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REVIEW ARTICLE

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# Comparative effectiveness of hypoglossal nerve stimulation and alternative treatments for obstructive sleep apnea: a systematic review and meta-analysis

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## Summary

Continuous positive airway pressure (CPAP) is the primary therapeutic modality for obstructive sleep apnea (OSA) management. However, despite efforts to encourage patients to comply with CPAP usage, long-term adherence remains low. Consequently, surgical intervention for OSA is considered a secondary option for patients who exhibit non-compliance with CPAP. Therefore, we conducted systematic review and meta-analysis assessed the relative effectiveness of hypoglossal nerve stimulation (HNS) treatment and alternative surgical interventions for managing OSA. Five databases were searched. Studies were included if they measured polysomnography parameters and assessed sleep apnea-related quality of life (Epworth Sleepiness Scale [ESS]) both before and after HNS, and compared these outcomes with control, CPAP, or airway surgery (uvulopalatopharyngoplasty, expansion sphincter pharyngoplasty, or tongue base surgery) groups. A total of 10 studies (2209 patients) met the inclusion criteria. Compared to other airway surgeries, the rates of post-treatment apnea–hypopnea index (AHI) < 10 and < 15 events/h were significantly lower in the HNS group (odds ratio [OR] 5.33, 95% confidence interval [CI] 1.21–23.42; and 2.73, 95% CI 1.30–5.71, respectively). Additionally, postoperative AHI was significantly lower in the HNS group than in all other airway surgery groups (AHI: mean difference [MD] −8.00, 95% CI −12.03 to−3.97 events/h). However, there were no significant differences in the rate of post-treatment AHI < 5 events/h (OR 1.93, 95% CI 0.74–5.06) or postoperative ESS score (MD 0.40, 95% CI−1.52 to 2.32) between the two groups. HNS is an effective option for selected patients with moderate-to-severe OSA and CPAP intolerance.

KEYWORDS
hypoglossal nerve, meta-analysis, obstructive, sleep apnea, systematic review, tongue

## 1 | INTRODUCTION

Obstructive sleep apnea (OSA) is characterised by repetitive episodes of upper airway collapse during sleep; it is a multifactorial disorder with a variety of associated symptoms and comorbidities. Notably, relationships among between cardiovascular complications, metabolic diseases, and cognitive impairment have been reported (Gosselin et al., 2019; Marin et al., 2005). The prevalence of OSA is heterogeneous, differing depending on evaluation criteria; it tends to be underdiagnosed, affecting 13%–33% of males and 6%–19% of females worldwide (Chang et al., 2022). Continuous positive airway pressure (CPAP) is the primary therapeutic modality for OSA management. However, despite efforts to encourage patients to comply with CPAP usage, long-term adherence remains low, with only 40%–60% of patients following the treatment (Rotenberg et al., 2016; Sawyer et al., 2011). Consequently, surgical intervention for OSA is considered a secondary therapeutic option for patients who exhibit non-compliance with CPAP treatment (Aurora et al., 2010; Sundaram et al., 2005). Upper airway surgery can also be considered as an alternative treatment to CPAP for managing a significant proportion of patients suffering from OSA (Rotenberg et al., 2016; Weaver & Grunstein, 2008).

Hypoglossal nerve stimulation (HNS) is a surgical treatment option that differs from other surgical approaches that alter the airway structure. As the hypoglossal nerve affects genioglossus protrusion and pharyngeal muscle tone, airway patency can be maintained through electrical stimulation of the nerve. HNS has emerged as an effective surgical intervention for OSA treatment. In this meta-analysis, we aimed to compare the effectiveness of HNS with other surgical options as alternative treatment methods to CPAP.

## 2 | METHODS

This research was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021). The study protocol was prospectively registered in the Open Science Framework (https://osf.io/m76fd/).

### 2.1 | Search strategy and selection of studies

A comprehensive search for relevant studies published in electronic databases, including PubMed, SCOPUS, Embase, Web of Science, and the Cochrane database, up to March 2023 was conducted using the following search terms: 'hypoglossal nerve stimulation', 'electrical stimulation', 'hypoglossal neurostimulation', 'hypoglossal nerve', 'sleep apnea', 'obstructive sleep apnea', and 'upper airway stimulation'. Studies using airway surgeries such as uvulopalatopharyngoplasty, expansion sphincter pharyngoplasty, and tongue base surgery were also searched for. The PICO (Population, Intervention, Comparison, and Outcome) framework for this study was as follows: Patients with moderate-to-severe OSA and inadequate CPAP adherence; Intervention with HNS; Comparison to airway surgeries such as uvulopalatopharyngoplasty, expansion sphincter pharyngoplasty, or tongue base surgery (or a control [no treatment]); and Outcome assessment based on the apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and Epworth Sleepiness Scale (ESS).

Two independent reviewers, M.A.B and S.H.K, screened all abstracts and titles to select relevant studies, excluding those that did not meet the criteria. For studies with potentially relevant content, full-text versions were obtained when abstracts alone were insufficient for conclusive determination of eligibility. In cases of discrepancies in the decision-making process at each stage, a third reviewer (S.W.K) was consulted to reach a consensus on the literature to be included in the final analysis. The inclusion criteria consisted of randomised controlled trials (RCTs) or cohort articles consistent with the PICO framework. Studies involving patients undergoing additional upper airway-affecting procedures, such as head and neck surgery, as well as duplicated reports, were deemed ineligible for inclusion. Additionally, studies with unclear reporting or quantifiable data for the outcomes of interest, or where extraction and calculation of the outcomes were not feasible from the published results, were also excluded from the analysis. Ultimately, 10 articles met the inclusion criteria for the meta-analysis. Figure 1 presents an overview of the search methodology employed to select these studies.

### 2.2 | Data extraction and risk of bias assessment

Data from the included studies were extracted using standardised forms and verified by two independent reviewers (Hwang et al., 2022; Hwang et al., 2023; Kim et al., 2022). Post-treatment measurements included the polysomnography (PSG) outcomes and quality of life scores after HNS. The outcomes included PSG and disease-specific quality of life during the postoperative period (Heiser et al., 2022; Huntley et al., 2018; Huntley et al., 2019; Huntley et al., 2021; Mehra et al., 2020; Pengo et al., 2016; Shah et al., 2018; Stewart et al., 2021; Walia et al., 2020; Woodson et al., 2014). The HNS group and other groups (control, CPAP, and all other airway surgeries, such as uvulopalatopharyngoplasty [UPPP], expansion sphincter pharyngoplasty, or tongue base surgery) were compared during the follow-up period.

The main outcome measures in this study were the AHI, ODI, and ESS score. The secondary outcome measures included the percentages of AHI < 5, < 10, and < 15 events/h, and the success rate based on the Sher criteria after HNS. Success based on the Sher criteria was defined as a drop in postoperative AHI by 50% or to a value < 20 events/h (Huntley et al., 2017). The data extracted from the studies included patient numbers, scale scores, and $p$ values derived from comparisons between pre- and post-treatment observations.

In non-RCTs, the quality of each study was assessed using the Newcastle–Ottawa Scale, which ranges from 0 to 9, as presented in Table S1. This 'star system' was used to evaluate each included study based on the selection of study groups, comparability of the groups, and ascertainment of outcomes of interest. For RCTs, the Cochrane Risk of Bias tool was employed to assess the risk of bias.

### 2.3 | Statistical analysis

A meta-analysis of the selected studies was conducted using R statistical software (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria). The means and standard deviations of continuous measures were compared between the control and treatment groups; the effect size was represented by the mean difference (MD) for such

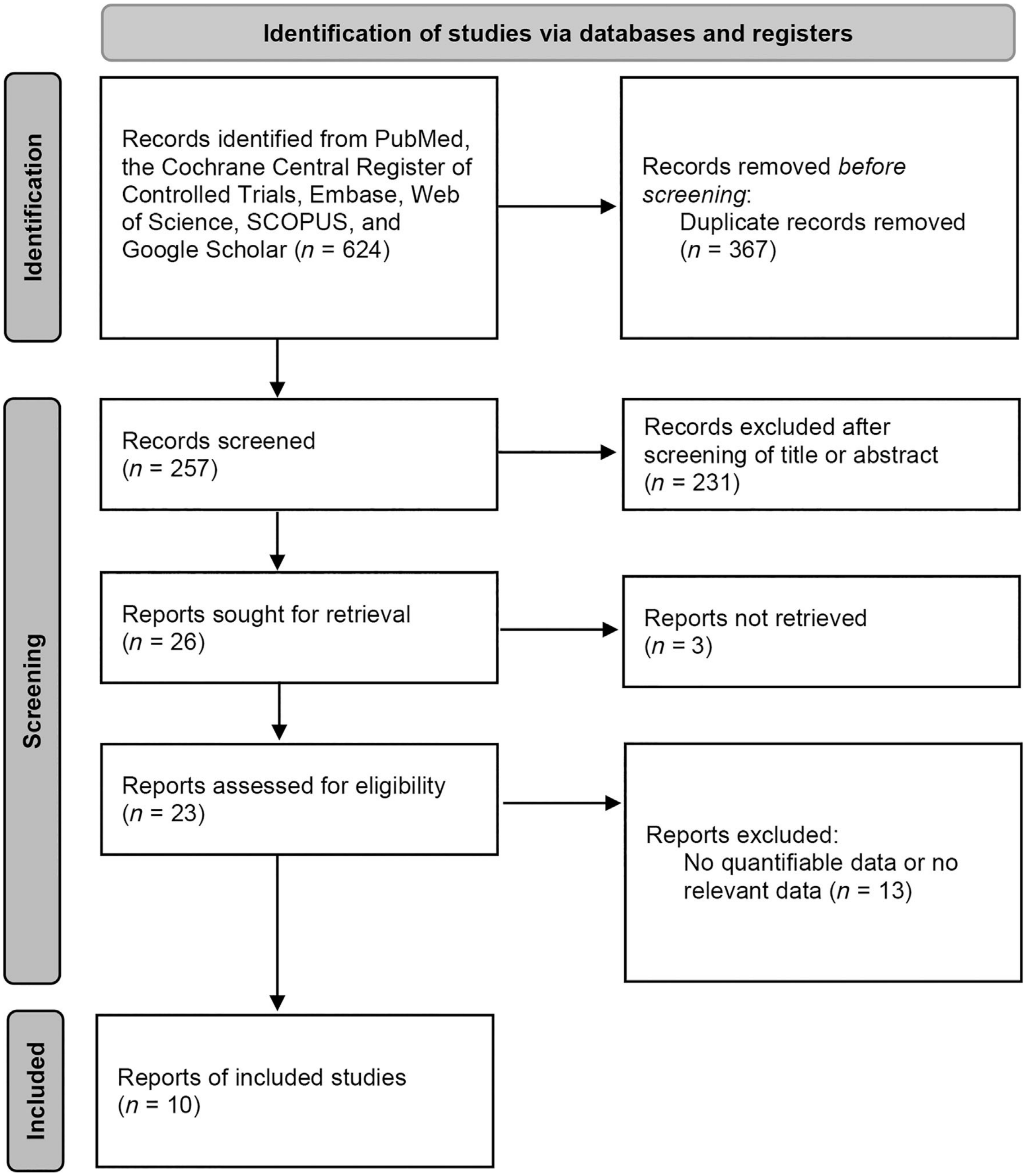


**FIGURE 1** Flowchart depicting the article search and selection processes.

variables, i.e., the difference between the means of the treatment and control groups. The MD was computed in cases where all studies used the same outcomes and units of measure. Rate-related outcomes were analysed based on odds ratios (ORs).

Heterogeneity was calculated with the $I^2$ test and ranged from 0 (no heterogeneity) to 100 (maximum heterogeneity). When significant heterogeneity among outcomes was found (defined as $I^2 > 50$), the random-effects model was used. Outcomes that did not show significant heterogeneity ($I^2 < 50$) were analysed with a fixed-effects model. A funnel plot and Egger's test were used to identify publication bias.

## 3 | RESULTS

A total of 10 studies involving 2209 participants were included in the review, as depicted in Figure 1. Patient characteristics could not be fully assessed due to incomplete reporting of variables by the included studies. A summary of the study characteristics is presented in Table 1, while the bias assessment results are described in Tables S2 and S3. However, due to the limited number of studies included in each analysis, it was not possible to perform the Egger's test or draw Begg funnel plots to identify publication bias.

**TABLE 1** Summary of studies included in the meta-analysis.

| Reference | Study design | Nation | Sample size, *n* | Age, years, mean (SD) | Sex, male/female | Severity | Other characteristics | BMI, kg/m$^2$, mean (SD) | Type of application | Variables | Comparison | Follow-up PSG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Woodson et al., 2014 | RCT | USA | 23 | 57.1 (10.0) | 21/2 | Moderate-to-severe OSA and intolerance or inadequate adherence to CPAP | | 28.4 (2.4) | Inspire Medical Systems, Minneapolis, MN, USA | Postoperative ESS, postoperative AHI, postoperative ODI | Placebo | Attended full PSG |
| Pengo et al., 2016 | RCT | UK | 36 | 50.8 (11.2) | 30/6 | OSA with an ODI ≥ 15 events/h or with an ODI ≥ 5 events/h plus an ESS > 10 points | | 29.6 | Overnight transcutaneous electrical stimulation of the pharyngeal dilators during a single night (bilaterally) | Postoperative AHI, postoperative ODI | Placebo | Attended full PSG |
| Huntley et al., 2018 | Cohort | USA | 108 | 61.67 (11.92) | 78/30 | Moderate-to-severe OSA with an AHI > 15 events/h, inability to tolerate CPAP therapy | | 29.5 (3.96) | Inspire Medical Systems, Minneapolis, MN, USA | Rate of postoperative AHI < 5, 10, and 15 events/h and surgical success[a], postoperative ESS, postoperative AHI | ESP /all airway surgery | Attended full PSG |
| Shah et al., 2018 | Cohort | USA | 40 | 62.4 (8.9) | 30/10 | Moderate-to-severe OSA (AHI 20–65 events/h), inability to adhere to CPAP, BMI ≤ 32 kg/m$^2$ | History of prior upper airway surgery for OSA: 35% | 28.0 (2.1) | Inspire Medical Systems, Minneapolis, MN, USA | Rate of postoperative AHI < 5, 10, and 15 events/h and surgical success[a], postoperative ESS | UPPP/all airway surgery | Attended full PSG |
| Huntley et al., 2018 | Cohort | USA | 100 | 61.92 (12.04) | 70/30 | Moderate-to-severe OSA with an AHI ≥ 15 events/h, inability to tolerate CPAP | | 29.38 (4.06) | Inspire Medical Systems, Minneapolis, MN, USA | Rate of postoperative AHI < 5, 10, and 15 events/h and surgical success[a], postoperative AHI | TORS/all airway surgery | Attended full PSG |
| Mehra et al., 2020 | Cohort | USA | 230 | 57.5 (10.8) | 194/36 | OSA with a preoperative AHI between 15 and 65 events/h and < 25% central and mixed apneas, CPAP intolerance, and the absence of complete concentric collapse at the soft palate during drug-induced sleep endoscopy | Any OSA surgery: 119 (52%) | 29.8 (3.9) | UAS system (Inspire Medical Systems, Minneapolis, MN, USA) | Postoperative ESS, postoperative AHI | Placebo | Type III home sleep apnea test |

**TABLE 1** (Continued)

| Reference | Study design | Nation | Sample size, *n* | Age, years, mean (SD) | Sex, male/female | Severity | Other characteristics | BMI, kg/m$^2$, mean (SD) | Type of application | Variables | Comparison | Follow-up PSG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Walia et al., 2020 | Cohort | Netherlands | 402 | 58.8 (11.4) | 167/35 | Intolerance or suboptimal adherence to PAP, history of moderate-to-severe OSA (AHI ≥ 15 events/h), and for whom there was observed absence of circumferential airway collapse with drug-induced sedation endoscopy | | 28.9 (3.4) | UAS system (Inspire Medical Systems, Minneapolis, MN, USA) | Postoperative ESS | CPAP | NR |
| Huntley et al., 2019 | Cohort | USA | 698 | 59.5 (10.8) | 613/85 | Moderate-to-severe OSA, BMI < 35 kg/m$^2$, and without complete concentric collapse of the velopharynx | | NR | Inspire Medical Systems, Minneapolis, MN, USA | Postoperative ESS, postoperative AHI | All airway surgery | Attended full PSG or type III home sleep apnea test |
| Stewart et al., 2021 | Cohort | USA | 345 | 60 (11) | 255/90 | NR | | 30 (7) | Inspire Medical Systems, Minneapolis, MN, USA | Rate of postoperative AHI < 5, 10, and 15 events/h and surgical success[a], postoperative AHI | TORS, ESP/all airway surgery | Attended full PSG or type III home sleep apnea test |
| Heiser et al., 2022 | Cohort | Germany | 227 | 57.8 (11.6) | 179/48 | Patients using the same treatment exclusively for ≥12 months and if they had pathological sleepiness, with an ESS ≥11 | | 29.5 (3.7) | Inspire Medical Systems, Minneapolis, MN, USA | Rate of postoperative AHI < 5, 10, and 15 events/h, postoperative ESS, postoperative AHI | CPAP | Type III home sleep apnea test |

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index (kg/m$^2$); CPAP, continuous positive airway pressure; ESP, expansion sphincter pharyngoplasty; ESS, Epworth Sleepiness Scale; NR, not reported; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSG, polysomnography; RCT, randomised controlled trial; TORS, transoral robotic base of tongue resection; UAS, upper airway stimulation; UPPP, Uvulopalatopharyngoplasty.

[a]Surgical success: defined as a drop in postoperative AHI by 50% and to a value <20 events/h.

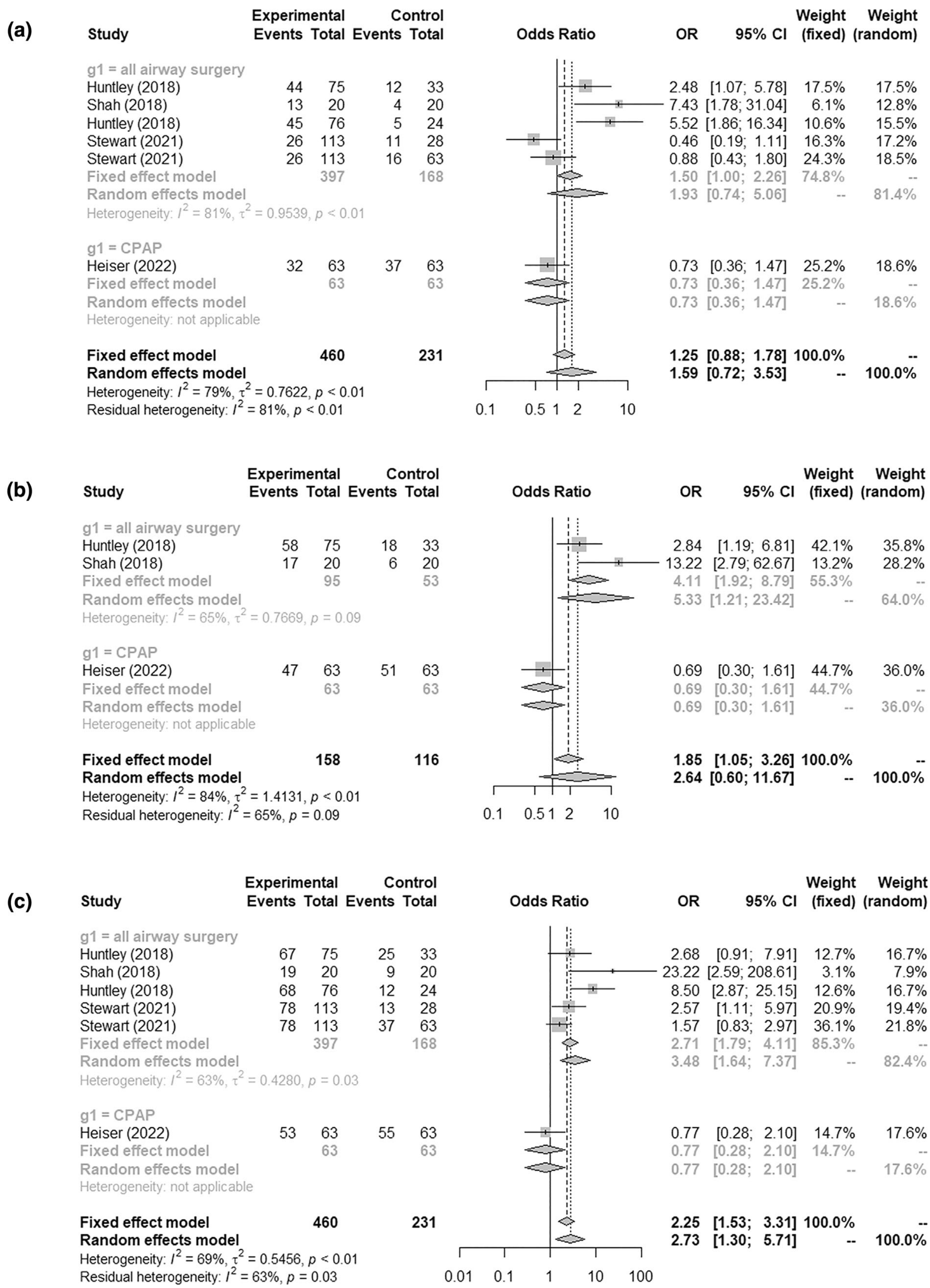


**FIGURE 2** Comparison of hypoglossal nerve stimulation, all other airway surgeries, and continuous positive airway pressure in terms of the rates of postoperative apnea–hypopnea index < 5 (a), < 10 (b), and < 15 events/h (c).

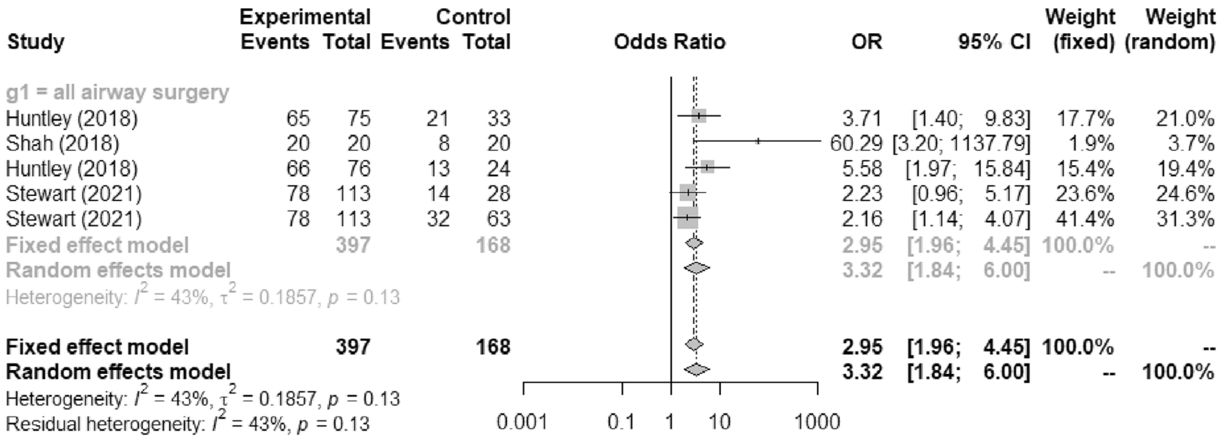


**FIGURE 3** Comparison of hypoglossal nerve stimulation and all other airway surgeries in terms of the success rate.

### 3.1 | Comparison of HNS and all other airway surgeries: rates of postoperative AHI < 5, < 10, and < 15 events/h, success rate, and postoperative AHI and ESS scores

Six studies were included in the meta-analysis. The rates of post-treatment AHI < 10 and 15 events/h were significantly lower in the HNS group than in all other airway surgery groups (OR 5.3275, 95% confidence interval [CI] 1.2117–23.4228; and OR 3.4806, 95% CI 1.6434–7.3718, respectively; Figure 2). The rates of success rate based on Sher criteria were significantly higher in the HNS group than in all other airway surgery groups (OR 2.9546, 95% CI 1.9634–4.4462; Figure 3). In addition, postoperative AHI was significantly lower in the HNS group than in all other airway surgery groups (MD −8.0000, 95% CI −12.0344 to −3.9656; Figure 4a). However, there was no significant difference in the rate of post-treatment AHI < 5 events/h (OR 1.9286, 9%% CI 0.7352–5.0597; Figure 2) or postoperative ESS (MD 0.3968, 95% CI −1.5231 to 2.3167) between the two groups; Figure 4b).

### 3.2 | Comparison of HNS and control (no operation or no CPAP): postoperative AHI, ESS scores, and ODI

Three studies were included in the meta-analysis. The AHI, ESS score, and ODI after HNS were significantly lower (MD −12.8394, 95% CI −16.1475 to −9.5312 [Figure 4a]; MD −5.3929, 95% CI −6.6078 to −4.1781 [Figure 4b]; and MD −11.8384, 95% CI −17.4476 to −6.2292, respectively) than in the control group (Figure 4c).

### 3.3 | Comparison of HNS and CPAP: rates of postoperative AHI < 5, < 10, and < 15 events/h, and postoperative AHI and ESS scores

Two studies were included in the meta-analysis. There were no significant differences in the rate of post-treatment AHI < 5 (OR 0.7254, 95% CI 0.3588–1.4665; Figure 2a), < 10 (OR 0.6912, 95% CI 0.2963–1.6121; Figure 2b), or < 15 events/h (OR 0.7709, 95% CI 0.2827–2.1025; Figure 2c), or in postoperative AHI (MD 1.5000, 95% CI −1.0145 to 4.0145; Figure 4a) or ESS scores (MD −1.8236, 95% CI −4.5634 to 0.9163; Figure 4b) between the two groups (Figure 2). However, the comparison of CPAP results was mainly based on a single study and the results should thus be interpreted cautiously.

### 3.4 | Comparison of effectiveness among HNS, all other airway surgeries, CPAP, and control (no operation or no CPAP)

A total of 10 studies were included in the meta-analysis. The ORs for post-treatment AHI < 10 and 15 events/h were significantly lower for HNS versus CPAP, and for HNS versus all other airway surgeries (0.6912 versus 5.3275, $p = 0.0190$; and 0.7709 versus 3.4806, $p = 0.0184$, respectively; Figure 2b, c). In addition, the MD in postoperative AHI of HNS versus CPAP was significantly different from those in HNS versus all other airway surgeries and control (1.5000 versus −8.0000 and −12.8394, $p < 0.0001$/−1.8236 versus 0.3968 and −5.3929, $p < 0.0001$; Figure 4a). These results suggest that HNS could be as effectiveness as CPAP, and superior to all other airway surgeries, in reducing AHI. Regarding daytime sleepiness, all treatment modalities, including HNS, all other airway surgeries, and CPAP, may have similar effectiveness.

### 3.5 | Sensitivity analysis

Sensitivity analyses were conducted to assess the impact of each individual study on the pooled outcomes by excluding one study at a time and then repeating the meta-analysis. The results of these sensitivity analyses were consistent with the analysis including all studies.

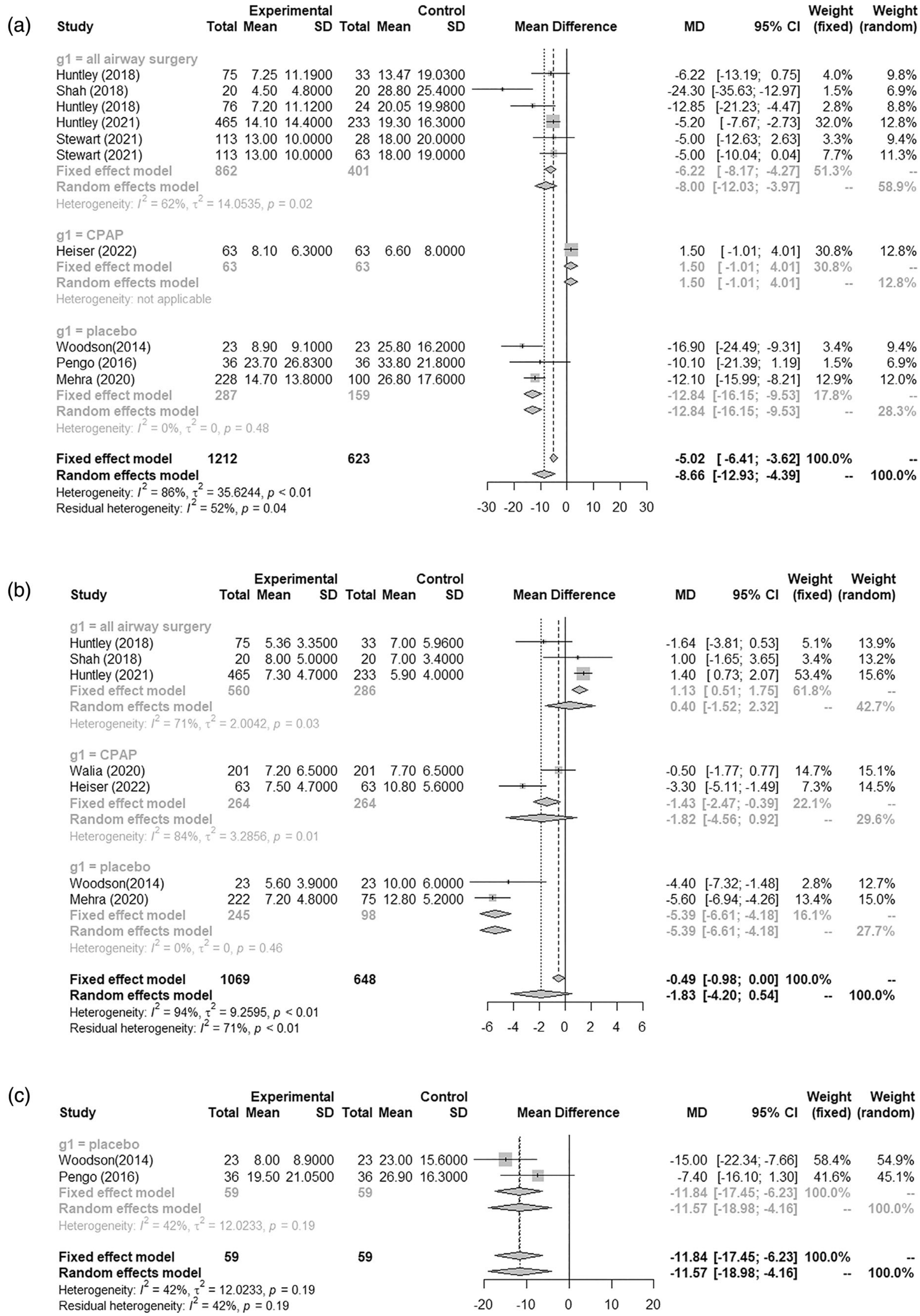


**FIGURE 4** Comparison of hypoglossal nerve stimulation and all other airway surgeries, continuous positive airway pressure (CPAP), and control (no operation or no CPAP) in terms of the mean difference in postoperative apnea–hypopnea index (a), Epworth Sleepiness Scale scores (b), and oxygen desaturation index (c).

## 4 | DISCUSSION

Currently, CPAP is the primary treatment for OSA due to its well-documented effectiveness and low overall morbidity (Chang et al., 2022). In comparison to other treatment modalities, CPAP has more supportive data regarding its efficacy in managing OSA, especially for severe cases involving multilevel and multifactorial pathophysiology. Although the effectiveness of CPAP therapy is well-established, patient adherence is not optimal. Several factors may contribute to poor adherence, including challenges associated with chronic use of nasal or oronasal interfaces. Consequently, a considerable proportion of individuals with sleep apnea receive inadequate treatment when CPAP therapy is the only option considered (Dedhia et al., 2015).

Alternative treatment modalities for managing sleep apnea include oral appliance therapy, positional therapy, weight reduction, behavioural adjustments, and upper airway reconstructive surgery. The conventional strategy for managing OSA involves identifying the level/s of upper airway obstruction and addressing it by eliminating redundant tissue in the palate, oropharynx, and tongue base, or more recently by reconstructing the palatine and pharyngeal musculature. However, clinically, patient-specific multilevel surgery is not generally used; instead, UPPP is commonly applied (Huntley et al., 2021).

Although these surgical approaches have proven effective for certain individuals, they have been less effective in terms of achieving a consistent and long-lasting reduction in AHI, particularly in patients diagnosed with moderate-to-severe OSA (Sundaram et al., 2005). Moreover, the potential advantages of conventional surgical interventions targeting the upper airway should be carefully assessed in relation to their associated risks and morbidity. This is particularly important considering the limited availability of reliable data and variability of surgical procedures. The upper airway and pharynx are sensitive areas, and complications arising from surgical procedures may be irreversible, further emphasising the need for caution when considering these interventions.

In the present study, HNS showed equal or superior results to other conventional upper airway surgeries. Additionally, the overall postoperative AHI was significantly lower in the HNS group than in all other airway surgery groups. It is noteworthy that HNS can be distinguished from alternative airway surgical interventions, including UPPP, expansion sphincter pharyngoplasty, and tongue base surgeries. HNS is only used in extrapharyngeal interventions, which minimises the risks of severe throat pain, bleeding, dysphagia, taste disturbances, and other unfavourable outcomes related to pharyngeal mucosal distortion.

In previous studies, conventional airway surgeries were associated with a respiratory distress rate of 11% and postoperative complication rates of 3%–5% (Brietzke et al., 2017). In contrast, HNS was not associated with either complication. The typical postoperative adverse effects associated with HNS are temporary tongue weakness and temporary dysphagia, occurring at a rate of 1%–2% (Heiser et al., 2019). Due to the low risk of postoperative morbidity and complications, hospital stays after HNS are shorter than those after traditional airway surgery (Gouveia et al., 2017; Kezirian et al., 2004). Moreover, unlike most pharyngeal surgeries, HNS is reversible (Dedhia et al., 2015).

Hypoglossal nerve stimulation can be optimised through titration while performing PSG. Therefore, unlike traditional airway surgeries, where the results of surgery are difficult to predict, it is possible to adjust the treatment according to the patient's condition, similar to CPAP. The adaptability and adjustability of the treatment may aid the long-term management of sleep apnea as the patient's condition and needs evolve over time. Assessment of the device in the office setting could offer insight into the number of hours of usage and stimulation settings, similar to downloadable CPAP data.

This review had some limitations. First, half of the included studies were retrospective, and RCTs were scarce; thus, there is a possibility of selection bias. Second, the outcomes of the analysed studies may have been influenced by various factors, including the patients' baseline characteristics, implant types, and operator expertise. Additionally, preoperative management, postoperative care, and patient adherence to treatment may have varied across the studies, thus increasing heterogeneity. However, controlling for all of these variables in the context of a meta-analysis is impractical. To overcome this limitation, further clinical trials employing comparable treatment protocols are necessary. Third, differences in postoperative follow-up PSG methods among reports may have increased heterogeneity. Fourth, performing titration can affect the compliance of PSG, but in the studies that we included, the reports reporting CPAP results lacked mention of whether titration was performed. Lastly, most subjects in the included studies were from Western countries. As upper airway anatomy can differ at the skeletal level, studies that take these differences into account are needed for generalizability of the results.

## 5 | CONCLUSIONS

Hypoglossal nerve stimulation could be an effective alternative option for patients with moderate-to-severe OSA who are intolerant to CPAP.

### AUTHOR CONTRIBUTIONS

**Do Hyun Kim:** Methodology; investigation; funding acquisition; writing – original draft; writing – review and editing; project administration; visualization. **Sung Won Kim:** Conceptualization; supervision; writing – review and editing; funding acquisition; investigation. **Jae Sang Han:** Methodology; data curation; investigation; validation; writing – review and editing. **Geun-Jeon Kim:** Methodology; validation; investigation; writing – review and editing; data curation; formal analysis. **Jeong Hae Park:** Methodology; validation; writing – review and editing; investigation; data curation; resources. **Mohammed Abdullah Basurrah:** Investigation; methodology; validation; writing – review and editing; data curation. **Sun Hong Kim:** Methodology; validation; writing – review and editing; investigation; data curation. **Se Hwan Hwang:** Conceptualization; supervision; visualization; writing – review and editing; funding acquisition; project administration.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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