Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

**Review Article**

J Exp Clin Med
2024; 41(2): 407-416
**doi:** 10.52142/omujecm.41.2.30

# Hypoglossal nerve stimulation in the treatment of obstructive sleep apnea in down syndrome patients: A systematic review and meta-analysis

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**Received:** 17.02.2024 • **Accepted/Published Online:** 18.04.2024 • **Final Version:** 19.05.2024

**Abstract**

Obstructive sleep apnea (OSA) is highly prevalent in individuals with Down syndrome (DS), affecting more than 50% of this population during childhood and reaching up to 100% in adulthood. This disorder poses significant clinical consequences, including impaired cognitive function, developmental delay, and cardiovascular complications. To address this, direct hypoglossal nerve stimulation (HNS) has been approved as a treatment modality for OSA. Recent studies have shown a significant positive correlation between HNS voltage and post-apnea-hypopnea index (AHI) levels in DS and non-DS patients. However, concerns regarding the reliability of some findings have been raised, emphasizing the need for further research to underline the usefulness of HNS in treating OSA in DS patients. This meta-analysis provides a comprehensive review and analysis of the available case reports, case series, and cohort studies to evaluate the safety and efficacy of HNS in treating OSA in Down syndrome patients.

**Keywords:** OSA, down syndrome, apnea, hypoglossal nerve, stimulation

## 1. Introduction

Down syndrome, also known as trisomy 21, is the most common chromosomal anomaly in the world. This syndrome poses a high risk for a variety of diseases, such as cardiac, renal, and neural diseases (1). Among these disorders, it is found that obstructive sleep apnea (OSA), a disorder that is characterized by episodes of a complete (apnea) or partial collapse (hypopnea) of the upper airway with an associated decrease in oxygen saturation or arousal from sleep (2), is specifically highly prevalent in Down's syndrome patients. Indeed, OSA affects more than 50% of this population during childhood, reaching up to 100% in adulthood (3, 4).

A combination of abnormalities contributes to this liability of Down syndrome patients, either anatomical, including macroglossia, adenotonsillar hypertrophy, midface hypoplasia, or associated disorders such as hypotonia, obesity, hypothyroidism, and gastroesophageal reflux (5, 6). Therefore, as this disorder could further negatively affect the quality of life among these patients, it is recommended to perform polysomnography in all Down syndrome patients as a screening test for OSA (7).

Various treatment modalities have been introduced as treatment methods for OSA. Direct stimulation of the hypoglossal nerve (CN XII) (HNS) was approved as a treatment modality for OSA in 2014 for patients who are unable to tolerate continuous positive airway pressure (CPAP) (8). This method aids in enhancing the tongue's tone, preventing retroglossal collapse and obstruction. This improves upper airway and respiratory functions, leading to positive responses in sleep apnea, snoring, sleepiness, and quality of life (9, 10).

The adherence to such treatment modality is promising, and the finding of a method to improve the quality of life in Down syndrome patients with OSA is crucial, as leaving OSA non-

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treated or even insufficiently controlled in these patients could have devastating outcomes, including daytime sleepiness, impaired cognitive function, developmental delay, mood, attention, and learning problems, as well as sudden death attributable to cardiovascular complications (11).

This study is an updated systematic review and meta-analysis demonstrating the efficacy, safety, and possible adverse events associated with HNS for OSA in the Down syndrome population. Such a study is needed to underline the usefulness of HNS in treating such life-compromising disorder in Down syndrome patients.

## 2. Methods

This systematic review and meta-analysis adhered to the preferred reporting items for systematic reviews and meta-analysis statements PRISMA guidelines (12).

### 2.1. Data sources and search strategy

We searched PubMed, Scopus, WOS, and Cochrane systematically from commencement until September 2023 using the following search strategy with no search restrictions: "((Hypoglossal nerve stimulation OR Upper airway stimulation OR Nerve stimulation) AND (Sleep Apnea OR OSA OR Obstructive sleep apnea)) AND (Down syndrome OR Down OR trisomy 21)". We exported 145 studies after removing duplicates and compiled them on the Rayyan website (www.rayyan.ai) to initiate the screening process.

Three independent authors (YH, BY, TE) performed the abstract and full-text screening after removing duplicates using Zotero. Any conflict was resolved by consensus. A manual search was also conducted for the reference list of included studies for other eligible studies.

### 2.2. Inclusion and exclusion criteria

The criteria to include studies were: 1) Population - individuals with Down syndrome and OSA, without age limitations. 2) Intervention - HNS. 3) Language - English language only 4) Study design: Randomized clinical trials, prospective or retrospective cohort studies, case reports, and case series. Studies that were conducted on patients with OSA but not Down syndrome, interventions other than HNS, reviews, commentaries, animal models, and articles not available in English or as full text were excluded.

### 2.3. Data extraction

Three independent review authors (YH, BY, OA) extracted the following data: Study ID, Study Design, the patients' baseline criteria, number of participants, and characteristics of the interventions (frequency, operative time, duration of device usage, outcome measures).

### 2.4. Outcome of interest

HNS is a promising approach for treating OSA in patients with Down syndrome. The following data were extracted before analysis: Apnea-hypopnea index (AHI) and nadir oxygen saturation level as the primary outcome. In addition, quality of life was extracted as a secondary outcome using the two scores FOSQ-10 & OSA-18 and the intensity and frequency of stimulation. Continuous variables were pooled into median and interquartile ranges. Categorical variables were summarized using frequency and percentage. The paired t-test was used to compare baseline and different follow-up measures regarding AHI, $SaO_2$, OSA-18, and Arousal Index.

### 2.5. Risk of Bias assessment

The revised Joanna Briggs Institute (JBI) and the National Institutes of Health (NIH) checklist for case reports and case series were used to assess the quality of the included studies. For one non-comparative prospective single-arm cohort study, we used a modified version of the Newcastle Ottawa Scale (NOS) published by a previous study (13). According to this modified version, scores 5 and 6 were considered high quality. This modified version included from the selection part three domains – representativeness of exposed cohorts, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study, and three domains from the outcome part – ascertainment of the outcome, follow-up, and loss of follow-up rate. JBI consisted of the following domains: demographic characteristics, history, diagnosis, investigation interventions, post-intervention clinical condition, and adverse events. It also provided takeaway lessons. NIH tool for case series assessed the following domains: the study question, the description of the study population if the cases were consecutive and comparable, the description of the intervention, outcome measurement, length of follow-up, statistical methods clearness, and description of the results.

NIH scores the quality of evidence as poor, fair, or good, while JBI scores depend on percentages. Two authors independently assessed the quality of the evidence, and a third author resolved conflicts.

### 2.6. Statistical analysis

The data analysis was conducted using Rstudio. The mean and standard deviation (SD) were used to describe continuous variables, while categorical variables were represented using numbers (N) and percentages (%). To compare two or more categorical data, the Chi-square test was employed. The results were deemed significant if the P-value was less than 0.05.

## 3. Results

We collected 108 studies from multiple databases, as illustrated in **Fig. 1**. Of these, 78 were deemed duplicates and removed. During the abstract screening, 30 studies underwent screening, with 16 excluded, leaving only 14 for full-text screening. After a comprehensive evaluation of these 14 studies, we included 10 articles for inclusion in the meta-analysis. A summary of the included studies is demonstrated in **Table 1**.

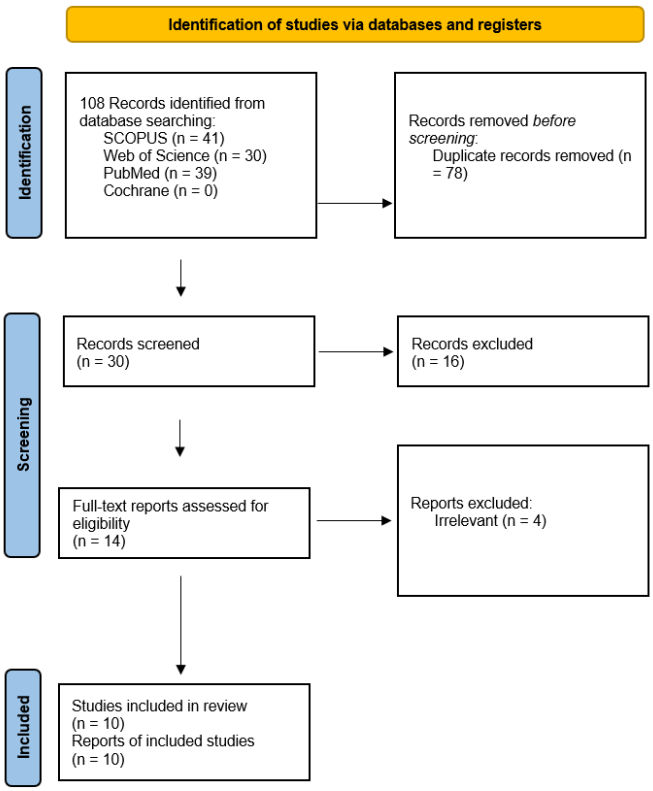


**Fig. 1.** PRISMA Flow Diagram for the selection and screening of the studies

### 3.1. Demographics

A total number of 82 Down syndrome patients diagnosed with OSA were retrieved from the included studies. In our analysis, the demographic characteristics of the participants were as follows: the median age was 14.9 (10.5 to 37.3) years. The median Body Mass Index (BMI) was 24.0 (20.1 and 24.4) kg/m$^2$. Males were 55 (67.1%), while females constituted 27 (33%) participants. Furthermore, the parameters for the stimulator voltage were summarized with a median of 1.72 (0.7 to 2.1) volts. Additionally, the device usage time per night had a median of 9.05 (8.2 to 10.5) hours. These results comprehensively overview the study's participant characteristics and key variables.

### 3.2. Quality Assessment

Our research mainly consisted of case series, and all five studies included had good quality scores (ranging from 7-9) based on the NIH tool, as shown in **Table 2**. However, the quality of the four case reports varied significantly. Two scored poorly, with only two out of five points, while the other two studies had good quality scores of 4 and 5 points, respectively, as shown in **Table 3**. The single prospective cohort study we included scored five out of six points on the modified NOS, as shown in **Table 4.**

### 3.3. Primary Outcomes

HNS significantly improved the Apnea-Hypopnea Index (AHI), which decreased significantly after the intervention (P value = 0.000). Furthermore, we evaluated the effects of HNS on oxygen saturation ($SaO_2$ NADIR) in obstructive sleep apnea patients. The results showed a non-significant change (P value = 0.75). Moreover, the HNS significantly improved sleep-related quality of life in Obstructive Sleep Apnea (OSA) patients, measured by the OSA-18 questionnaire, as shown in **Fig. 2**.

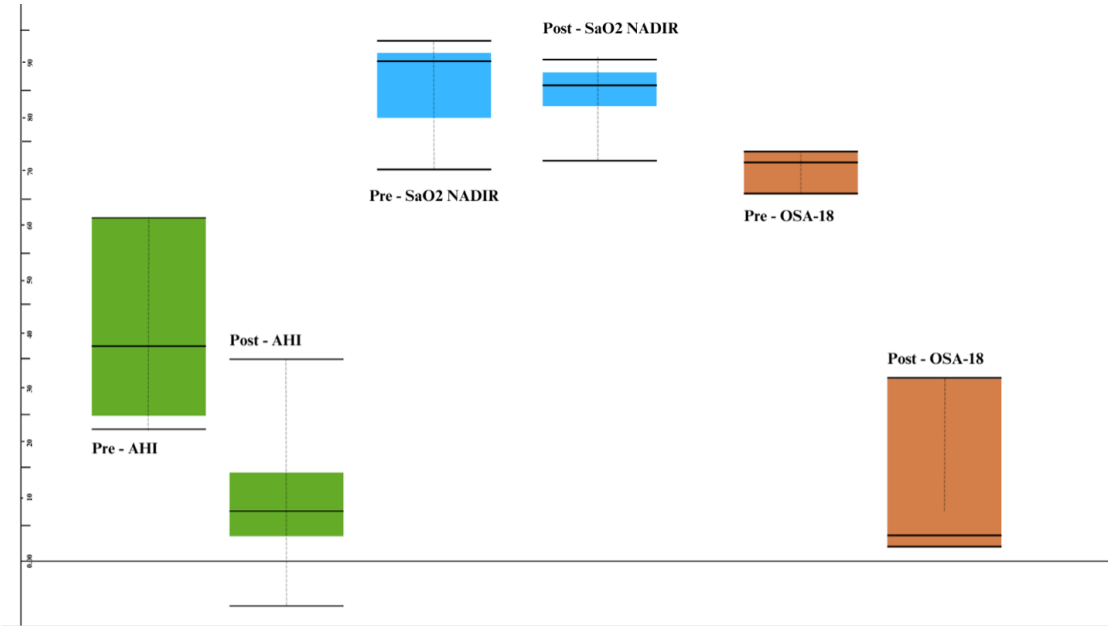


**Fig. 2.** Shows Box Plots of before and after Hypoglossal Nerve Stimulation (HNS) for Apnea-Hypopnea Index (AHI), oxygen saturation levels (SaO2 NADIR) and Obstructive Sleep Apnea -18 (OSA-18

**Table 1.** Summary of the included studies' characteristics

| Study ID | Study design | Population | Mean age (SD) | Gender | Primary outcomes | Mean voltage of stimulator (SD) | Mean duration of device usage hour/night (SD) | Adverse events mentioned | Follow-up duration | Risk of bias | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Li 2019 | Case report | 3 | 37.3 (8.3) | 3 (100%) | To assess stability (AHI) and adverse events of the surgery | 2.1 (0.22) | 8.2 | No | 2-9 months | Good | HNS resulted in significant reductions in the AHI during titration polysomnography and improved quality of sleep |
| Karlik 2020 | Case series | 3 | 10.5 (1.7) | 1 (33.3%) | To detail the anesthetic management during HNS | N/A | N/A | No | Not mentioned | Good | Anesthetic HNS placement is an extremely rewarding case with a significant lifelong impact in a particularly complicated but gratifying patient population. |
| Caloway 2020 | Case series | 20 | 15.7 (0.9) | 13 (65%) | To assess safety and monitor for adverse events. | N/A | 9.1 (0.3) | Yes (two patients were readmitted and required revision surgery) | 2 Months | Good | It showed significant reduction of the AHI and improvement in OSA-related QOL. |
| Stenerson 2021 | Case series | 4 | 12.3 (1.5) | 2 (50%) | To assess stability (by AHI), growth (BMI), and QoL (OSA-18) | 0.7 (0.35) | N/A | No | 44-58 Months | Good | Hypoglossal nerve stimulators offer potentially long-lasting therapeutic benefit to patients |
| Van De Perck 2019 | Case report | 1 | 23 | 1 (100%) | To report on the successful application of upper airway stimulation (UAS) therapy in an adult Down syndrome patient with OSA | 1.2 | 9.4 | No | N/A | Good | Respiration-synchronized electrostimulation of the hypoglossal nerve using UAS therapy may have a potential value in well-selected |
| Diercks 2016 | Case report | 1 | 14 | 1 (100%) | To report the effectiveness and safety of HNS in DS patient with OSA | 1.4 (0.05) | 9 | No | 5 months, but will be followed up for up to 12 months | Fair | In a carefully selected adolescent patient with DS, the nerve stimulator was effective in relieving upper airway obstruction and was well tolerated. |
| Yu 2022 | Prospective single-group multicenter cohort study | 42 | 15.1 (3) | 28 (66.7%) | To evaluate the safety and effectiveness of upper airway stimulation for adolescent patients with Down syndrome and severe OSA. | N/A | 9 (1.8) | Yes (tongue or oral discomfort, reoperation) | 12 months | Good | Upper airway stimulation was able to be safely performed for 42 adolescents who had Down syndrome and persistent severe OSA. |
| Diercks 2018 | Case series | 6 | 14.7 (2.1) | 4 (66.7%) | To determine the safety and effectiveness of HNS in DS patients with OSA. | 1.72 (0.22) | 8.7 (1.5) | Yes (readmission due to various adverse events) | 12 months | Good | Hypoglossal nerve stimulation was well tolerated and effective in the study population, |
| Scheffler 2023 | Case report | 1 | 31 | 1 (100%) | To describe the effectiveness of HNS in a patient with a pharyngeal flap. | 1.85 (1.03) | 10 | No | 48 months | Poor | HGNS can be a viable option for patients with moderate to severe OSA in the presence of a pharyngeal flap and may be able to achieve adequate control of OSA symptoms |
| Kay 2021 | Case report | 1 | 13 | 1 (100%) | To assess HNS efficacy with home-based sleep testing is discussed. | 1.8 (0.12) | 10.5 | No | 2 months | Poor | HNS is clinically efficient in in a patient with DS and OSA, which was confirmed with a home sleep apnea test. |

**Table 2.** Quality assessment results of the included case series using NIH

| NIH quality assessment tool for case series studies criteria met | Study ID | | | | |
|---|---|---|---|---|---|
| | Karlik 2020 | Caloway 2020 | Stenerson 2021 | Diercks 2018 | Li 2019 |
| Was the study question or objective clearly stated? | Yes | Yes | Yes | Yes | Yes |
| Was the study population clearly and fully described including a case definition? | Yes | Yes | Yes | Yes | Yes |
| Were the cases consecutive? | Yes | Yes | Yes | Yes | Yes |
| Were the subjects comparable? | No | No | Yes | No | Yes |
| Were the interventions clearly described? | Yes | Yes | Yes | Yes | Yes |
| Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes |
| Was the length of follow-up adequate? | No | No | No | No | No |
| Were statistical methods well-described? | Yes | Yes | Yes | Yes | Yes |
| Were the results well-described? | Yes | Yes | Yes | Yes | Yes |
| **Quality (total score)** | 7 | 7 | 8 | 7 | 8 |
| **Quality= Good/Fair/Poor** | Good | Good | Good | Good | Good |

**Table 3.** Quality assessment results of the included case reports using JBI

| The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports | Study ID | | | |
|---|---|---|---|---|
| | Van De Perck 2019 | Diercks 2016 | Scheffler 2023 | Kay 2021 |
| Were the patient's demographic characteristics clearly described? | Yes | Yes | Yes | Yes |
| Was the patient's history clearly described and presented as at a timeline? | Yes | Yes | No | Yes |
| Was the current clinical condition of the patient on presentation clearly described? | Yes | Yes | No | No |
| Were adverse events (harms) or unanticipated events identified and described? | Yes | No | No | No |
| Does the case report provide takeaway lessons? | Yes | Yes | Yes | No |
| **Quality (total score)** | 5 | 4 | 2 | 2 |

**Table 4.** Quality assessment of the single arm prospective cohort study using modified NOS.

| Study | Selection | | | Outcome | | | Total quality score | Modified Total quality score |
|---|---|---|---|---|---|---|---|---|
| | Representativeness of exposed cohort | Ascertainment of exposure | Demonstration that the outcome of interest was not present at the start of the study | Ascertainment of outcome | Follow-up | Loss of follow-up rate | | |
| **Yu 2022** | * | * | | * | * | * | 5/9 | 5/6 |

The paired t-tests conducted for the Apnea-Hypopnea Index (AHI) revealed significant improvements in sleep apnea severity following the HNS. At the 12-month mark, a notable significant reduction in AHI was observed (P value = 0.0005). Similarly, the 2-month follow-up demonstrated a substantial but non-significant decrease in AHI (P value = 3.86). Furthermore, the analysis of $SaO_2$ levels between the baseline and the 6-month follow-up showed no statistically significant changes (P value = 0.83). A paired t-test of the OSA-18 scores between the baseline and the 6-month follow-up showed a statistically significant improvement (P value = 0.012). Moreover, in assessing the Arousal Index between the baseline and the last follow-up, the paired t-test revealed no statistically significant changes (P value = 0.51), as shown in **Table 5**.

Our analysis revealed a robust positive correlation (r = 0.763) between Stimulator Parameters (Voltage) and the post-intervention AHI. The corresponding p-value of 0.0459 attests to the statistical significance of this correlation. These results indicate a significant association between the voltage levels of the stimulator parameters and the observed alterations in the AHI after HNS intervention, see **Fig. 3 (A)**. The correlation coefficient (r = 0.796, p = 0.032) indicates a strong, significant, positive relationship between hypoglossal nerve stimulation voltage and obstructive sleep apnea patients' BMI, as shown in **Fig. 3 (B)**. The correlation between the change in OSA-18 scores and the change in $SaO_2$ NADIR is strong (r = 0.85) but not statistically significant (p = 0.35), as shown in **Fig. 3 (C)**.

Adverse events post-HNS in Down syndrome patients with obstructive sleep apnea included rash at the surgical site, acute insomnia, readmission, reoperation, and tongue or oral pain/discomfort, as shown in **Fig. 4**. Notably, readmission was the most frequent event, emphasizing the need for careful monitoring and management in this patient group.

**Table 5.** The results of paired t-tests comparing different measures at baseline and various follow-up time points, including the t-value, degrees of freedom (df), p-value, confidence interval (CI), and mean difference (MD) for each measure. The measures include AHI (Apnea-Hypopnea Index), SaO2 (Oxygen Saturation), OSA-18 (Obstructive Sleep Apnea - 18 Questionnaire), and Arousal Index

| Measure | Comparison | t-Value | Degrees of Freedom (df) | P-Value | Confidence Interval (CI) | Mean Difference (MD) |
|---|---|---|---|---|---|---|
| **AHI** | Baseline vs. Post 12 Months | 5.3 | 9 | 0.0005 | 96% CI: 14.5 to 36.13 | 25.3 |
| **AHI** | Baseline vs. 2 Months | 8.53 | 27 | 3.86 | 95% CI: 16.3 to 26.6 | 21.5 |
| **SaO2** | Baseline vs. 6 Months | 0.22 | 6 | 0.83 | 95% CI: -5.04 to 6.43 | 0.53 |
| **OSA-18** | Baseline vs. 6 Months | 2.7 | 19 | 0.012 | 95% CI: 0.2 to 1.65 | - |
| **Arousal Index** | Baseline vs. Last Follow-up | 1 | 1 | 0.51 | 95% CI: -109.1 to 127.3 | 9.1 |

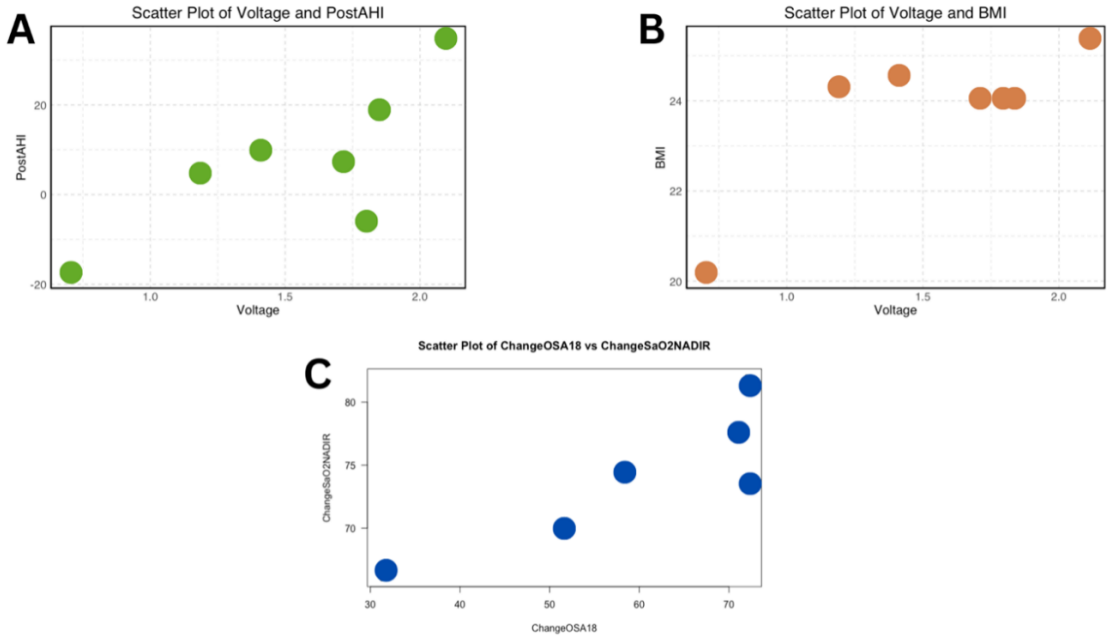


**Fig. 3.** Presents scatter plots illustrating (A) the observed robust positive correlation (r = 0.763) between Stimulator Parameters (Voltage) and the post-intervention Apnea Hypopnea Index (AHI) (B) the observed robust positive correlation (r = 0.796) between Stimulator Parameters (Voltage) and patients' BMI (C) the observed robust positive correlation (r = 0.85) between the change in OSA-18 scores and the change in SaO2 NADIR

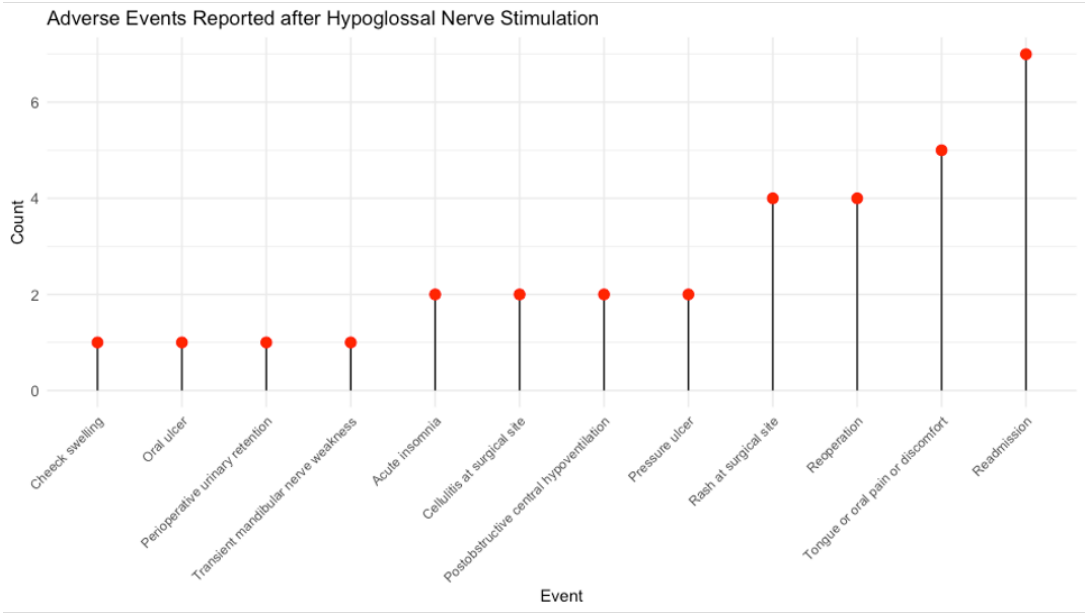


**Fig. 4.** shows the counts of adverse events following HNS in Down syndrome participants with OSA

## 4. Discussion

DS is the most common genomic disorder of intellectual disability, trisomy of chromosome 21, and survivable autosomal aneuploidy. The lifetime prevalence of DS is rising significantly as the global population continues to grow and the improvements in the survival of children with DS. The life expectancy of individuals with DS in the USA has increased from an estimated mean of 26 years and a median of 4 years in 1950 to 53 and 58 years, respectively, in 2010 (14). OSA is a complex disorder with significant clinical consequences for patients with DS. OSA is frequently observed in patients with DS and, when present, tends to be more severe. This increased prevalence might be attributed to common anatomic abnormalities and a greater risk of additional comorbidities such as hypotonia and obesity (15).

This study systematically investigated the therapeutic effectiveness of HNS for OSA in adolescents with DS. This study contributes valuable insights to the literature by addressing a pertinent knowledge gap. While Liu et al. (2022) conducted a systematic review of this subject, concerns were raised regarding the reliability of their findings (16). This was attributed to a methodological flaw in which a group of patients was duplicated and treated as distinct entities in the analysis, compromising the credibility of their outcomes.

However, meta-analysis is a powerful analytical approach for identifying the overall measures and summarizing knowledge. This is controversial because even minor violations of certain presumptions can lead to misleading conclusions. Therefore, reproducibility is required for obtaining reliable results (17). Considering these concerns, our primary objective was to present updated results using an alternative analysis approach to enhance the robustness and reliability of the findings.

Our findings align with those of the meta-analysis conducted by Liu et al. In 2022, supporting the effectiveness of HNS in reducing the AHI, where a mean of 17.4 reduction in the AHI score was significant ($p < 0.001$) (16). Furthermore, a significant 64% reduction in the AHI mean from $42 \pm 19.43$ to $13.12 \pm 9.61$ was reported by Baptista et al. In patients without DS (18). Our study demonstrated a remarkable median AHI reduction from 36.8 pre-HNS to 6.6 post-HNS, with ($P < 0.0001$). Paired t-tests at 2 and 12 months from baseline revealed non-significant ($p = 0.386$) and significant ($p = 0.0005$) differences, respectively. Our study highlights the importance of long-term follow-up in evaluating the sustained effectiveness of HNS in adolescents with DS and OSA. However, a more extended follow-up period is essential to elaborate on cognitive development benefits and potential impacts.

Recognizing the unique stage of rapid fat accumulation in adolescents with DS (19), we emphasize investigating variations in the stimulation voltage intensity and its impact on efficacy in a wide range of BMI. The Food and Drug Administration (FDA) recommends HNS for OSA in non-DS adults with AHI <50 events/h, BMI <32 kg/m², and no circumferential airway collapse at the level of the velopharynx (19, 20).

The stimulation intensity showed non-significant changes in AHI (persistently reduced) over four years in non-DS patients (8). Unlike Diercks et al. (2016) and Zhu et al. (2020), our study revealed a significant positive correlation between the HNS voltage and post-AHI levels. This contradicts their observation of an inverse relationship between HNS voltage and post-AHI level in patients with DS and no effect on AHI in non-DS patients, respectively (21, 22). This discrepancy emphasizes the complexity of individual responses to HNS and stresses the need for further investigation of these relationships in diverse populations, specifically in patients with DS.

Oxygen saturation ($O_2$ sat) represents the percentage of the reversible linkage between hemoglobin (Hb) and oxygen, which depends on many factors, including partial pressure of the inspired oxygen, the adequacy of ventilation and gas exchange, the concentration of Hb, and the affinity of Hb to oxygen which normally ranges between 95 and 98% at sea level (23, 24).

Regarding O2 sat, our results indicated a median reduction of four points from 90 to 86 post-HNS, although this change was clinically and statistically ($p = 0.75$) insignificant. The paired t-test at 6 months from baseline also showed an insignificant improvement ($p = 0.83$) in the $O_2$ sat levels. This suggests that while HNS may significantly improve AHI, its impact on oxygen saturation levels may be less pronounced.

Our study assessed the reduction in AHI and explored the impact on participants' quality of life using the OSA-18 questionnaire, which has a sensitivity of 56% and a specificity of 73% (25). Three studies reported baseline OSA-18 with a mean of $70.7 \pm 37$ (Caloway et al. 2020; Stenerson et al. 2021; Yu et al. 2022). After 6 months, Caloway et al. Reported a mean of $2.45 \pm 1.2$, changing from a baseline of $74 \pm 1.9$, and at 12 months, 2 studies, Yu et al. And Diercks et al. Reported OSA-18 of $31.3 \pm 10.8$ and $1.5 \pm 0.6$, respectively. A paired t-test at six months post-baseline demonstrated a significant reduction in OSA-18 scores ($p = 0.012$), indicating the improved sleep-related quality of life. Moreover, Liu et al. Results also show a significant reduction in OSA-18 post-HNS ($p < 0.001$) (16). Moreover, correlation analysis revealed insignificant associations between OSA-18 scores and oxygen saturation levels ($p = 0.35$).

However, only one study by Yu et al. Reported a baseline Epworth Sleepiness Scale (ESS) with a mean of $10 \pm 7.3$ reduced at 12 months to a mean of $5 \pm 4.9$. Therefore, we recommend that future researchers use the ESS questionnaire in addition to the OSA-18.

The paired t-test for the arousal index between the baseline and the last follow-up was insignificant ($p = 0.51$), indicating

that HNS did not significantly change arousal levels throughout the study. This suggests that HNS primarily influences the physiological aspects (AHI) of sleep without significantly improving the arousal patterns.

The reported adverse events included readmission, tongue or oral pain, reoperation, and rash at the surgical sites, with cellulitis at the surgical site and acute insomnia being less frequently reported (only in two patients each). Among these, the most serious adverse events were readmission, reoperation, and cellulitis at the surgical site. Fortunately, device migration, as noted in non-DS patients, did not occur; however, long-term follow-up is needed to confirm the absence, and prophylactic measures are necessary (26).

Moreover, dysphagia, which is a common complaint in traditional upper airway surgeries, was not reported in any of the included studies (26). Acute insomnia presents a paradoxical outcome and affects only a limited number of patients. It is associated with worse patient outcomes and is accompanied by depression (27). It is crucial to evaluate whether the length of the device wire is sufficient; therefore, we can prophylactically prevent or reduce complications. Device migration can be avoided by selecting the appropriate surgical site and ensuring adequate anchoring. Oral pain can be reduced by titrating the voltage. Fortunately, no permanent injuries, life-threatening illnesses, or deaths have been reported in the literature.

Our findings support the efficacy of HNS as a treatment option for OSA in adolescents with DS. The significant reduction in AHI and enhancement in quality of life, as measured by the OSA-18 and ESS questionnaires, suggests that HNS can be considered an effective and well-tolerated alternative to CPAP therapy.

### 4.1. **Limitations and Future Recommendations:**

This review may be limited by certain factors, including restricted sample sizes (mainly case reports), and the absence of control groups in any of these studies raises concerns about potential research bias. Moreover, there needs to be a more comprehensive understanding regarding the safety of HNS therapy and the factors contributing to adverse events. Furthermore, the assessments did not include data on adolescent tolerance to electrical stimulation, underscoring the importance of thoroughly evaluating the safety aspects of HNS therapy to mitigate adverse outcomes. Lastly, the follow-up duration for the study participants was generally limited, leaving the long-term consequences of HNS on adolescents with DS and OSA uncertain. Given these limitations, there is a crucial need for large-scale, prospective, randomized, controlled, multicenter studies to provide more robust evidence on the safety and efficacy of HNS therapy in this population.

## 5. Conclusion

In conclusion, this study addressed the therapeutic effect of HNS on OSA in patients with DS. Our study utilized a different analysis approach to enhance reliability, aligned with previous findings supporting the effectiveness of the HNS in reducing AHI. Notably, a significant median reduction in AHI from 36.8 to 6.6 post-HNS was observed, demonstrating sustained effectiveness over 12 months. This underscores the importance of long-term follow-up in evaluating HNS outcomes. Significant reductions in AHI, improvements in OSA-18 scores, and positive effects on quality-of-life indicators suggest that HNS could be a well-tolerated alternative to continuous positive airway pressure therapy. Future research should explore the safety aspects, underlying mechanisms of adverse events, and long-term consequences of HNS in adolescents with DS and OSA.

**Conflict of interest**

All authors declare they have no commercial associations that might pose a conflict of interest in relation to the manuscript.

**Funding**

No specific funding was received for this work.

**Acknowledgments**

None to declare.

**Authors' contributions**

Concept: Y.J.A., H.K.A., Z.K., O.A., I.MA., Design: Y.J.A., H.K.A., Z.K., O.A., I.MA., Data Collection or Processing: B.Y.M., A.M.A., J.H.J., O.A., T.E., Y.H., H.K.A., Analysis or Interpretation: Y.J.A., H.K.A., B.Y.M., I.MA., T.E., Literature Search: B.Y.M., Y.H., A.M.A., Y.J.A., H.K.A., O.A., Z.K., J.H.J. Writing: B.Y.M., Y.H., A.M.A., Y.J.A., H.K.A., O.A., Z.K., J.H.J.

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