderate to severe obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg*. 2009;140(6):917-923.
1791. Riley RW, Powell NB, Guilleminault C. Inferior Sagittal Osteotomy of the Mandible with Hyoid Myotomy-Suspension - a New Procedure for Obstructive Sleep-Apnea. *Otolaryng Head Neck*. 1986;94(5):589-593.
1792. Awad M, Gouveia C, Zaghi S, Camacho M, Liu SYC. Changing practice: Trends in skeletal surgery for obstructive sleep apnea. *J Cranio Maxill Surg*. 2019;47(8):1185-1189.
1793. Song SA, Chang ET, Certal V, et al. Genial tubercle advancement and genioplasty for obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope*. 2017;127(4):984-992.
1794. Chen SC, Shi S, Xia YH, et al. Changes in Sleep Characteristics and Airway Obstruction in OSAHS Patients with Multi-Level Obstruction following Simple UPPP, UPPP-GA, or UPPP-TBA: A Prospective, Single-Center, Parallel Group Study. *Orl J Oto-Rhino-Lary*. 2014;76(4):179-188.
1795. Wootten CT, Shott SR. Evolving Therapies to Treat Retroglossal and Base-of-Tongue Obstruction in Pediatric Obstructive Sleep Apnea. *Arch Otolaryngol*. 2010;136(10):983-987.
1796. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: a review of 306 consecutively treated surgical patients. *Otolaryngol Head Neck Surg*. 1993;108(2):117-125.
1797. Vilaseca I, Morello A, Montserrat JM, Santamaria J, Iranzo A. Usefulness of uvulopalatopharyngoplasty with genioglossus and hyoid advancement in the treatment of obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2002;128(4):435-440.

1798. Richard W, Kox D, den Herder C, van Tinteren H, de Vries N. One stage multilevel surgery (uvulopalatopharyngoplasty, hyoid suspension, radiofrequent ablation of the tongue base with/without genioglossus advancement), in obstructive sleep apnea syndrome. *Eur Arch Oto-Rhino-L.* 2007;264(4):439-444.
1799. Liu SY, Awad M, Riley RW. Maxillomandibular Advancement: Contemporary Approach at Stanford. *Atlas Oral Maxillofac Surg Clin North Am.* 2019;27(1):29-36.
1800. Troell RJ, Riley RW, Powell NB, Li K. Surgical management of the hypopharyngeal airway in sleep disordered breathing. *Otolaryngol Clin North Am.* 1998;31(6):979-1012.
1801. Kezirian EJ, Goldberg AN. Hypopharyngeal surgery in obstructive sleep apnea: an evidence-based medicine review. *Arch Otolaryngol Head Neck Surg.* 2006;132(2):206-213.
1802. Foltan R, Hoffmannova J, Pretl M, Donev F, Vlk M. Genioglossus advancement and hyoid myotomy in treating obstructive sleep apnoea syndrome - A follow-up study. *J Cranio Maxill Surg.* 2007;35(4-5):246-251.
1803. Song SA, Wei JM, Buttram J, et al. Hyoid surgery alone for obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope.* 2016;126(7):1702-1708.
1804. Kuscu O, Suslu AE, Ozer S, Gunaydin RO, Ogretmenoglu O, Onerci M. Sole effect of genioglossus advancement on apnea hypopnea index of patients with obstructive sleep apnea. *Acta Oto-Laryngol.* 2015;135(8):835-839.
1805. Kao YH, Shnyder Y, Lee KC. The efficacy of anatomically based multilevel surgery for obstructive sleep apnea. *Otolaryng Head Neck.* 2003;129(4):327-335.
1806. Kotecha BT, Hannan SA, Khalil HMB, Georgalas C, Bailey P. Sleep nasendoscopy: a 10-year retrospective audit study. *Eur Arch Oto-Rhino-L.* 2007;264(11):1361-1367.
1807. Metes A, Hoffstein V, Mateika S, Cole P, Haight JSJ. Site of Airway-Obstruction in Patients with Obstructive Sleep-Apnea before and after Uvulopalatopharyngoplasty. *Laryngoscope.* 1991;101(10):1102-1108.
1808. Kezirian EJ, Maselli J, Vittinghoff E, Goldberg AN, Auerbach AD. Obstructive sleep apnea surgery practice patterns in the United States: 2000 to 2006. *Otolaryng Head Neck.* 2010;143(3):441-447.
1809. Omur M, Ozturan D, Elez F, Unver C, Derman S. Tongue base suspension combined with UPPP in severe OSA patients. *Otolaryng Head Neck.* 2005;133(2):218-223.
1810. Handler E, Hamans E, Goldberg AN, Mickelson S. Tongue suspension: an evidence-based review and comparison to hypopharyngeal surgery for OSA. *Laryngoscope.* 2014;124(1):329-336.
1811. DeRowe A, Gunther E, Fibbi A, et al. Tongue-base suspension with a soft tissue-to-bone anchor for obstructive sleep apnea: preliminary clinical results of a new minimally invasive technique. *Otolaryngol Head Neck Surg.* 2000;122(1):100-103.
1812. Woodson BT. A tongue suspension suture for obstructive sleep apnea and snorers. *Otolaryng Head Neck.* 2001;124(3):297-303.
1813. Woodson BT, DeRowe A, Hawke M, et al. Pharyngeal suspension suture with Repose bone screw for obstructive sleep apnea. *Otolaryng Head Neck.* 2000;122(3):395-401.
1814. Sorrenti G, Piccin O, Latini G, Scaramuzzino G, Mondini S, Rinaldi Ceroni A. Tongue base suspension technique in obstructive sleep apnea: personal experience. *Acta Otorhinolaryngol Ital.* 2003;23(4):274-280.
1815. Thomas AJ, Chavoya M, Terris DJ. Preliminary findings from a prospective, randomized trial of two tongue-base surgeries for sleep-disordered breathing. *Otolaryng Head Neck.* 2003;129(5):539-546.
1816. Bostanci A, Turhan M. A systematic review of tongue base suspension techniques as an isolated procedure or combined with uvulopalatopharyngoplasty in obstructive sleep apnea. *Eur Arch Oto-Rhino-L.* 2016;273(10):2895-2901.

1817. Woodson BT, Steward DL, Mickelson S, Huntley T, Goldberg A. Multicenter study of a novel adjustable tongue-advancement device for obstructive sleep apnea. *Otolaryng Head Neck*. 2010;143(4):585-590.
1818. Tsou YA, Huang CW, Wu TF, Hung LW, Chang WD. The effect of tongue base suspension with uvulopalato-pharyngoplasty on sleep quality in obstructive sleep apnea. *Sci Rep*. 2018;8(1):8788.
1819. den Herder C, van Tinteren H, de Vries N. Hyoidthyroidpexia: A surgical treatment for sleep apnea syndrome. *Laryngoscope*. 2005;115(4):740-745.
1820. Riley R, Guilleminault C, Powell N, Derman S. Mandibular Osteotomy and Hyoid Bone Advancement for Obstructive Sleep-Apnea - a Case-Report. *Sleep*. 1984;7(1):79-82.
1821. Riley RW, Powell NB, Guilleminault C. Obstructive Sleep-Apnea and the Hyoid - a Revised Surgical-Procedure. *Otolaryng Head Neck*. 1994;111(6):717-721.
1822. Bowden MT, Kezirian EJ, Utley D, Goode RL. Outcomes of hyoid suspension for the treatment of obstructive sleep apnea. *Arch Otolaryngol*. 2005;131(5):440-445.
1823. Verse T, Baisch A, Maurer JT, Stuck BA, Hörmann K. Multilevel surgery for obstructive sleep apnea: short-term results. *Otolaryngol Head Neck Surg*. 2006;134(4):571-577.
1824. Askar SM, El-Anwar MW, Awad A. Expansion Hyoidthyroidpexy: Combined Hyoid Surgery Techniques for Obstructive Sleep Apnea: All in One. *Otolaryng Head Neck*. 2019;160(2):355-358.
1825. O'Malley BW, Weinstein GS, Snyder W, Hockstein NG. Transoral robotic surgery (TORS) for base of tongue neoplasms. *Laryngoscope*. 2006;116(8):1465-1472.
1826. Friedman M, Hamilton C, Samuelson CG, et al. Transoral robotic glossectomy for the treatment of obstructive sleep apnea-hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2012;146(5):854-862.
1827. Cammaroto G, Montevercchi F, D'Agostino G, et al. Tongue reduction for OSAHS: TORSs vs coblations, technologies vs techniques, apples vs oranges. *Eur Arch Otorhinolaryngol*. 2017;274(2):637-645.
1828. Miller SC, Nguyen SA, Ong AA, Gillespie MB. Transoral robotic base of tongue reduction for obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope*. 2017;127(1):258-265.
1829. Samutsakorn P, Hirunwiwatkul P, Chaitusaney B, Charakorn N. Lingual tonsillectomy with palatal surgery for the treatment of obstructive sleep apnea in adults: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2018;275(4):1005-1013.
1830. Hoff PT, D'Agostino MA, Thaler ER. Transoral Robotic Surgery in Benign Diseases Including Obstructive Sleep Apnea: Safety and Feasibility. *Laryngoscope*. 2015;125(5):1249-1253.
1831. Lin HS, Rowley JA, Folbe AJ, Yoo GH, Badr MS, Chen W. Transoral robotic surgery for treatment of obstructive sleep apnea: factors predicting surgical response. *Laryngoscope*. 2015;125(4):1013-1020.
1832. Catalfumo FJ, Golz A, Westerman ST, Gilbert LM, Joachims HZ, Goldenberg D. The epiglottis and obstructive sleep apnoea syndrome. *Journal of Laryngology and Otology*. 1998;112(10):940-943.
1833. Torre C, Camacho M, Liu SY, Huon LK, Capasso R. Epiglottis collapse in adult obstructive sleep apnea: A systematic review. *Laryngoscope*. 2016;126(2):515-523.
1834. Vonk PE, Ravesloot MJL, Kasius KM, van Maanen JP, de Vries N. Floppy epiglottis during drug-induced sleep endoscopy: an almost complete resolution by adopting the lateral posture. *Sleep Breath*. 2020;24(1):103-109.
1835. Kwon OE, Jung SY, Al-Dilajjan K, Min JY, Lee KH, Kim SW. Is epiglottis surgery necessary for obstructive sleep apnea patients with epiglottis obstruction? *Laryngoscope*. 2019;129(11):2658-2662.
1836. Dedhia RC, Rosen CA, Soose RJ. What is the role of the larynx in adult obstructive sleep apnea? *Laryngoscope*. 2014;124(4):1029-1034.

1837. Cassano M. Endoscopic coblator-assisted epiglottoplasty in 'obstructive sleep apnoea syndrome' patients. *Clin Otolaryngol*. 2017;42(5):1112-1114.
1838. Golz A, Goldenberg D, Westerman ST, et al. Laser partial epiglottidectomy as a treatment for obstructive sleep apnea and laryngomalacia. *Ann Oto Rhinol Laryn*. 2000;109(12):1140-1145.
1839. Oomen KPQ, Modi VK. Epiglottopexy with and without lingual tonsillectomy. *Laryngoscope*. 2014;124(4):1019-1022.
1840. Kayhan FT, Kaya KH, Koc AK, et al. Multilevel Combined Surgery With Transoral Robotic Surgery for Obstructive Sleep Apnea Syndrome. *J Craniofac Surg*. 2016;27(4):1044-1048.
1841. Vicini C, Montevecchi F, Tenti G, Canzi P, Dallan I, Huntley TC. Transoral robotic surgery: Tongue base reduction and supraglottoplasty for obstructive sleep apnea. *Operative Techniques in Otolaryngology-Head and Neck Surgery*. 2012;23(1):45-47.
1842. Hershey HG, Stewart BL, Warren DW. Changes in Nasal Airway-Resistance Associated with Rapid Maxillary Expansion. *Am J Orthod Dentofac*. 1976;69(3):274-284.
1843. Harvold EP, Tomer BS, Vargervik K, Chierici G. Primate Experiments on Oral Respiration. *Am J Orthod Dentofac*. 1981;79(4):359-372.
1844. Baratieri C, Alves M, de Souza MMG, Araujo MTD, Maia LC. Does rapid maxillary expansion have long-term effects on airway dimensions and breathing? *Am J Orthod Dentofac*. 2011;140(2):146-156.
1845. Chang Y, Koenig LJ, Pruszyński JE, Bradley TG, Bosio JA, Liu DW. Dimensional changes of upper airway after rapid maxillary expansion: A prospective cone-beam computed tomography study. *Am J Orthod Dentofac*. 2013;143(4):462-470.
1846. Warren DW, Hershey HG, Turvey TA, Hinton VA, Hairfield WM. The Nasal Airway Following Maxillary Expansion. *Am J Orthod Dentofac*. 1987;91(2):111-116.
1847. Iwasaki T, Saitoh I, Takemoto Y, et al. Improvement of nasal airway ventilation after rapid maxillary expansion evaluated with computational fluid dynamics. *Am J Orthod Dentofac*. 2012;141(3):269-278.
1848. Gorgulu S, Gokce SM, Olmez H, Sagdic D, Ors F. Nasal cavity volume changes after rapid maxillary expansion in adolescents evaluated with 3-dimensional simulation and modeling programs. *Am J Orthod Dentofac*. 2011;140(5):633-640.
1849. Vinha PP, Faria AC, Xavier SP, Christino M, de Mello FV. Enlargement of the Pharynx Resulting From Surgically Assisted Rapid Maxillary Expansion. *J Oral Maxil Surg*. 2016;74(2):369-379.
1850. Camacho M, Chang ET, Song SJA, et al. Rapid Maxillary Expansion for Pediatric Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis. *Laryngoscope*. 2017;127(7):1712-1719.
1851. Cistulli PA, Palmisano RG, Poole MD. Treatment of obstructive sleep apnea syndrome by rapid maxillary expansion. *Sleep*. 1998;21(8):831-835.
1852. Machado AJ, Zancanella E, Crespo AN. Rapid maxillary expansion and obstructive sleep apnea: A review and meta-analysis. *Med Oral Patol Oral*. 2016;21(4):E465-E469.
1853. Vale F, Albergaria M, Carrilho E, et al. Efficacy of Rapid Maxillary Expansion in the Treatment of Obstructive Sleep Apnea Syndrome: A Systematic Review with Meta-Analysis. *J Evid-Based Dent Pr*. 2017;17(3):159-168.
1854. Vinha PP, Eckeli AL, Faria AC, Xavier SP, de Mello FV. Effects of surgically assisted rapid maxillary expansion on obstructive sleep apnea and daytime sleepiness. *Sleep Breath*. 2016;20(2):501-508.
1855. Carlson C, Sung J, McComb RW, Machado AW, Moon W. Microimplant-assisted rapid palatal expansion appliance to orthopedically correct transverse maxillary deficiency in an adult. *Am J Orthod Dentofac*. 2016;149(5):716-728.

1856. Yoon A, Guilleminault C, Zaghi S, Liu SYC. Distraction Osteogenesis Maxillary Expansion (DOME) for adult obstructive sleep apnea patients with narrow maxilla and nasal floor. *Sleep Med.* 2020;65:172-176.
1857. Suri L, Taneja P. Surgically assisted rapid palatal expansion: A literature review. *Am J Orthod Dentofac.* 2008;133(2):290-302.
1858. Monini S, Malagola C, Villa MP, et al. Rapid Maxillary Expansion for the Treatment of Nasal Obstruction in Children Younger Than 12 Years. *Arch Otolaryngol.* 2009;135(1):22-27.
1859. Quo SD, Hyunh N, Guilleminault C. Bimaxillary expansion therapy for pediatric sleep-disordered breathing. *Sleep Med.* 2017;30:45-51.
1860. Riley RW, Powell NB, Guilleminault C. Maxillary, mandibular, and hyoid advancement for treatment of obstructive sleep apnea: a review of 40 patients. *J Oral Maxillofac Surg.* 1990;48(1):20-26.
1861. Barrera JE. Skeletal Surgery for Obstructive Sleep Apnea. *Sleep Med Clin.* 2018;13(4):549-558.
1862. Gottsauner-Wolf S, Laimer J, Bruckmoser E. Posterior Airway Changes Following Orthognathic Surgery in Obstructive Sleep Apnea. *J Oral Maxil Surg.* 2018;76(5).
1863. Dattilo DJ, Drooger SA. Outcome assessment of patients undergoing maxillofacial procedures for the treatment of sleep apnea: comparison of subjective and objective results. *J Oral Maxillofac Surg.* 2004;62(2):164-168.
1864. Prinsell JR. Maxillomandibular advancement surgery in a site-specific treatment approach for obstructive sleep apnea in 50 consecutive patients. *Chest.* 1999;116(6):1519-1529.
1865. Abdelwahab M, Poomkonsarn S, Ren X, et al. A Comprehensive Strategy for Improving Nasal Outcomes After Large Maxillomandibular Advancement for Obstructive Sleep Apnea. *Facial Plast Surg Aesthet Med.* 2021;23(6):437-442.
1866. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev.* 2010;14(5):287-297.
1867. Camacho M, Noller MW, Del Do M, et al. Long-term Results for Maxillomandibular Advancement to Treat Obstructive Sleep Apnea: A Meta-analysis. *Otolaryngol Head Neck Surg.* 2019;160(4):580-593.
1868. Kezirian EJ, Goding GS, Malhotra A, et al. Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes. *J Sleep Res.* 2014;23(1):77-83.
1869. Friedman M, Jacobowitz O, Hwang MS, et al. Targeted hypoglossal nerve stimulation for the treatment of obstructive sleep apnea: Six-month results. *Laryngoscope.* 2016;126(11):2618-2623.
1870. Heiser C, Sommer JU, Hofauer B, et al. Bilateral vs Unilateral Hypoglossal Nerve Stimulation in Patients With Obstructive Sleep Apnea. *OTO Open.* 2022;6(3):2473974X221109794.
1871. Van de Heyning PH, Badr MS, Baskin JZ, et al. Implanted upper airway stimulation device for obstructive sleep apnea. *Laryngoscope.* 2012;122(7):1626-1633.
1872. Vanderveken OM, Maurer JT, Hohenhorst W, et al. Evaluation of Drug-Induced Sleep Endoscopy as a Patient Selection Tool for Implanted Upper Airway Stimulation for Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine.* 2013;9(5):433-438.
1873. Certal VF, Zaghi S, Riaz M, et al. Hypoglossal nerve stimulation in the treatment of obstructive sleep apnea: A systematic review and meta-analysis. *Laryngoscope.* 2015;125(5):1254-1264.
1874. Kompelli AR, Ni JS, Nguyen SA, Lentsch EJ, Neskey DM, Meyer TA. The outcomes of hypoglossal nerve stimulation in the management of OSA: A systematic review and meta-analysis. *World J Otorhinolaryngol Head Neck Surg.* 2019;5(1):41-48.
1875. Thaler E, Schwab R, Maurer J, et al. Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. *Laryngoscope.* 2020;130(5):1333-1338.

1876. Woodson BT, Gillespie MB, Soose RJ, et al. Randomized Controlled Withdrawal Study of Upper Airway Stimulation on OSA: Short- and Long-term Effect. *Otolaryng Head Neck*. 2014;151(5):880-887.
1877. Woodson BT, Soose RJ, Gillespie MB, et al. Three-Year Outcomes of Cranial Nerve Stimulation for Obstructive Sleep Apnea: The STAR Trial. *Otolaryng Head Neck*. 2016;154(1):181-188.
1878. Gillespie MB, Soose RJ, Woodson BT, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Patient-Reported Outcomes after 48 Months of Follow-up. *Otolaryng Head Neck*. 2017;156(4):765-771.
1879. Heiser C, Maurer JT, Hofauer B, Sommer JU, Seitz A, Steffen A. Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study. *Otolaryng Head Neck*. 2017;156(2):378-384.
1880. Steffen A, Sommer UJ, Maurer JT, Abrams N, Hofauer B, Heiser C. Long-term follow-up of the German post-market study for upper airway stimulation for obstructive sleep apnea. *Sleep Breath*. 2020;24(3):979-984.
1881. Boon M, Huntley C, Steffen A, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Results from the ADHERE Registry. *Otolaryng Head Neck*. 2018;159(2):379-385.
1882. Huntley C, Topf MC, Christopher V, Doghramji K, Curry J, Boon M. Comparing Upper Airway Stimulation to Transoral Robotic Base of Tongue Resection for Treatment of Obstructive Sleep Apnea. *Laryngoscope*. 2019;129(4):1010-1013.
1883. Shah J, Russell JO, Waters T, Kominsky AH, Trask D. Uvulopalatopharyngoplasty vs CN XII stimulation for treatment of obstructive sleep apnea: A single institution experience. *Am J Otolaryng*. 2018;39(3):266-270.
1884. Huntley C, Vasconcellos A, Doghramji K, Hofauer B, Heiser C, Boon M. Upper Airway Stimulation in Patients Who Have Undergone Unsuccessful Prior Palate Surgery: An Initial Evaluation. *Otolaryng Head Neck*. 2018;159(5):938-940.
1885. Kezirian EJ, Heiser C, Steffen A, et al. Previous Surgery and Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea. *Otolaryng Head Neck*. 2019;161(5):897-903.
1886. Steffen A, Abrams N, Suurna MV, Wollenberg B, Hasselbacher K. Upper-Airway Stimulation Before, After, or Without Uvulopalatopharyngoplasty: A Two-Year Perspective. *Laryngoscope*. 2019;129(2):514-518.
1887. Bohorquez D, Mahmoud AF, Yu JL, Thaler ER. Upper airway stimulation therapy and sleep architecture in patients with obstructive sleep apnea. *Laryngoscope*. 2020;130(4):1085-1089.
1888. Hofauer B, Philip P, Wirth M, Knopf A, Heiser C. Effects of upper-airway stimulation on sleep architecture in patients with obstructive sleep apnea. *Sleep Breath*. 2017;21(4):901-908.
1889. Costantino A, Rinaldi V, Moffa A, et al. Hypoglossal nerve stimulation long-term clinical outcomes: a systematic review and meta-analysis. *Sleep Breath*. 2020;24(2):399-411.
1890. Kent DT, Carden KA, Wang L, Lindsell CJ, Ishman SL. Evaluation of Hypoglossal Nerve Stimulation Treatment in Obstructive Sleep Apnea. *Jama Otolaryngol*. 2019;145(11):1044-1052.
1891. Hasselbacher K, Hofauer B, Maurer JT, Heiser C, Steffen A, Sommer JU. Patient-reported outcome: results of the multicenter German post-market study. *Eur Arch Oto-Rhino-L*. 2018;275(7):1913-1919.
1892. Sarber KM, Chang KW, Epperson MV, et al. Hypoglossal Nerve Stimulation in Veterans with Obstructive Sleep Apnea. *Laryngoscope*. 2020;130(9):2275-2280.
1893. Mahmoud AF, Thaler ER. Outcomes of Hypoglossal Nerve Upper Airway Stimulation among Patients with Isolated Retropalatal Collapse. *Otolaryng Head Neck*. 2019;160(6):1124-1129.
1894. Withrow K, Evans S, Harwick J, Kezirian E, Strollo P, Investigators AR. Upper Airway Stimulation Response in Older Adults with Moderate to Severe Obstructive Sleep Apnea. *Otolaryng Head Neck*. 2019;161(4):714-719.

1895. Zhu ZJ, Hofauer B, Wirth M, et al. Selective upper airway stimulation in older patients. *Resp Med*. 2018;140:77-81.
1896. Evans SS, Richman J, Cho DY, Withrow K. Increasing preoperative apnea severity improves upper airway stimulation response in OSA treatment. *Laryngoscope*. 2020;130(2):556-560.
1897. Dedhia RC, Shah AJ, Bliwise DL, et al. Hypoglossal Nerve Stimulation and Heart Rate Variability: Analysis of STAR Trial Responders. *Otolaryngol Head Neck Surg*. 2019;160(1):165-171.
1898. Steffen A, Chamorro R, Buyny L, et al. Upper airway stimulation in obstructive sleep apnea improves glucose metabolism and reduces hedonic drive for food. *J Sleep Res*. 2019;28(5).
1899. Walia HK, Thompson NR, Strohl KP, et al. Upper Airway Stimulation vs Positive Airway Pressure Impact on BP and Sleepiness Symptoms in OSA. *Chest*. 2020;157(1):173-183.
1900. ElShebiny T, Venkat D, Strohl K, Hans MG, Alonso A, Palomo JM. Hyoid Arch Displacement with Hypoglossal Nerve Stimulation. *Am J Resp Crit Care*. 2017;196(6):790-792.
1901. Elshebiny T VD, Strohl M, Strohl K, Ponsky D, Palomo Airway Evaluation in Response to Hypoglossal Nerve Stimulation: A Case Report. *J Dent Sleep Med*. 2017;4(1):15-17.
1902. Goding GS, Tesfayesus W, Kezirian EJ. Hypoglossal Nerve Stimulation and Airway Changes under Fluoroscopy. *Otolaryng Head Neck*. 2012;146(6):1017-1022.
1903. Oliven A, Tov N, Geitini L, et al. Effect of genioglossus contraction on pharyngeal lumen and airflow in sleep apnoea patients. *Eur Respir J*. 2007;30(4):748-758.
1904. Steffen A, Kilic A, Konig IR, Suurna MV, Hofauer B, Heiser C. Tongue motion variability with changes of upper airway stimulation electrode configuration and effects on treatment outcomes. *Laryngoscope*. 2018;128(8):1970-1976.
1905. Vanderveken OM, Beyers J, Op de Beeck S, et al. Development of a Clinical Pathway and Technical Aspects of Upper Airway Stimulation Therapy for Obstructive Sleep Apnea. *Front Neurosci-Switz*. 2017;11.
1906. Kezirian EJ. Acclimation settings with identical or similar sensation and functional thresholds. *Laryngoscope*. 2016;126:S20-S21.
1907. Huntley C, Kaffenberger T, Doghramji K, Soose R, Boon M. Upper Airway Stimulation for Treatment of Obstructive Sleep Apnea: An Evaluation and Comparison of Outcomes at Two Academic Centers. *Journal of Clinical Sleep Medicine*. 2017;13(9):1075-1079.
1908. Heiser C, Knopf A, Bas M, Gahleitner C, Hofauer B. Selective upper airway stimulation for obstructive sleep apnea: a single center clinical experience. *Eur Arch Oto-Rhino-L*. 2017;274(3):1727-1734.
1909. Heiser C. Advanced titration to treat a floppy epiglottis in selective upper airway stimulation. *Laryngoscope*. 2016;126:S22-S24.
1910. Meleca JB, Kominsky AH. Reconfiguration of Upper Airway Stimulation Devices Utilizing Awake Endoscopy. *Laryngoscope*. 2020;130(10):2494-2498.
1911. Safiruddin F, Vanderveken OM, de Vries N, et al. Effect of upper-airway stimulation for obstructive sleep apnoea on airway dimensions. *Eur Respir J*. 2015;45(1):129-138.
1912. Lin HC, Weaver EM, Lin HS, Friedman M. Multilevel Obstructive Sleep Apnea Surgery. *Adv Otorhinolaryngol*. 2017;80:109-115.
1913. Kezirian EJ. Nonresponders to pharyngeal surgery for obstructive sleep apnea: insights from drug-induced sleep endoscopy. *Laryngoscope*. 2011;121(6):1320-1326.
1914. Ravesloot MJ, de Vries N. One hundred consecutive patients undergoing drug-induced sleep endoscopy: results and evaluation. *Laryngoscope*. 2011;121(12):2710-2716.
1915. Weaver EM. Sleep apnea devices and sleep apnea surgery should be compared on effectiveness, not efficacy. *Chest*. 2003;123(3):961-962; author reply 962.



1916. Hobson JC, Robinson S, Antic NA, et al. What is "success" following surgery for obstructive sleep apnea? The effect of different polysomnographic scoring systems. *Laryngoscope*. 2012;122(8):1878-1881.
1917. Jung SY, Rhee EH, Al-Dilaijan KF, Kim SW, Min JY. Impact of AASM 2012 Recommended Hypopnea Criteria on Surgical Outcomes for Obstructive Sleep Apnea. *Laryngoscope*. 2020;130(3):825-831.
1918. MacKay S, Carney AS, Catcheside PG, et al. Effect of Multilevel Upper Airway Surgery vs Medical Management on the Apnea-Hypopnea Index and Patient-Reported Daytime Sleepiness Among Patients With Moderate or Severe Obstructive Sleep Apnea: The SAMS Randomized Clinical Trial. *JAMA*. 2020;324(12):1168-1179.
1919. Lin HC, Friedman M, Chang HW, Gurpinar B. The efficacy of multilevel surgery of the upper airway in adults with obstructive sleep apnea/hypopnea syndrome. *Laryngoscope*. 2008;118(5):902-908.
1920. Mulholland GB, Jeffery CC, Ziai H, et al. Multilevel Palate and Tongue Base Surgical Treatment of Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Laryngoscope*. 2019;129(7):1712-1721.
1921. Andsberg U, Jessen M. Eight years of follow-up--uvulopalatopharyngoplasty combined with midline glossectomy as a treatment for obstructive sleep apnoea syndrome. *Acta Otolaryngol Suppl*. 2000;543:175-178.
1922. Hou J, Yan J, Wang B, et al. Treatment of obstructive sleep apnea-hypopnea syndrome with combined uvulopalatopharyngoplasty and midline glossectomy: outcomes from a 5-year study. *Respir Care*. 2012;57(12):2104-2110.
1923. Neruntarat C. Genioglossus advancement and hyoid myotomy: short-term and long-term results. *J Laryngol Otol*. 2003;117(6):482-486.
1924. Neruntarat C, Chantapant S. Radiofrequency surgery for the treatment of obstructive sleep apnea: short-term and long-term results. *Otolaryngol Head Neck Surg*. 2009;141(6):722-726.
1925. Steward DL, Weaver EM, Woodson BT. Multilevel temperature-controlled radiofrequency for obstructive sleep apnea: extended follow-up. *Otolaryngol Head Neck Surg*. 2005;132(4):630-635.
1926. Yüksel A, Ugur KS, Kizilbulut G, et al. Long-term results of one staged multilevel surgery with tongue suspension surgery or one level palatal surgery for treatment of moderate and severe obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2016;273(5):1227-1234.
1927. Baisch A, Maurer JT, Hormann K. The effect of hyoid suspension in a multilevel surgery concept for obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2006;134(5):856-861.
1928. Sun X, Yi H, Cao Z, Yin S. Reorganization of sleep architecture after surgery for OSAHS. *Acta Otolaryngol*. 2008;128(11):1242-1247.
1929. Yang MC, Hsu YB, Lan MY, Lan MC. The comparison of multilevel surgery (hyoid myotomy and suspension with uvulopalatopharyngoplasty) with CPAP in moderate to severe OSAS patients. *Eur Arch Otorhinolaryngol*. 2020.
1930. Yi HL, Sun XQ, Chen B, et al. Z-palatopharyngoplasty plus genioglossus advancement and hyoid suspension for obstructive sleep apnea hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2011;144(3):469-473.
1931. Kezirian EJ, Malhotra A, Goldberg AN, White DP. Changes in obstructive sleep apnea severity, biomarkers, and quality of life after multilevel surgery. *Laryngoscope*. 2010;120(7):1481-1488.
1932. Emara TA, Omara TA, Shouman WM. Modified genioglossus advancement and uvulopalatopharyngoplasty in patients with obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2011;145(5):865-871.

1933. Hsu PP, Brett RH. Multiple level pharyngeal surgery for obstructive sleep apnoea. *Singapore Med J*. 2001;42(4):160-164.
1934. Miller FR, Watson D, Boseley M. The role of the Genial Bone Advancement Trephine system in conjunction with uvulopalatopharyngoplasty in the multilevel management of obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2004;130(1):73-79.
1935. Steward DL. Effectiveness of multilevel (tongue and palate) radiofrequency tissue ablation for patients with obstructive sleep apnea syndrome. *Laryngoscope*. 2004;114(12):2073-2084.
1936. Chiffer RC, Schwab RJ, Keenan BT, Borek RC, Thaler ER. Volumetric MRI analysis pre- and post-Transoral robotic surgery for obstructive sleep apnea. *Laryngoscope*. 2015;125(8):1988-1995.
1937. Rohrer JW, Eller R, Santillan PG, Barrera JE. Geniotubercle advancement with a uvulopalatal flap and its effect on swallow function in obstructive sleep apnea. *Laryngoscope*. 2015;125(3):758-761.
1938. Brietzke SE, Ishman SL, Cohen S, Cyr DD, Shin JJ, Kezirian EJ. National Database Analysis of Single-Level versus Multilevel Sleep Surgery. *Otolaryngol Head Neck Surg*. 2017;156(5):955-961.
1939. Chan CY, Han HJ, Lye WK, Toh ST. Complications and Pain in Obstructive Sleep Apnoea - Comparing Single and Multilevel Surgery. *Ann Acad Med Singapore*. 2018;47(3):101-107.
1940. Kezirian EJ, Weaver EM, Yueh B, et al. Incidence of serious complications after uvulopalatopharyngoplasty. *Laryngoscope*. 2004;114(3):450-453.
1941. Baker AB, Xiao CC, O'Connell BP, Cline JM, Gillespie MB. Uvulopalatopharyngoplasty: Does Multilevel Surgery Increase Risk? *Otolaryngol Head Neck Surg*. 2016;155(6):1053-1058.
1942. Li HY, Wang PC, Hsu CY, Lee SW, Chen NH, Liu SA. Combined nasal-palatopharyngeal surgery for obstructive sleep apnea: simultaneous or staged? *Acta Otolaryngol*. 2005;125(3):298-303.
1943. Busaba NY. Same-stage nasal and palatopharyngeal surgery for obstructive sleep apnea: is it safe? *Otolaryngol Head Neck Surg*. 2002;126(4):399-403.
1944. Pang KP. One-stage nasal and multi-level pharyngeal surgery for obstructive sleep apnoea: safety and efficacy. *J Laryngol Otol*. 2005;119(4):272-276.
1945. Kieff DA, Busaba NY. Same-day discharge for selected patients undergoing combined nasal and palatal surgery for obstructive sleep apnea. *Ann Otol Rhinol Laryngol*. 2004;113(2):128-131.
1946. Elasmfour A, Miyazaki S, Itasaka Y, Yamakawa K, Ishikawa K, Togawa K. Evaluation of uvulopalatopharyngoplasty in treatment of obstructive sleep apnea syndrome. *Acta Otolaryngol Suppl*. 1998;537:52-56.
1947. Friedman M, Lin HC, Gurpinar B, Joseph NJ. Minimally invasive single-stage multilevel treatment for obstructive sleep apnea/hypopnea syndrome. *Laryngoscope*. 2007;117(10):1859-1863.
1948. Eun YG, Kwon KH, Shin SY, Lee KH, Byun JY, Kim SW. Multilevel surgery in patients with rapid eye movement-related obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2009;140(4):536-541.
1949. van Maanen JP, Ravesloot MJ, Witte BI, Grijseels M, de Vries N. Exploration of the relationship between sleep position and isolated tongue base or multilevel surgery in obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2012;269(9):2129-2136.
1950. Li S, Wu D, Shi H. Treatment of obstructive sleep apnea hypopnea syndrome caused by glossoptosis with tongue-base suspension. *Eur Arch Otorhinolaryngol*. 2013;270(11):2915-2920.
1951. Plzak J, Zabrodsky M, Kastner J, Betka J, Klozar J. Combined bipolar radiofrequency surgery of the tongue base and uvulopalatopharyngoplasty for obstructive sleep apnea. *Arch Med Sci*. 2013;9(6):1097-1101.
1952. van Maanen JP, Witte BI, de Vries N. Theoretical approach towards increasing effectiveness of palatal surgery in obstructive sleep apnea: role for concomitant positional therapy? *Sleep Breath*. 2014;18(2):341-349.
1953. Salapatas AM, Bonzelaar LB, Hwang MS, et al. Impact of Minimally Invasive Multilevel Surgery on Mild/Moderate OSA. *Otolaryngol Head Neck Surg*. 2016;155(4):695-701.

1954. Li HY, Lee LA, Kezirian EJ. Efficacy of Coblation Endoscopic Lingual Lightening in Multilevel Surgery for Obstructive Sleep Apnea. *JAMA Otolaryngol Head Neck Surg.* 2016;142(5):438-443.
1955. Missale F, Fragale M, Incandela F, et al. Outcome predictors for non-resective pharyngoplasty alone or as a part of multilevel surgery, in obstructive sleep apnea-hypopnea syndrome. *Sleep Breath.* 2019.
1956. Elshaug AG, Moss JR, Southcott AM, Hiller JE. Redefining success in airway surgery for obstructive sleep apnea: a meta analysis and synthesis of the evidence. *Sleep.* 2007;30(4):461-467.
1957. Janson C, Gislason T, Bengtsson H, et al. Long-term follow-up of patients with obstructive sleep apnea treated with uvulopalatopharyngoplasty. *Arch Otolaryngol.* 1997;123(3):257-262.
1958. Riley RW, Powell NB, Li KK, Troell RJ, Guilleminault C. Surgery and obstructive sleep apnea: Long-term clinical outcomes. *Otolaryng Head Neck.* 2000;122(3):415-421.
1959. Pang KP, Pang EB, Pang KA, Rotenberg B. Anterior palatoplasty in the treatment of obstructive sleep apnoea - a systemic review. *Acta Otorhinolaryngo.* 2018;38(1):1-6.
1960. Sharma S, Wormald JCR, Fishman JM, Andrews P, Kotecha BT. Rhinological interventions for obstructive sleep apnoea - a systematic review and descriptive meta-analysis. *J Laryngol Otol.* 2019;133(3):168-176.
1961. Mechanick JI, Kushner RF, Sugerman HJ, et al. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. *Surg Obes Relat Dis.* 2008;4(5):S109-S184.
1962. Wong AM, Barnes HN, Joosten SA, et al. The effect of surgical weight loss on obstructive sleep apnoea: A systematic review and meta-analysis. *Sleep Medicine Reviews.* 2018;42:85-99.
1963. Lee HM, Kim HY, Suh JD, et al. Uvulopalatopharyngoplasty reduces the incidence of cardiovascular complications caused by obstructive sleep apnea: results from the national insurance service survey 2007-2014. *Sleep Med.* 2018;45:11-16.
1964. Zhan X, Li L, Wu C, et al. Effect of uvulopalatopharyngoplasty (UPPP) on atherosclerosis and cardiac functioning in obstructive sleep apnea patients. *Acta Otolaryngol.* 2019;139(9):793-797.
1965. Pang KP, Plaza G, Baptista JP, et al. Palate surgery for obstructive sleep apnea: a 17-year meta-analysis. *Eur Arch Otorhinolaryngol.* 2018;275(7):1697-1707.
1966. Kuhlo W, Doll E, Franck MC. [Successful management of Pickwickian syndrome using long-term tracheostomy]. *Dtsch Med Wochenschr.* 1969;94(24):1286-1290.
1967. Guilleminault C, Simmons FB, Motta J, et al. Obstructive Sleep-Apnea Syndrome and Tracheostomy - Long-Term Follow-up Experience. *Archives of Internal Medicine.* 1981;141(8):985-989.
1968. Simmons FB, Guilleminault C, Dement WC, Tilkian AG, Hill M. Surgical management of airway obstructions during sleep. *Laryngoscope.* 1977;87(3):326-338.
1969. Aulakh PK, Westerman DE, Dedhia RC. The Longest Obstructive Apnea You Have Ever Seen: A Patient With New-Onset Autonomic Dysfunction. *Journal of Clinical Sleep Medicine.* 2018;14(5):893-895.
1970. Haapaniemi JJ, Laurikainen EA, Halme P, Antila J. Long-term results of tracheostomy for severe obstructive sleep apnea syndrome. *Orl-J Oto-Rhin-Laryn.* 2001;63(3):131-136.
1971. Kim SH, Eisele DW, Smith PL, Schneider H, Schwartz AR. Evaluation of patients with sleep apnea after tracheotomy. *Arch Otolaryngol.* 1998;124(9):996-1000.
1972. Motta J, Guilleminault C, Schroeder JS, Dement WC. Tracheostomy and Hemodynamic Changes in Sleep-Induced Apnea. *Annals of Internal Medicine.* 1978;89(4):454-458.
1973. Thatcher GW, Maisel RH. The long-term evaluation of tracheostomy in the management of severe obstructive sleep apnea. *Laryngoscope.* 2003;113(2):201-204.

1974. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC. Sleep-Induced Apnea Syndrome - Prevalence of Cardiac-Arrhythmias and Their Reversal after Tracheostomy. *Am J Med.* 1977;63(3):348-358.
1975. Weitzman ED, Kahn E, Pollak CP. Quantitative-Analysis of Sleep and Sleep-Apnea before and after Tracheostomy in Patients with the Hypersomnia-Sleep Apnea Syndrome. *Sleep.* 1980;3(3-4):407-423.
1976. Weitzman ED, Pollack CP, Borowiecki B. Hypersomnia-Sleep Apnea Due to Micrognathia - Reversal by Tracheoplasty. *Arch Neurol-Chicago.* 1978;35(6):392-395.
1977. Partinen M, Jamieson A, Guilleminault C. Long-Term Outcome for Obstructive Sleep-Apnea Syndrome Patients - Mortality. *Chest.* 1988;94(6):1200-1204.
1978. He J, Kryger MH, Zorick FJ, Conway W, Roth T. Mortality and Apnea Index in Obstructive Sleep-Apnea - Experience in 385 Male-Patients. *Chest.* 1988;94(1):9-14.
1979. Camacho M, Certal V, Brietzke SE, Holty JE, Guilleminault C, Capasso R. Tracheostomy as treatment for adult obstructive sleep apnea: a systematic review and meta-analysis. *Laryngoscope.* 2014;124(3):803-811.
1980. Conway WA, Victor LD, Magilligan DJ, Fujita S, Zorick FJ, Roth T. Adverse-Effects of Tracheostomy for Sleep-Apnea. *Jama-J Am Med Assoc.* 1981;246(4):347-350.
1981. Organization WH. Obesity and Overweight. <https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight>. Published 2020. Updated 03/03/2020. Accessed 03/03/2020, 2020.
1982. Lettieri CJ, Eliasson AH, Andrada T, Khramtsov A, Raphaelson M, Kristo DA. Obstructive sleep apnea syndrome: are we missing an at-risk population? *J Clin Sleep Med.* 2005;1(4):381-385.
1983. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care.* 2008;31 Suppl 2:S303-309.
1984. Rajala R, Partinen M, Sane T, Pelkonen R, Huikuri K, Seppalainen AM. Obstructive sleep apnoea syndrome in morbidly obese patients. *J Intern Med.* 1991;230(2):125-129.
1985. Rasheid S, Banasiak M, Gallagher SF, et al. Gastric bypass is an effective treatment for obstructive sleep apnea in patients with clinically significant obesity. *Obes Surg.* 2003;13(1):58-61.
1986. Bakker JP, Tavakkoli A, Rueschman M, et al. Gastric Banding Surgery versus Continuous Positive Airway Pressure for Obstructive Sleep Apnea: A Randomized Controlled Trial. *Am J Respir Crit Care Med.* 2018;197(8):1080-1083.
1987. Feigel-Guiller B, Drui D, Dimet J, et al. Laparoscopic Gastric Banding in Obese Patients with Sleep Apnea: A 3-Year Controlled Study and Follow-up After 10 Years. *Obes Surg.* 2015;25(10):1886-1892.
1988. Quintas-Neves M, Preto J, Drummond M. Assessment of bariatric surgery efficacy on Obstructive Sleep Apnea (OSA). *Rev Port Pneumol (2006).* 2016;22(6):331-336.
1989. Sarkhosh K, Switzer NJ, El-Hadi M, Birch DW, Shi X, Karmali S. The impact of bariatric surgery on obstructive sleep apnea: a systematic review. *Obes Surg.* 2013;23(3):414-423.
1990. Haines KL, Nelson LG, Gonzalez R, et al. Objective evidence that bariatric surgery improves obesity-related obstructive sleep apnea. *Surgery.* 2007;141(3):354-358.
1991. Zhang YX, Wang WY, Yang CC, Shen JH, Shi ML, Wang B. Improvement in Nocturnal Hypoxemia in Obese Patients with Obstructive Sleep Apnea after Bariatric Surgery: a Meta-Analysis. *Obesity Surgery.* 2019;29(2):601-608.
1992. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA.* 2004;292(14):1724-1737.
1993. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. *Am J Med.* 2009;122(6):535-542.

1994. Hariri K, Kini SU, Herron DM, Fernandez-Ranvier G. Resolution of Symptomatic Obstructive Sleep Apnea Not Impacted by Preoperative Body Mass Index, Choice of Operation Between Sleeve Gastrectomy and Roux-en-Y Gastric Bypass Surgery, or Severity. *Obes Surg*. 2018;28(5):1402-1407.
1995. Miras AD, Kamocka A, Patel D, et al. Obesity surgery makes patients healthier and more functional: real world results from the United Kingdom National Bariatric Surgery Registry. *Surg Obes Relat Dis*. 2018;14(7):1033-1040.
1996. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. *JAMA*. 2020;323(14):1389-1400.
1997. Keenan BT, Kim J, Singh B, et al. Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. *Sleep*. 2018;41(3).
1998. Tam S, Woodson BT, Rotenberg B. Outcome measurements in obstructive sleep apnea: beyond the apnea-hypopnea index. *Laryngoscope*. 2014;124(1):337-343.
1999. Weaver EM, Kapur V, Yueh B. Polysomnography vs self-reported measures in patients with sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2004;130(4):453-458.
2000. Browaldh N, Bring J, Friberg D. SKUP(3) RCT; continuous study: Changes in sleepiness and quality of life after modified UPPP. *Laryngoscope*. 2016;126(6):1484-1491.
2001. Justin GA, Chang ET, Camacho M, Brietzke SE. Transoral Robotic Surgery for Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis. *Otolaryngol Head Neck Surg*. 2016;154(5):835-846.
2002. Meccariello G, Cammaroto G, Montevercchi F, et al. Transoral robotic surgery for the management of obstructive sleep apnea: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2017;274(2):647-653.
2003. Murphey AW, Kandl JA, Nguyen SA, Weber AC, Gillespie MB. The Effect of Glossectomy for Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. 2015;153(3):334-342.
2004. Boyd SB, Chigurupati R, Cillo JE, Jr., et al. Maxillomandibular Advancement Improves Multiple Health-Related and Functional Outcomes in Patients With Obstructive Sleep Apnea: A Multicenter Study. *J Oral Maxillofac Surg*. 2019;77(2):352-370.
2005. Tsui WK, Yang Y, McGrath C, Leung YY. Improvement in quality of life after skeletal advancement surgery in patients with moderate-to-severe obstructive sleep apnoea: a longitudinal study. *Int J Oral Maxillofac Surg*. 2020;49(3):333-341.
2006. Zaghi S, Holty JEC, Certal V, et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea A Meta-analysis. *Jama Otolaryngol*. 2016;142(1):58-66.
2007. Wang M, Liu SY, Zhou B, Li Y, Cui S, Huang Q. Effect of nasal and sinus surgery in patients with and without obstructive sleep apnea. *Acta Otolaryngol*. 2019;139(5):467-472.
2008. Farrar J, Ryan J, Oliver E, Gillespie MB. Radiofrequency ablation for the treatment of obstructive sleep apnea: a meta-analysis. *Laryngoscope*. 2008;118(10):1878-1883.
2009. Gao YN, Wu YC, Lin SY, Chang JZ, Tu YK. Short-term efficacy of minimally invasive treatments for adult obstructive sleep apnea: A systematic review and network meta-analysis of randomized controlled trials. *J Formos Med Assoc*. 2019;118(4):750-765.
2010. Llewellyn CM, Noller MW, Camacho M. Cautery-assisted palatal stiffening operation for obstructive sleep apnea: A systematic review and meta-analysis. *World J Otorhinolaryngol Head Neck Surg*. 2019;5(1):49-56.
2011. Veer V, Yang WY, Green R, Kotecha B. Long-term safety and efficacy of radiofrequency ablation in the treatment of sleep disordered breathing: a meta-analysis. *Eur Arch Otorhinolaryngol*. 2014;271(11):2863-2870.

2012. Atef A, Mosleh M, Hesham M, Fathi A, Hassan M, Fawzy M. Radiofrequency vs laser in the management of mild to moderate obstructive sleep apnoea: does the number of treatment sessions matter? *J Laryngol Otol.* 2005;119(11):888-893.
2013. Ishman SL, Benke JR, Cohen AP, Stephen MJ, Ishii LE, Gourin CG. Does surgery for obstructive sleep apnea improve depression and sleepiness? *Laryngoscope.* 2014;124(12):2829-2836.
2014. Steward DL, Weaver EM, Woodson BT. A comparison of radiofrequency treatment schemes for obstructive sleep apnea syndrome. *Otolaryngol Head Neck Surg.* 2004;130(5):579-585.
2015. Walker-Engstrom ML, Wilhelmsson B, Tegelberg A, Dimenas E, Ringqvist I. Quality of life assessment of treatment with dental appliance or UPPP in patients with mild to moderate obstructive sleep apnoea. A prospective randomized 1-year follow-up study. *J Sleep Res.* 2000;9(3):303-308.
2016. Franklin KA, Anttila H, Axelsson S, et al. Effects and side-effects of surgery for snoring and obstructive sleep apnea--a systematic review. *Sleep.* 2009;32(1):27-36.
2017. Conradt R, Hochban W, Heitmann J, et al. Sleep fragmentation and daytime vigilance in patients with OSA treated by surgical maxillomandibular advancement compared to CPAP therapy. *J Sleep Res.* 1998;7(3):217-223.
2018. Santamaria JD, Prior JC, Fleetham JA. Reversible reproductive dysfunction in men with obstructive sleep apnoea. *Clin Endocrinol (Oxf).* 1988;28(5):461-470.
2019. Shin HW, Park JH, Park JW, et al. Effects of surgical vs. nonsurgical therapy on erectile dysfunction and quality of life in obstructive sleep apnea syndrome: a pilot study. *J Sex Med.* 2013;10(8):2053-2059.
2020. Dahlof P, Ejnell H, Hallstrom T, Hedner J. Surgical treatment of the sleep apnea syndrome reduces associated major depression. *International Journal of Behavioral Medicine.* 2000;7(1):73-88.
2021. Klonoff H, Fleetham J, Taylor DR, Clark C. Treatment outcome of obstructive sleep apnea. Physiological and neuropsychological concomitants. *J Nerv Ment Dis.* 1987;175(4):208-212.
2022. Li HY, Huang YS, Chen NH, Fang TJ, Liu CY, Wang PC. Mood improvement after surgery for obstructive sleep apnea. *Laryngoscope.* 2004;114(6):1098-1102.
2023. Xiao Y, Han D, Zang H, Wang D. The effectiveness of nasal surgery on psychological symptoms in patients with obstructive sleep apnea and nasal obstruction. *Acta Otolaryngol.* 2016;136(6):626-632.
2024. Malhotra A, Ayappa I, Ayas N, et al. Metrics of sleep apnea severity: beyond the apnea-hypopnea index. *Sleep.* 2021;44(7).
2025. Kezirian EJ, Weaver EM, Criswell MA, de Vries N, Woodson BT, Piccirillo JF. Reporting results of obstructive sleep apnea syndrome surgery trials. *Otolaryngol Head Neck Surg.* 2011;144(4):496-499.
2026. Binar M, Karakoc O. Anterior Palatoplasty for Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg.* 2018;158(3):443-449.
2027. Pirklbauer K, Russmueller G, Stiebellehner L, et al. Maxillomandibular advancement for treatment of obstructive sleep apnea syndrome: a systematic review. *J Oral Maxillofac Surg.* 2011;69(6):e165-176.
2028. Fairburn SC, Waite PD, Vilos G, et al. Three-dimensional changes in upper airways of patients with obstructive sleep apnea following maxillomandibular advancement. *J Oral Maxillofac Surg.* 2007;65(1):6-12.
2029. Noller MW, Guillemineault C, Gouveia CJ, et al. Mandibular advancement for adult obstructive sleep apnea: A systematic review and meta-analysis. *J Craniomaxillofac Surg.* 2017;45(12):2035-2040.

2030. Tsui WK, Yang Y, Cheung LK, Leung YY. Distraction osteogenesis as a treatment of obstructive sleep apnea syndrome: A systematic review. *Medicine (Baltimore)*. 2016;95(36):e4674.
2031. Minni A, Cialente F, Ralli M, et al. Uvulopalatopharyngoplasty and barbed reposition pharyngoplasty with and without hyoid suspension for obstructive sleep apnea hypopnea syndrome: A comparison of long-term functional results. *Bosn J Basic Med Sci*. 2020.
2032. Camacho M, Nesbitt NB, Lambert E, et al. Laser-Assisted Uvulopalatoplasty for Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis. *Sleep*. 2017;40(3).
2033. Marti S, Sampol G, Munoz X, et al. Mortality in severe sleep apnoea/hypopnoea syndrome patients: impact of treatment. *Eur Respir J*. 2002;20(6):1511-1518.
2034. Lysdahl M, Haraldsson PO. Long-term survival after uvulopalatopharyngoplasty in nonobese heavy snorers: a 5- to 9-year follow-up of 400 consecutive patients. *Arch Otolaryngol Head Neck Surg*. 2000;126(9):1136-1140.
2035. Keenan SP, Burt H, Ryan CF, Fleetham JA. Long-term survival of patients with obstructive sleep apnea treated by uvulopalatopharyngoplasty or nasal CPAP. *Chest*. 1994;105(1):155-159.
2036. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg*. 2011;128(1):305-310.
2037. Chin CH, Lin PW, Lin HC, Friedman M, Lin MC. Effects of OSA Surgery on Leptin and Metabolic Profiles. *Otolaryngol Head Neck Surg*. 2019;161(6):1048-1055.
2038. Fehrm J, Friberg D, Bring J, Browaldh N. Blood pressure after modified uvulopalatopharyngoplasty: results from the SKUP(3) randomized controlled trial. *Sleep Med*. 2017;34:156-161.
2039. Islam S, Taylor CJ, Ormiston IW. Effects of maxillomandibular advancement on systemic blood pressure in patients with obstructive sleep apnoea. *Br J Oral Maxillofac Surg*. 2015;53(1):34-38.
2040. Boyd SB, Walters AS, Waite P, Harding SM, Song Y. Long-Term Effectiveness and Safety of Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea. *J Clin Sleep Med*. 2015;11(7):699-708.
2041. Lee LA, Huang CG, Chen NH, Wang CL, Fang TJ, Li HY. Severity of obstructive sleep apnea syndrome and high-sensitivity C-reactive protein reduced after relocation pharyngoplasty. *Otolaryngol Head Neck Surg*. 2011;144(4):632-638.
2042. Choi JH, Yi JS, Lee SH, et al. Effect of upper airway surgery on heart rate variability in patients with obstructive sleep apnoea syndrome. *J Sleep Res*. 2012;21(3):316-321.
2043. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. *JACC Cardiovasc Imaging*. 2014;7(10):1025-1038.
2044. Peng Y, Zhang L, Hu D, et al. Reduction of internal carotid artery intima-media thickness in patients with moderate-to-severe obstructive sleep apnea syndrome after nasal surgery and uvulopalatopharyngoplasty. *Acta Otolaryngol*. 2016;136(5):514-521.
2045. Lin CC, Wang YP, Lee KS, Liaw SF, Chiu CH. Effect of uvulopalatopharyngoplasty on leptin and endothelial function in sleep apnea. *Ann Otol Rhinol Laryngol*. 2014;123(1):40-46.
2046. Kinoshita H, Shibano A, Sakoda T, et al. Uvulopalatopharyngoplasty decreases levels of C-reactive protein in patients with obstructive sleep apnea syndrome. *Am Heart J*. 2006;152(4):692 e691-695.
2047. Zohar Y, Talmi YP, Frenkel H, et al. Cardiac function in obstructive sleep apnea patients following uvulopalatopharyngoplasty. *Otolaryngol Head Neck Surg*. 1992;107(3):390-394.
2048. Partinen M, Guilleminault C. Daytime sleepiness and vascular morbidity at seven-year follow-up in obstructive sleep apnea patients. *Chest*. 1990;97(1):27-32.
2049. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of Sleep-Disordered Breathing With Cognitive Function and Risk of Cognitive Impairment: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2017;74(10):1237-1245.

2050. Olaithe M, Bucks RS. Executive dysfunction in OSA before and after treatment: a meta-analysis. *Sleep*. 2013;36(9):1297-1305.
2051. Rojo-Sanchis C, Almerich-Silla JM, Paredes-Gallardo V, Montiel-Company JM, Bellot-Arcis C. Impact of Bimaxillary Advancement Surgery on the Upper Airway and on Obstructive Sleep Apnea Syndrome: a Meta-Analysis. *Sci Rep*. 2018;8(1):5756.
2052. Chinnadurai S, Jordan AK, Sathe NA, Fonnesbeck C, McPheeters ML, Francis DO. Tonsillectomy for Obstructive Sleep-Disordered Breathing: A Meta-analysis. *Pediatrics*. 2017;139(2).
2053. Marcus CL, Moore RH, Rosen CL, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med*. 2013;368(25):2366-2376.
2054. Dahlof P, Norlin-Bagge E, Hedner J, Ejnell H, Hetta J, Hallstrom T. Improvement in neuropsychological performance following surgical treatment for obstructive sleep apnea syndrome. *Acta Otolaryngol*. 2002;122(1):86-91.
2055. Lin WC, Huang CC, Chen HL, et al. Longitudinal brain structural alterations and systemic inflammation in obstructive sleep apnea before and after surgical treatment. *J Transl Med*. 2016;14(1):139.
2056. Canessa N, Castronovo V, Cappa SF, et al. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med*. 2011;183(10):1419-1426.
2057. Lojander J, Kajaste S, Maasilta P, Partinen M. Cognitive function and treatment of obstructive sleep apnea syndrome. *J Sleep Res*. 1999;8(1):71-76.
2058. Decary A, Rouleau I, Montplaisir J. Cognitive deficits associated with sleep apnea syndrome: a proposed neuropsychological test battery. *Sleep*. 2000;23(3):369-381.
2059. Pang KP, Pang EB, Pang KA, Vicini C, Chan YH, Rotenberg BW. Upper airway surgery for obstructive sleep apnea reduces blood pressure. *Laryngoscope*. 2018;128(2):523-527.
2060. Li L, Zhan X, Wang N, et al. Does airway surgery lower serum lipid levels in obstructive sleep apnea patients? A retrospective case review. *Med Sci Monit*. 2014;20:2651-2657.
2061. Qian Y, Zou J, Xu H, et al. Association of upper airway surgery and improved cardiovascular biomarkers and risk in OSA. *Laryngoscope*. 2020;130(3):818-824.
2062. Gunbey E, Karabulut I, Karabulut H, Zaim M. Impact of Multilevel Surgical Treatment on Mean Platelet Volume in Patients With Obstructive Sleep Apnea Syndrome. *J Craniofac Surg*. 2015;26(4):1287-1289.
2063. Simsek G, Haytuglu S, Muluk NB, Arikan OK, Cortuk M, Kiraz K. Mean Platelet Volume Decreases in Adult Patients With Obstructive Sleep Apnea After Uvulopalatal Flap Surgery. *J Craniofac Surg*. 2015;26(7):2152-2154.
2064. Friedman M, Bliznikas D, Vidyasagar R, Woodson BT, Joseph NJ. Reduction of C-reactive protein with surgical treatment of obstructive sleep apnea hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2006;135(6):900-905.
2065. Constantinidis J, Erelidias S, Angouridakis N, Konstantinidis I, Vital V, Angouridaki C. Cytokine changes after surgical treatment of obstructive sleep apnoea syndrome. *Eur Arch Otorhinolaryngol*. 2008;265(10):1275-1279.
2066. Eun YG, Kim MG, Kwon KH, Shin SY, Cho JS, Kim SW. Short-term effect of multilevel surgery on adipokines and pro-inflammatory cytokines in patients with obstructive sleep apnea. *Acta Otolaryngol*. 2010;130(12):1394-1398.
2067. Mutlu M, Vuralkan E, Akin I, et al. Alteration of serum levels of inflammatory cytokines and polysomnographic indices after uvulopalatal flap surgery in obstructive sleep apnea. *Ear Nose Throat J*. 2017;96(2):65-68.
2068. Vuralkan E, Mutlu M, Firat IH, et al. Changes in serum levels of MDA and MMP-9 after UPF in patients with OSAS. *Eur Arch Otorhinolaryngol*. 2014;271(5):1329-1334.



2069. Peng YK, Zhang LC, Hu DF, et al. Reduction of internal carotid artery intima-media thickness in patients with moderate-to-severe obstructive sleep apnea syndrome after nasal surgery and uvulopalatopharyngoplasty. *Acta Oto-Laryngol*. 2016;136(5):514-521.
2070. Lee MY, Lin CC, Lee KS, et al. Effect of uvulopalatopharyngoplasty on endothelial function in obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2009;140(3):369-374.
2071. Yang HB, Wang Y, Dong MM. Effect of Han-uvulopalatopharyngoplasty on flow-mediated dilatation in patients with moderate or severe obstructive sleep apnea syndrome. *Acta Otolaryngol*. 2012;132(7):769-772.
2072. Partinen M, Guilleminault C. Daytime Sleepiness and Vascular Morbidity at 7-Year Follow-up in Obstructive Sleep-Apnea Patients. *Chest*. 1990;97(1):27-32.
2073. Chen SY, Chergn YG, Lee FP, et al. Risk of Cerebrovascular Diseases After Uvulopalatopharyngoplasty in Patients With Obstructive Sleep Apnea: A Nationwide Cohort Study. *Medicine (Baltimore)*. 2015;94(41):e1791.
2074. Pietzsch JB, Liu S, Garner AM, Kezirian EJ, Strollo PJ. Long-Term Cost-Effectiveness of Upper Airway Stimulation for the Treatment of Obstructive Sleep Apnea: A Model-Based Projection Based on the STAR Trial. *Sleep*. 2015;38(5):735-744.
2075. Pietzsch JB, Richter AK, Randerath W, et al. Clinical and Economic Benefits of Upper Airway Stimulation for Obstructive Sleep Apnea in a European Setting. *Respiration*. 2019;98(1):38-47.
2076. Ulfberg J, Carter N, Talback M, Edling C. Excessive daytime sleepiness at work and subjective work performance in the general population and among heavy snorers and patients with obstructive sleep apnea. *Chest*. 1996;110(3):659-663.
2077. Leger D, Stepnowsky C. The economic and societal burden of excessive daytime sleepiness in patients with obstructive sleep apnea. *Sleep Med Rev*. 2020;51:101275.
2078. Zhang XQ, Liu LJ, Li XY, et al. Effect of minimally invasive surgery on the sleep quality and work ability of patients with obstructive sleep apnea-hypopnea syndrome. *Sleep Breath*. 2020.
2079. Roland PS, Rosenfeld RM, Brooks LJ, et al. Clinical practice guideline: Polysomnography for sleep-disordered breathing prior to tonsillectomy in children. *Otolaryngol Head Neck Surg*. 2011;145(1 Suppl):S1-15.
2080. Teo DT, Mitchell RB. Systematic review of effects of adenotonsillectomy on cardiovascular parameters in children with obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2013;148(1):21-28.
2081. O'Brien LM, Gozal D. Autonomic dysfunction in children with sleep-disordered breathing. *Sleep*. 2005;28(6):747-752.
2082. Chervin RD, Ruzicka DL, Giordani BJ, et al. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. *Pediatrics*. 2006;117(4):e769-778.
2083. O'Brien LM, Mervis CB, Holbrook CR, et al. Neurobehavioral implications of habitual snoring in children. *Pediatrics*. 2004;114(1):44-49.
2084. Suratt PM, Barth JT, Diamond R, et al. Reduced time in bed and obstructive sleep-disordered breathing in children are associated with cognitive impairment. *Pediatrics*. 2007;119(2):320-329.
2085. Mitchell RB, Kelly J. Behavior, neurocognition and quality-of-life in children with sleep-disordered breathing. *Int J Pediatr Otorhinolaryngol*. 2006;70(3):395-406.
2086. Gozal D, Wang M, Pope DW, Jr. Objective sleepiness measures in pediatric obstructive sleep apnea. *Pediatrics*. 2001;108(3):693-697.
2087. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome. *Pediatrics*. 2012;130(3):576-584.
2088. Chervin RD, Archbold KH, Dillon JE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. *Pediatrics*. 2002;109(3):449-456.

2089. Galland BC, Dawes PJ, Tripp EG, Taylor BJ. Changes in behavior and attentional capacity after adenotonsillectomy. *Pediatr Res*. 2006;59(5):711-716.
2090. Chervin RD, Ruzicka DL, Archbold KH, Dillon JE. Snoring predicts hyperactivity four years later. *Sleep*. 2005;28(7):885-890.
2091. Chervin RD, Archbold KH. Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. *Sleep*. 2001;24(3):313-320.
2092. Brietzke SE, Katz ES, Roberson DW. Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature. *Otolaryngol Head Neck Surg*. 2004;131(6):827-832.
2093. Burghard M, Brozek-Madry E, Krzeski A. Sleep disordered breathing in children - Diagnostic questionnaires, comparative analysis. *Int J Pediatr Otorhinolaryngol*. 2019;120:108-111.
2094. Sen T, Spruyt K. Pediatric Sleep Tools: An Updated Literature Review. *Front Psychiatry*. 2020;11:317.
2095. Michelet D, Julien-Marsollier F, Vacher T, et al. Accuracy of the sleep-related breathing disorder scale to diagnose obstructive sleep apnea in children: a meta-analysis. *Sleep Med*. 2019;54:78-85.
2096. Patel AP, Meghji S, Phillips JS. Accuracy of clinical scoring tools for the diagnosis of pediatric obstructive sleep apnea. *Laryngoscope*. 2020;130(4):1034-1043.
2097. Rosen CL, Wang R, Taylor HG, et al. Utility of symptoms to predict treatment outcomes in obstructive sleep apnea syndrome. *Pediatrics*. 2015;135(3):e662-671.
2098. Howard NS, Brietzke SE. Pediatric tonsil size: objective vs subjective measurements correlated to overnight polysomnogram. *Otolaryngol Head Neck Surg*. 2009;140(5):675-681.
2099. Hwang SH, Guilleminault C, Park CS, Kim TW, Hong SC. Usefulness of adenotonsillar size for prediction of severity of obstructive sleep apnea and flow limitation. *Otolaryngol Head Neck Surg*. 2013;149(2):326-334.
2100. Nolan J, Brietzke SE. Systematic review of pediatric tonsil size and polysomnogram-measured obstructive sleep apnea severity. *Otolaryngol Head Neck Surg*. 2011;144(6):844-850.
2101. Tang A, Benke JR, Cohen AP, Ishman SL. Influence of Tonsillar Size on OSA Improvement in Children Undergoing Adenotonsillectomy. *Otolaryngol Head Neck Surg*. 2015;153(2):281-285.
2102. Biederman J, Faraone SV, Monuteaux MC, Plunkett EA, Gifford J, Spencer T. Growth deficits and attention-deficit/hyperactivity disorder revisited: impact of gender, development, and treatment. *Pediatrics*. 2003;111(5 Pt 1):1010-1016.
2103. Mitchell RB, Archer SM, Ishman SL, et al. Clinical Practice Guideline: Tonsillectomy in Children (Update). *Otolaryngol Head Neck*. 2019;160:S1-S42.
2104. Friedman NR, Parikh SR, Ishman SL, et al. The current state of pediatric drug-induced sleep endoscopy. *Laryngoscope*. 2017;127(1):266-272.
2105. Boudewyns A, Verhulst S, Maris M, Saldien V, Van de Heyning P. Drug-induced sedation endoscopy in pediatric obstructive sleep apnea syndrome. *Sleep Med*. 2014;15(12):1526-1531.
2106. Kirkham E, Ma CC, Filipek N, et al. Polysomnography outcomes of sleep endoscopy-directed intervention in surgically naive children at risk for persistent obstructive sleep apnea. *Sleep Breath*. 2020;24(3):1143-1150.
2107. Durr ML, Meyer AK, Kezirian EJ, Rosbe KW. Drug-induced sleep endoscopy in persistent pediatric sleep-disordered breathing after adenotonsillectomy. *Arch Otolaryngol Head Neck Surg*. 2012;138(7):638-643.
2108. Baldassari CM, Lam DJ, Ishman SL, et al. Expert Consensus Statement: Pediatric Drug-Induced Sleep Endoscopy. *Otolaryngol Head Neck Surg*. 2021;165(4):578-591.

2109. Amos JM, Durr ML, Nardone HC, Baldassari CM, Duggins A, Ishman SL. Systematic Review of Drug-Induced Sleep Endoscopy Scoring Systems. *Otolaryngol Head Neck Surg.* 2018;158(2):240-248.
2110. Wilcox LJ, Bergeron M, Reghunathan S, Ishman SL. An updated review of pediatric drug-induced sleep endoscopy. *Laryngoscope Investig Otolaryngol.* 2017;2(6):423-431.
2111. Chervin RD, Weatherly RA, Garetz SL, et al. Pediatric sleep questionnaire: prediction of sleep apnea and outcomes. *Arch Otolaryngol Head Neck Surg.* 2007;133(3):216-222.
2112. Franco RA, Jr., Rosenfeld RM, Rao M. First place--resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. *Otolaryngol Head Neck Surg.* 2000;123(1 Pt 1):9-16.
2113. Aurora RN, Zak RS, Karipoot A, et al. Practice Parameters for the Respiratory Indications for Polysomnography in Children. *Sleep.* 2011;34(3):379-388.
2114. Venekamp RP, Hearne BJ, Chandrasekharan D, Blackshaw H, Lim J, Schilder AGM. Tonsillectomy or adenotonsillectomy versus non-surgical management for obstructive sleep-disordered breathing in children. *Cochrane Db Syst Rev.* 2015(10).
2115. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy Outcomes in Treatment of Obstructive Sleep Apnea in Children A Multicenter Retrospective Study. *Am J Resp Crit Care.* 2010;182(5):676-683.
2116. Mitchell RB, Kelly J. Outcome of adenotonsillectomy for obstructive sleep apnea in obese and normal-weight children. *Otolaryng Head Neck.* 2007;137(1):43-48.
2117. Todd CA, Bareiss AK, McCoul ED, Rodriguez KH. Adenotonsillectomy for Obstructive Sleep Apnea and Quality of Life: Systematic Review and Meta-analysis. *Otolaryng Head Neck.* 2017;157(5):767-773.
2118. Maris M, Verhulst S, Wojciechowski M, Van de Heyning P, Boudewyns A. Outcome of adenotonsillectomy in children with Down syndrome and obstructive sleep apnoea. *Arch Dis Child.* 2017;102(4):331-+.
2119. Trosman SJ, Eleff DJ, Krishna J, Anne S. Polysomnography results in pediatric patients with mild obstructive sleep apnea: Adenotonsillectomy vs. watchful waiting. *Int J Pediatr Otorhi.* 2016;83(4):25-30.
2120. Volsky PG, Woughter MA, Beydoun HA, Derkay CS, Baldassari CM. Adenotonsillectomy vs Observation for Management of Mild Obstructive Sleep Apnea in Children. *Otolaryng Head Neck.* 2014;150(1):126-132.
2121. Lewis TL, Johnson RF, Choi J, Mitchell RB. Weight Gain after Adenotonsillectomy: A Case Control Study. *Otolaryng Head Neck.* 2015;152(4):734-739.
2122. Kheirandish-Gozal L, Bhattacharjee R, Bandla HPR, Gozal D. Antiinflammatory Therapy Outcomes for Mild OSA in Children. *Chest.* 2014;146(1):88-95.
2123. Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. *Pediatrics.* 2008;122(1):E149-E155.
2124. Liming BJ, Ryan M, Mack D, Ahmad I, Camacho M. Montelukast and Nasal Corticosteroids to Treat Pediatric Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Otolaryng Head Neck.* 2019;160(4):594-602.
2125. Liming BJ, Ryan M, Mack D, Ahmad I, Camacho M. Montelukast and Nasal Corticosteroids to Treat Pediatric Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg.* 2019;160(4):594-602.
2126. FDA.GOV. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug>. Accessed July 11, 2022.
2127. Arganbright JM, Lee JC, Weatherly RA. Pediatric drug-induced sleep endoscopy: An updated review of the literature. *World J Otorhinolaryngol Head Neck Surg.* 2021;7(3):221-227.

2128. Caloway CL, Diercks GR, Keamy D, et al. Update on hypoglossal nerve stimulation in children with down syndrome and obstructive sleep apnea. *Laryngoscope*. 2020;130(4):E263-E267.
2129. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep*. 1999;22(5):667-689.
2130. Loube DI, Gay PC, Strohl KP, Pack AI, White DP, Collop NA. Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: a consensus statement. *Chest*. 1999;115(3):863-866.
2131. Asghari A, Mohammadi F, Kamrava SK, Jalessi M, Farhadi M. Evaluation of quality of life in patients with obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2013;270(3):1131-1136.
2132. Kang JM, Kang SG, Cho SJ, et al. The quality of life of suspected obstructive sleep apnea patients is related to their subjective sleep quality rather than the apnea-hypopnea index. *Sleep Breath*. 2017;21(2):369-375.
2133. Wu H, Yuan X, Wang L, Sun J, Liu J, Wei Y. The Relationship Between Obstructive Sleep Apnea Hypopnea Syndrome and Inflammatory Markers and Quality of Life in Subjects With Acute Coronary Syndrome. *Respir Care*. 2016;61(9):1207-1216.
2134. Quan SF, Chan CS, Dement WC, et al. The association between obstructive sleep apnea and neurocognitive performance--the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep*. 2011;34(3):303-314B.
2135. Vazir A, Hastings PC, Papaioannou I, et al. Variation in severity and type of sleep-disordered breathing throughout 4 nights in patients with heart failure. *Resp Med*. 2008;102(6):831-839.
2136. Fietze I, Glos M, Zimmermann S, Penzel T. Long-term variability of the apnea-hypopnea index in a patient with mild to moderate obstructive sleep apnea. *J Clin Sleep Med*. 2020;16(2):319-323.
2137. Sforza E, Roche F, Chappelle C, Pichot V. Overnight Variability of Apnea-Hypopnea Index in Obstructive Sleep Apnea Using Ambulatory Polysomnography. *Front Physiol*. 2019;10:849.
2138. Magalang UJ, Chen N-H, Cistulli PA, et al. Agreement in the scoring of respiratory events and sleep among international sleep centers. *Sleep*. 2013;36(4):591-596.
2139. Azarbarzin A, Sands SA, Stone KL, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J*. 2019;40(14):1149-1157.
2140. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest*. 2010;137(1):95-101.
2141. Djonlagic I, Saboisky J, Carusona A, Stickgold R, Malhotra A. Increased sleep fragmentation leads to impaired off-line consolidation of motor memories in humans. *PLoS one*. 2012;7(3):e34106.
2142. Bhattacharjee R, Khalyfa A, Khalyfa AA, et al. Exosomal Cargo Properties, Endothelial Function and Treatment of Obesity Hypoventilation Syndrome: A Proof of Concept Study. *J Clin Sleep Med*. 2018;14(5):797-807.
2143. Gongol B, Shang F, He M, et al. Serum miR-92a is Elevated in Children and Adults with Obstructive Sleep Apnea. *J Mol Biomark Diagn*. 2020;11(4).
2144. Khalyfa A, Gozal D, Kheirandish-Gozal L. Plasma Exosomes Disrupt the Blood-Brain Barrier in Children with Obstructive Sleep Apnea and Neurocognitive Deficits. *Am J Respir Crit Care Med*. 2018;197(8):1073-1076.
2145. Koch H, Schneider LD, Finn LA, et al. Breathing Disturbances Without Hypoxia Are Associated With Objective Sleepiness in Sleep Apnea. *Sleep*. 2017;40(11).
2146. Smith JH, Baumert M, Nalivaiko E, McEvoy RD, Catcheside PG. Arousal in obstructive sleep apnoea patients is associated with ECG RR and QT interval shortening and PR interval lengthening. *J Sleep Res*. 2009;18(2):188-195.

2147. Sulit L, Storfer-Isser A, Kirchner HL, Redline S. Differences in polysomnography predictors for hypertension and impaired glucose tolerance. *Sleep*. 2006;29(6):777-783.
2148. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea - New pathways for targeted therapy. *Sleep Med Rev*. 2018;37:45-59.
2149. Pien GW, Ye L, Keenan BT, et al. Changing Faces of Obstructive Sleep Apnea: Treatment Effects by Cluster Designation in the Icelandic Sleep Apnea Cohort. *Sleep*. 2018;41(3).
2150. Kim J, Keenan BT, Lim DC, Lee SK, Pack AI, Shin C. Symptom-Based Subgroups of Koreans With Obstructive Sleep Apnea. *J Clin Sleep Med*. 2018;14(3):437-443.
2151. Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J*. 2014;44(6):1600-1607.
2152. Khosla S, Deak MC, Gault D, et al. Consumer Sleep Technology: An American Academy of Sleep Medicine Position Statement. *J Clin Sleep Med*. 2018;14(5):877-880.
2153. Cai Y, Tripuraneni P, Gulati A, et al. Patient-Defined Goals for Obstructive Sleep Apnea Treatment. *Otolaryngol Head Neck Surg*. 2022:1945998221075298.
2154. Gulati A, Stephens EM, Cai Y, Chang JL. Characterizing Decisional Conflict in Patients Presenting to Sleep Surgery Clinic and an Exploration of Resource Limitations. *Laryngoscope*. 2021;131(10):2384-2390.
2155. Ishman SL, Tang A, Cohen AP, et al. Decision Making for Children with Obstructive Sleep Apnea without Tonsillar Hypertrophy. *Otolaryngol Head Neck Surg*. 2016;154(3):527-531.
2156. Bergeron M, Duggins A, Chini B, Ishman SL. Clinical outcomes after shared decision-making tools with families of children with obstructive sleep apnea without tonsillar hypertrophy. *Laryngoscope*. 2019;129(11):2646-2651.
2157. Fung CH, Martin JL, Liang LJ, et al. Efficacy of a patient decision aid for improving person-centered decision-making by older adults with obstructive sleep apnea. *J Clin Sleep Med*. 2021;17(2):121-128.