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Hypoglossal nerve stimulation for obstructive sleep apnea in adults: An updated systematic review and meta-analysis

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ABSTRACT

Objectives: This study aims to evaluate the efficacy of Apnex, Inspire, and ImThera hypoglossal nerve stimulation (HGNS) devices in changing the severity of obstructive sleep apnea (OSA).

Method: ology: A systematic search was conducted across the databases to collect baseline and postoperative outcome measures. Articles were then filtered and data from post-filtration was extracted. The efficacy of each device was assessed individually, and the reported outcomes were analyzed at short-term (≤1 year) and long-term (>1 year) intervals.

Results: A total of 30 papers were included; 26 were single-arm studies encompassing 549 middle-aged overweight patients. Four RCTs included 273 participants. Results show that HGNS is an effective and safe treatment option. The Inspire device significantly improved, reducing the apnea-hypopnea index (AHI) by −20.14 events/h in the short term and −15.91 events/h in the long term. It also decreased the oxygen desaturation index (ODI) by −14.16 events/h (short term) and −12.95 events/h (long term). Patient-reported outcomes showed decreased Epworth Sleepiness Scale (ESS) scores by −5.02 (short term) and −4.90 (long term) and improved Functional Outcomes of Sleep Questionnaire (FOSQ) scores by 3.58 (short term) and 3.28 (long term). The Apnex and the ImThera devices featured similar improvements but to a lesser extent.

Conclusion: Hypoglossal nerve stimulation is a safe and effective treatment for patients with OSA, exhibiting high adherence and satisfaction rates. However, it is important to note the potential for refining selection criteria to include a wider spectrum of patients with OSA.

1. Introduction

Obstructive Sleep Apnea (OSA) is a sleep-related breathing disorder characterized by recurrent upper airway obstruction during sleep resulting from insufficient motor tone in the tongue and/or airway dilator muscles [1]. It manifests as an airflow interruption lasting at least 10 s (apnea) or a significant but incomplete flow reduction associated with desaturation, arousal, or both (hypopnea) [2]. It causes several complications, including hypoxemia, hypercapnia, and intrathoracic pressure changes [3–5]. OSA is a common and underdiagnosed medical condition [6].It affects 26 % of individuals between 30 and 70 years in the U.S [7]. Benjafield et al. reported that approximately 1 billion adults aged 30–69 years have mild to severe OSAS, and 425 million adults aged between 30 and 69 years have moderate to severe OSAS globally [8]. The prevalence of OSA is increasing worldwide, matching the increased prevalence of obesity around the globe [9,10].

Polysomnography (PSG) is the gold standard diagnostic test for OSA. It quantifies the number of obstructive airway events per sleep hour,

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known as the Apnea-Hypopnea Index (AHI). An AHI of less than 5 events per hour is considered normal, indicating the absence of significant obstructive sleep-disordered breathing [11]. It also assesses the Oxygen Desaturation Index (ODI), which measures the frequency of oxygen desaturation events during sleep. ODI quantifies the number of times per hour that the oxygen saturation level drops by a predetermined threshold, reflecting the severity of OSA [12].

Patient-reported outcomes (PROs) have an important role in evaluating the impact of OSA on patients' daily activities and quality of life. There are 2 widely used questionnaires for assessing (PROs). Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ). ESS measures the subjective tendency to sleep during the day in various situations providing valuable insights into the severity of daytime sleepiness [13]. FQSQ is a multidimensional questionnaire that assesses functional impairments across several domains including general productivity, vigilance, social interactions, mental and physical activities, driving as well as sexual and emotional wellbeing [14].

Currently, there is no effective pharmacotherapy for OSA [15] Treatment options range from Continuous Positive Airway Pressure (CPAP) therapy and Mandibular Advancement Devices (MADs) to surgical interventions [16]. CPAP is more effective than MAD in reducing AHI, Oxygen Desaturation Index (ODI), and daytime sleepiness [17]. It is considered the gold standard for OSA treatment and is the first-choice treatment for patients with moderate to severe OSA [18].

Hypoglossal Nerve Stimulation (HNS) was first described in 2001 and was successfully used to decrease OSA severity in a small patient cohort [19]. The contraction of the upper airway dilator muscles, primarily the Genioglossus (innervated by the Hypoglossal Nerve, Cranial Nerve XII), maintains upper airway patency [20], which enhances upper airway neuromuscular tone and reduces the collapsibility that occurs with OSA [21]. HNS is indicated in patients with moderate to severe OSA who have been non-adherent or intolerant of CPAP and have a BMI of $\leq$32 kg/m^2 [17].

Clinical results have been published on different HNS systems, each working via a different mechanism. In 2011, Apex Medical reported a significant decrease in symptoms and OSA severity following implantation with their system (HGNS, Apnex Medical Inc., St. Paul, MN, USA), but this device did not enter clinical practice. The Inspire Medical System® (Inc., Maple Grove, MN) stimulates the genioglossus muscle fibers of the tongue and is currently the only FDA-approved HNS device for OSA. The ImThera® system stimulates both tongue protrusors and retractors to stiffen the posterior aspect of the tongue and pharyngeal walls [20]. Recently, the new Genio™ system (Nyxoah SA, Mont-Saint-Guibert, Belgium) has been developed to stimulate both branches of the hypoglossal nerve. This system does not require any leads (connective wires between the sensor/cuff electrodes and the pulse generator) and necessitates only a single incision without any tunneling. Furthermore, the energy battery is placed externally [22].

The objective of this study is to perform a comprehensive systematic review and meta-analysis of all the available published clinical trials, to evaluate the efficacy and safety of (HGNS) therapy. The investigation aimed to assess both short-term and long-term outcomes associated with HGNS, to provide an updated thorough analysis of exciting evidence about this approach.

2. Methodology

2.1. Study design:

This research was conducted following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines, and the protocol was pre-registered on PROSPERO (CRD42024538949). The design of this research followed the PICOS framework as follows: Population (Patients with obstructive sleep apnea with failed continuous positive airway pressure (CPAP) therapy, Intervention (Hypoglossal nerve stimulator device (Apnex, Inspire, ImThera, Genio device: Nyxoah)), Comparator: post-implantation values in patients who received the implant was compared with their baseline values before implantation (in single-arm studies) or against a control group (in RCTs) which includes patients who did not receive the HNS implant or those who received the implant but have not had the device activated. Outcomes (polysomnography parameters (Apnea-Hypopnea Index (AHI), Oxygen Desaturation Index (ODI)) and patient-reported outcomes (Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ). Study design included (clinical trials; randomized and non-randomized).

2.2. Search strategy

On March 1, 2024, PubMed, Web of Science (WoS), ScienceDirect, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov were searched for studies reporting the implantation of HNS devices (Apnex, Inspire, ImThera, and Genio device: Nyxoah) in patients with OSA. The following keywords were used to identify relevant articles: (" Hypoglossal nerve stimulation" OR "upper airway stimulation" OR "inspire upper airway stimulation" OR "Hypoglossal stimulator device" OR "HGNS" OR "Implantable Neurostimulator "OR "Electrical Stimulation Therapy" OR "Electrotherapy") AND ("Obstructive Sleep Apnea" OR "Sleep Hypopnea" OR "Sleep-Disordered Breathing" OR "Inadequate Sleep" OR "Insufficient Sleep" OR "Sleep Debt" OR "Sleep Fragmentation" OR "Obstructive Sleep Apnea Syndrome OR "Sleep Apnea Hypopnea Syndrome" OR "OSAHS" OR "Upper Airway Resistance OR "Nasal Airway Obstruction" OR "Sleep Disorders"). Additionally, Medical Subject Headings (MeSH) terms were used to identify all potentially relevant articles based on these indexed terms.

A manual search was also conducted following the screening of the articles to identify any potentially missing relevant articles through three approaches: (a)screening the reference list of the included articles, (b) screening "similar articles" to the included ones, through the "similar articles" options on PubMed, (c) reviewing the included articles in the previously conducted meta-analysis.

2.3. Eligibility criteria

Studies were included if they met the following criteria [1]: The recruited individuals were adults (>18y) with obstructive sleep apnea who received an implantation of one of the following devices: (Apnex, Inspire, ImThera, Genio device (Nyxoah), [2], Clinical trial studies, [3], English papers. No restrictions were set on the date of publication.

On the other hand, studies were excluded if they had one of the following criteria [1]:Patients receiving HNS by other means (not using the mentioned devices), [2],Non-clinical trial studies, [3],Patients with concurrent health conditions (e.g., Down syndrome), [4], Patients with other implantations (e.g., pacemakers), [5], Patients with special situations (e.g., veterans), [6], Pediatric patients, [7],Non-English papers, [8], Non-human models, [9], Unavailable full texts.

2.4. Study selection

Following retrieval of the studies from the database search, citations were imported to EndNote for duplication removal, after which, citations were exported into an Excel Sheet for screening. First, the titles and abstracts of retrieval studies were screened against our prespecified eligibility criteria. Then, potentially relevant studies underwent full-text screening. This process was carried out by two sets of two independent reviewers [M.S. and M.K.; S.O. and A.D.] and any discrepancies were solved through discussion with a third reviewer [W.A].

2.5. Data extraction

A pilot data extraction process was conducted using Google Forms to design the data extraction form. The extracted data was organized in a

Microsoft Excel spreadsheet. The form comprises five main sections. The first part includes the baseline characteristics of the included studies (name of the first author, year of publication, country, name of the journal, and the study design) and included participants (sample size, age, gender, BMI). The second part included data on the intervention (type of device, nightly hours of device usage, follow-up duration, and any co-interventions). The third part includes data on patients' history of OSA (type of apnea, duration of symptoms before treatment, diagnostic tools used for OSA, and any prior treatments (before HGNS therapy). The fourth part includes data on outcome measures post-implantation and at baseline (AHI, ODI, ESS, FQSQ). The fifth part includes data about the reported complications and adverse events, patient compliance with the treatment, and the changes in cardiovascular comorbidities (if reported). The data extraction process was carried out by two reviewers independently [W.A. M.S.M.K. S.O. and A.D.] and any conflict was resolved through discussion with the senior author.

2.6. Quality assessment

The methodological quality of the included studies was evaluated using the ROBINS-I tool for assessment of the non-randomized studies [23], while the Cochrane Risk of Bias Tool was used for assessment of the randomized controlled trials. This process was carried out by two sets of two reviewers [M.S. and M.K.; W.A. and A.D.] and any discrepancies were solved by group discussion.

2.7. Data synthesis

The collected data were quantitatively synthesized, and data regarding the primary outcomes (AHI, ODI) and secondary outcomes (ESS, FQSQ) were stratified into subgroups based on the specific HGNS device used (Apnex, Inspire, ImThera) The reported outcomes of each device were assessed at various follow-up duration. In studies that reported the outcomes at multiple visits, data from the last visit were included in the analysis. Given that the reported outcomes of the included studies were presented at different follow-up durations, these durations were categorized into short-term outcomes (one year or less) and long-term outcomes (more than one year). The analysis was conducted between post-implantation values and baseline measurements in single-arm studies. In randomized controlled trials (RCTs), the comparison was made between the study group (patients receiving the implant) and the control group (which includes patients without the hypoglossal nerve stimulation implant or those with an inactive device) In studies that reported the outcomes of interest in graphs, data were extracted with the help of Web Plot Digitizer [24] R version 4.3.1was used to calculate the treatment effect size [25,26]. Cochrane's χ^2 test (Cochrane's Q) and I^2 quantified heterogeneity. A fixed-effects model was used assuming similar effect sizes across studies. If significant heterogeneity is observed (χ^2 test $p < 0.1$, $I^2 > 50$ %), a random-effects model was applied. If heterogeneity persists, a meta-regression was conducted to explore potential sources of heterogeneity. Outcome measures were reported as mean and standard deviation (SD) or as median and interquartile range if not normally distributed. Qualitative variables were presented as counts and percentages. The qualitative synthesis included summarizing the occurrence of adverse events and complications of the procedure, we also summarized the adherence rate and the success rate among the included studies.

2.8. Publication bias

Publication bias was assessed using funnel plotting and publication bias testing (using both Eggers and rank correlation test) for outcomes with >10 studies according to Egger et al., 1997 [27].

3. Results

3.1. Search results

The systematic search resulted in a total of (854) papers, following the removal of 124 duplicates, the remaining 730 studies were screened by title and abstract. Subsequently, 216 potential full texts were assessed for eligibility resulting in a total of [30] met the predefined criteria. The PRISMA flowchart [28] illustrates the literature search, screening process, and reasons for exclusion (Fig. 1).

3.2. Baseline characteristics of the included studies

A total of 30 papers (26 single-arm studies and 4 RCTs) were included in the analysis. The total sample size across these studies was 867 patients. The study population predominantly consisted of middle-aged (mean = 55 ± 9.2), overweight (mean BMI = 29 ± 3.9) patients. with a male-to-female ratio of 4:1. In the single-arm studies the average follow-up duration was 14 ± 12.6 months, with a median of 12 months and a range of 6–60 months. The duration of the randomized phase varied across studies. For instance, the study conducted by Schwartz AR in 2023 had a randomization phase of 16 weeks, while the studies conducted by Heiser C in 2021 and Woodson BT in 2014 both had a randomization phase of 1 week. The fourth RCT was included only in the qualitative analysis. The general characteristics of the included studies are summarized in Table 1. The inclusion and exclusion criteria for each study are illustrated in Table 1 in Supplementary Material 1.

3.3. Outcome assessment

The effectiveness of each device was evaluated using polysomnography parameters, primarily the Apnea-Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI). Secondary outcomes were assessed to determine the impact of the therapy on quality of life, using the Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ). The analysis was conducted between post-implantation values and baseline measurements in single-arm studies and between the study group and the control group in the RCTs. The safety of the procedure was qualitatively assessed by summarizing the reported adverse events. Both baseline and post-implantation values, in addition to the success rate and adherence to therapy, are reported in Table 2. Risk of bias summary using the ROBIN-1 tool and Cochrane Risk of Bias Tool are depicted in Figs. 2 and 3 respectively. Reported adverse events as well as quality assessment details of the included studies are illustrated in Tables 2 and 3, in Supplementary Material 1.

4. Quantitative analysis

4.1. Assessment of (AHI) at short term

Using the random effects model, we observed a significant mean difference in the (AHI) in the short term (MD: −20.11; (95 % [CI]: −23.13 to −17.10)). Detailed analysis of the subgroups revealed the following mean differences for each device: (Inspire: (MD: −20.15; (95 % [CI]: −23.55 to −16.74)), Apnex: (MD: −21.66; (95 % [CI]: −28.74 to −14.58)), ImThera: MD: (−18.30; (95 % [CI]: [−35.65 to −0.95])). Significant heterogeneity was detected across the subgroups, with an I^2 statistic of 66 % (P-value <0.01) as illustrated in Fig. 4.

4.2. Assessment of (ODI) at short term

Using the random effects model, we determined that the overall mean difference in (ODI) reduction across the studies included was (MD: −13.05; (95 % [CI]: −18.44 to −9.66)). The subgroup analysis yielded the following mean reductions: Inspire: (MD: −14.13; (95 % [CI]-18.35 to −9.90)), Apnex: (MD: −6.38; (95 % [CI]: −13.06 to 0.30)), ImThera:

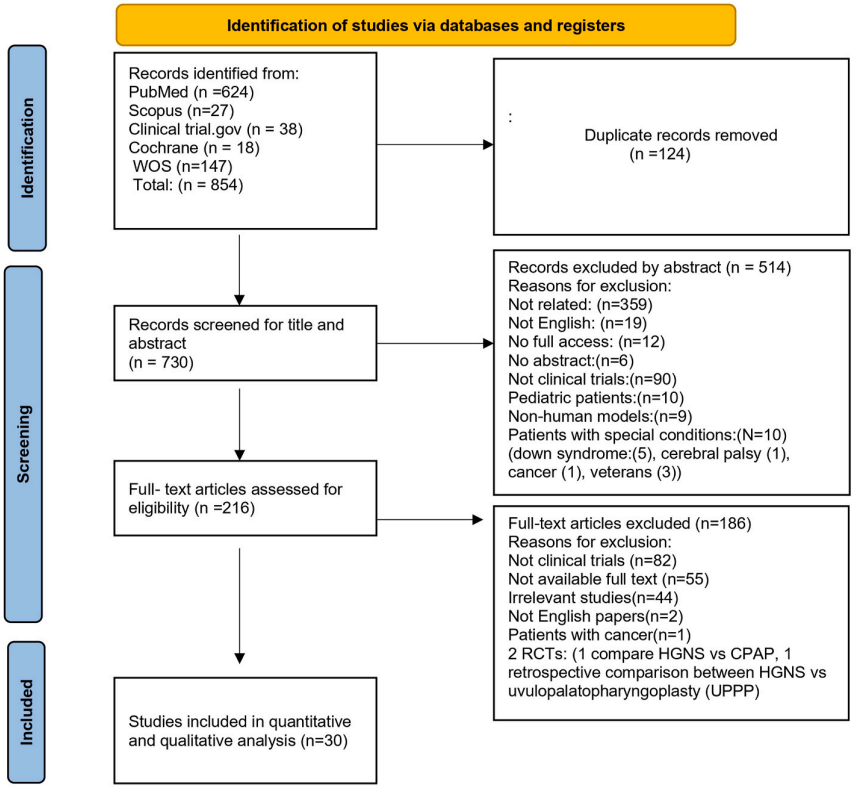

Fig. 1. PRISMA chart of study filtration and inclusion.

(MD: −12.47; (95 % [CI]: −18.96 to −6.51)). Significant heterogeneity was observed among the subgroups, as indicated by an I^2 statistic of 65 % (P-value <0.01) as illustrated in Fig. 5.

4.3. Assessment of (ESS) at short term:

Using the random effects model, we found a significant reduction in the (ESS) score across the included studies, the overall mean difference in ESS score reduction was (MD: −5.06; (95 % [CI]: −5.79 to −4.33)). The subgroup analysis yielded the following results: Inspire: (MD: −5.49; (95 % [CI]: −6.33 to −4.64)), Apnex: (MD: −4.13; (95 % [CI]: −5.81 to −2.44)), ImThera: (MD: −3.43; (95 % [CI]: −5.12 to −1.73)). No significant heterogeneity was detected across the studies, as indicated by an I^2 statistic of 38 % (P-value = 0.07) as illustrated in Fig. 6.

4.4. Assessment of (FQSQ) at short term:

Using the fixed effects model, we observed a significant improvement in the (FOSQ) score among patients who underwent HGNS therapy across the studies included. The overall mean difference was (MD: 3.28; (95 % [CI]: 2.81 to 3.75)). Analysis for each device individually revealed the following: Inspire: (MD:3.58; (95 % [CI]: 3.02 to 4.15)), Apnex: (MD: 2.59; (95 % [CI]: 1.75 to 3.43)). No data was available regarding the ImThera devices. No significant heterogeneity was detected among the subgroups, as indicated by an I^2 statistic of 56 % (P-value = 0.06) as illustrated in Fig. 7.

4.5. Assessment of (AHI, ODI, ESS) at long term:

Using the random-effects model to evaluate the longitudinal outcomes in patients undergoing HGNS therapy, we observed a statistically significant improvement in the long-term outcomes. This improvement is evidenced by a significant reduction in the AHI, ODI, and ESS scores. The available studies predominantly focus on the Inspire device, with a lack of data concerning the long-term outcomes associated with the Apnex and ImThera devices. The total mean reduction in AHI was (MD: −15.60; (95 % [CI]: −21.72 to −9.48)). Concurrently, the total mean reduction in ODI was (MD: −12.75; (95 % [CI]: −18.91 to −6.58)). The ESS score exhibited a total mean reduction of (MD: −4.86; (95 % [CI]: −5.42 to −4.29)). Significant heterogeneity was observed among the studies reporting the AHI and ODI indices, as indicated by an I2 statistic of 87 % (P < 0.01) and 82 % (P < 0.01), respectively. However, the studies reporting the ESS score did not exhibit significant heterogeneity, with an I^2 value of 22 % (P = 0.26) as illustrated in Fig. 8.

4.6. Assessment of (FQSQ) at long term:

Using the common-effects model, we observed a statistically significant improvement in the (FQSQ) score. The mean difference was (MD:3.28; (95 % [CI]: 2.99 to 3.67)). No significant heterogeneity was detected, as evidenced by I^2 statistic of 0, (P = 0.56). It is of note that all studies reporting the FQSQ outcome originated from the Stimulation Therapy for Apnea Reduction (STAR) study, with various follow-up durations, as illustrated in Fig. 9.

4.7. Assessment of (AHI, ODI, ESS, FQSQ) in randomized controlled trials:

Three Randomized Controlled Trials (RCTs) were identified in the literature that compared HGNS therapy with a control group (the fourth RCT was not included in the quantitative analysis) [56]. Each study incorporated a randomized phase as part of the clinical trial, where patients with implanted devices were randomized into either a device "ON" group or a device "OFF" group, as conducted by Schwartz AR et al.

Table 1
General characteristics of the included studies.

Study, Year	Device	Sample size analyzed	Age mean ± SD	Mean BMI ± SD
Schwartz AR, 2001 [28]	inspire	8	49.9 ± 8.1	28.4 ± 4.5
Steffen A, 2017 (German post market study 12 months) [38]	Inspire	1y = 56	56.8 ± 9.1	28.8 ± 3.6
Steffen A.2020 (German post-market study, 3 years [39])	Inspire	2y = 41, 3y = 38	56.8 ± 9.1	28.8 ± 3.6
Heiser C,2016 (German post-market study, 6 months) [40]	Inspire	initial 60, M6 = 56	56.8 ± 9.1	28.8 ± 3.6
Heiser C, 2017[41]	inspire	31	59.6 ± 10.9	28.8 ± 3.1
Steffen A,2022 [42]	Inspire	29	53.07 ± 8.16	29.21 ± 4.41
Steffen A.2017 [43]	Inspire	35	57 ± 9.3	28.4 ± 4.8
Steffen A,2019 [44]	Inspire	25	52.6	29.4 ± 4.9
Heiser C,2017 [45]	Inspire	20	57 ± 12	28.1 ± 13.1
Eastwood PR,2011 [46]	Apnex	21 (at 6-month n = 19, at 3months n = 17)	53.6 ± 9.2	32.7 ± 3.6
Eastwood PR.2020 [31]	The Genio™ system	22	55.9 ± 12)	27.4 ± 3
Strollo PJ Jr,2015 (STAR trial, 18 months) [47]	Inspire	M18 = 123	54.5 ± 10.2	28.4 ± 92.6
Strollo PJ Jr, 2014 (STAR trial,12 months) [48]	Inspire	initial = 126, M12 = 124	54.5 ± 10.2	28.4 ± 92.6
Woodson BT, 2016 (STAR trial, 3 years) [49]	Inspire	M24 = 111, M36 = 116,	54.5 ± 10.2	28.4 ± 92.6
Woodson BT, 2018 (STAR trial, 5 years) [50]	Inspire	M60 = 97	54.5 ± 10.2	28.4 ± 92.6
Gillespie MB,2017 (STAR trial, 4 years) [51]	Inspire	M48 = 91	54.5 ± 10.2	28.4 ± 92.6
Philip P, 2018 [52, 53]	Inspire	10	52 ± 9.4	28.8 ± 3.3
Bachour A,2020 [54]	Inspire	15	53 ± 6	29.7 ± 1.3
Zhu Z, 2018 [55]	Inspire	31 M6 = 27, M12 = 25	70 ± 9.1	30.1 ± 3.8
Pries R,2022 [52]	inspire	16	56.8-	29 ± 3.9
Schwab RJ, 2018 [56]	Inspire	13	53 ± 15	27.77 ± 1.57
Van de Heyning PH,2012 (part I) [57]	Inspire	20	55.7 ± 8.1	29.8 ± 2.7
Van de Heyning PH,2012 (part II) [57]	Inspire	8	53.6 ± 11.9	28.9 ± 2.1
Mwenge GB,2013 [58]	ImThera aura6000	10	50.3 ± 9.6	31 ± 3
Friedman M, 2016 [59]	ImThera aura6000	initial 47, M6 43	54.9 ± 11.1	30.8 ± 3.7
Kezirian EJ,2014 [60]	Apnex	31	52.4 ± 9.4	32.4 ± 3.6
Vanderveken OM,2013 [61]	Inspire	16	55 ± 11	28 ± 2
Schwartz AR,2023 [62]	ImThera	92 treatment, 46 control	58.3 treatment, 56.6 control	29.94 treatment, 29.62 control
Heiser C, 2021[63]	Inspire	43 treatments, 43 controls	58.3 treatment, 56.6 control	29.2 treatment, 29.5 control
Woodson BT,2014 [64]	Inspire	23 treatments, 23 controls	57.1 Treatment, 52.7 control	10.0 Treatment, 10.4 control
Dedhia RC.2019 [65]	Inspire	16 treatments, 16 withdrawals	54 ± 11	28 ± 2

OSA: obstructive sleep apnea SD: standard deviation, CPAP: continuous positive airway pressure, BMI: body mass index, CCC: complete concentric collapse, DISE: drug induced sleep endoscopy, COPD: chronic obstructive pulmonary disease, MI: myocardial infarction, CSA: central sleep apnea, NYHA: New York Heart Association.

[53]. Alternatively, after a period of device activation, patients were randomized into a "therapy maintenance" group or a "therapy withdrawal" group, as conducted by Heiser C et al. [54] and Woodson BT et al. [55]. All included RCTs used the Inspire device, with the exception of the study conducted by Schwartz AR et al., which used the ImThera device. All reported outcomes were short-term outcomes. We used a random-effects model for the analysis of AHI, ODI, and ESS outcomes (Figure (10)), and the FQSQ outcome (Figure (11)). We observed a significant improvement in the reported outcomes in the treatment group compared to the control group. The mean difference of AHI reduction was (MD: −11.08; (95 % [CI]: −14.21 to −7.19)). For ODI, the mean difference was (MD: −12.16; (95 % [CI]: −17.96 to −6.83)). For ESS, the mean difference was (MD: −4.36; (95 % [CI]: −5.20 to −3.51)). The improvement of the FQSQ score had a mean difference of (MD:1.48; (95 % [CI]: 0.48 to 2.51)). No significant heterogeneity was detected, as indicated by the I2 statistics of 33 % (P = 0.22), 15 % (P = 0.28), 0 % (P = 0.87), and 0 % (P = 0.69) for AHI, ODI, ESS, and FQSQ, respectively.

4.8. Publication bias assessment

Publication bias assessment was conducted using funnel plotting and statistical tests, including Egger's regression test and rank correlation test, for outcomes with more than 10 studies, specifically AHI, ODI, and ESS at short-term period. It is important to note that the assessment of publication bias for the long-term period (Fig. 6) was not conducted due to the fundamental differences in the outcomes and the unavailability of sufficient studies (<10 studies for each outcome) to assess each outcome individually. The funnel plots visually examined the symmetry of the data distribution and indicated no evidence of publication bias for all the assessed outcomes. Moreover, the rank correlation test and Egger's test confirmed the absence of bias. Detailed information regarding the assessment of publication bias for each outcome is provided in Supplementary Material 2.

4.9. Heterogeneity assessment

In this study, a comprehensive meta-regression analysis was conducted to investigate the relationship between various predictors and the effect size of studies evaluating AHI, ODI, and ESS at both short-term and long-term follow-up periods. Each group of studies was analyzed separately to assess the impact of baseline sample size, post-implantation sample size, mean BMI, mean age, and duration of follow-up on the effect size. The results revealed that none of these predictors exhibited a significant influence on the effect size across all groups in the short-term outcomes (all p-values >0.05). However, in the long-term evaluation of the AHI outcome, both mean age and mean BMI of the participants were found to significantly influence the effect size. Conversely, none of the predictors demonstrated a significant influence

Table 2
Clinical outcomes of each study.

Study	Follow up duration	AHI- pre	AHI-post	ODI-pre	ODI-post	ESS-pre	ESS-post	FQSQ-pre	FQSQ-post	response rate[a]	adherence
Schwartz AR, 2001 [28]	6 months	51.6 ± 21.8	22.6 ± 16.7								
Steffen A, 2017 (German post-market study,12 months) [38]	12 months	31.2 ± 13.2	13.8 ± 14.8	27.6 ± 16.4	13.7 ± 14.9	12.4 ± 5.7	6.5 ± 4.5	13.2 ± 3.6	17.5 ± 3	73 %	43.4 ± 13.6 h/ week
Steffen A.2020 (German post-market study,3 years) [39]	2 years		28.9 ± 13.8		24.8 ± 17		5.3 ± 4.6			76 %	40.3 ± 14.7 h/ week
	3 years		30 ± 13.7		25.8 ± 16.7		6 ± 3.2			62 %	41.0 ± 13.9 h/ week
Heiser C,2016 (German post-market study,6 months) [40]	6 months		15.6 ± 16.46		13.22 ± 18.68		8.41 ± 4.31			68 %	42.9 ± 1.9 h/week
Heiser C, 2017 [41]	2 months	32.9 ± 11.2	11.5 ± 14.1	30.7 ± 13	13.7 ± 12.2	12.6 ± 5.6	8.6 ± 5				
	3 months		10.3 ± 13		13.8 ± 13.8		6.8 ± 4.8				
	6 months		7.6 ± 5.3		11.7 ± 8.8		5.9 ± 4.8			96.8 %	6.0 ± 2.2 h/night
	12 months		7.1 ± 5.9		9.9 ± 8		5.9 ± 5.2			96.8 %	
Steffen A,2022 [42]	6 months	25.92 ± 8.4	15.6 ± 16.46	14.21 ± 7.97	13.22 ± 18.68	13.72 ± 4.33	8.41 ± 4.31				5.56 ± 1.76 h/ night
Steffen A.2017 [43]	12 months	36 ± 12.1	7 ± 23	27.3 ± 17.3	5.1 ± 15.5	13 ± 3.3	8 ± 4			82.9 %	
Steffen A,2019 [44]	12 months	32.8 ± 15.4	13.6 ± 17.5	20.1 ± 18.5	10.3 ± 17.3	12.5 ± 4.9	6.6 ± 4.3			84.0 %	
	2 years		11.2 ± 10		10.7 ± 13.1		5.4 ± 3.9			80.0 %	
Heiser C,2017 [45]	12 months	28.9 ± 7.6	6.6 ± 5.1							74 %	
Eastwood PR,2011 [46]	3 months	43.1 ± 17.5	19 ± 10.7	16.8 ± 14.4	8 ± 7.8	12.1 ± 4.7	7.9 ± 4	14.4 ± 2	17 ± 2		
	6 months		19.5 ± 16.7		9.1 ± 16.7		8.1 ± 4.4		16.7 ± 2.2	67 %	5.8 ± 1.6 h/night
Eastwood PR.2020 [31]	6 months	23.7 ± 12.2	12.9 ± 10.1	19.1 ± 11.2	9.8 ± 6.9	11 ± 5.3	8 ± 5.4	15.3 ± 3.3	17.2 ± 3	57.9 %	91 % reported adherence >5 days a week and 77 % reported a nightly use of >5 h per night.
Strollo PJ Jr,2015 (STAR trial) [47]	18 months	32 ± 11.8	14.1 ± 14.4	28.9 ± 12	12.7 ± 15.5	11.6 ± 5	7 ± 4	14.3 ± 3.2	17.3 ± 3	64 %	
Strollo PJ Jr, 2014 (STAR trial) [48]	12 months	32 ± 11.8	15.3 ± 16.1	28.9 ± 12	13.9 ± 15.7	11.6 ± 5	7 ± 4.2	14.3 ± 3.2	17.3 ± 2.9	66 %	
Woodson BT, 2016 (STAR trial) [49]	3 years	32 ± 11.8	11.5 ± 13.9	28.9 ± 18.2	9.1 ± 11.7	11.6 ± 5	7 ± 5	14.3 ± 3.2	17.4 ± 3.5	74 %	
Woodson BT, 2018 (STAR trial) [50]	5 years	32 ± 1.8	12.4 ± 16.3	28.9 ± 18.2	9.9 ± 14.5	11.6 ± 5	6.9 ± 4.7	14.3 ± 3.2	18 ± 2.2	75 %	
Gillespie MB,2017 (STAR trail) [51]	4 years	32 ± 11.8	11.5 ± 14			11.6 ± 5	7.3 ± 4.9	14.3 ± 3.2	17.5 ± 2.9		

(*continued on next page*)

Table 2 (*continued*)

Study	Follow up duration	AHI- pre	AHI-post	ODI-pre	ODI-post	ESS-pre	ESS-post	FQSQ-pre	FQSQ-post	response rate[a]	adherence
Philip P, 2018 [53]	6 months	46.7 ± 12.2	14.5 ± 8.9	38.1 ± 21.2	10.5 ± 9.9	15.9 ± 3.5	10 ± 6.1				
Bachour A,2020 [54]	18 months	29.2 ± 14	27.3 ± 23.3	20.9 ± 19.3	16.5 ± 17.3	11 ± 4.5	7.3 ± 5.2				3:35 ± 2:01 (hours: minutes) per day
Zhu Z, 2018 [55]	6 months	28.4 ± 10.6	6 ± 6.9	25.3 ± 13.2	5.5 ± 8.2	12 ± 5	7 ± 5.3				
	12 months		7.2 ± 4.6	7.3	4.5 ± 6	5				68 %	
Pries R,2022 [52]	6 months	33 ± 11.3	18 ± 16.7	19 ± 14.7	10 ± 13.7	14 ± 5.5	9 ± 5.2				45.8 h/ week
Schwab RJ, 2018 [56]	12 months	33.47 ± 10.42	21.36 ± 17.47								
Van de Heyning PH,2012 part I [57]	6 months	43.6 ± 18.4	41.6 ± 18.6	30.1 ± 24	41.3 ± 18.6					30 %	
Van de Heyning PH,2012 part II [57]	6 months	38.9 ± 9.8	10 ± 11	32.1 ± 15.1	9.5 ± 10.2					87.5 %	
Mwenge GB,2013 [58]	3 months	41.5 ± 13.1	14.3 ± 8.8	23.1 ± 10.2	7.6 ± 4.1	9.4 ± 4.4	5.6 ± 5.4				
	12 months		13.2 ± 5.5		7.8 ± 5.3		7 ± 4			76.9 %	
Friedman M, 2016 [59]	6 months	34.9 ± 2.5	25.4 ± 23.1	32.4 ± 22.3	23.6 ± 22.3	12 ± 4.8	8.3 ± 4.4			35 %	
Kezirian EJ,2014 [60]	6 months	45.4 ± 17.5	20.8 ± 17.6	20.9 ± 17.3	10.7 ± 17.1	12.1 ± 4.6	8.3 ± 3.6	14.2 ± 2	16.8 ± 2.4		
	12 months		25.3 ± 20.6		15.7 ± 19.6		7.9 ± 3.8		17 ± 2.4	55.%	
Vanderveken OM,2013 [61]	6 months	37.6 ± 11.4	11.6 ± 11.7			8.2 ± 5	6.4 ± 4.3			62 %	
Heiser C, 2021 [63]	1 week	Treatment 3.7 ± 8.5 control 6.9 ± 9.2	Treatment 10 ± 9 Control 21 ± 11.8			Treatment 7 ± 4.2 control 7 ± 4.6	Treatment 7.5 ± 4.9 control 12 ± 4.3	Difference in treatment 17.0 ± 3.2 Difference in control 14.9 ± 3.6	(Treatment group 73.3 % control group 29.5 %)[b]		
Schwartz AR,2023 [62]	4 months	Treatment 39.2 ± 10.1, control 35.4 ± 8.8	Treatment 24.1 ± 20.04 control 32 ± 16.78	Treatment 37.9 ± 10.11 control 36 ± 9.5	Treatment 26.3 ± 20.4 control 33.8 ± 17.07	difference in treatment −4.4 ± 4.2 difference in control −1.1 ± 3.5	Difference in treatment 2.5 ± 3.0 Difference in control 1.1 ± ± 3.2	52.3 %		82 % used the device 5 or more nights/w	
Woodson BT,2014[c] [64]	1 week	Treatment 7.2 ± 5 control 7.6 ± 4	Treatment 8.9 ± 9.1 control 25.8 ± 16	Treatment 6.3 ± 5.4 control 6 ± 3.7	Treatment 8 ± 8.9 control 23 ± 15.6	Treatment 5.9 ± 3.4 control 6.9 ± 4.6		Treatment 5.6 ± 3.9 control 10 ± 6		Treatment 17.9 ± 2.9 control 17 ± 3.5	
Dedhia RC.2019[c] [65]	1 week	Treatment 7 ± 5 Control 7 ± 4	Treatment 8.9 ± 9.1 control 25.8 ± 16								

IPG: implant pulse generator, AE; adverse events, AHI: apnea hypopnea index, ODI: oxygen desaturation index, ESS: Epworth Sleepiness Scale, FOSQ: Functional Outcomes of Sleep Quest.

[a] Calculated according to Sher criteria.

[b] Response rate was defined as AHI ≤15 (ITT), (not according to Sher criteria).

[c] The same study with different outcome of interest.

on the effect size of the ESS outcome at the long-term follow-up (all p-values >0.05). It is important to note that due to an insufficient number of studies available for the long-term evaluation of ODI, a meta-regression analysis could not be conducted (number of studies < number of moderators). Comprehensive results from the meta-regression analysis are provided in Supplementary Material 3.

4.9.1. *Safety profile:*

In the included studies, the majority of adverse events reported were non-serious. There were no instances of life-threatening complications or permanent impairment related to the procedure. Furthermore, no deaths attributable to the procedure were reported. The most frequently reported device-related non-serious adverse events were patients experiencing the stimulation sensation as “painful” or “uncomfortable”,

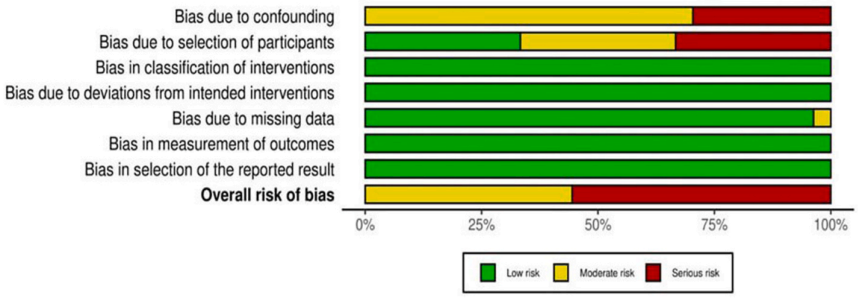

Fig. 2. Risk of bias summary for the non-randomized clinical trials using ROBIN-1 tool.

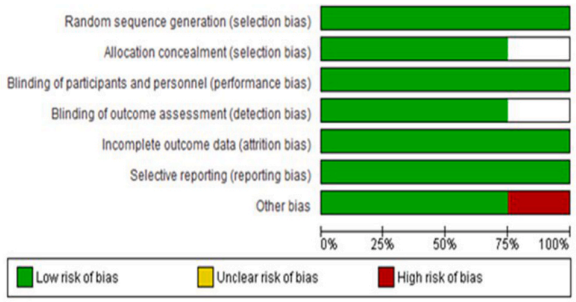

Fig. 3. Risk of bias summary for RCTs using Cochrane Risk of Bias Tool.

Table 3
Summarization of the reported adverse events.

Nature of the adverse events	Type of the adverse event	Percentage
Commonly reported adverse events	Perception of the stimulation sensation	33 %
	intermittent tongue sores and abrasions	27 %
	pain at the incision site	24 %
	numbness and paresthesia at the incision sites	13.2 %
	temporary tongue weakness	12.5 %
	bleeding	7 %
	postoperative infection	6 %
	device malfunction and cuff dislodgement	5 %
	postoperative hematoma	4 %
	anesthesia complications	1 %
Serious adverse events[a]	device malfunction	7.8 %
	painful stimulation	0.7 %
	pain	2.8 %
	infection	3 %
	hematoma and bleeding	2 %
	device migration	1.6 %
Less commonly reported non serious adverse events	dysarthria, local edema, painful swallowing, tongue fasciculation, the twiddler phenomenon, and fever	

[a] These adverse events were described as serious in their corresponding studies.

reported in 33 % of cases. However, this was temporary as patients acclimated to the therapy. The second most common non-serious adverse event was intermittent tongue sores and abrasions, primarily on the ventral surface of the tongue due to movement over mandibular dentition. These abrasions were transient and self-limited and were successfully managed in most cases with plastic dental guards. A detailed illustration of the reported adverse events is depicted in Table 3. More details regarding reported adverse outcomes for each study are illustrated in Table 2 in Supplemantary Material 1.

It is important to note that the incidence of adverse effects tends to be higher in the first year following the Hypoglossal Nerve Stimulation (HNS) procedure, with a significant decrease in the long term. The STAR trial, which represents the longest trial to date, reported that only 8 patients (6 % of the sample) experienced device-related adverse events. These events were primarily related to device malfunction, displacement, or cuff dislodgement, all of which were successfully managed through repositioning or replacement. Discomfort due to electrical stimulation was reported only 5 times during the fifth year, compared to 81 times during the first year. Additionally, tongue abrasion was reported 2 times during the fifth year, in contrast to 28 times in the first year. It appears that while adverse events can occur, the majority resolve and the overall safety profile of HNS appears favorable for OSA patients.

4.9.2. Adherence:

The included studies reported high adherence among patients to nightly HNS device use. On average, patients used the device for approximately 5.7 h per night, with a median of 5.8 h [IQR 6.1–5.4] hours. Notably, the STAR trial, reported patient self-reported rates of nightly device use as follows: 86 % at 1 year, 81 % at 3 years, 81 % at 4 years, and 80 % at 5 years.

4.9.3. Success rate

In the included studies the success rate among patients undergoing HNS therapy was defined according to the Sher criteria, which required a 50 % reduction in AHI and an overall AHI <20. Patients meeting these criteria were considered responders to therapy. In the included studies, the rates of responders among patients who received the Inspire device were as follows: 69.4 % at 6 months, 93.5 % at 12 months, 64 % at 18 months, 77 % at 2 years, 70 % at 3 years and 75 % at 5 years. For the Apnex device, the rates were 67 % at 6 months and 55 % at 12 months. And for ImThera device the rate of responders was 76.9 % at 6 months and 35 % at 12 months.

4.9.4. Genu device

A single clinical trial investigating the efficacy and safety of the Genu device was identified. The study, conducted by Eastwood PR et al., in 2020 [22] involved a cohort of 27 patients who were implanted with the device and followed up for 6 months. The mean age of the participants was 55.9 ± 12.0 years, and the mean BMI was 27.4 ± 3.0 kg/mˆ2. Of the initial cohort, only 22 patients completed the protocol. Significant improvements were observed in both PSG parameters and patient-reported outcomes. AHI decreased from 23.7 ± 12.2 to 12.9 ± 10.1 events/hour, representing a mean change of 10.8 events/hour ($p < 0.001$). ODI decreased from 19.1 ± 11.2 to 9.8 ± 6.9 events/hour a mean change of 9.3 events/hour ($p < 0.001$). ESS score decreased from 11.0 ± 5.3 to 8.0 ± 5.4, a mean change of 3.3 ($p = 0.011$), while the FOSQ-10 score increased from 15.3 ± 3.3 to 17.2 ± 3.0, a mean change of 1.9 (95 % [CI]: 0.4 to 3.4, median 1.0; $p = 0.016$). In terms of adherence, 91 % of patients reported using the device for more than 5 days a week, and 77 % reported nightly use of more than 5 h. No serious adverse events related to the device were reported during the 6-month post-implantation

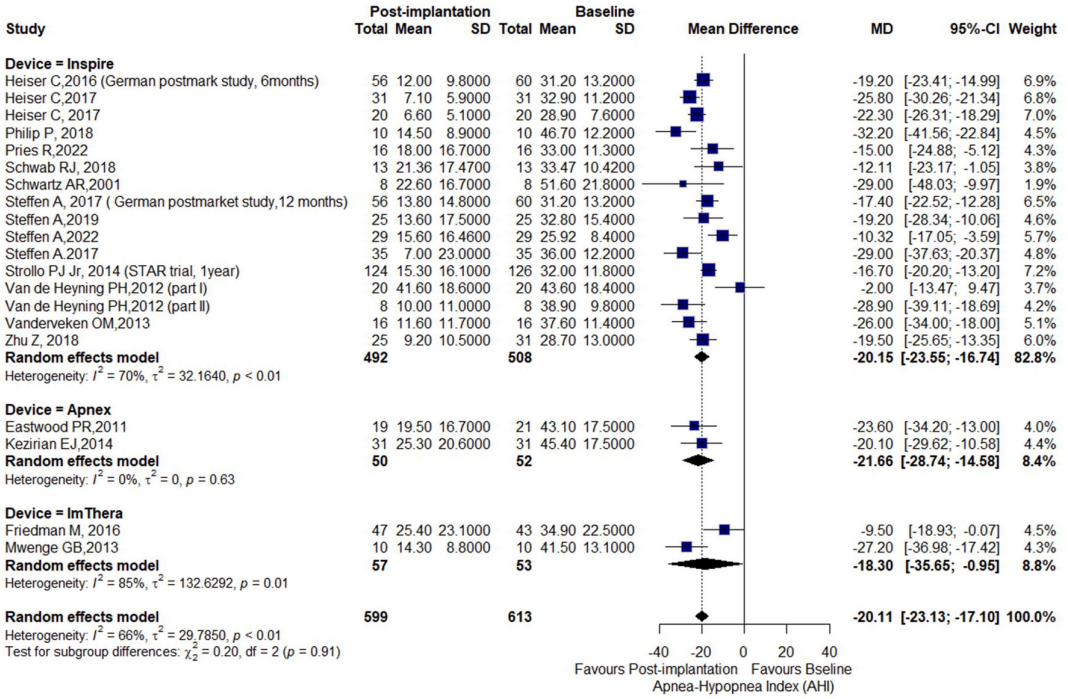

Fig. 4. Assessment of (AHI) at short term.

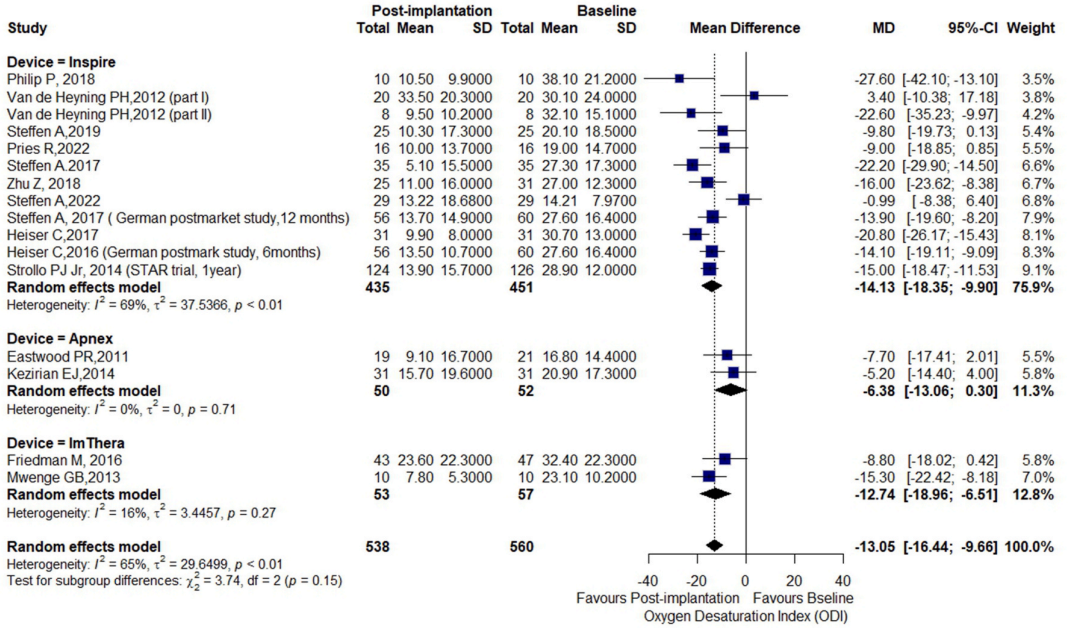

Fig. 5. Assessment of (ODI) at short term.

period. Further details regarding the reported adverse events are presented **in** Table (2) **in** Supplementary Material 1.

4.9.5. Effect of HGNS therapy on cardiovascular risk:

A secondary analysis of the STAR trial was conducted on a cohort of 46 patients, classified as responders based on Sher criteria [56]. This analysis aimed to investigate the impact of HGNS therapy on Heart Rate Variability (HRV), a recognized marker for autonomic dysfunction. The pathophysiological effect of OSA on adverse cardiovascular outcomes is primarily mediated by autonomic dysfunction, which is triggered by recurrent airway obstruction and cyclical hypoxia. During sleep, OSA patients experience spikes in sympathetic activity, leading to periodic elevations in blood pressure, thereby detrimentally impacting cardiovascular health. A moderate to strong correlation was observed between the reduction in Apnea-Hypopnea Index (AHI) and the improvement in HRV (r = 0.39, P = 0.03). The HRV during sleep exhibited a decrease

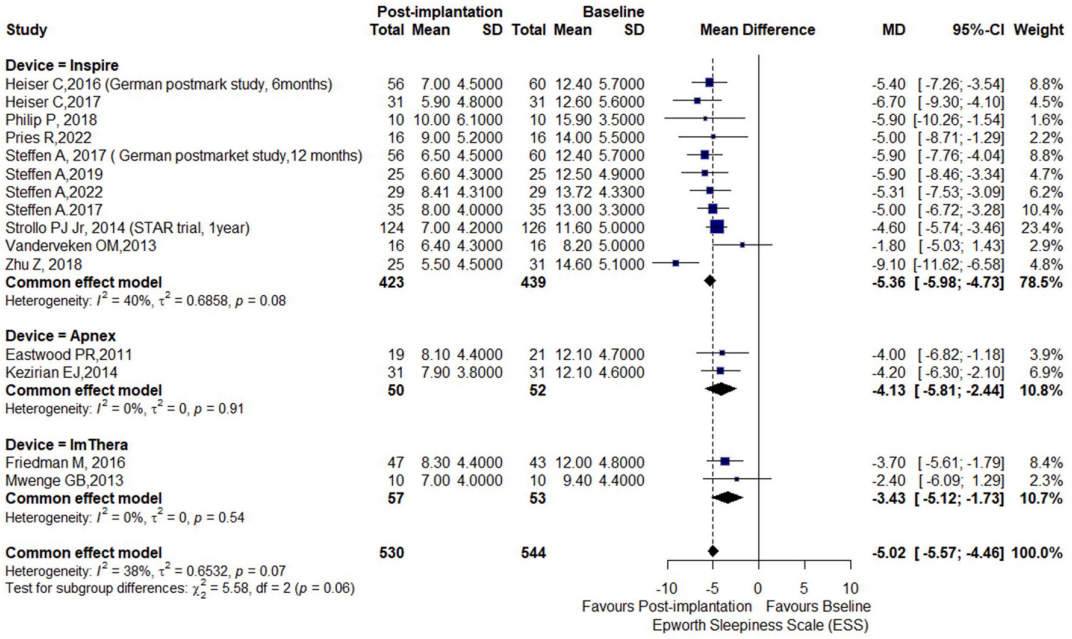

Fig. 6. Assessment of (ESS) at short term.

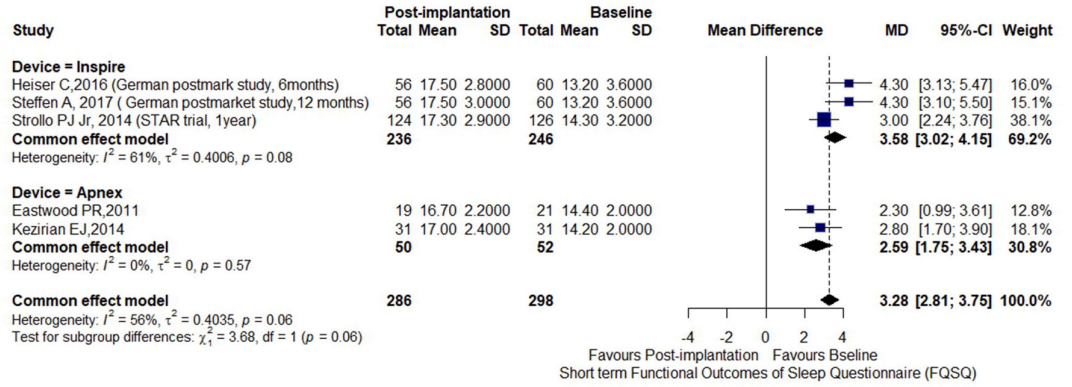

Fig. 7. Assessment of (FQSQ) at short term.

from (mean ± SD: 0.074 (0.025) to 0.065 (0.022) at the 12-month (p = 0.03), indicating the stabilization of HRV during sleep in this subset of responders from the STAR trial.

5. Discussion

This systematic review and meta-analysis of 30 clinical trials investigates the efficacy and safety of different hypoglossal nerve stimulation (HGNS) devices for patients with obstructive sleep apnea (OSA), who were intolerant to continuous positive airway pressure (CPAP) therapy. The results indicate that HGNS is an effective and safe treatment option for this population. The Inspire device showed significant improvements in key outcomes. In the short term, it reduced the AHI by −20.14 events per hour and in the long term by −15.91 events per hour. It also reduced the oxygen desaturation index ODI by −14.16 events per hour in the short term and by −12.95 events per hour in the long term. Patient-reported outcomes showed a decrease in the ESS score by −5.02 in the short term and by −4.90 in the long term, as well as an improvement in the FOSQ score by 3.58 in the short term and by 3.28 in the long term. Regarding the Apnex device, short-term results revealed reductions in AHI by −21.66 events per hour, ODI by −6.38 events per hour, and ESS by −4.13. The FOSQ score improved by 2.59. However, there was no available data on the long-term effects of the Apnex device on PSG parameters or patient-reported outcomes. For the ImThera device, the short-term reduction in AHI was −18.30 events per hour, ODI was −12.47 events per hour, and ESS was −3.43. No data was found regarding the effect of the ImThera device on the FOSQ score. It is noteworthy that no significant differences in efficacy were observed among the three devices. Our findings are consistent with previous meta-analyses examining the effects of HNS on OSA. Costantino et al. reported a significant reduction in AHI by −17.88 and a decrease in ODI by −14.79 at 12 months follow-up. Additionally, they noted an improvement in the ESS score, with a reduction of −5.01 at the same duration [57]. Similarly, a meta-analysis conducted by Certal et al. reported mean improvements in AHI, ODI, and ESS scores at 12 months of −17.51, −13.73, and −4.42, respectively [58].

Gaining insights from the patient's perspective and understanding the impact of treatment on patient-reported outcomes are vital aspects

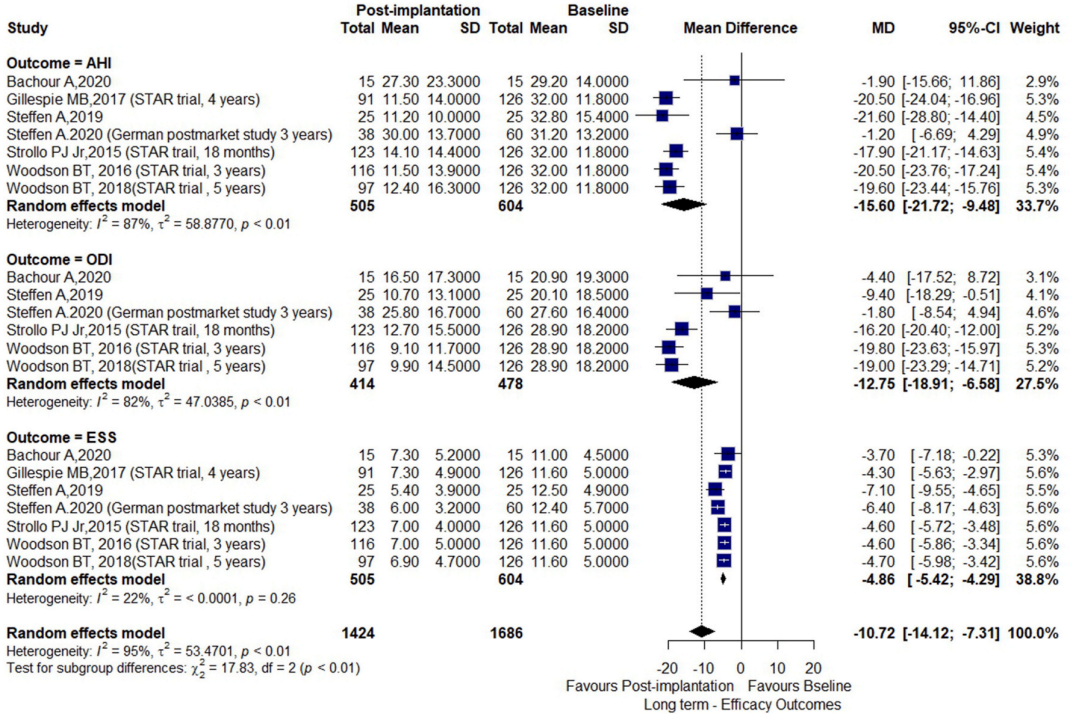

Fig. 8. Assessment of (AHI, ODI, ESS) at long term.

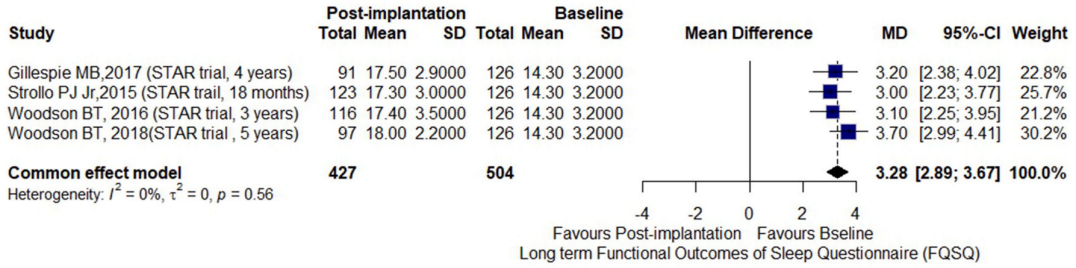

Fig. 9. Assessment of (FQSQ) at long term.

of clinical decision-making and assessing treatment effectiveness. A recent meta-analysis conducted by Braun et al. focusing on patient-reported outcomes found that the mean improvement in the ESS score was −4.59 and in the FOSQ score was 2.84, which are closely aligned with our study results [59]. It is worth noting that the observed reduction in ESS score with PAP treatment, as indicated by prior meta-analyses, is typically in the range of 2–3 points [60]. Thus, findings from Braun et al.'s meta-analysis demonstrate a more substantial improvement in ESS score, suggesting that HGNS therapy may offer a more effective alternative for patients who are intolerant to PAP therapy. Our study revealed highly favorable adherence rates among patients undergoing HGNS. The adherence rate was approximately 5.7 h per night, with a median of 5.8 h, which aligns with the findings reported by Costantino et al. in their meta-analysis (median usage of 5.8 h per night, IQR 5.5–6.2). Interestingly, the only clinical trial compared the efficacy of HGNS with CPAP showed higher mean disease alleviation (MDA) in the HGNS therapy group compared to the CPAP group (59 % vs. 51 %), although the treatment efficacy was higher in the CPAP group compared to the HGNS group (82 % vs. 76 %). These differences were attributed to the higher adherence rate in the HGNS group (5.04 ± 2.58 h/night) compared to the CPAP group (4.03 ± 2.12 h/night). Consequently, the HGNS group exhibited an overall remaining AHI of 14 events per hour of sleep after 12 months, while the CPAP group had 18 events per hour of sleep. This suggests that despite the superiority of CPAP in reducing the severity of OSA, its treatment benefits are limited by the low adherence rate compared to HGNS therapy [61].

Numerous scientific studies have provided evidence supporting the effectiveness of HGNS therapy compared to surgical modalities [62]. (63) [64](65). However, a study conducted by Steffen et al. suggests that in cases where patients with persistent OSA after upper airway stimulation (UAS) implantation exhibit obstruction at the level of the velum and oropharynx, an additional uvulo-palato-pharyngo-plasty procedure should be considered. This approach has shown higher response rates and better outcomes in patients undergoing HGNS therapy. It is important to note that this additional procedure is not indicated for all patients undergoing UAS therapy [35].

According to the FDA report, the criteria for patients undergoing HGNS therapy include moderate to severe OSA (AHI between 15 and 65), age >22 years, BMI <32 kg/m^2, and absence of complete concentric collapse (CCC) at the soft palate level [66]. It is important to note that despite meeting these criteria, approximately one third of patients in this study did not meet the criteria for responsiveness according to the

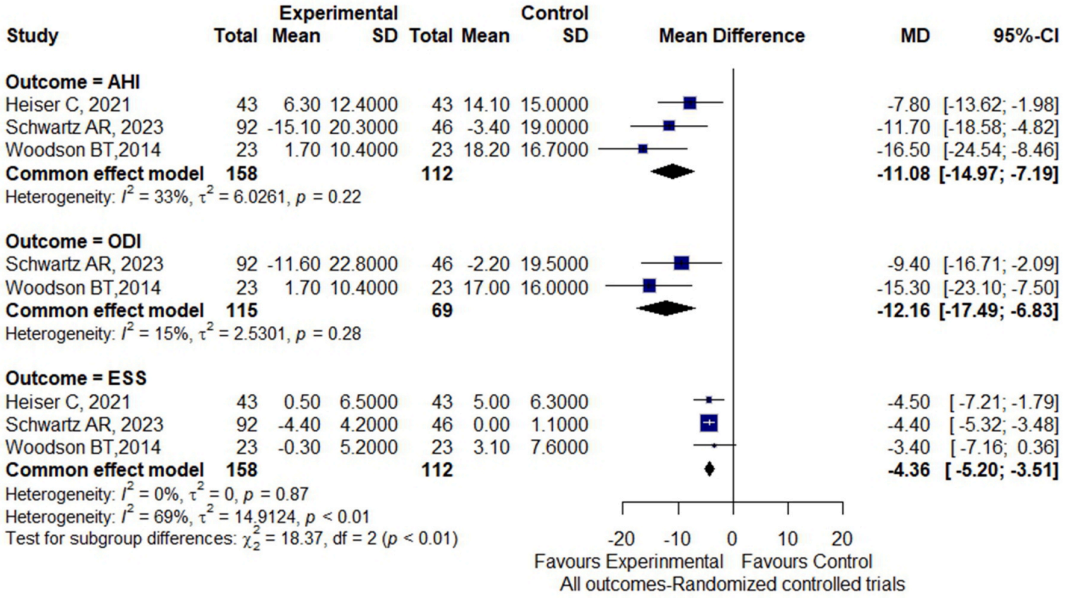

Fig. 10. Assessment of (AHI, ODI, ESS) in randomized controlled trials.

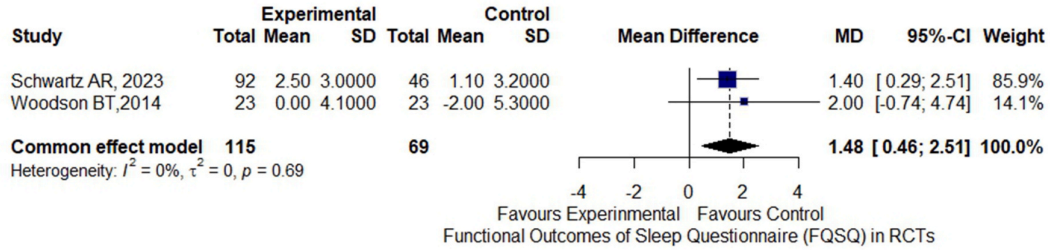

Fig. 11. Assessment of (FQSQ) in randomized controlled trials.

Sher criteria. This finding is consistent with the ADHERE registry, which reported that about one third of patients had residual OSA even after therapy [67]. Additionally, the German post-market study reported a 73 % participant response rate at 12 months [29] and the STAR trial reported a 66 % response rate in OSA [39]. It is evident that multiple factors influence the effectiveness of treatment modalities for OSA. Although these factors are not the primary focus of our study, a review of the literature and the papers included in our study provide some insights into these factors. Based on our findings, it seems that the effectiveness of the treatment is primarily influenced by individual patient factors, rather than the specific surgical procedure or type of device used. The ADHERE registry, the largest international observational study to date, provides valuable suggestions into these factors. The registry found that age was a statistically significant predictor of therapy success, with each one-year increase in age correlating with a 4 % increase in the odds of OSA treatment success. These findings align with a controlled clinical trial conducted by Zhu Z et al. which reported a significant reduction in AHI, ODI, and e ESS in patients aged over 64 years. The results were comparable to those of younger patients, despite the comorbidities associated with the elderly [46]. Furthermore, the ADHERE registry reported an association between age and increased adherence to UAS therapy. As for each year increase in age, there was a 9 % increased odds ratio of UAS usage. Again, this was also reported by Zhu Z et al. who reported that therapy adherence evaluated as the nightly usage duration of HGNS device, tended to be higher among older subjects than in the controlled group at 6-months (p = 0.178) and 12-month (p = 0.057) visits [46]. Notably, the ADHERE registry also reported that for each 1-unit increase in BMI, there was 9 % reduced odds of OSA treatment success. Additionally, for each unit increase in BMI, the odds of UAS adherence were 10 % lower. These findings are supported by other studies [32,48,52,68].

Another possible predictor factor for response therapy is the baseline sleep efficacy as demonstrated in a recent randomized controlled trial conducted by Schwartz AR who found that patients with a baseline sleep efficacy greater than 85 % had a higher response rate compared to those with a sleep efficacy less than 85 %. Specifically, the response rate at 4 months was 20 % in patients with baseline sleep efficacy greater than 85 %, while it was only 5 % in patients with sleep efficacy less than 85 % [53]. The ADHERE registry identified sex as a potential predictor for response to therapy in patients with OSA, as female sex has been associated with a three-fold higher odds of treatment success with UAS compared to males. Although this difference did not reach statistical significance, it suggests a potential trend toward better treatment outcomes for females [67]. Patient anatomy also should be considered during patient selection, as many studies show that patients with a greater increase of retro-glossal airways are better responders to therapy [69](47). Many studies proved that patients who exhibit anterior tongue motion of the tongue were better responders to therapy. This can be achieved by bilateral stimulation (e.g. Genu device) but also can be achieved in some patients with unilateral HGNS due to the cross innervation between both sides in some patients. Thus, considering the patient anatomy may be of help in predicting therapy response [22,33,

34,36,37,70].

This meta-analysis is subject to several limitations: Firstly, it was the authors' assumption to categorize outcomes into short-term (less than one year) and long-term (more than one year). Although many studies, including the STAR trial, [40–42,71], and the German post-market study [30], often compare the final visit outcomes with the 12-month reported outcomes besides the baseline values. Secondly, it is important to acknowledge that not all of the included studies in the meta-analysis reported the response rate or the complication rates associated with HGNS therapy. This lack of reporting introduces a potential limitation, as the reported statistics may either overestimate or underestimate the true values of the proportion of patients who experienced positive outcomes and/or adverse events. Thirdly, while HGNS therapy has been demonstrated as a safe and effective treatment for OSA, with high satisfaction levels reported by both patients and physicians, it is important to remember that these data are not based on randomized controlled trials. Consequently, these results may be subject to confounding. Only four RCTs that studied the efficacy of HGNS therapy in comparison to a control group were identified in the literature. Two of these RCTs were conducted on patients who were already identified as responders to HGNS therapy, which may increase the risk of confounding. Furthermore, it is important to note that most of the clinical trials included in the meta-analysis were sponsored by the companies that manufacture the HGNS device. This could potentially introduce reporting bias and influence the interpretation of the results [72]. Finally, there is a lack of long-term studies, as the longest study duration included in this meta-analysis was five years. This duration may not be sufficient to capture the full effects and potential complications of HGNS therapy over a longer period.

6. Conclusion

Hypoglossal nerve stimulation exhibits a favorable safety and efficacy profile as a treatment modality for improving the severity of OSA and enhancing patient-reported outcomes. However, the evaluation of HNS effectiveness in reducing the AHI compared to CPAP is premature due to the lack of comparative clinical trials. Nevertheless, HNS users exhibit a higher adherence rate compared to individuals undergoing CPAP therapy. Our findings suggest the potential for refining the selection criteria beyond the current criteria imposed by the FDA. However, to comprehensively evaluate the patient selection criteria, as well as the efficacy and safety of this treatment approach, further RCTs and long-term studies are needed.

CRediT authorship contribution statement

Warda A. Alrubasy: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. **Mohammad T. Abuawwad:** Data curation, Formal analysis, Methodology, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Mohammad J.J. Taha:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Mohammed Khurais:** Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **Muhammad Sabrah Sayed:** Investigation, Methodology, Project administration, Resources, Software. **Amneh M. Dahik:** Project administration, Resources, Software, Supervision, Validation, Writing – review & editing. **Noha Keshk:** Data curation, Formal analysis, Investigation, Resources, Software. **Sameh Abdelhadi:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Hashem Abu Serhan:** Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing.

Data availability statement

Data available upon request by email to the corresponding author.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2024.107826.

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