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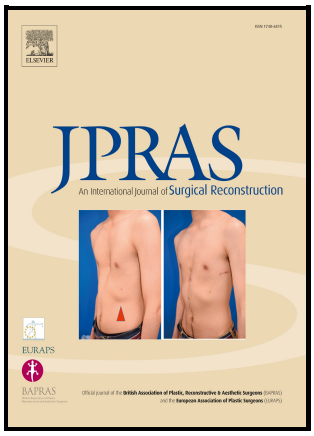


# Nasal airway obstruction in patients with cleft lip nasal deformity: a systematic review

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**Nasal airway obstruction in patients with cleft lip nasal deformity: a systematic review**

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**Abstract (249 of 250 words)**

**Background:** Cleft lip nasal deformity (CLND)-associated nasal airway obstruction (CL-NAO) may be inadequately characterized, with its functional implications subsequently underappreciated and neglected. The purpose of this systematic review is to (1) summarize the available assessment results in CL-NAO, (2) evaluate the reliability of current assessment tools, and (3) identify ongoing gaps and inconsistencies for future study.

**Methods:** A systematic search of the MEDLINE, EMBASE, and Scopus databases was performed for articles studying CL-NAO. Articles focusing on noncleft populations or surgical technique were excluded. Extracted data included information about study design, patient demographics, medical history, and assessment scores.

**Results:** Twenty-six articles met criteria for inclusion. Assessments included patient-reported outcome measures (PROMs), anatomic characterizations of CLND, and nasal airflow and resistance studies. Objective assessments were generally more reliable than subjective assessments in CLND. Unilateral CLND was better represented in the literature than bilateral CLND. For unilateral CLND, the cleft side was more obstructed than the noncleft side with stereotyped patterns of anterior nasal deformity but varied patterns of middle and posterior deformity. Overall, there was considerable heterogeneity in study design regarding stratification of CLND cohorts by age, cleft phenotype and laterality, and surgical history.

**Conclusions:** A wide range of subjective and objective assessment tools were used to characterize CL-NAO, including PROMs, anatomic measurements, and airflow and resistance metrics. Overall, objective assessments of CL-NAO were more reliable than subjective surveys, which may be the result of variable expectations regarding nasal patency in the CLND population combined with large heterogeneity in study design.

**Keywords (4 of 6 keywords):** Cleft Lip; Cleft Palate; Cleft Lip Nasal Deformity; Nasal Airway Obstruction

## 1. INTRODUCTION

Nasal airway obstruction (NAO) impacts patients' well-being and productivity as well as mood, energy, sleep, recreation, and quality of life.[1,2] Etiologies are wide, ranging from inflammatory disease to anatomic abnormalities.[2–4] Orofacial cleft, e.g., cleft lip with/without cleft palate, is a developmental abnormality with characteristic nasal features—cleft lip nasal deformity (CLND). CLND has recently been associated with NAO as well as airway obstruction at multiple anatomic levels leading to an increased risk of mouth breathing and sleep-disordered breathing.[5–7] In unilateral cases (uCLND), the caudal septum is classically described as deviated to the noncleft side with the columella shortened on the cleft side; in bilateral cases (bCLND), the columella is shortened overall with grossly decreased tip projection.[8,9] Because of these distinctive characteristics, a persistent question arises: Does cleft lip-associated NAO (CL-NAO) exhibit dissimilar behavior compared to non-cleft patients with NAO (NC-NAO)?

Although NC-NAO has been studied extensively using patient-reported outcome measures (PROMs) and airflow studies,[3,10,11] CL-NAO remains poorly characterized. A primary challenge inherent to studying CL-NAO stems from the staged nature of CLND surgical repair. Repair typically begins with primary rhinoplasty (at initial lip repair) followed by intermediate rhinoplasty (between 4–10 years of age) and secondary/definitive rhinoplasty (after skeletal maturity).[8] However, there is high variability in surgical decision-making to perform these procedures, not to mention a plethora of available surgical techniques. Consequently, efforts to characterize CL-NAO face the challenge of cohort heterogeneity regarding surgical history. Despite multiple staged surgeries, adults with CLND continue to report nasal obstruction as a primary complaint.[12] Thus, the underlying deformities may be inadequately addressed with current treatment, and there is a need for improved understanding of CL-NAO to refine surgical management and improve outcomes. The purpose of this systematic review is to (1) summarize the available assessment results in CL-NAO, (2) evaluate the reliability of current assessment tools, and (3) identify ongoing gaps and inconsistencies for future study.

## 2. METHODS

### *2.1 Search Strategy and Risk of Bias Assessment*

A systematic search of the MEDLINE, EMBASE, and Scopus databases was performed for CL-NAO using methodology from the 2020 Primary Reporting Items for Systematic Reviews and Meta-analyses guidelines.[13] Search terms were "Cleft" AND ("Nasal Obstruction" OR "Nasal Airway Obstruction") in the title or abstract of studies published prior to June 12, 2023. All studies were imported into Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia). Duplicates were removed, and two authors individually screened articles for inclusion with conflicts settled by a third author. Inclusion criteria were English language full-text articles studying CL-NAO. Exclusion criteria were studies focused only on NC-NAO or surgical techniques, video reports, and articles without full-texts available. The Newcastle-Ottawa Scale was used for quality assessment.[14]

### *2.3 Data Extraction and Analysis*

Extracted information from the articles included study design, year, sample size, and interventions. Primary outcomes were assessment scores, anatomic metrics describing CLND, and airflow parameters. Summary statistics in this review were presented as mean (standard deviation; SD) or median (interquartile range; IQR). Lastly, extracted demographic information and medical history

of study cohorts included age, sex, laterality of cleft, cleft phenotype (e.g., isolated cleft lip or cleft lip and palate), and inclusion/exclusion criteria. As bCLND confers relatively symmetric nasal anatomy compared to uCLND, the two are thought to exhibit different airflow behaviors. Thus, when applicable, the results were presented separately for (1) CLND overall (combining uCLND and bCLND), (2) uCLND alone, and (3) bCLND alone. Additionally, when able, isolated cleft palate—which arises from a different embryological event than cleft lip—was excluded because it does not typically involve the characteristic CLND.[15] To capture CL-NAO prior to definitive surgical intervention, when able, only results from patients without prior definitive or secondary rhinoplasty were included.

## 3. RESULTS

### *3.1 Overview of Study Selection*

The initial search identified one hundred ninety-eight unique articles, of which twenty-six met final criteria for inclusion (Figure 1). Of the included articles, two were fair quality and twenty-four were poor quality on the Newcastle-Ottawa Scale,[14] where a score of 6–9 reflects "good," 3–5 "fair," and 0–2 "poor" regarding the quality of patient selection, comparability of groups, and quality of outcomes and exposures. Despite these quality ratings, the articles were felt to be adequate for inclusion because the ratings were in large part due to study design challenges inherent to studying CLND; as shown in Table 1, many studies focused exclusively on CLND without a comparison control group or planned intervention. Most studies also did not control for age or sex due to relatively small sample size. Overall, the articles covered a wide breadth of assessments for CL-NAO with most articles utilizing more than one metric. These included subjective assessment of nasal obstruction using PROMs, anatomic metrics, and functional evaluations of nasal airflow and resistance. The studies demonstrated high variability in cohort stratification by cleft laterality, cleft phenotype, age, and surgical history. Details of each article and their cohorts and assessments are shown in Table 1.

### *3.2 Patient-Reported Outcome Measures (PROMs):*

Among fourteen articles reporting PROMs, ten used the Nasal Obstruction Symptom Evaluation (NOSE), three used a Visual Analog Scale (VAS), one study used the Standardized Cosmesis and Health Nasal Outcomes Survey (SCHNOS), and one used the Rhinoplasty Outcomes Evaluation (ROE). Two articles used in-house questionnaires that assessed nasal obstruction, though the full questionnaires themselves were not available.

#### *3.2.1 Nasal Obstruction Symptom Evaluation (NOSE)*

NOSE is most frequently used as a quality of life or disease severity measure for patients with NC-NAO,[16] but it has also been adopted by the International Consortium for Health Outcomes Measurement for assessing nasal obstructive symptoms in CLND.[17] Severity on NOSE is generally graded from mild (5–25) to moderate (30–50), severe (55–75), and extreme (80–100).[18] However, there is large variation in how these results can be presented. For example, although most articles in this review reported total NOSE scores, Sobol et al[19] reported isolated scores from each domain of NOSE (Table 2). In addition, Chaithanyaa et al[20] and Carlson et al[21] provided only the distribution of patients within each severity group rather than the numerical scores themselves (Table 2). As such, the results from NOSE in this review are more suitable for comparison by overall severity grade rather than by numerical scores. Moreover, some studies presented aggregate results for all patients with CLND (uCLND and bCLND combined),[19–24] whereas others

presented results for uCLND alone;[7,25–27] there were no studies on bCLND alone (Table 2). In what follows, the results are presented first for uCLND and bCLND combined followed by for uCLND alone. Highlighted results are summarized in Table 2.

NOSE scores for six studies reporting aggregate CLND results (uCLND and bCLND combined) showed variable results (Table 2). Half of the studies (Braun et al[22], Van Zijl et al[23], and Chaithanyaa et al[20]) found that CL-NAO severity was moderate to severe (corresponding to 30–75 on NOSE) while the other half (Carlson et al[21], Sobol et al[19], and Zhang et al[24]) found that CLND-NAO severity was mild to none (corresponding to <30 on NOSE). Notably, these three studies that reported mild to no nasal obstruction were all associated with younger cohorts of mean age <18 years.[19,21,24] In addition, the studies by Carlson et al[21] and Zhang et al[24] permitted a parental proxy for completing the survey.

The four studies that focused solely on uCLND suggested that overall, uCLND was associated with severe obstruction (corresponding to 55–75 on NOSE), although results were also variable (Table 2). Both Frank-Ito et al[7] and Russel et al[25] reported NOSE scores in the severe range, with median NOSE scores of 67.5 (IQR=30) and 65 (IQR=33.75) respectively. Wang et al[26] examined the effects of two different treatment arms (combined Le Fort 1 osteotomy/septoplasty versus osteotomy alone) on nasal obstruction. For this article, the preoperative NOSE scores from each treatment arm were extracted to reflect untreated CLND. However, despite two seemingly similar preoperative cohorts, the combined surgery group had severe obstruction while the single surgery group had mild obstruction, suggesting high selection bias between the treatment arms (Table 2). In another study, Pinto et al[27] compared NOSE scores at five-year follow up between patients who had undergone primary cleft rhinoplasty and those without any prior nasal surgery. As neither group had undergone definitive rhinoplasty, both were considered appropriate for inclusion. At five-year follow up, obstruction severity was worse in the group with no prior nasal surgery than the group that underwent primary cleft rhinoplasty ($p<0.01$).[27]

### *3.2.2 Visual Analog Scale (VAS)*

The Visual Analog Scale (VAS) is a basic psychometric measure scored from 0 (no symptoms) to 10 (worst symptoms possible) that is frequently used to characterize symptomatic burden; in NAO, VAS indicates obstruction severity. Three studies used VAS to evaluate CL-NAO.[23,28,29] Moren et al[28] found that uCLND was associated with significantly worse nasal obstruction symptoms than noncleft healthy controls for bilateral nasal obstruction (median scaled VAS=5.25 versus 0.9, $p<0.001$). Van Zijl et al[23] evaluated unilateral nasal obstruction in CLND (combined uCLND and bCLND) using VAS and found that mean VAS=5.5 (SD=2.7) on the left and mean VAS=6.4 (SD=2.8) on the right. Although there was no breakdown of scores based on cleft versus noncleft side within the uCLND group or comparison between uCLND and bCLND, this study demonstrated one of the primary strengths of VAS over other PROMs: the ability to assess unilateral symptoms. Saito et al[29] also used VAS to assess results for CLND (combined uCLND and bCLND) after maxillary distraction osteogenesis, but no specific VAS scores were reported.

### *3.2.3 Other Patient-Reported Outcome Measures*

A variety of other PROMs were used to assess CL-NAO (Table 1). Russel et al[25] used SCHNOS to characterize CL-NAO. SCHNOS consists of cosmetic (C) and obstructive (O) domains, with the obstructive domain graded from mild (0–40) to moderate (45–75) and severe (75–100)

obstruction.[30] Russel et al[25] found that median SCHNOS-O in uCLND was 60 (IQR=10), corresponding to moderate obstruction. Oommen et al[31] administered the Rhinoplasty Outcome Evaluation (ROE) in a cohort of combined uCLND and bCLND undergoing workup for secondary rhinoplasty. ROE is a survey typically used to quantify patient satisfaction after rhinoplasty regarding nasal appearance, nasal function, and overall quality of life.[32] ROE contains six questions, each scored 0–4, where a higher score is a better outcome.[32,33] Oommen et al[31] found that preoperatively the mean score for nasal obstruction was 1.61 (SD=0.5). Peroz et al[34] and Seixas et al[35] used in-house questionnaires to assess nasal function in CLND. The survey by Peroz et al[34] asked several questions including: "To what level is your nose obstructed?" and "To what extent would you like to improve the function of the nose?" In Seixas et al[35], the questionnaire was composed of three domains: nasal obstruction, oronasal breathing, and respiratory symptoms), though the specific questions were not available.

### *3.3 Anatomic Features of Cleft Lip Nasal Deformity*

Twelve studies characterized nasal anatomy in CLND; of these articles, five were based on in-office evaluation (physical examination, nasal endoscopy, and photogrammetry), ten used computed tomography-derived measurements, and five used supplementary diagnostic assessments including acoustic rhinometry and rhinomanometry (Table 1). Although rhinomanometry is primarily used to measure nasal pressure and airflow, these parameters can be used to predict minimum nasal cross-sectional areas using the pressure-flow technique previously described by Warren et al.[36]

#### *3.3.1 In-Office Evaluation of Nasal Anatomy*

All studies that described nasal anatomy based on in-office evaluation focused on uCLND alone. The findings were consistent with expectations: in nearly all cases, the dorsum deviated to the noncleft side, the septum deviated to the noncleft side, the columella was shortened on the cleft side, and the alar base and nasal tip were the most deformed parts of the nasal airway.[6,27,28] In one study, the cleft side in 15% of uCLND patients was too narrow for insertion of a 4 mm endoscope.[28]

#### *3.3.2 Computed Tomography Generated Anatomic Measurements*

Computed tomography (CT) has increasingly been incorporated into routine preoperative evaluation of CLND for surgical planning. Of ten studies using CT, eight reported CT-derived anatomic measurements. Highlighted results are summarized in Table 3. These included descriptions of septal morphology, measurements of septal deviation and inferior turbinate size, and estimations of nasal cavity volume based on three-dimensional reconstruction of CT images.

Two studies reporting results for CLND overall (combined uCLND and bCLND) found that compared to noncleft healthy patients, CLND was associated with smaller bilateral nasal volumes and worse septal deviation.[37,38] Farzal et al[37] reported that total bilateral nasal volumes in CLND were ~30% smaller than in age-matched noncleft healthy patients ($p<0.05$). Massie et al[38] reported that the septal deviation at three locations from anterior to posterior (anterior nasal spine, posterior nasal spine, and anterior/posterior nasal spine midpoint) was worse in CLND than in age-matched noncleft healthy patients for all locations (all $p<0.05$).

CT-derived measurements were used to describe nasal anatomy in seven studies examining uCLND alone. Three articles evaluated nasal volumes. Of these, Yan et al[39] conducted the largest

study and found that the cleft side nasal volume was smaller than the noncleft side volume ($p<0.0001$). This finding was supported by Friel et al[40] and Russel et al[25], albeit with smaller cohorts (Table 3); Friel et al[40] reported 38.7% smaller nasal volumes on the cleft side than the noncleft side. Although not significantly different ($p=0.06$), Farzal et al[37] noted that the cleft side did have a smaller mean nasal volume compared to the noncleft side (Table 3). Regarding the nasal septum in uCLND, Marcus et al[6] and Massie et al[38] found that the anterior septal deviation was toward the noncleft side for all patients (mean deviation=8.9°), but the behavior of the middle and posterior septum was more variable. In Massie et al[38], the site of maximal septal deviation was ipsilateral to the cleft side in 63.6% of patients but contralateral in 36.4%. Massie et al[38] and Friel et al[40] both identified the midpoint between the anterior and posterior nasal spine as having worse septal deviation than the anterior or posterior nasal spines (Table 3). This midpoint also accounted for the maximal septal deviation in 78% of cases.[38] Similarly, the nasal midpoint was more stenotic than at the anterior and posterior nasal spines ($p<0.001$).[38] Dentino et al[41] characterized inferior turbinate size in uCLND and found that when measured along three evenly spaced cross sections from anterior to posterior along the length of the inferior turbinate, the inferior turbinate on the noncleft side was larger than that on the cleft side ($p=0.003$). Yan et al[39] explored the relationship between septum-inferior turbinate position on unilateral nasal cavity volumes in uCLND. By categorizing uCLND patients into having one of three septum-turbinate positions on the cleft side as such: type 1 (no contact), type 2 (partial contact), and type 3 (complete contact), the authors found that type 3 was associated with significantly decreased cleft side nasal volume compared to types 1 and 2.[39]

When comparing uCLND and bCLND nasal anatomy, Farzal et al[37] found no significant difference between bilateral nasal cavity sizes ($p=0.72$). However, Massie et al[38] found that uCLND had worse septal deviation at the posterior nasal spine than bCLND by nearly 3 mm ($p<0.01$).[33]

### *3.3.3 Anatomic Measurements Using Acoustic Rhinometry and Rhinomanometry*

Acoustic rhinometry (AR) and rhinomanometry (RM) are two diagnostic techniques that allow for the characterization of nasal anatomy. Whereas acoustic rhinometry allows direct measurement of nasal cross-sectional area, rhinomanometry (anterior RM-A or posterior RM-P) can be used to estimate minimum cross-sectional area using the pressure-flow technique.[36] In this review, three studies used AR and two used RM to describe the nasal anatomy in CLND (Table 4).

As shown in Table 4, results using AR and RM to determine bilateral minimum nasal cross-sectional areas in CLND were overall consistent across studies despite different techniques (Fukushiro et al[42], Kunkel et al[43], Seixas et al[26,35], and Wang et al[26]). The range of minimum bilateral cross-sectional areas in these studies was ~0.5–0.8 $cm^2$. When comparing uCLND and bCLND, there was no consistent pattern in nasal cavity dimensions. Fukushiro et al[42] found no significant difference between bilateral minimum cross-sectional areas between uCLND and bCLND but found that bCLND patients more frequently had subnormal nasal cross-sectional areas (clinically defined as <0.4 $cm^2$ for RM-P and <0.5 $cm^2$ for RM-A)[36,42] than uCLND patients (Table 4). On the other hand, Kunkel et al[43] found that bilateral nasal volumes in bCLND were much larger than those in uCLND, while minimum cross-sectional areas were comparable (Table 4). When considering unilateral nasal cavities in uCLND, both minimum cross-sectional area and nasal volume on the cleft side were smaller than on the noncleft side.[43] In uCLND, Wahlmann et

al[44] also found that the cleft side was the site of subnormal minimum cross-sectional area 85% of the time compared to 15% on the noncleft side.

### *3.4 Nasal Resistance and Airflow*

In this review, two studies[25,29] reported nasal resistance and airflow using rhinomanometry, one study[26] used acoustic rhinometry to perform conversion from cross-sectional areas to estimate nasal resistance,[26] and three studies[7,25,45] used computational fluid dynamics (CFD) modeling. CFD technique has become increasingly popular for describing nasal airflow in detail to study NAO.[7,25,45–54] In Saito et al[29], Russel et al[25], and Frank-Ito et al[7], the unilateral nasal resistance in uCLND on the cleft side was consistently greater than on the noncleft side. Likewise, unilateral airflow and airflow partitioning on the cleft side was less than on the noncleft side (Russel et al[25], Frank-Ito et al[7]); based on nasal airflow at a resting inspiratory rate of 15 L/min, Russel et al[25] found that in uCLND, median airflow on the cleft side was 1.27 (IQR=3.30) L/min versus median=13.73 (IQR=3.29) L/min on the noncleft side, corresponding to airflow partitioning of 8.5% on the cleft side and 91.5% on the noncleft side. In Frank-Ito et al[7], the median airflow partitions were 39.3% on the cleft side and 60.7% on the noncleft side.

Although the trends described above regarding cleft and noncleft sides in uCLND were consistent across different techniques for quantifying nasal resistance and airflow dynamics, the numerical airflow parameter values themselves were only comparable when similar techniques were used. For example, Saito et al[29] and Russel et al[25] reported similar bilateral nasal resistance using RM-A (mean=0.57, SD=0.11 Pa-s/mL and median=0.88, IQR=2.64 Pa-s/mL, respectively). However, even within the same study but using different methods for determining nasal resistance, Russel et al[25] found that bilateral nasal resistance calculated by CFD was median=0.10 (IQR=0.12) Pa-s/mL compared to median=0.88 (IQR=2.64) by rhinomanometry. Likewise, calculations of bilateral nasal resistance based on acoustic rhinometry measurements by Wang et al[26] were approximately an order of magnitude larger than those by other methods. Demonstrating the unique features of CFD analysis, Tillis et al[45] performed virtual surgery in CLND and analyzed subsequent nasal airflow behavior.

## 4. DISCUSSION

To our knowledge, this systematic review is the first to study subjective and objective measures of NAO in the CLND population. A wide range of ages and cleft phenotypes were represented in these articles. Most studies used PROMs and CT-derived anatomic measurements to assess the severity of CL-NAO. There were no articles on bCLND alone, whereas there were twelve articles on uCLND alone and fourteen studies on both uCLND and bCLND (Table 1). For uCLND in these cohorts, the anterior nasal deformity reliably featured anterior septal deviation toward the noncleft side, dorsal deviation to the noncleft side, and shortened columella on the cleft side.[6,27,28,38] However, the middle and posterior third of the nasal cavities were not as stereotyped. These regions contained the largest septal deviations and worst regions of stenosis, which could occur on either side (cleft or noncleft).[6,7,38,40] Perhaps it is this region of the middle to posterior nasal cavity that is inadequately addressed in cleft rhinoplasty, leaving adult CLND patients with persistent nasal obstruction despite multiple nasal surgeries; further anatomic studies are necessary to better describe the middle to posterior deformity. The cleft side was smaller than the noncleft side with regards to unilateral nasal volume and cross-sectional area, and the majority of airflow passed through the noncleft side due to higher nasal resistance on the cleft side. Notably, no studies

emphasized external nasal valve collapse as a primary contribution to nasal obstruction, despite the known external nasal deformity in CLND; this is likely due to challenges inherent to characterizing the dynamic nature of this anatomic region, especially using CT imaging. Overall, uCLND was better characterized in the literature than bCLND, likely due to its relatively higher prevalence. The relative severity of nasal obstructive symptoms and nasal cavity size between uCLND and bCLND remains unclear.[37,42,43]

Results from PROMs for assessing CL-NAO were highly variable. As the recommended survey for assessment of CLND-NAO by International Consortium for Health Outcomes Measurement, NOSE was the most commonly administered PROM. However, NOSE scores were strikingly heterogeneous in the included articles, fluctuating between mild/no obstruction to severe obstruction in seemingly similar cohorts. In what follows, we identify two explanations for this inconsistency.

Firstly, these variations may in part be due to the many challenges inherent to studying CLND. There was highly variable in study design regarding (1) stratification by cohort cleft phenotypes and surgical history, (2) specific reported outcomes (i.e., mean/median composite score, mean/median individual question score, percentage cohort breakdown by severity), and (3) method of data collection leading to selection and response bias. Heterogeneity in surgical history may lead to an inaccurate representation of untreated CL-NAO. To help overcome this problem, the current review excluded populations with prior definitive rhinoplasty, but as shown by Pinto et al[27], even primary rhinoplasty can have downstream effects on NOSE scores. In addition, Sobol et al[19] found that age and specific cleft pathology (e.g., isolated cleft lip or complete cleft lip and palate) affected CLND-NAO severity. Although some articles only enrolled subjects with age >17 to control for anatomic changes with growth, the age ranges in other articles varied widely. Articles reporting lower NOSE scores tended to also be associated with younger cohort ages, suggesting age dependence.[19,21,24] The circumstances for CLND-NAO evaluation are also likely to have an effect on PROM scores—NOSE scores from routine annual visits (such as in Zhang et al[24]) tended to be lower than those from pre-operative evaluations, which likely capture more symptomatic patients requiring surgical intervention. Improved stratification in future studies would improve the reliability of inter-study comparisons and could allow for meta-analyses.

Secondly, PROMs themselves may be poor markers of NAO severity in the CLND population due to the intrinsic significant nasal deformity with which CLND patients are born. As such, CLND patients may have different expectations for nasal patency compared to NC-NAO. While the CLND cohorts encompassed a range of NOSE severity similar to that of NC-NAO,[10] nasal resistances in CL-NAO (determined using RM) were higher than those reported in the literature for NC-NAO—by more than a factor of 10.[25,55] Thus, the utility of PROMs may be limited in CL-NAO, or the NOSE may be inadequate for assessing CL-NAO .

Objective metrics demonstrated better inter-study reliability than PROMs in this review. Metrics of nasal anatomy were comparable among similar CLND populations between different studies. Trends identified by nasal resistance and airflow analysis were also consistent across different studies, although the numerical values themselves depended on measurement technique. For example, nasal resistance measurements using AR, RM, and CFD were different, but the trends identified when using each technique were similar. The discrepancies between numeric values

when using different techniques to measure airflow metrics have previously been described and are likely due to inconsistencies in experimental setup related to fixed conditions of airflow rate or nasal pressure.[56]

Overall, in CL-NAO, subjective measures appear to have limited utility, whereas objective metrics more reliably represent CL-NAO severity, particularly when assessing trends in the context of an intervention or when making comparison between different CLND groups. For reference, in NC-NAO, prior authors have favored subjective measures over objective measures of nasal obstruction because objective measures are felt to capture only a single moment in time, rather than an average of symptoms over weeks, thus inadequately capturing the dynamic effects of nasal cycling.[57] However, with increased symptomatic severity in NC-NAO, there is also higher correlation between subjective and objective measures. This is likely because the static contribution to nasal obstruction overwhelms the effects of nasal cycling in these cases. In CL-NAO, the high degree of nasal resistance relative to that in NC-NAO is perhaps the reason why there is greater consistency among objective assessment tools. On the other hand, CLND patients with significant nasal deformity likely have different expectations regarding the sensation of nasal patency, thus leading to the variability in subjective scores described in this study.

## 5. CONCLUSION

This systematic review presents a critical overview of published literature regarding CL-NAO. A wide range of subjective and objective assessment tools were used including PROMs, anatomic measurements, and airflow and resistance metrics. Overall, objective assessments of CLND-NAO were more reliable than subjective surveys, which may be due to variable expectations regarding nasal patency in the CLND population combined with large heterogeneity in study design. Necessary changes to future study design include the need to (1) define standardized classifications schemes for CLND pathology with appropriate grouping of cohorts, (2) further explore objective assessments for CL-NAO, borrowing techniques from the robust non-cleft NAO literature, and (3) design a new subjective nasal obstruction measure specifically for CLND that more adequately reflects and concerns and symptoms of this population.

## 6. ACKNOWLEDGEMENTS/FUNDING

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## 7. CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report.

## 8. ETHICAL APPROVAL

Not required

## 8. FIGURE LEGENDS

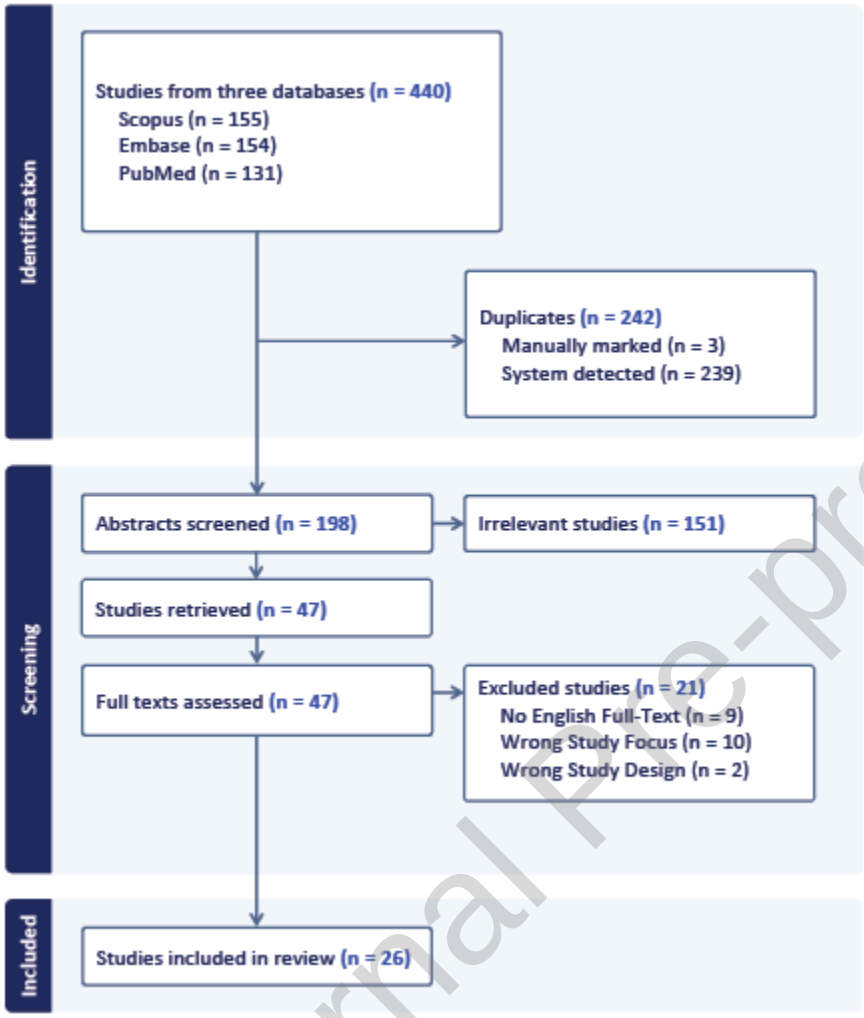


Figure 1. PRISMA diagram of search strategy with twenty-six included articles.



## 9. TABLES

Table 1. Included articles with study design, cohort information, interventions, and assessments.

| Author, Year | Study Design | Cohort Breakdown | Control (Y/N) | Age | Sex | Intervention | Assessments |
|---|---|---|---|---|---|---|---|
| Braun, 2023 | Cross Sectional | 32 CLP<br>22 CP<br>9 CL | N | Mean 43.7 years<br><br>Range 19–93 years | 23 M, 40 F | None | NOSE |
| Carlson, 2023 | Retrospective Cohort | 61 uCLP<br>19 bCLP | N | Mean 8 years<br><br>Range 7–16.2 years | 42 M, 38 F | Secondary Rhinoplasty | NOSE |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Chaithanyaa, 2011 | Prospective Cohort | 7 uCLP<br>3 bCLP | N | Mean 20.4 years<br><br>Range 15–40 years | 3 M, 7 F | Secondary Rhinoplasty | NOSE, PE |
| Dentino, 2016 | Retrospective Cohort | 53 uCLP | N | Mean 12.2 (SD=0.8) years | 21 M, 32 F | None | CT |
| Farzal, 2016 | Retrospective Case Control | 10 uCLP<br>10 bCLP | Y | Mean 8.3 (SD=1.2) years | 14 M, 6 F | None | CT |
| Frank-Ito, 2019 | Retrospective Case Control | 8 uCLP | Y | Range 15–46 years | 2 M, 6 F | None | NOSE, CT, CFD |
| Friel, 2015 | Retrospective Case Control | 22 uCLP | Y | Mean 10.8 years<br><br>Range 6.8–17.9 years | N/A | None | CT |
| Fukushiro, 2005 | Prospective Case Control | 16 uCLP<br>17 bCLP<br>20 CP (excluded) | Y | Range 18–35 years | 32 M, 21 F | None | RMM |
| Kunkel, 1997 | Retrospective Case Control | 23 uCLP<br>17 bCLP | Y | Range 7–38 years | N/A | None | AR |
| Marcus, 2019 | Retrospective Cohort | 25 uCLND | N | Mean 21 years<br><br>Range 15–32 years | N/A | None | PE, CT |
| Massie, 2016 | Retrospective Case Control | 11 uCLP<br>13 bCLP | Y | Mean 21 (SD=5) years<br><br>Range 15–33 years | 19 M, 5 F | None | CT |
| Moren, 2013 | Cross Sectional | 83 uCLP | Y | Range 20-47 years | 45 M, 38 F | None | PE, VAS |
| Oommen, 2019 | Prospective Cohort | 19 uCLND<br>7 bCLND | N | Mean 20 years<br><br>Range 18–23 years | 15 M, 11 F | Secondary Rhinoplasty | ROE |
| Peroz, 2017 | Cross Sectional | 83 uCLP | Y | Range 20-47 years | 46 M, 37 F | None | AR, RMM, In-House Questionnaire |
| Pinto, 2018 | Retrospective Case Control | 40 uCLP | N | N/A | N/A | None | NOSE, PE |
| Russel, 2023 | Prospective Cohort | 5 uCLND | N | Mean 20 years<br><br>Range 18–23 years | 3 M, 2 F | Secondary Rhinoplasty | NOSE, SCHNOS-O, CT, RMM |

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|---|---|---|---|---|---|---|---|
| Saito, 2006 | Prospective Cohort | 9 uCLP<br>4 bCLP | N | Mean 18.5 years<br><br>Range 11.8–33.6 years | 9 M, 4 F | Distraction Osteogenesis | VAS, RMM |
| Seixas, 2022 | Retrospective Cohort | 235 uCLP<br>196 bCLP<br>34 CP (excluded) | N | Mean 24.4 (SD=5.2) years<br><br>Range 18–45 years | 317 M, 218 F | Orthognathic Surgery | RMM, In-House Questionnaire |
| Sobol, 2016 | Cross Sectional | 38 CL+/-A<br>79 CLP<br>59 CP | Y | Mean 13.4 (SD=2) years<br><br>Range 9.9–17 years | 106 M, 70 F | None | NOSE |
| Starbuck, 2014 | Retrospective Cohort | 29 uCLP<br>21 bCLP | N | Mean 11 years<br><br>Range 7–18 years | 37 M, 13 F | None | CT |
| Tillis, 2022 | Experimental Case Study | 1 uCLP | N | 15 years | 1 F | Virtual Surgery | CT, CFD |
| van Zijl, 2018 | Prospective Cohort | 81 uCLND<br>22 bCLND | N | Mean 23 years<br><br>Range 17–68 years | 68 M, 55 F | None | NOSE, VAS |
| Wahlmann, 1998 | Prospective Cohort | 23 uCL(P) | N | N/A | N/A | None | AR |
| Wang, 2017 | Prospective Cohort | 23 uCLP | N | Mean 20.5 years<br><br>Range 18–25 years | 13 M, 10 F | Le Fort I Osteotomy +/- Rhinoplasty | NOSE, PE, AR |
| Yan, 2021 | Retrospective Cohort | 234 uCLA | N | Range 9–17 years | 132 M, 102 F | None | CT |
| Zhang, 2019 | Cross Sectional | 34 Submucosal<br>37 Veau 1<br>106 Veau 2<br>178 Veau 3<br>92 Veau 4<br>9 CLA | N | Mean 10.1 (SD=4.5) years | 255 M, 201 F | None | NOSE |

Abbreviations: Cleft Lip/Palate (CLP), Cleft Palate (CP), Cleft Lip (CL), Cleft Lip/Alveolus (CLA), Cleft Lip Nasal Deformity (CLND), Nasal Obstruction Symptom Evaluation (NOSE), Physical Examination (PE), Computer Tomography (CT), Computational Fluid Dynamics (CFD), Rhinomanometry (RMM), Acoustic Rhinometry (AR), Visual Analog Scale (VAS), Standardized Cosmesis and Health Nasal Outcomes Survey (SCHNOS)

Table 2. Summarized results from Nasal Obstruction Symptom Evaluation.

| Author, Year | Cohort | Total Cohort Size | Reported Data | Summarized Results |
|---|---|---|---|---|
| Braun, 2023 | uCLND and bCLND | 63 | Mean (SD) composite NOSE | Composite NOSE mean=36.3 (SD=26.4) |
| Van Zijl, 2018 | uCLND and bCLND | 103 | Mean (SD) composite NOSE | Composite NOSE mean=34.2 (SD=29.4) |
| Chaithanyaa, 2011 | uCLND and bCLND | 10 | Composite NOSE severity distribution | Composite NOSE distribution:<br>80% moderate<br>20% severe |
| Carlson, 2023* | uCLND and bCLND | 80 | Composite NOSE severity distribution | Composite NOSE distribution:<br>76.3% mild<br>18.8% moderate<br>3.8% significant<br>0% severe |
| Sobol, 2016* | uCLND and bCLND (sorted by phenotype) | 176 | Individual domain NOSE severity distribution | Summarized individual NOSE domain distributions:<br>Nasal Congestion 49.4–71.0% none to mild<br>Nasal Blockage 76.3–92.1% none to mild<br>Nasal Breathing 67.6–86.8% none to mild<br>Trouble Sleeping 74–89.5% none to mild<br>Exercise limitation 81.6–94.7% none to mild |
| Zhang, 2019 | uCLND and bCLND | 456 | Mean (SD) composite NOSE | Composite NOSE mean=19.75 (SD=20.25) |
| Frank-Ito, 2019 | uCLND | 8 | Median (IQR) composite NOSE | Composite NOSE median=67.5 (IQR=30) |
| Russel, 2023 | uCLND | 5 | Median (IQR) composite NOSE | Composite NOSE median=65 (IQR=33.75) |
| Wang, 2017 | uCLND (pre-op for LF1 alone versus LF1/S) | 23 | Mean (SD) composite NOSE | Pre-op LF1: Composite NOSE mean=13.15 (SD=8.45)<br>Pre-op LF1/S: Composite NOSE mean=76.65 (SD=8.05) |
| Pinto, 2018 | uCLND (5-year follow up after NNS versus 1°CR) | 40 | Mean (SD) composite NOSE | NNS: Composite NOSE mean=70.8 (SD=17.2)<br>1°CR: Composite NOSE mean=21.9 (SD=9.4) |

*Parental proxy permitted

Abbreviations: Cleft Lip Nasal Deformity (CLND), Nasal Obstruction Symptom Evaluation (NOSE), LeFort I Osteotomy (LF1), Septoplasty (S), No Nasal Surgery (NNS), Primary Cleft Rhinoplasty (1°CR)

Table 3. Summarized Results of Computed Tomography-Derived Anatomic Metrics

| Author, Year | Cohort | Total Cohort Size | Reported Data | Summarized Results |
|---|---|---|---|---|
| Farzal, 2016 | uCLND and bCLND | 20 | Mean (SD) unilateral and bilateral nasal volume | Bilateral uCLND nasal volume=7.10 (SD=2.60) $cm^3$<br>Unilateral uCLND cleft nasal volume=3.33 (SD=1.34) $cm^3$; noncleft=3.77 (SD=1.35) $cm^3$<br>Bilateral bCLND nasal volume=6.72 (SD=2.12) $cm^3$ |
| Massie, 2016 | uCLND and bCLND | 24 | Mean (SD) septal deviation at ANS/MNS/PNS; maximal septal deviation | ANS septal deviation=2.1 (SD=0.5) mm<br>MNS septal deviation=4.4 (SD=0.6) mm<br>PNS septal deviation (not reported)<br>Maximal septal deviation=5.6 (SD=0.7) mm |
| Yan, 2021 | uCLND | 234 | Mean (SD) unilateral nasal volume (by septum-inferior turbinate relationship) | Unilateral type 1 cleft nasal volume=6.03 (SD=0.24) $cm^3$; noncleft=6.63 (SD=0.22) $cm^3$<br>Unilateral type 2 cleft nasal volume=5.91 (SD=0.21) $cm^3$; noncleft=6.74 (SD=0.28) $cm^3$<br>Unilateral type 3 cleft nasal volume=4.31 (SD=0.19) $cm^3$; noncleft=6.69 (SD=0.23) $cm^3$ |
| Friel, 2015 | uCLND | 22 | Mean unilateral nasal volumes at anterior, middle, and posterior nasal cavity thirds; mean septal deviation at ANS/MNS/PNS | Unilateral anterior cleft nasal volume=1.57 $cm^3$; noncleft=1.96 $cm^3$<br>Unilateral middle cleft side nasal volume=1.80 $cm^3$; noncleft=2.60 $cm^3$<br>Unilateral posterior cleft side nasal volume=2.53 $cm^3$, noncleft=3.62 $cm^3$<br>ANS septal deviation=4.99 mm<br>MNS septal deviation=5.71 mm<br>PNS septal deviation=5.37 mm |
| Russel, 2023 | uCLND | 5 | Median (IQR) unilateral nasal volumes | Unilateral cleft nasal volume=5.27 (IQR=2.92) $cm^3$<br>Unilateral noncleft nasal volume=10.70 (IQR=4.13) $cm^3$ |
| Marcus, 2019 | uCLND | 25 | Mean anterior septal deviation angle | Anterior septal deviation angle=8.9° |
| Dentino, 2016 | uCLND | 53 | Mean (SD) unilateral IT CSA along anterior/middle/posterior thirds | Unilateral anterior cleft IT CSA=10.3 (SD=4.0) $mm^2$; noncleft=12.6 (SD=5.3) $mm^2$<br>Unilateral middle cleft IT CSA=10.4 (SD=4.1) $mm^2$; noncleft=13.2 (SD=5.0) $mm^2$<br>Unilateral posterior cleft IT CSA=8.4 (SD=3.9) $mm^2$; noncleft=9.6 (SD=3.6) $mm^2$ |

Abbreviations: Cleft Lip Nasal Deformity (CLND), Anterior Nasal Spine (ANS), Midpoint of Anterior/Posterior Nasal Spine (MNS), Posterior Nasal Spine (PNS), Inferior Turbinate (IT), Cross Sectional Area (CSA)

Table 4. Summarized Results of Acoustic Rhinometry and Rhinomanometry-Derived Anatomic Metrics

| Author, Year | Cohort | Total Cohort Size | Diagnostic Technique | Select Reported Data | Summarized Results |
|---|---|---|---|---|---|
| Fukushiro, 2005 | uCLND and bCLND | 33 | RM-A, RM-P | Mean (SD) bilateral mCSA (RM-A and RM-P); % patients with subnormal unilateral mCSA* (RM-A and RM-P) | Bilateral uCLND mCSA (RM-A)=0.57 (SD=0.19) $cm^2$<br>Bilateral uCLND mCSA (RM-P)=0.47 (SD=0.16) $cm^2$<br>Bilateral bCLND mCSA (RM-A)=0.57 (SD=0.21) $cm^2$<br>Bilateral bCLND mCSA (RM-P)=0.51 (SD=0.21) $cm^2$<br>Subnormal unilateral mCSA (RM-A): 31% uCLND, 59% bCLND<br>Subnormal unilateral mCSA (RM-P): 19% uCLND, 41% bCLND |
| Kunkel, 1997 | uCLND and bCLND | 40 | AR | Mean (SD) unilateral nasal volume (AR); mean (SD) unilateral mCSA (AR) | uCLND cleft nasal volume=6.9 (SD=1.7) $cm^3$<br>uCLND noncleft nasal volume=12.4 (SD=4.3) $cm^3$<br>uCLND cleft mCSA=0.31 (SD=0.1) $cm^2$<br>uCLND noncleft mCSA=0.52 (SD=0.1) $cm^2$<br>bCLND right nasal volume=11.3 (SD=3.9) $cm^3$<br>bCLND left nasal volume=11.3 (SD=4.1) $cm^3$<br>bCLND right mCSA=0.47 (SD=0.2) $cm^2$<br>bCLND left mCSA=0.46 (SD=0.2) $cm^2$ |
| Seixas, 2022 | uCLND and bCLND | 431 | RM-A, RM-P | Mean (SD) bilateral mCSA (RM-A and RM-P) | Bilateral uCLND mCSA (RM-A)=0.56 (SD=0.17) $cm^2$<br>Bilateral uCLND mCSA (RM-P)=0.52 (SD=0.18) $cm^2$<br>Bilateral bCLND mCSA (RM-A)=0.0.59 (SD=0.21) $cm^2$<br>Bilateral bCLND mCSA (RM-P)=0.54 (SD=0.18) $cm^2$ |
| Wang, 2017 | uCLND (pre-op for LF1 alone versus LF1/S) | 23 | AR | Mean (SD) bilateral nasal volume (AR); mean (SD) bilateral mCSA | Bilateral nasal volume (LF1)=12.78 (SD=2.84) cm3<br>Bilateral nasal volume (LF1/S)=13.29 (SD=4.15) cm3<br>Bilateral mCSA (LF1)=0.47 (SD=0.09) cm2<br>Bilateral mCSA (LF1/S)=0.47 (SD=0.10) cm2 |

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|---|---|---|---|---|---|
| Wahlmann, 1998 | uCLND | 23 | AR | % subnormal unilateral mCSA* (AR) on cleft versus noncleft sides | Subnormal unilateral mCSA (AR): 85% on cleft side, 15% noncleft side |

* Threshold for subnormal mCSA is <0.50 cm² for RM-A and <0.40 cm² for RM-P and AR, as defined by Hinton et al and Fukushiro et al

Abbreviations: Cleft Lip Nasal Deformity (CLND), Rhinomanometry (RM, -Anterior, -Posterior), Minimum Cross-Sectional Area (mCSA), Acoustic Rhinometry (AR), LeFort I Osteotomy (LF1), Septoplasty (S)

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