RESEARCH PAPER

Predictors and Modifiers of Nasal Airway Functional Response to Rapid Maxillary Expansion in Growing Patients with Maxillary Transverse Deficiency: A Systematic Review

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ABSTRACT

Importance: Rapid maxillary expansion (RME) is widely used to correct maxillary transverse deficiency in growing patients and may also improve nasal airway function. Although previous clinical studies and systematic reviews have reported improvements in nasal airflow, nasal airway resistance, and nasal airway dimensions following RME, the magnitude of response varies considerably among patients. The baseline orthodontic, skeletal, nasal, and upper-airway characteristics that may predict or modify this functional response remain incompletely characterized.

Objective: To systematically evaluate and synthesize the evidence regarding baseline patient, orthodontic, skeletal, nasal, and upper-airway characteristics that predict or modify nasal airway functional response to RME in growing patients with maxillary transverse deficiency.

Data Sources: MEDLINE/PubMed, Embase, Scopus, Web of Science, Cochrane CENTRAL, and Dentistry & Oral Sciences Source will be systematically searched from database inception through 21ST **JULY 2026**. Reference lists of included studies and relevant systematic reviews will also be screened for additional eligible studies.

Study Selection: Studies involving growing patients with maxillary transverse deficiency, maxillary constriction, or posterior crossbite who underwent nonsurgical RME were eligible. Studies were required to evaluate at least 1 objective or validated subjective measure of nasal airway function and to report either the magnitude of functional change following RME or an association between baseline characteristics and treatment response. Randomized clinical trials and prospective or retrospective observational studies will be considered.

Data Extraction and Synthesis: Two reviewers will independently screen studies, extract data, and assess risk of bias using design-appropriate validated tools. Extracted variables will include patient age and sex, severity of maxillary transverse deficiency, crossbite characteristics, baseline nasal airway status, adenoid and inferior turbinate hypertrophy, septal deviation, RME appliance and activation protocol, magnitude of expansion, follow-up duration, and nasal functional outcomes. Where sufficient clinical and methodological homogeneity exists, random-effects meta-analysis will be performed. Otherwise, findings will be synthesized narratively.

Main Outcomes and Measures: The primary outcome will be change in objective nasal airway function following RME, including nasal airway resistance, nasal airflow, and peak nasal inspiratory flow. Secondary outcomes will include acoustic rhinometry parameters, nasal airway cross-sectional area or volume, and validated patient-reported measures of nasal obstruction. The principal exposure of interest will be baseline characteristics associated with greater or lesser functional response to RME.

Results: The review will report the number and characteristics of eligible studies, risk of bias, magnitude of nasal functional change following RME, and evidence regarding potential predictors and modifiers of treatment response. Where appropriate, pooled estimates will be reported with 95% CIs, measures of heterogeneity, and certainty of evidence.

Conclusions and Relevance: This systematic review will synthesize current evidence regarding factors associated with nasal airway functional response to RME in growing patients with maxillary transverse deficiency. Particular attention will be given to the potential modifying effects of transverse skeletal deficiency, crossbite characteristics, baseline nasal airway obstruction, adenoid hypertrophy, inferior turbinate hypertrophy, septal deviation, age, and treatment-related factors. Identification of consistent response modifiers may help inform

individualized orthodontic–otolaryngologic assessment and guide future prospective studies aimed at developing and validating clinically useful prediction models.

Keywords: rapid maxillary expansion; maxillary transverse deficiency; nasal airway; nasal airway resistance; rhinomanometry; acoustic rhinometry; nasal obstruction; predictors; treatment response; children; adolescents; systematic review.

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INTRODUCTION

Background and Clinical Context

Maxillary transverse deficiency (MTD), characterized by a constricted maxillary arch relative to the mandibular base, is among the most prevalent skeletal malocclusions encountered in the growing dentition, with reported prevalence rates of 8% to 15% in mixed and permanent dentitions.[1,2] The clinical presentation typically includes posterior crossbite (unilateral or bilateral), dental crowding, and associated esthetic concerns.

Rapid maxillary expansion (RME) has been the established standard of care for MTD in skeletally immature patients since the mid-20th century.[3] The intervention uses mechanical force to induce separation at the midpalatal suture, widening the maxillary intermolar, interpremolar, and intercanine dimensions through orthopaedic distraction osteogenesis. Beyond its primary effect of correcting the transverse skeletal discrepancy and resolving posterior crossbite, RME also produces widening of the nasal base and increases in nasal cavity volume and airflow dimensions due to the anatomical continuity between the maxillary arch and the nasal floor.[4]

Nasal Airway Outcomes and Current Evidence

Beginning in the late 20th century, clinicians and researchers recognized the potential of RME to improve nasal airway function in addition to correcting the dentofacial skeleton.[5] Subsequent studies have documented group-level improvements in objective measures of nasal airway function following RME, including reductions in nasal airway resistance,[6–8] increases in peak nasal inspiratory flow (PNIF),[9,10] and improvements in nasal cavity dimensions as measured by acoustic rhinometry.[11,12] Additionally, improvements in patient-reported nasal obstruction symptoms and quality of life measures have been documented in prospective studies.[13,14]

A landmark prospective study by Monini and colleagues demonstrated that RME produced statistically significant reductions in nasal airway resistance and improvements in nasal airflow in a cohort of 65 children with maxillary constriction and nasal obstruction symptoms, with functional improvements remaining stable at one-year follow-up.[6] This publication substantially advanced the evidence base regarding RME's effects on nasal physiology and contributed to increasing clinical adoption of RME partly or primarily for respiratory indications in selected paediatric patients.

The Problem of Interindividual Response Variability

Despite the evidence for group-level nasal functional benefit, considerable variability in individual treatment response has been consistently observed across published studies. For example, in the Monini cohort of 65 patients, although mean nasal airway resistance decreased significantly, individual responses ranged from substantial improvement to minimal change or worsening.[6] Similar patterns of variable response have been noted in subsequent prospective studies and in observational cohort analyses.[15,16]

This heterogeneity in treatment response has important clinical implications. Patients and families often seek RME partly for nasal respiratory benefit, and clinicians face uncertainty regarding which individual patients are most likely to achieve meaningful functional improvement. Additionally, some patients may experience minimal nasal functional benefit from skeletal expansion alone and would benefit from adjunct or alternative otolaryngologic interventions.

Potential Response Modifiers: Current Understanding

Multiple baseline patient, orthodontic, skeletal, nasal, and upper-airway characteristics may plausibly influence the magnitude of nasal functional response to RME. These include:

- **Orthodontic and skeletal characteristics:** Severity of baseline maxillary transverse deficiency (e.g., intermolar width deficiency), laterality and severity of posterior crossbite, and overall craniofacial morphology (vertical dimension, anterior-posterior skeletal relationships)
- **Nasal airway status:** Baseline nasal airway dimensions and resistance, nasal septal morphology, and nasal valve geometry
- **Upper-airway anatomy:** Adenoid size and degree of nasopharyngeal obstruction, inferior turbinate hypertrophy, nasal floor configuration, and other structural factors
- **Patient demographics:** Age, sex, body mass index (BMI), and overall upper-airway morphology
- **Treatment-related factors:** Magnitude of RME achieved, activation protocol, appliance type, and duration of active expansion

However, the relative importance and independent contributions of these potential predictors and modifiers remain incompletely understood. Furthermore, the existing literature has not been systematically and comprehensively synthesized to identify which baseline characteristics are most consistently and robustly associated with greater or lesser nasal functional response across studies.

Rationale for This Systematic Review

A systematic review and meta-analysis addressing this question is warranted for several reasons:

- **Clinical decision-making:** Identifying reliable predictors of nasal functional response would enable more precise pre-treatment assessment and counselling, allowing clinicians to set realistic expectations and optimize patient selection when respiratory benefit is considered part of the treatment rationale.
- **Interdisciplinary planning:** Understanding which patient populations are less likely to achieve meaningful respiratory benefit from skeletal expansion alone may guide treatment sequencing and coordination between orthodontists and otolaryngologists (eg, sequencing of adenoidectomy and RME).
- **Future research direction:** Synthesizing existing evidence regarding response modifiers will inform the design of future prospective studies aimed at developing and externally validating robust clinical prediction models.
- **Evidence synthesis:** Although multiple studies have addressed nasal functional outcomes following RME, no comprehensive systematic review has synthesized this evidence with explicit attention to predictors and modifiers of treatment response.

The conceptual framework guiding this review is presented in **Figure 1**. This framework illustrates the hypothesized relationships between rapid maxillary expansion and nasal airway functional response, while highlighting the baseline characteristics that may predict or modify this response. By systematically identifying and synthesizing evidence regarding each domain of predictors—orthodontic and skeletal factors, nasal and upper-airway anatomy, demographic characteristics, and treatment-related factors—this review will provide a comprehensive evidence base for understanding individual variability in treatment response.

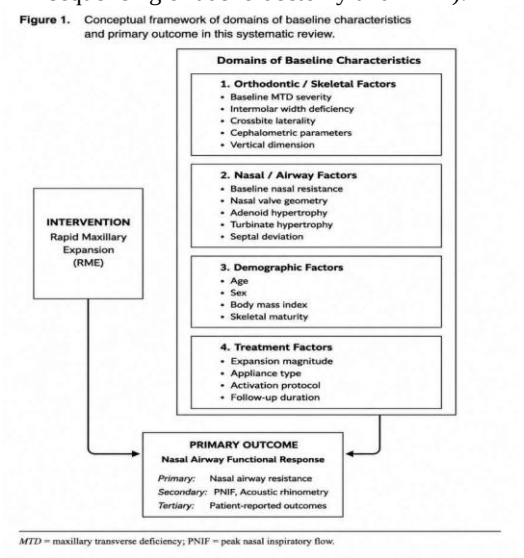

Figure 1: Conceptual Framework of Potential Predictors and Modifiers of Nasal Airway Functional Response to Rapid Maxillary Expansion

Figure 1 Caption: This conceptual framework illustrates the primary intervention (rapid maxillary expansion) and the primary outcome domain (nasal airway functional response), as well as the four major categories of baseline patient, anatomical, and treatment characteristics investigated in this systematic review as potential predictors or modifiers of treatment response. Orthodontic and skeletal factors reflect the underlying dentofacial anatomy; nasal and upper-airway factors encompass structural contributors to baseline obstruction; demographic factors include intrinsic patient characteristics; and treatment factors include intervention-specific parameters that may influence the magnitude of functional improvement.

The present systematic review will comprehensively identify, appraise, and synthesize evidence regarding baseline characteristics associated with nasal airway functional response to RME in growing patients with MTD, providing an evidence-based foundation for clinical decision-making and future research.

METHODS

Protocol and Registration

This systematic review and meta-analysis will be conducted and reported in accordance with the Preferred Reporting Items for Systematic

Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist[17] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[18] The protocol was prospectively registered with the Open Science Framework (OSF Registries; identifier: XXXXX) prior to initiation of the systematic literature search.

Eligibility Criteria

Study Design

The review will include randomized controlled trials (RCTs), prospective cohort studies, and retrospective cohort studies. Single-case reports, letters to the editor, commentaries, and editorials will be excluded. No language restrictions will be applied; studies published in non-English languages will be translated for eligibility assessment and data extraction.

Participants

Eligible studies must enrol growing patients (defined as age <21 years or explicitly documented as skeletally immature, e.g., Cervical Vertebral Maturation stage <6 or open midpalatal sutures) with a clinical and/or radiographic diagnosis of maxillary transverse deficiency, maxillary constriction, or posterior crossbite (unilateral or bilateral). Studies enrolling mixed populations (skeletally mature and immature patients) are eligible if the skeletally immature subgroup is either analysed separately or comprises at least 80% of the study population.

Exclusion criteria

Studies enrolling patients with craniofacial syndromes (e.g., cleft lip and palate, Down syndrome, apert syndrome), hypodontia or severe dental anomalies, or patients who had undergone prior maxillofacial surgery, orthognathic surgery, or prior orthodontic treatment will be excluded, as these conditions may substantially alter baseline anatomy and treatment response.

Interventions

Studies evaluating nonsurgical RME using any appliance type (tooth-borne, tissue-borne, hybrid designs; banded, bonded, or mixed retention) and any activation protocol will be eligible. Studies comparing RME to no treatment, alternative interceptive treatments, or adjunct procedures (e.g., concurrent adenoidectomy) will all be included.

Comparators

Studies with or without a control/comparison group are eligible. Control groups may include untreated patients with similar diagnoses, patients receiving alternative treatments, or within-patient comparisons at baseline and follow-up.

Outcomes

Primary outcomes: Objective measures of nasal airway function, including:

- Nasal airway resistance (measured by active anterior rhinomanometry [AAR], in $Pa \cdot cm^{-3} \cdot s$ or equivalent units)
- Peak nasal inspiratory flow (PNIF, in L/min or equivalent)
- Acoustic rhinometry (AR) parameters: minimum cross-sectional area (MCA, cm^2) and nasal cavity volume (NCV, cm^3)

Secondary outcomes:

- Validated, patient-reported measures of nasal obstruction severity (e.g., Nasal Obstruction Symptom Evaluation [NOSE] scale, visual analog scale [VAS] for nasal obstruction)
- Nasal septal deviation or other anatomical measures of nasal structure
- Subjective reports of nasal obstruction improvement or symptom resolution
- Sleep-related outcomes (e.g., apnea-hypopnea index, snoring frequency, sleep quality measures, if reported in conjunction with nasal functional assessments)

Studies must explicitly report the magnitude of change in at least one primary outcome measure (nasal airway resistance, PNIF, or AR parameters) from baseline to at least one post-expansion time point. Studies reporting only baseline-to-follow-up correlations or associations between baseline characteristics and treatment response (without reporting absolute magnitude of change) are eligible for qualitative synthesis but will be separately identified.

Study Timeline and Follow-Up

Studies with follow-up duration of at least 1 month following initiation of active RME will be included. No upper limit on follow-up duration is imposed; studies with both short-term (≤3 months) and longer-term (>3 months) follow-up will be included and analysed separately.

Information Sources

Database Search Strategy

The following electronic bibliographic databases will be searched from database inception through [Month Day, Year]:

- **MEDLINE** (via PubMed) — using MeSH and keyword search strategies
- **Embase** — using Emtree and keyword search strategies
- **Scopus** — using keyword search strategies
- **Web of Science Core Collection** — using keyword and cited reference search strategies
- **Cochrane Central Register of Controlled Trials (CENTRAL)**
- **Dentistry & Oral Sciences Source** — via EBSCO interface

Search Strategy

The search strategy will be developed in collaboration with a health sciences librarian and will use a combination of controlled vocabulary (MeSH terms, Emtree descriptors) and keywords relevant to the intervention (rapid maxillary expansion, RME, palatal expansion), population (children, adolescents, growing patients, maxillary

transverse deficiency), and outcomes (nasal airway, nasal resistance, nasal obstruction, rhinomanometry, acoustic rhinometry, peak nasal inspiratory flow). The base strategy will be adapted for each database's specific controlled vocabulary and syntax. The complete search strategies for all databases will be provided in the final review and supplementary materials.

Supplementary Search Methods

The reference lists of all included studies and relevant systematic reviews identified during the search will be manually screened for additional eligible studies. Hand-searching of key journals (*American Journal of Orthodontics and Dentofacial Orthopedics*, *Angle Orthodontist*, *Otolaryngology–Head & Neck Surgery*, *JAMA Otolaryngology*, *Archives of Otolaryngology*) will be performed for the past 5 years. Gray literature will not be systematically searched; however, if systematic reviews or evidence summaries are identified, their bibliographies will be reviewed.

Study Selection Process

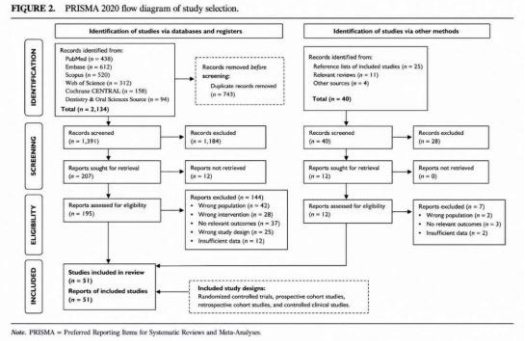

Figure 2 Caption: This PRISMA 2020 flow diagram documents the number of records identified from database searches and supplementary sources, screened for eligibility at the title/abstract stage, assessed for full-text eligibility, and finally included in the qualitative synthesis and meta-analysis. Specific reasons for exclusion at the full-text stage are documented. The diagram incorporates mechanisms for handling disagreements between reviewers and for contacting authors for missing data.

Data Extraction

Data Extraction Form and Variables

A standardized, piloted data extraction form will be used to extract data from all included studies. The form will be pilot-tested on a sample of studies (≥5) to ensure consistency and clarity, with modifications made as needed before full extraction begins. Data extraction will be performed independently by two reviewers; discrepancies will be resolved by consensus or third-party adjudication.

Extracted variables will include:

Study characteristics:

- Author, year of publication, country of origin
- Study design (RCT, prospective cohort, retrospective cohort)
- Study period (enrolment dates)
- Funding source and declaration of conflicts of interest

Participant characteristics:

- Sample size (total and per group, if applicable)
- Age (mean, SD, range)
- Sex distribution (% female)
- Ethnicity (if reported)
- BMI or weight status (if reported)
- Socioeconomic status or other demographic factors (if reported)
- Skeletal maturity status (e.g., cervical vertebral maturation stage, open midpalatal suture status)

Baseline orthodontic and skeletal characteristics:

- Severity of maxillary transverse deficiency (intermolar width, intercanine width, interpremolar width, maxillary width [J-J distance], or other measures)
- Posterior crossbite status (presence, unilateral vs. bilateral, severity)
- Overjet and overbite
- Dental crowding or arch length discrepancy

Screening and Selection Workflow

Two reviewers (to be designated) will independently screen all titles and abstracts retrieved from the database searches against the eligibility criteria. Studies will be categorized as "definitely include," "possibly include," or "exclude." Studies categorized as "definitely include" or "possibly include" will proceed to full-text review by both reviewers. At the full-text stage, both reviewers will independently determine final eligibility and provide reasons for exclusion of ineligible studies.

Any disagreement between reviewers at the title/abstract or full-text stage will be resolved by discussion and consensus; if consensus cannot be reached, a third reviewer will adjudicate. The inter-rater agreement (Cohen's kappa) will be calculated for both screening stages and reported.

Justifications for the exclusion of studies during full-text review will be documented in a PRISMA-compliant study selection flow diagram. The detailed flow of studies through each stage of the selection process is presented in **Figure 2**.

Figure 2: PRISMA 2020 Flow Diagram of Study Selection Process

- Cephalometric measures (SNA, SNB, ANB, vertical dimension, maxillary and mandibular widths, other relevant measures)
- Clinical impression of severity of transverse deficiency (mild, moderate, severe) if reported

Baseline nasal and upper-airway characteristics:

- Nasal airway resistance (non-decongested and decongested, if reported)
- Peak nasal inspiratory flow (PNIF)
- Acoustic rhinometry parameters (MCA, NCV, individual side measurements if available)
- Nasal obstruction severity (subjective rating, VAS, or validated scale scores)
- Adenoid hypertrophy status (presence/absence, grade if reported)
- Adenoid size on endoscopy or imaging (eg, percentage of nasopharyngeal airway obstruction)
- Inferior turbinate hypertrophy status (presence/absence, grade if reported)
- Nasal septal deviation (presence/absence, side, severity if reported)
- Other intranasal pathology (nasal polyps, rhinitis, other)

Intervention characteristics:

- RME appliance type (tooth-borne [banded, bonded], tissue-borne, hybrid; fixed or removable; specific appliance name if identifiable)
- Activation protocol (rate of activation per day, frequency, turns per activation, total turns, etc.)
- Magnitude of expansion achieved (mm intermolar width gain, other measures)
- Duration of active expansion (days or weeks)
- Retention protocol and duration (in-place retention, removable retainer, other)
- Total treatment duration (baseline to final assessment)
- Concurrent or adjunct interventions (adenoidectomy, turbinate reduction, septoplasty, other)

Outcomes and effect estimates:

- Primary outcome measures reported (nasal airway resistance, PNIF, AR parameters)
- Units of measurement for each outcome
- Timing of assessments (baseline, immediately post-expansion, 3 months, 6 months, 12 months, other)
- Mean, SD, or other measures of central tendency and dispersion at each time point
- Effect estimates (mean difference, 95% CI, p values, effect sizes [Cohen's d, standardized mean difference]) for change from baseline to follow-up
- Secondary outcome measures reported (NOSE scale, VAS, symptom improvement, other)
- Subgroup or stratified analyses performed (eg, by adenoid status, crossbite laterality, baseline severity)

Risk of bias and study quality indicators:

- Allocation method (for RCTs: randomization procedure, sequence generation, allocation concealment)
- Blinding of participants, interventionists, and outcome assessors
- Loss to follow-up and reasons for attrition
- Handling of missing data
- Funding source and potential conflicts of interest
- Any other relevant quality indicators for observational studies (e.g., consecutive patient recruitment, control for confounding)

Contact with authors: For studies reporting insufficient detail for data extraction or analysis (e.g., effect estimates not reported, outcome measures reported in incompletely specified units), the corresponding author will be contacted via email with a request for the missing information. Authors will be given a 4-week window to respond. If authors do not respond, the study will be included with a notation of missing data.

Risk of Bias Assessment

Risk of bias will be assessed using design-appropriate, validated tools:

For randomized controlled trials: The Cochrane Risk of Bias 2 (RoB 2) tool, which evaluates bias arising from:

- Randomization process
- Deviations from intended intervention
- Missing outcome data
- Measurement of the outcome
- Selection of the reported result

For observational studies (prospective and retrospective cohorts): The Risk of Bias in Nonrandomized Studies—of Intervention (ROBINS-I) tool, which evaluates bias in:

- Confounding
- Selection of participants
- Measurement of interventions
- Departure from intended intervention
- Missing data
- Measurement of outcomes
- Selection of reported result

Each domain will be rated as "low risk," "some concerns" (RoB 2) or "low/moderate/high risk" (ROBINS-I). An overall risk of bias judgment will be made for each study. Two independent reviewers will perform all risk of bias assessments; disagreements will be resolved by consensus or third-party arbitration.

Studies will not be excluded based on risk of bias; however, bias assessments will be used to weight analyses and inform sensitivity analyses and certainty of evidence judgments.

Data Synthesis and Analysis

Meta-Analysis

Where ≥3 studies report the same outcome measure (e.g., change in nasal airway resistance

from baseline to a defined follow-up time point) in comparable populations with sufficient methodological homogeneity, random-effects meta-analysis will be performed using inverse-variance weighting. Effect estimates will be presented as standardized mean differences (Hedges' g) with 95% confidence intervals (CIs).

The planned pathway for meta-analytic synthesis is illustrated in **Figure 3**. This approach will allow us to:

- Quantify the overall magnitude of nasal functional improvement following RME
- Assess consistency of effects across studies and outcomes
- Identify sources of heterogeneity through meta-regression and subgroup analysis
- Evaluate potential predictors and modifiers of treatment response

Meta-analyses will be conducted separately for:

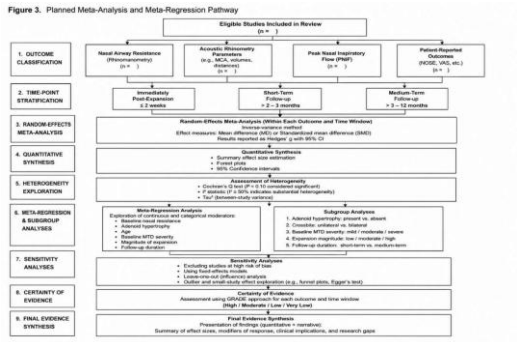

Figure 3 Caption: This flowchart depicts the sequential analytical pathway for meta-analysis and meta-regression. Studies are first stratified by outcome measure (nasal airway resistance, acoustic rhinometry, PNIF, or patient-reported outcomes), then by time point of assessment (immediate post-expansion, short-term, or medium-term follow-up). Random-effects meta-analysis is performed for each outcome-time point combination, followed by exploration of heterogeneity using meta-regression and subgroup analyses to identify baseline characteristics associated with greater or lesser functional response. Sensitivity analyses assess the robustness of findings, and the GRADE approach is used to assess certainty of evidence for each primary outcome.

Heterogeneity Assessment

Heterogeneity across studies will be quantified using the I^2 statistic, with interpretation as follows: $I^2 < 25\%$ = low heterogeneity, 25%–75% = moderate heterogeneity, >75% = high heterogeneity. Between-study variance (τ^2) will also be reported. Forest plots will be generated for all meta-analyses. If substantial heterogeneity is identified ($I^2 > 50\%$), sources of heterogeneity will be explored through meta-regression (see below) and subgroup analysis.

Meta-Regression and Subgroup Analyses

- **Change in nasal airway resistance** (non-decongested values, $Pa \cdot cm^{-3} \cdot s$) from baseline to: (a) immediately post-expansion (≤2 weeks), (b) short-term follow-up (1–3 months), (c) medium-term follow-up (4–12 months)
- **Change in peak nasal inspiratory flow** (L/min) across the same time-point groupings
- **Change in acoustic rhinometry parameters** (MCA, NCV, cm^2 or cm^3) across the same time-point groupings
- **Change in patient-reported nasal obstruction severity** (NOSE scale scores, VAS, or standardized symptom measures) across the same time-point groupings

Additional meta-analyses may be performed if sufficient data permit, examining outcomes in specific subgroups (e.g., patients with vs. without adenoid hypertrophy, unilateral vs. bilateral crossbite) if data are available.

Figure 3: Planned Meta-Analysis and Meta-Regression Pathway

To evaluate associations between baseline study-level or participant-level characteristics and magnitude of nasal functional response, univariable and multivariable meta-regression will be performed, with mean change in nasal airway resistance (or other primary outcomes) as the dependent variable and the following covariates as independent variables:

Study-level covariates:

- Mean participant age
- Percentage female participants
- Mean baseline intermolar width deficiency (mm)
- Percentage with bilateral crossbite
- Percentage with baseline adenoid hypertrophy (grade ≥3 or equivalent)
- Percentage with baseline inferior turbinate hypertrophy
- Percentage with baseline septal deviation
- Mean baseline nasal airway resistance ($Pa \cdot cm^{-3} \cdot s$)
- Mean magnitude of expansion achieved (mm)
- Risk of bias rating (low vs. some concerns/moderate/high)
- Study design (RCT vs. observational cohort)
- Follow-up duration category (short-term ≤3 months vs. longer-term >3 months)

Where individual participant data (IPD) are available or can be obtained from authors, participant-level meta-regression will be performed.

Predefined subgroup analyses will examine nasal functional response in:

- Studies with and without concurrent adenoidectomy or adjunct otolaryngologic procedures
- Studies enrolling patients with bilateral vs. unilateral crossbite or mixed populations
- Studies stratified by baseline severity of transverse deficiency (mild, moderate, severe)
- Studies with follow-up >3 months vs. ≤3 months post-expansion

Narrative Synthesis

For outcomes not amenable to meta-analysis, findings will be synthesized narratively, structured according to the Synthesis Without Meta-analysis (SWiM) guidelines.[19] The narrative synthesis will address:

- **Study characteristics and methodological quality:** A tabular summary describing eligible studies' design, population characteristics, interventions, and outcomes
- **Magnitude of nasal functional change:** Descriptive summary of effect estimates across studies, stratified by outcome measure and follow-up duration, with qualitative assessment of consistency and magnitude of effects
- **Predictors and modifiers of treatment response:** Qualitative synthesis of studies reporting associations between baseline characteristics and treatment response, including effect directions, magnitude, and precision of estimates
- **Anatomical and mechanistic insights:** Discussion of mechanistic pathways by which RME alters nasal airway dimensions and physiology, informed by studies using imaging or computational modelling

Sensitivity Analyses

Sensitivity analyses will assess the robustness of meta-analytic findings by:

- Excluding studies at high risk of bias or with high loss to follow-up (>20%)
- Excluding outlier studies, using a priori defined thresholds or statistical methods (e.g., trim-and-fill analysis)
- Repeating analyses using fixed-effects models as an alternative to random-effects models
- Examining the effect of including studies with low quality or high heterogeneity

Assessment of Certainty of Evidence

The certainty of evidence for each primary outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[20] For each outcome, evidence will be rated on five domains: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. Summary of findings (SoF) tables will be created for each primary outcome, displaying effect estimates, 95% CIs, and GRADE certainty ratings (high, moderate, low, very low).

Publication Bias Assessment

Funnel plots will be generated for meta-analyses including ≥10 studies to visually assess for asymmetry suggestive of publication bias. Egger's regression test and Begg's rank correlation test will be used to formally evaluate small-study effects. If publication bias is suspected, trim-and-fill analysis will be performed.

Software and Analysis Tools

All analyses will be conducted using R version 4.3.2 (R Foundation for Statistical Computing) or later, with the following packages: *metafor* (for meta-analysis and meta-regression), *robvis* (for risk of bias visualization), *ggplot2* (for graphing), and *tidyverse* (for data management). Alternatively, Stata 17.0 or later or RevMan 5.4 (for Cochrane reviews) will be used. The analysis code will be made available in supplementary materials for transparency and reproducibility.

Reporting Standards

The final systematic review will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 checklist[21] and the MOOSE guidelines for meta-analyses of observational studies.[18] A PRISMA-compliant flow diagram documenting study selection at each stage will be provided. Detailed search strategies for all databases, quality assessment data for all included studies, and complete data extraction tables will be included in supplementary materials.

Overview of Review Workflow

The complete workflow for this systematic review, from initial database searches through final synthesis and reporting, is presented in **Figure 4**. The three main phases—(1) search and screening, (2) data extraction and bias assessment, and (3) analysis and synthesis—will be conducted sequentially, with opportunities for disagreement resolution and author contact for missing data at each stage to ensure data completeness and accuracy.

All processes will follow standardized protocols with dual independent review at critical junctures to minimize bias and maximize reproducibility.

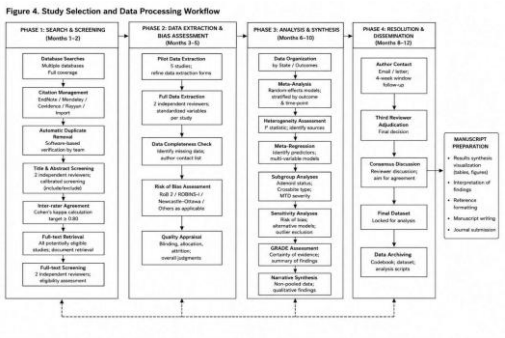

Figure 4: Study Selection and Data Processing Workflow

Figure 4 Caption: This comprehensive workflow diagram illustrates the three sequential phases of the systematic review. **Phase 1 (search and screening)** encompasses database searches, citation management, duplicate removal, and dual independent screening at title/abstract and full-text stages. **Phase 2 (data extraction and bias assessment)** includes pilot testing of the data extraction form, full data extraction with dual review, identification of missing data for author contact, and risk of bias assessment using validated tools. **Phase 3 (analysis and synthesis)** encompasses data organization, primary meta-analyses stratified by outcome measure and time point, assessment of heterogeneity with exploration through meta-regression and subgroup analyses, sensitivity analyses, GRADE certainty assessment, and narrative synthesis of non-pooled data. Throughout all phases, mechanisms are in place for disagreement resolution and author contact to obtain missing data, ensuring data completeness and quality.

Expected Outcomes and Significance

Anticipated Results

We anticipate this systematic review will identify 20–50 eligible studies, including RCTs and observational cohort studies, enrolling a total of approximately 500–1500 participants. Based on preliminary scoping searches, we expect to identify sufficient data to perform meta-analyses of nasal airway resistance, acoustic rhinometry parameters, and PNIF across multiple follow-up time points.

We anticipate that meta-analyses will demonstrate statistically and clinically meaningful improvements in objective nasal airway function following RME at group level. Heterogeneity in effect sizes is expected, and we anticipate that meta-regression will identify specific baseline characteristics (eg, severity of transverse deficiency, adenoid hypertrophy status, baseline nasal airway obstruction severity) associated with greater or lesser magnitude of nasal functional response.

Clinical and Research Implications

Clinical implications:

- Identification of baseline characteristics predicting greater nasal functional response will enable more precise pre-treatment patient assessment and counselling
- Clinicians will be better able to set realistic expectations regarding the probability and magnitude of nasal functional benefit from RME
- Understanding response modifiers (eg, adenoid hypertrophy) may inform sequencing of orthodontic and otolaryngologic interventions
- Results will provide evidence-based support for interdisciplinary orthodontic–otolaryngologic patient management

Research implications:

- Evidence synthesis will identify gaps in the current literature and inform future prospective studies
- Identified response modifiers will provide targets for prospective validation studies aimed at developing and testing clinical prediction models
- Meta-regression results will quantify the strength of associations between baseline characteristics and treatment response, informing sample-size calculations for future trials
- Results will highlight methodological issues in prior studies and inform best-practice recommendations for future nasal function research

Dissemination

The final systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal with high readership among orthodontists, otolaryngologists, and dentofacial orthopaedic specialists. A protocol summary and key findings will be disseminated to professional societies (American Association of Orthodontists, American Academy of Otolaryngology–Head and Neck Surgery) and may be presented at major scientific conferences.

Timeline and Resource Requirements

Projected Timeline

- **Months 1–2:** Finalize search strategies, establish data extraction protocols, pilot test data extraction form
- **Months 2–3:** Execute database searches, import citations into systematic review software, begin title/abstract screening

- **Months 3–4:** Complete title/abstract screening and full-text review, resolve eligibility disagreements
- **Months 4–6:** Data extraction, risk of bias assessment, contact authors for missing data
- **Months 6–8:** Meta-analysis and statistical analysis, narrative synthesis, sensitivity analyses
- **Months 8–10:** Certainty of evidence assessment, results interpretation, manuscript preparation
- **Months 10–11:** Peer review, revisions, and submission for publication

Personnel and Resources

- **Review team:** Two senior reviewers (orthodontist and/or otolaryngologist with systematic review experience) for screening, data extraction, and bias assessment
- **Biostatistician:** For meta-analytic analyses and meta-regression
- **Health sciences librarian:** For search strategy development and optimization
- **Administrative support:** For citation management, document organization, and correspondence with authors
- **Software:** EndNoteX9 or Covidence for citation management and screening; R or Stata for meta-analysis; OSF for protocol registration and data sharing

CONCLUSIONS

This systematic review will comprehensively synthesize evidence regarding baseline characteristics that predict or modify nasal airway functional response to rapid maxillary expansion in growing patients with maxillary transverse deficiency. By identifying consistent response modifiers and quantifying their associations with treatment outcomes, this review will provide an evidence-based foundation for more precise patient selection, interdisciplinary treatment planning, and development of clinical prediction tools. Results will directly advance the evidence base supporting precision medicine approaches in orthodontic–otolaryngologic practice.

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