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REVIEW ARTICLES

Obstructive sleep apnea in children with nonsyndromic cleft palate: a systematic review

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Study Objectives: To characterize obstructive sleep apnea in children with nonsyndromic cleft palate based on polysomnographic parameters relative to primary palatoplasty.

Methods: A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following databases were searched: PubMed, Scopus, CINAHL, and Cochrane. Studies were only considered for inclusion if they examined exclusively patients with nonsyndromic cleft palate and reported polysomnogram data.

Results: Seven studies met inclusion criteria, providing information on a total of 151 patients with a weighted mean age of 5.2 ± 5.0 years (range 0.1–12 years). Five studies presented data from either the pre- or postoperative period. Two studies investigated both pre- and postpalatoplasty polysomnogram data, and neither observed a significant change in apnea-hypopnea index (AHI) values following surgery (mean preoperative AHI of 2.7 events/h, mean improvement of 0.6 events/h). The entire cohort had a prepalatoplasty weighted mean AHI of 11.4 events/h (range 1.5–16.1) and postpalatoplasty AHI of 1.5 events/h (range 0.2–5.2). Interpretation of polysomnographic data was limited by heterogeneity; however, the AHI values for children with nonsyndromic cleft palate largely demonstrated mild to moderate obstructive sleep apnea following palatoplasty.

Conclusions: The full effect of cleft palate repair on obstructive sleep apnea in children with nonsyndromic cleft palate remains understudied. While published data are heterogenous, few studies support the worsening of obstructive AHI after palatoplasty in children with nonsyndromic cleft palate. Further studies with standardized polysomnographic parameters are needed to provide guidance for management of this population.

Keywords: cleft palate, palatoplasty, pediatric, obstructive sleep apnea, apnea-hypopnea index

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Children with cleft palate have been reported to have a high risk of obstructive sleep apnea both before and after palatoplasty. However, current literature frequently fails to differentiate syndrome status when reporting polysomnographic data in the cleft palate population. Therefore, we conducted a systematic review investigating obstructive polysomnogram parameters in strictly nonsyndromic children with cleft palate.

Study Impact: This systematic review did not identify substantial worsening of obstructive sleep apnea in patients with nonsyndromic cleft palate undergoing palatoplasty. Furthermore, it lays the foundation for future investigations to better characterize obstructive sleep apnea in children with cleft palate based on syndrome status, as these likely represent distinct populations in terms of obstructive sleep disorders.

INTRODUCTION

Cleft palate is one of the most common congenital malformations in newborns, observed in approximately 0.49–2.51 per 1,000 births.[1–4] The standard treatment of cleft palate includes surgical repair with palatoplasty,[5] which the American Cleft Palate–Craniofacial Association recommends completion of by 18 months of age to optimize long-term speech outcomes.[6] Among conditions that may affect children with cleft palate, studies have suggested that this population is at risk of obstructive sleep apnea (OSA) both before and after palatoplasty.[7–9] In children, OSA can lead to serious negative sequalae, including neurocognitive deficits, behavioral problems, worse quality of life, and cardiopulmonary problems in cases of severe disease.[10–12] The reported prevalence of polysomnogram (PSG)-diagnosed OSA in children with cleft palate is nearly 3 times higher than that of noncleft chilldren[10]; however, studies often do not distinguish these values based on whether the child has an associated syndrome. Therefore, it is critical to understand the nuances of OSA risk in children with cleft palate in order to appropriately counsel families and manage patients both before and after palatoplasty.

Cleft palate can either manifest as an isolated pathology without genetic changes (nonsyndromic cleft palate) or in conjunction with another anatomic anomaly or syndrome (syndromic cleft palate). Prior studies estimate that approximately 30% of patients with cleft palate fall within this "syndromic" category.[13,14] Patients with certain anomalies (eg, Pierre-Robin sequence or Treacher Collins syndrome) are often predisposed to OSA at baseline due to associated craniofacial anomalies, such as maxillary hypoplasia or micrognathia.[15,16] However, the current literature describing OSA in patients with cleft palate frequently fails to investigate differences between children

with nonsyndromic vs syndromic cleft palate. Furthermore, the impact of palatoplasty on OSA parameters is poorly defined. Concerns of increased OSA risk in patients with syndromic cleft palate may not be equally observed in the nonsyndromic cleft palate population, highlighting a potential gap in knowledge and ability to accurately counsel caregivers.

Given the lack of consensus detailing the risk of OSA in pediatric patients with nonsyndromic cleft palate, we conducted a systematic review to analyze the body of published literature to better understand how OSA has been examined in this subgroup. This will be accomplished by using studies that include PSG data, the gold-standard diagnostic tool for OSA,[17] in order to provide a consistent and objective measurement to compare across populations. Furthermore, we will present these data in the context of patient palatoplasty status to investigate how this procedure relates to OSA parameters. The aim of this project is to characterize the literature describing reported PSG variables of solely patients with nonsyndromic cleft palate, both pre- and postpalatoplasty, to better inform clinicians and caregivers of the risk of OSA in this population.

METHODS

Search criteria

A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] The search was developed by the research team and executed by 2 trained clinical research fellows (W.N.J. and N.S.P.). The following databases were used: PubMed (National Library of Medicine, National Institutes of Health), Scopus (Elsevier), CINAHL (EBSCOHost), and Cochrane (Cochrane Library). Search terms were devised to include concepts related to palatoplasty, nonsyndromic cleft palate, OSA, and PSG. This strategy used a combination of subject headings (eg, Medical Subject Headings [MeSH] in PubMed) and keywords. The PubMed search strategy was adjusted for the other 3 databases by the MeSH terms being replaced with appropriate subject headings and similar keywords when available. The databases were searched from inception through July 22, 2021. The reference lists of relevant and citing articles were manually searched to confirm the search strategy and identify additional articles. Search strategy details are included in Appendix S1 in the supplemental material. The systematic review was registered with PROSPERO for study originality: ID# CRD42021269486.

Selection criteria

All article types, including double- or single-blinded randomized controlled trials, double- or single-blinded randomized comparison trials, nonrandomized controlled trials, and prospective or retrospective observational studies, were considered for inclusion. Studies were only considered for inclusion if they (1) comprised exclusively children with nonsyndromic cleft palate and (2) contained PSG data before or after palatoplasty, or both. Exclusion criteria were revision palatoplasties, studies which included only patients with syndromic cleft palate, and PSG data presented in relation to other surgical procedures such as mandibular distraction or pharyngoplasty. Exclusion criteria also included non–English-language studies and nonpediatric populations.

Data extraction

All articles from the initial search strategy were imported into the Covidence software (Veritas Health Innovation, Melbourne, Australia). Title and abstract screening and subsequent full-text review were conducted independently by 2 of the authors (W.N.J. and N.S.P.), and discrepancies were resolved by a third collaborator (S.A.N). Two reviewers (W.N.J. and N.S.P.) independently extracted the data and compared for accuracy. Author, year of publication, demographics, including age and sex, were recorded. The outcome measures extracted included PSG data such as apnea-hypopnea index (AHI) and obstructive AHI (oAHI), age at time of palatoplasty, and timing of pre- and postpalatoplasty PSGs. For reference, AHI measures both central and obstructive apneic events, whereas oAHI represents only obstructive apneic events.

Level of evidence

The level of evidence for the included articles was evaluated according to the Oxford Center for Evidence-Based Medicine.[19] The risk of bias was then assessed using the *Cochrane Handbook for Systematic Reviews of Interventions*, version 6.2.[20] Since all studies were nonrandomized controlled trials, the Risk of Bias in Non-Randomized Studies–of Interventions (ROBINS-I) tool was used.[21] Two authors (W.N.J. and N.S.P.) independently performed a risk assessment on the included studies, and disagreements were resolved by discussion between authors. Risk of bias was graded as "low," "unclear," or "high," across 6 categories: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of reported results.

Statistical analysis

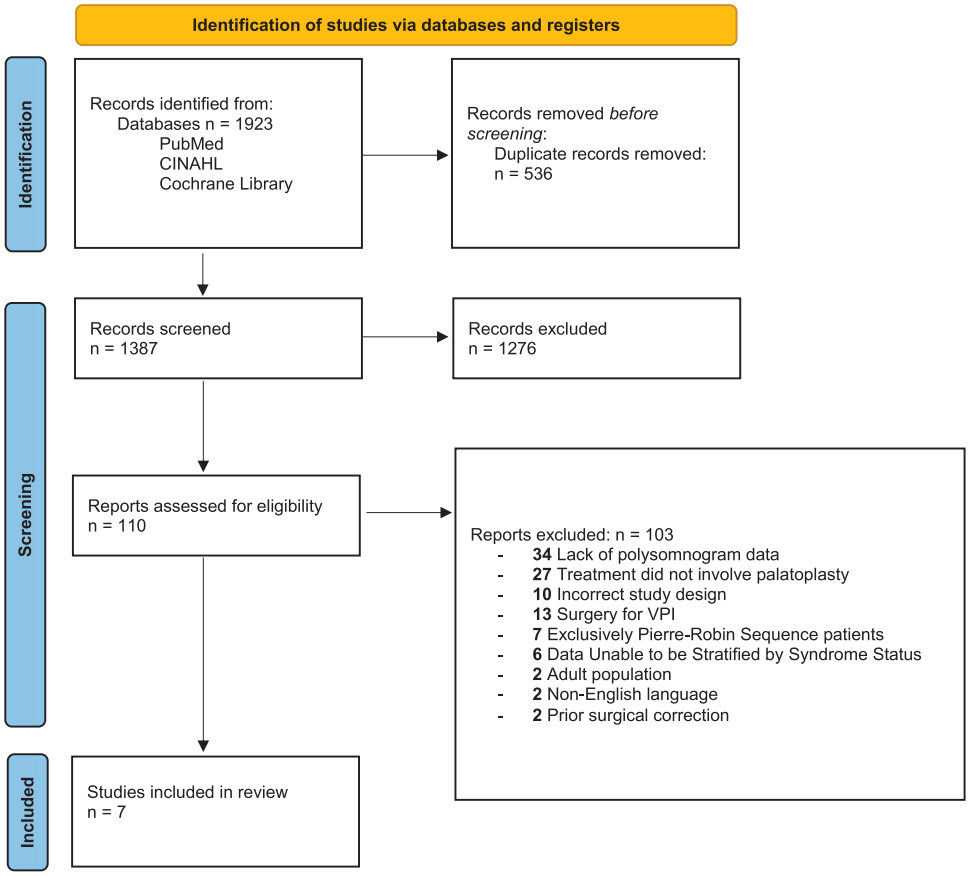
Categorical data are presented by absolute and relative frequencies with percentages. Continuous data are summarized by mean ± standard deviation (SD) or range (minimum, maximum). Given the heterogeneity and lack of adequate data in outcome metrics, no meta-analysis or statistical tests were performed. Consequently, the results are presented as an integrated qualitative review.

RESULTS

Search results and study characteristics

The literature search yielded 1,387 unique manuscripts, of which title and abstract screening excluded 1,276, leaving 110 studies that underwent full-text review. In total, 7 studies met full inclusion criteria and were analyzed in the final systematic review.[22–28] A PRISMA diagram outlining the comprehensive search process is detailed in **Figure 1**. These studies all included data that were able to be stratified to include PSG findings for patients with strictly nonsyndromic cleft palate. The included studies were published between the years of 1987 and 2021 across 5 unique countries and were designed either as prospective cohort or retrospective case-control studies. Critical appraisal indicated an acceptably low

Figure 1—PRISMA diagram.



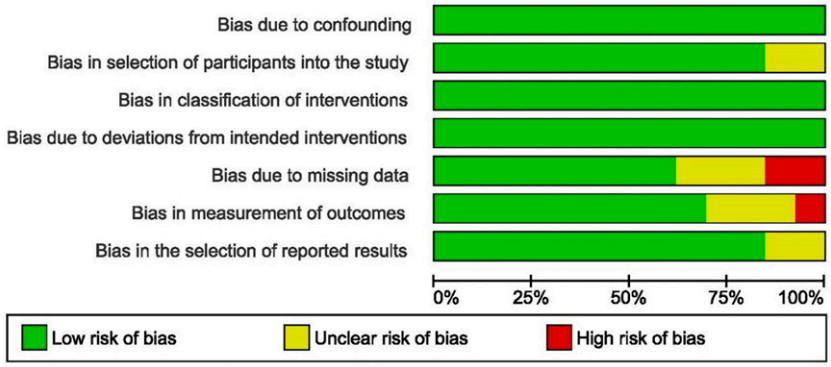
Description of systematic review search process. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, VPI = Velopharyngeal Insufficiency.

risk of bias for the majority of included studies (Figure 2), with the greatest potential for bias in the categories of "missing data" and "selection of reported results." Studies included in the final systematic review were all classified as either evidence level 3 or level 4 according to the Oxford Level of Evidence scale.

Study data

The 7 included studies that reported PSG data on patients with strictly nonsyndromic cleft palate are shown in Table 1.[22–28] These studies described PSG characteristics in 151 children who had a weighted mean ± SD age of 5.2 ± 5.0 years (range 0.1–12).

Figure 2—Risk of bias.



Assessment of risk of bias of the included manuscripts.

Table 1—Systematic review of studies including PSG scores in patients with nonsyndromic cleft palate.

Study (Year)	OLE	Study Design	Patients (n)	Age at PSG, Years (SD)/ [Range]	Pre-Op AHI (SD)	Pre-Op oAHI, (SD)/[Range]	Post-Op AHI, (SD)/[Range]	Post-Op oAHI (SD)
Akita et al (2006)[22]	3	Prospective cohort	8	1.6 (0.14)	3.0 (2.1)	NR	2.8 (1.5)	NR
Cielo et al (2016)[23]	3	Prospective cohort	15	0.3 (0.1)	NR	1.2 [0.2–4.6]	NR	NR
MacLean et al (2012)[24]	3	Prospective cohort	35	0.2 (0.2)	16.1 (1.9)	7.2 (1.2)	NR	NR
Orr et al (1987)[25]	3	Prospective cohort	10	NR	1.5 (0.8)	0.6 (0.5)	1.0 (0.6)	0.6 (0.5)
Rose et al (2002)[26]	3	Prospective cohort	43	12.1 (3.8)	NR	NR	0.2 (0.2)	NR
Sert et al (2021)[27]	4	Retrospective case-control	17	4.1 [2.1–7.1]	NR	NR	5.2 [1.1–28.5]	NR
Sobral et al (2018)[28]	4	Retrospective case-control	23	[7–12]*	NR	NR	1.1 (0.8)	0.3 (0.4)

*No mean age reported by the manuscript. AHI = apnea-hypopnea index, NR = not reported, oAHI = obstructive apnea-hypopnea index, OLE = Oxford level of evidence, Post-Op = postoperative, Pre-Op = preoperative, PSG = polysomnogram, SD = standard deviation.

The reported age at palatoplasty in this cohort ranged from 0.3 to 1.8 years. Two studies included PSG data on patients who had not yet undergone palatoplasty,[23,24] 3 investigated patients who had previously undergone palatoplasty,[26–28] and 2 included PSG data for both pre- and postoperative patients.[22,25]

Among the entire patient cohort, the weighted mean preoperative AHI was 11.4 events/h (range 1.5–16.1) and the weighted mean postoperative AHI was 1.5 events/h (range 0.2–5.2). The weighted mean preoperative oAHI of these patients was 4.5 events/h (range 0.6–7.6) and the weighted mean postoperative oAHI was 0.37 events/h (range 0.1–0.6). It should be noted that the preoperative AHI and oAHI values are skewed higher by the patients described by MacLean et al,[24] who demonstrated a mean AHI and oAHI of 16.1 and 7.6 events/h, respectively. Timing of PSG relative to palatoplasty varied considerably, with 4 studies capturing PSG data within weeks or months of the procedure[22–25] and the remaining providing PSG data obtained months to years following surgery.[26–28]

Neither of the 2 studies that investigated both pre- and postpalatoplasty AHI values in patients with nonsyndromic cleft palate (Akita et al,[22] Orr et al[25]) detected a significant change in AHI when comparing presurgical with postsurgical values. Akita et al[22] studied 8 patients with nonsyndromic cleft palate (age 1.6 ± 0.1 years) before and after cleft palate repair, capturing PSG data at an interval of 7.0 ± 1.5 months. This study cohort had a prepalatoplasty AHI of 3.0 ± 2.1 events/h and postpalatoplasty AHI of 2.8 ± 1.5 events/h, an improvement that was not determined to be statistically significant. Orr et al[25] captured PSG data in 10 patients with cleft palate on 3 separate occasions: 1 to 2 days preoperatively, 2 to 3 days postoperatively, and finally at 3 months postoperatively. These data were presented for each individual patient, but when calculated, the mean preoperative AHI was 1.5 ± 0.8 events/h, immediate postoperative AHI was 2.3 ± 3.6 events/h, and 3-month follow-up demonstrated a mean AHI of 0.5 ± 0.6 events/h.

Other relevant study outcomes

Beyond the standardized PSG values collected and documented above, each of the included manuscripts investigated other outcomes pertaining to patients with nonsyndromic cleft palate and OSA. Two studies, Rose et al[26] and Sobral et al,[28] examined patients who were multiple years postpalatoplasty and observed that their cohorts demonstrated "microsymptoms" of OSA, such as an increased Respiratory Distress Index or desaturation index, but these symptoms were not shown to be clinically pathologic. Sert et al[27] stratified PSG results by the Veau palate classification and found similar postoperative PSG characteristics despite a range of cleft severity. Two studies, Cielo et al[23] and MacLean et al,[24] observed that patients with nonsyndromic cleft palate demonstrated significantly lower AHI/oAHI scores compared with patients with syndromes, concluding that patients with syndromic cleft palate possess more severe OSA characteristics.

DISCUSSION

Consensus is lacking regarding the risk of OSA development in children with nonsyndromic cleft palate, both before and following palatoplasty. This population is unique from children with syndromic cleft palate, as many syndromes frequently present with other genetic (hypotonia) and craniofacial anomalies (micrognathia and midface hypoplasia), which increase the risk of OSA.[29,30] Our study presents the first systematic review concerning PSG characteristics in children with nonsyndromic cleft palate, particularly with respect to palatoplasty. Untreated OSA can have a significant negative long-term impact on a child's health. While it has been shown that patients with cleft palate are at risk of developing OSA,[24] the distinction between children with syndromic and nonsyndromic cleft palate remains understudied. The novel aim of this systematic review was to identify studies in the literature that make this important distinction.

To provide an objective measure for comparison, our systematic review only included literature with documented PSG findings in the targeted population. We identified 2 studies that described pre- and postoperative PSG data in patients with nonsyndromic cleft palate and 5 other studies that presented PSG data obtained either pre- or postpalatoplasty. Despite the heterogeneity of the

reported data on this topic, we did not find any evidence that palatoplasty contributes to a statistically significant worsening of OSA in this population. The included studies provided data on a range of patients who had previously undergone palatoplasty (follow-up range: 1–11 years), suggesting a minimal risk of OSA deterioration in nonsyndromic patients in the years following intervention. However, multiple studies did endorse the presence of "microsymptoms" among children years after palatoplasty, which may appear on PSG but lack clinical significance. This insight is relevant in that it provides guidance to clinicians who are counseling families regarding the likely course of their child's disease.

There has been a longstanding clinical concern that primary palatoplasty has the potential to induce symptoms of OSA.[31–33] A retrospective study published in 2012 noted an association between postpalatoplasty respiratory distress rates and the presence of preoperative OSA, recommending that patients undergo screening for obstructive sleep disorders prior to surgery.[34] Currently, it is unclear when and to what extent obstructive airway symptoms may develop after cleft repair, if at all. Children with cleft palate have generally been shown to be at high risk of OSA development before primary palate repair,[24] a risk that remains elevated postpalatoplasty.[35] It is unclear, however, whether this risk pertains to nonsyndromic children with cleft palate. The results of this literature review suggest that nonsyndromic children with cleft palate have mild to moderate OSA disease burden, especially in contrast to studies that incorporate AHI values from syndromic children with cleft palate. The presence of other craniofacial anomalies, such as maxillary or mandibular hypoplasia, predisposes children to OSA at baseline. For example, children with Pierre-Robin sequence have been shown to exhibit more severe PSG characteristics compared with children with nonsyndromic cleft palate.[10,24,36] Thus, this study underscores the importance of future studies to stratify PSG findings by syndrome status.

In our systematic review, we identified 2 papers that followed 18 patients before and after palatoplasty,[22,25] and neither study endorsed a significant worsening of AHI when comparing pre- with postoperative values. The remaining studies presented PSG data on children who had not yet undergone palatoplasty (50 patients) or had previously undergone palate repair (83 patients). The weighted mean AHI of the entire cohort was 11.4 events/h preoperatively and 1.5 events/h postoperatively, suggesting that postpalatoplasty patients had generally lower AHI scores after surgery or with growth. However, the preoperative data are likely skewed higher by 1 study that described patients with unusually severe OSA features.[24] These data also highlight the inconsistent timing of PSG attainment before and after palatoplasty, which limits the ability to develop strong clinical insight into this population's risk of OSA development. Future studies with long-term follow-up among patients with nonsyndromic cleft palate may provide more conclusive data on OSA trends over time.

The included manuscripts varied considerably in terms of study design and data presentation, making it challenging to provide concrete recommendations. One area of extensive variation was the timing of PSG attainment relative to palatoplasty date. For example, the PSG data documented by Orr et al[25] and Akita et al[22] were obtained in the perioperative period, whereas the Rose et al[26] and Sobral et al[28] studies captured PSG data many years postpalatoplasty. It has previously been shown that children with cleft palate may show signs of OSA at varying ages postsurgery.[10] Furthermore, patients in whom PSG was obtained in very early age, such as the mean age of 1.2 months captured by MacLean et al,[24] may be predisposed to more severe OSA given the differences in infant sleep structure, PSG normative values in this age group, and lack of time allowed for airway growth and development. Conversely, patients who are many years postsurgery, including those described by Rose et al[26] or Sobral et al,[28] may have developed other pathology contributing to OSA, such as adenotonsillar hypertrophy. Ideally, a prospective study would control for age and timing of PSG in relation to palatoplasty.

Other limitations of this systematic review must also be addressed. We identified only 2 studies that followed children pre- and postsurgically, limiting our ability to draw conclusions. The reviewed studies also frequently lacked comprehensive PSG data, and thus we were only able to report AHI and oAHI scores due to missing values, such as the Respiratory Distress Index and O_2 nadir. It is critical that future studies incorporate detailed and standardized PSG parameters to provide full insight into the OSA characteristics of this population. Multicenter prospective data regarding the prevalence of OSA in children with nonsyndromic cleft palate and the impact of palatoplasty on PSG parameters are needed to guide parental counseling and long-term management in this population.

CONCLUSIONS

The full effect of cleft palate repair on OSA in children with nonsyndromic cleft palate remains understudied. Our study represents the first comprehensive review of the available literature concerning PSG characteristics before and after palatoplasty in nonsyndromic patients. Although the published literature was not sufficient for meta-analysis, we did not find evidence supporting a worsening of OSA following primary palatoplasty in this population. Furthermore, we suggest that patients with nonsyndromic cleft palate likely exhibit different risks of developing OSA compared with syndromic patients, and future efforts should be made to stratify results by syndrome status to provide greater clarity. Subsequent projects should include standardized timing and PSG parameters to provide appropriate guidance for clinical management of OSA.

ABBREVIATIONS

AHI, apnea-hypopnea index
oAHI, obstructive apnea-hypopnea index
OSA, obstructive sleep apnea
PSG, polysomnogram
SD, standard deviation

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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. The authors report no conflicts of interest.