Systematic Review Article

Influence of rapid maxillary expansion on nocturnal enuresis in children: *A systematic review*

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ABSTRACT

Objectives: To evaluate the influence of rapid maxillary expansion (RME) on nocturnal enuresis (NE) in children to discuss whether RME can be indicated as an alternative treatment for NE in those patients.

Materials and Methods: An electronic search was performed in the following databases: PubMed/MEDLINE, Cochrane Library, Scopus, Science Direct, Google Scholar and LILACS. The literature review was blindly performed by two reviewers. References of each selected study were manually searched to identify articles that were not found by the electronic search. Kappa statistics were used to analyze interexaminer agreement after the selection of the articles. After reading the selected full-text articles, the studies that met the inclusion criteria were assessed qualitatively using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) and the Revised Cochrane risk-of-bias tool for randomized controlled trials-2 (RoB 2). The certainty level of evidence was assessed through the Grading of Recommendations, Assessment, Development and Evaluation tool. Kappa tests were used to analyze the interexaminer concordance level after the quality assessment of the studies.

Results: A total of 488 articles were found; however, after applying the inclusion and exclusion criteria, only 8 studies were selected for the systematic review. A low certainty level of evidence suggested that RME seems to promote a variable reduction in frequency or a remission of NE in children in both the short (4, 6, and 8 months) and long term (13, 36, 48, and 120 months).

Conclusions: Based on currently available information, RME seems to promote an improvement in NE in children. However, the low quality of the existing evidence weakens the recommendation. (*Angle Orthod.* 2021;91:680–691.)

KEY WORDS: Palatal expansion technique; Nocturnal enuresis; Respiration

INTRODUCTION

Rapid maxillary expansion (RME) is an orthopedic intervention widely used to treat maxillary constriction and skeletal posterior crossbites in the primary and mixed dentitions.[1] Recently, studies have suggested that RME not only treats transverse malocclusion but also improves nasal breathing of mouth breathers, as RME increases the palatal area, nasal cavity, and nasopharynx volumes and also reduces air resistance of the upper airway.[2–5] Considering that mouth breathing is associated with sleep disorders, several clinical studies have suggested that improvement in breathing after RME might promote other general health benefits, such as reduction of obstructive sleep apnea syndrome (OSAS)[6–8] and nocturnal enuresis (NE) episodes.[9–13]

NE is a sleep disorder that affects children older than 4 years and is characterized by two or more involuntary

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urination events during sleep per month in patients without nephrologic disorders.[12] Children with NE episodes may experience reduced quality of life due to sibling teasing and family or social disapproval, resulting in low self-esteem and possible psychoemotional problems. Treatment of NE includes behavioral, pharmacologic, and/or psychological therapy. The choice of treatment modality depends on the etiology.[14] In general, it begins with simple and conservative interventions, such as fluid restriction, wakening, reward systems, retention control training, and enuresis alarms. In cases of failure, psychotherapy associated or not with drugs such as desmopressin or tricyclic drugs can be used.[15]

The pathophysiology of NE seems to be associated with altered secretion of antidiuretic hormone (ADH) in patients with poor sleep hygiene and respiratory disturbances.[16,17] Considering that RME enlarges the upper airway width, oxygen saturation might increase during sleep. This contributes to the reduction in apnea and hypopnea frequency, induces the hypothalamus and the neurohypophysis to produce and secrete ADH, and might reduce or eliminate episodes of NE.[18]

Although previous studies[9–13] have suggested a correlation between the skeletal effects of RME, improvement in air permeability, and reduction or remission of NE episodes, the relationship between these variables is not yet fully understood, and the methodological heterogeneity and inconclusive results of these studies could bias the evidence and mislead practitioners. Thus, synthesis and qualitative assessment of the existing evidence may contribute to the decision-making process of whether RME should be indicated as an alternative treatment for NE in children and provide an overview of new research perspectives. The aim of this systematic review was to analyze the influence of RME on NE in children to discuss whether RME can be indicated as an alternative treatment for NE in those patients.

MATERIALS AND METHODS

Protocol and Registration

This systematic review was written as closely as possible according to the PRISMA guidelines and recommendations.[19] The protocol of this systematic review was registered in PROSPERO (CRD42019127386) and can be accessed at https://www.crd.york.ac.uk/prospero/.

Eligibility Criteria

The eligibility criteria were articles without restriction of language and year of publication; prospective studies and randomized controlled trials (RCTs); studies involving patients in the primary, mixed, or early permanent dentitions who underwent conventional RME; studies that analyzed the influence of RME on NE in the short (until 1 year of follow-up) or long term (more than 1 year of follow-up); and studies that analyzed the primary and secondary outcomes using questionnaires, laboratory tests, and/or medical examinations.

Exclusion criteria consisted of retrospective studies, studies that treated patients with history of previous orthodontic treatment, studies that associated RME with other orthodontic or medical treatment modalities; studies including patients diagnosed with urological, nephrologic, endocrine or neurologic disorders, cleft lip and palate, and/or craniofacial syndromes; and case reports, case series, expert opinions, literature reviews, and animal model experimental studies.

Information Sources

An extensive search of the available scientific literature was carried out both electronically and manually until March 2020. The electronic search was performed with the assistance of a librarian specialized in searches in the health sciences area databases. The databases searched included PubMed/MEDLINE, Cochrane library, Scopus, Science Direct, Google Scholar, and LILACS. Unpublished literature was also searched on ClinicalTrials.gov, the National Research Register, and ProQuest Dissertation Abstracts and Thesis database.

The references of each selected study were searched manually to identify articles that were not found by the electronic search. Contact with study authors was not necessary.

Search

The search strategy used in all databases included the combination of the following MeSH terms and synonyms: “palatal expansion technique”, “palatal expansion technic”, “maxillary expansion”, “enuresis”, and “nocturnal enuresis”. The search methodology is listed in Table 1.

Study Selection

Evaluation of the selected articles was staged in a two-step process to determine eligibility. First, two reviewers (Dr Padilha and Dr Barbalho) independently and blindly selected the studies by reading the title and abstract. Then, decisions for final eligibility were made based on full-text assessments by the same reviewers. Any disagreements between reviewers were solved by discussion or by introduction of a third reviewer (Dr Alves) to mediate when deemed necessary.

Data Collection Process

Data collection was done in duplicate. Key features of eligible articles were documented by each reviewer.

Table 1. Search Methodology for Electronic Systematic Review

Database	Search Strategy
PubMed/Medline	("palatal expansion technique" OR "maxillary expansion") AND ("enuresis" OR "nocturnal enuresis")
Cochrane library	("palatal expansion technique" OR "maxillary expansion" OR "palatal expansion technic") AND ("enuresis" OR "nocturnal enuresis")
Scopus	("maxillary expansion") AND ("enuresis" OR "nocturnal enuresis")
Science Direct	("maxillary expansion") AND ("enuresis" OR "nocturnal enuresis")
Google Scholar	("Palatal expansion technique" OR "maxillary expansion") AND ("enuresis" OR "nocturnal enuresis")
LILACS	("palatal expansion technic" OR "palatal expansion technique" OR "maxillary expansion") and ("enuresis" OR "enuresis, nocturnal")

Kappa tests were used to analyze interexaminer concordance level both after the selection of the articles and the quality assessment of the final studies.

Data Items

The primary data extracted from each study were as follows: author, year of publication, study design, sample size, study groups, dentition stage, type of expander, amount of expansion, follow-up period, respiratory disorders, and methods of assessment of respiratory disorders and NE. The characteristics of the included studies are summarized in Table 2.

Risk of Bias in Individual Studies

The non-randomized studies that met the inclusion criteria were assessed qualitatively using the Risk Of Bias In Non-randomized Studies for Intervention tool (ROBINS-I),[20] which is an updated version of the ACROBAT-NRSI.[21]

For the overall risk of bias, these studies were categorized according to the following: low risk of bias (the study was comparable with a well-performed randomized trial), moderate risk of bias (the study was sound for a non-randomized study but cannot be considered comparable with a well-performed randomized trial), serious risk of bias (the study had important problems), critical risk of bias (the study was too problematic to provide any useful evidence on the effects of the intervention), or no information (no information on which to base a judgement of risk of bias).

On the other hand, the Revised Cochrane Risk-of-Bias tool (RoB 2)[22] was used to qualitatively assess the selected randomized controlled clinical trial. The study could be categorized as "low" risk of bias, "some concerns," or "high" risk of bias.

Risk of Bias Across Studies

The level of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).[23] For the outcome examined, the GRADE assesses the study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Based on this assessment, the certainty of the evaluation of the outcome could be very low, low, moderate, or high quality.

Summary Measures

The main summary measures were the mean difference and the relative and absolute frequencies of the NE episodes recorded during the pre-expansion and postexpansion periods.

RESULTS

Study Selection

A total of 488 articles were found with the initial electronic search. After reading the titles and abstracts of these studies, 26 articles were selected. Only eight articles remained after removal of duplicates. No additional articles were found after the manual search in the references of those studies. Considering eight articles met the inclusion criteria, all were analyzed in this systematic review. The search process is illustrated in the flowchart (Figure 1). Kappa test was performed after article selection and showed an almost perfect interexaminer agreement of 0.85.[24]

Study Characteristics

The characteristics of each included study are summarized in Table 2. In general, the selected articles were published between 1990 and 2020 in medical and dental journals and consisted of seven non-randomized prospective studies[10–13,25–27] and one randomized controlled trial.[28]

The sample sizes of the studies were quite variable, and only one article[13] showed control group composed of untreated patients. The patients were either in the mixed or early permanent dentitions.[10–13,26] Separation of midpalatal suture was accomplished in all patients. The most widely used expander was the Hyrax-type.[12–14,28–30] The amount of expansion obtained ranged from 4 mm[25] to 8.2 mm,[13] and the reduction of NE episodes was analyzed in both the short (6 months[28] and 8 months[25]) and the long term (13 months,[26,27] 36 months,[12,13] 48 months,[10] and 120 months[11]) by means of questionnaires,[11–13] interviews with patients' parents,[10,25–27] registration of NE episodes

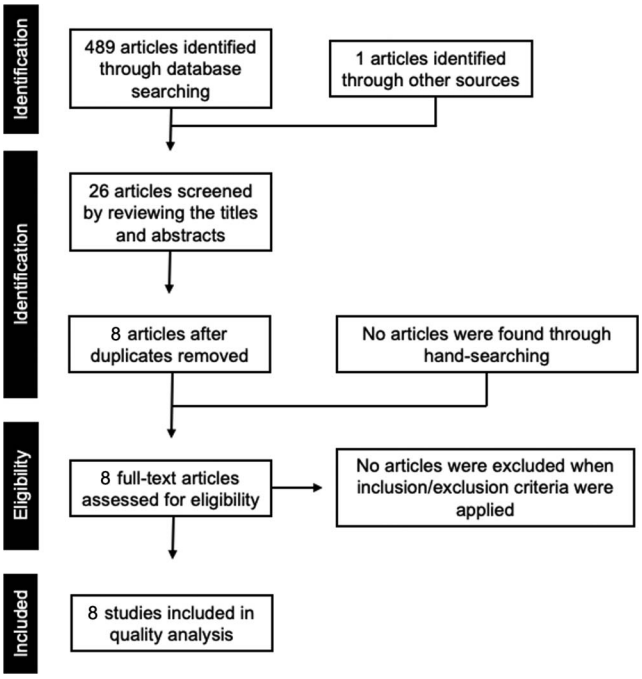

Figure 1. Flowchart adapted from PRISMA statement for systematic reviews.[19]

on a voiding chart,[28] registration of daytime voided volumes and nocturnal urine production via weighing of diapers or sheet covers,[28] polysomnography examinations,[27] and laboratory tests of osmolality of the blood plasma to quantify the level of ADH.[12]

Finally, participants of all studies were diagnosed with at least one of the following respiratory disorders: mouth breathing,[10,11,13,25,28] mixed breathing,[25] respiratory tract infections,[13] snoring,[13,26,28] adenoid hypertrophy,[10,24] amygdala hypertrophy,[10,13,25] nasal septum deviation,[25] and/or nasal obstruction.[25–27] The methods used for diagnosis were medical examinations,[10–12,25,26,28] rhinomanometry,[10–12,25,27] acoustic rhinomanometry,[26,27] polysomnography,[26,27] cone-beam computed tomography,[12] and/or anamnestic questionnaire.[13]

Risk of Bias Within Studies

The risk of bias of individual studies is shown in Table 3 and Figure 2. Kappa tests were performed after the quality assessment of the studies and showed an almost perfect interexaminer agreement of 0.83.[24]

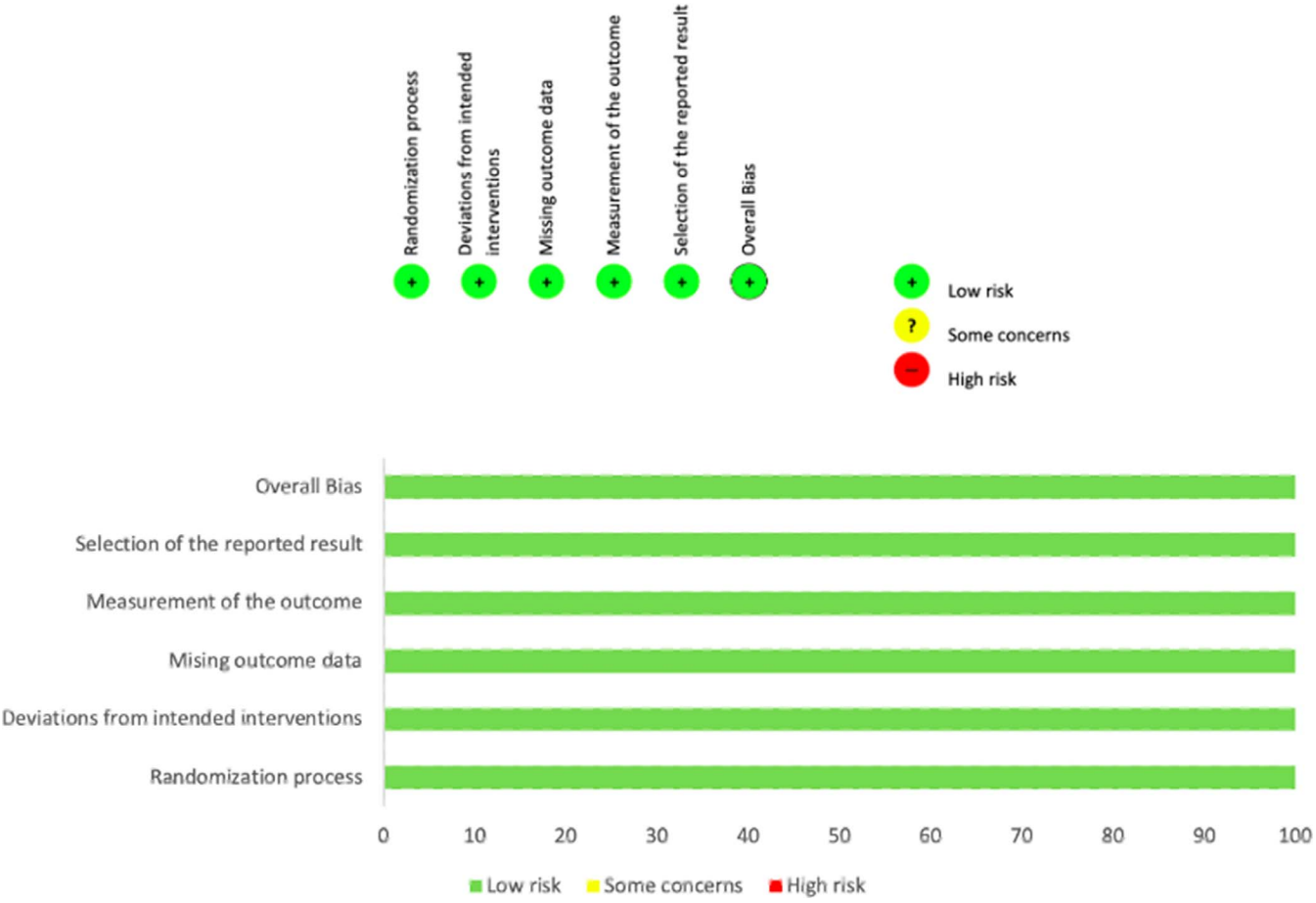

Figure 2. Summary of the risk of bias assessment for randomized controlled trials using RoB 2 tool.[22]

Table 2. Summary of Study Characteristics and Results of the Included Studies

Author	Study Design	Sample Size	Study Groups	Dentition Stage	Type of Expander	Amount of Expansion	Follow-up Period
Kurol et al., 1998	Prospective	10 patients	1 experimental group	Mixed or early permanent dentition	Hyrax	3.2–5 mm	48 mo
Usumez et al., 2003	Prospective	8 patients	1 experimental group	Mixed dentition	Acrylic splint expander	3–6 mm	8 mo
Schütz-Fransson and Kurol, 2008	Prospective	23 patients	1 experimental group	Mixed or early permanent dentition	Hyrax	6.5 mm	120 mo
Nevéus et al., 2014	Prospective	34 patients	1 experimental group	Mixed or early permanent dentition	Hyrax	Not reported	13 mo
Al-Taai et al., 2015	Prospective	19 patients	1 experimental group	Mixed or early permanent dentition	Hyrax	4.6 mm $\pm$ 1 mm	36 mo

Table 2. Extended

Respiratory Disorders	Method of Assessment of Respiratory Disorders	Method of Assessment of Nocturnal Enuresis	Results of Individual Studies
Mouth Breathing, Adenoid Hypertrophy, and/or Amygdala Hypertrophy	Otorhinolaryngological Examinations and Rhinomanometry	Application of Questionnaires to Patients' Parents	Assessment at pre-expansion period: 8 patients showed daily episodes of NE and 2 patients showed 3 or 4 episodes per week Assessment at 1 mo postexpansion: 3 patients reduced the number of NE episodes Assessment at 3 mo postexpansion: 6 patients ceased bedwetting, 1 patient showed 2 episodes of NE per week and 3 patients showed daily episodes Assessment at 48 mo postexpansion: 8 patients ceased bedwetting, 1 patient showed 2 episodes of NE per week, and 1 showed daily episodes
Mouth breathing, mixed breathing, nasal obstruction, nasal septum deviation, adenoid hypertrophy, and/or amygdala hypertrophy	Otorhinolaryngological examinations	Application of questionnaires to patients' parents	Assessment at 8 mo postexpansion: reduction of NE episodes per week after RME; no patient ceased bedwetting
Mouth breathing	Otorhinolaryngological examinations and rhinomanometry	Application of questionnaires to patients' parents and interviews using telephone	Assessment at 1 mo postexpansion: 50% of the patients showed reduction of NE episodes Assessment at 12 mo post-expansion: 6 patients ceased bedwetting, 5 patients reduced the NE episodes, and 10 patients did not show any improvement Assessment at 120 mo postexpansion: all patients stated that the NE episodes ceased in a period that ranged from 1 to 3 y after RME
Nasal obstruction and/or snoring	Otorhinolaryngological examinations, rhinomanometry, acoustic rhinomanometry, and polysomnography	Application of questionnaires to patients' parents	Assessment at pre-expansion period: mean of 5.48 ± 1.48 episodes of NE per week Assessment at expander installation: mean of 5.12 ± 1.73 episodes of NE per week Assessment at immediately postexpansion: mean of 3.09 ± 2.49 episodes of NE per week Assessment at 13 mo postexpansion: mean 2.63 ± 2.81 episodes of NE per week
Moderate nasal obstruction	Otorhinolaryngological examinations, rhinomanometry, cone-beam computed tomography	Application of questionnaires to patients' parents and blood plasma osmolality test	Assessment at 1 mo postexpansion: no significant reduction on the number of NE episodes was observed Assessment at 3 mo postexpansion: the NE episodes reduced from 2.21± 0.98 to 0.42 ± 0.40 per week Assessment at 12 mo postexpansion: the NE episodes reduced to 0.06 ± 0.1 per week Assessment at 36 mopost-expansion: all patients stated that the NE episodes ceased

Table 2. Continued

Author	Study Design	Sample Size	Study Groups	Dentition Stage	Type of Expander	Amount of Expansion	Follow-up Period
Hyla-Klekot et al., 2015	Prospective	41 patients	1 experimental group and 1 control group	Mixed or early permanent dentition	Not mentioned	4.6–8.2 mm	36 mo
Bazargani et al., 2016	Prospective	34 patients	1 experimental group	Mixed dentition	Hyrax	4 mm ± 1 mm	13 mo
Ring et al., 2020	Randomized clinical trial	38 patients	1 experimental group and 1 placebo group	Not specified	Hyrax and sham appliance	Not reported; the authors only state that expansion was performed until palatal surface of maxillary posterior teeth have contacted buccal surface of posterior mandibular teeth	6 mo

Risk of Bias Across Studies

The certainty of evidence was evaluated according to the GRADE approach. The level of evidence for influence of RME on reduction of NE was graded as low, and the strength of recommendation was weak. Reasons for downgrading the evidence are detailed in Table 4.

Results of Individual Studies

Eight studies were selected in this systematic review, and the results were described in Table 2.

Synthesis of Results

A meta-analysis was not possible. Methodologies of the selected studies were highly heterogeneous, posing a challenge for combining results together. In addition, some authors did not clearly describe the number of episodes of NE of patients during the pre-expansion and postexpansion phases.

DISCUSSION

Summary of Evidence

NE is considered a chronic health problem that compromises quality of life of children.[29] Therefore, it must be appropriately treated when diagnosed during childhood and adolescence.[29] A recent study found that children who responded successfully to medical treatment of NE showed significant improvement in quality of life and behavior compared with patients who did not.[30] In general, medical treatment of NE involves behavioral therapy, psychotherapy, use of urinary alarms, and/or drug therapy with desmopressin, anticholinergics, or tricyclic antidepressants.[31] The etiology of NE is still unclear and has been associated with genetic, psychological, and physiological factors, such as delay in normal bladder control, sleep apnea, and upper airway obstruction.[15–18] Considering RME significantly reduces nasal airway resistance, it has been suggested as a complementary alternative to NE treatment.[11]

In the 1990s, orthodontists suggested for the first time that RME might reduce NE episodes in mouth-breathing children with maxillary constriction.[9] Although some clinical studies have been performed over the past decades,[10–13,25–27] the present systematic review showed only one randomized controlled clinical trial[28] investigating this issue. It showed a low risk of bias for all domains assessed (Figure 2). It is important to highlight that scientific community encourages researchers to develop RCTs because that is the experimental study design in humans that shows the greatest scientific evidence.[32]

Table 2. Continued, Extended

Respiratory Disorders	Method of Assessment of Respiratory Disorders	Method of Assessment of Nocturnal Enuresis	Results of Individual Studies
Mouth breathing, amygdala hypertrophy, allergy, chronic respiratory tract infections, and/or snoring	Anamnestic questionnaire	Application of questionnaires to patients' parents	Assessment at 36 mo postexpansion: the experimental group showed a significant reduction on the NE episodes of 93.15%; remission of NE occurred in 50% of these children; the control group had 60% of reduction on the number of NE episodes, and remission occurred in 32% of these patients
Nasal obstruction	Rhinomanometry, acoustic rhinomanometry, and polysomnography	Application of questionnaires to patients' parents	Assessment at pre-expansion period: mean of 5.48 $\pm$ 1.73 episodes of NE per week Assessment immediately postexpansion: mean of 3.09 $\pm$ 2.49 episodes of NE per week Assessment at 13 mo postexpansion: mean of 2.3 $\pm$ 0.85 episodes of NE per week
Mouth breathing and snoring	Pediatric examinations	Registration of enuresis episodes on a voiding chart by parents and registration of daytime voided volume and nocturnal urine production via weighing of diapers or sheet covers	Assessment at 2 wk postexpansion: the patients showed a significant reduction of wet nights while the placebo group showed a nonsignificant reduction (no significant intergroup differences; assessment at 6 mo postexpansion: the whole group showed a reduction of 3.2 episodes of NE per week

The non-randomized prospective studies[10–12,25–27] analyzed in this systematic review showed risk of bias that varied from low to moderate (Table 3), resulting in a low level of certainty that weakens the recommendation of RME as an auxiliary treatment for NE (Table 4). Thus, the results of the selected studies must be interpreted with caution. However, the elaborate efforts in searching an unusually large number of databases provided some safeguard against missing relevant studies. Thus, the evidence summarized in this review is likely to be as good as it will get for the foreseeable future.

The lack of randomization and allocation concealment of participants was observed in the non-RCT studies (Table 3). These methodological flaws are commonly associated with increased risk of selection bias. Similarly, the lack of control group was observed in six studies.[10–12,25–27] A control group with untreated children would be important in these clinical studies to control confounding variables that might have contributed to the improvement of NE and a possible overestimation of RME effects, such as growth, psychological maturation, spontaneous reduction of adenoids, and/or improvement of sleep hygiene. Only one study[13] had a control group with untreated participants, two[12,27] used the expander passively during the pre-expansion period, and one[28] used the sham appliance to simulate a placebo effect.

All selected studies considered NE as the main eligibility criterion for patients' recruitment. However, some of these studies included patients without maxillary constriction in the sample[10,11,27] or did not cite whether patients had transverse malocclusions or normal occlusion.[12,13,25,26] Ideally, the presence of maxillary constriction should also be an eligibility criterion since recent studies have shown a correlation between transverse malocclusions, narrowing of the upper airways, OSAS, and NE.[33] In addition, the studies did not standardize the amount of maxillary expansion performed in the samples. This may be a problem because the minimum amount of expansion necessary to accomplish the skeletal effects on the palate and nasal cavity to improve air permeability and oxygen saturation to significantly reduce episodes of NE remains unknown.[34]

Only three studies[12,26,28] showed greater credibility regarding the cause and the diagnosis of NE in the sample, since the participants were submitted to previous nephrologic, neurologic, and pediatric evaluations. The participants of the other selected studies underwent only an otorhinolaryngological evaluation to diagnose respiratory disorders. Similarly, evaluations with otorhinolaryngologists are necessary in both the

Table 3. Assessment of Risk of Bias Using ROBINS-I

Study	Confounding	Selection Bias	Bias Classification of Interventions	Bias due to Deviations From Intended Interventions
Kurol, 1998	Serious risk of bias (lack of control group; discontinuations or switches were not described)	Serious risk of bias (selection into the study was very strongly related to intervention and outcome)	Serious risk of bias (lack of standardization of the amount of expansion)	Low risk of bias
Usumez, 2003	Serious risk of bias (lack of control group)	Serious risk of bias (selection related to intervention and outcome; some patients did not show respiratory disorders nor maxillary constriction with posterior crossbite)	Serious risk of bias (lack of standardization of the amount of expansion)	Low risk of bias
Schütz-Fransson, 2008	Critical risk of bias (lack of control group; periods of assessment were not described in details)	Serious risk of bias (selection related to intervention and outcome; patients did not show respiratory disorders, and some did not have maxillary constriction with posterior crossbite)	Serious risk of bias (lack of standardization of the amount of expansion)	Low risk of bias
Nevéus, 2014	Moderate risk of bias (the study did not have control group but patients used the expanders passively as placebo for 4 mo)	Serious risk of bias (selection related to intervention and outcome)	Serious risk of bias (lack of standardization of the amount of expansion)	Low risk of bias
Al-Taai, 2015	Moderate risk of bias (the study had a control group but patients used the expanders passively as placebo only for 30 d)	Serious risk of bias (selection related to intervention and outcome)	Serious risk of bias (lack of standardization of the amount of expansion)	Low risk of bias
Hyla-Klekot, 2015	Critical risk of bias (periods of assessment were not described in details; and discontinuations or switches were not described)	Serious risk of bias (selection related to intervention and outcome)	Critical risk of bias (no information of intervention was described)	No information
Bazargani, 2016	Moderate risk of bias (the study did not have control group but patients used the expanders passively as placebo for 30 d)	Serious risk of bias (selection related to intervention and outcome)	Serious risk of bias (lack of standardization of the amount of expansion)	Low risk of bias

pre-expansion and postexpansion periods to confirm the improvement in patients' nasal breathing. This is important since the reduction of NE episodes seems to be associated with improvement in sleep hygiene consequent to the improvement of nasal breathing after RME.[17,18]

The CONSORT statement emphasizes the importance of a detailed description of results to prevent reporting bias in clinical studies.[35] Some articles[10,11,13] of this systematic review did not clearly describe the improvement of NE using the mean or the absolute values of episodes observed in both the pre-expansion and postexpansion periods. In some cases, for example, the authors[10] reported that patients had NE episodes occasionally in the posttreatment period. The term *occasionally* confers subjectivity to the analysis, and the lack of quantification of NE episodes reduced the reliability of the results.

The most commonly used method to analyze the influence of RME on NE was interviews with the patients' parents using questionnaires. The parents were asked to report the daily, weekly, and monthly number of episodes of NE during a follow-up period that varied from 6 months[28] to 10 years.[13] Attention is required to the high risk of data underestimation associated with this method of analysis, because the quantification of NE episodes was dependent on the memory and the notification to parents regarding the occurrence of bedwetting.

Table 3. Extended

Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall
Low risk of bias	Serious risk of bias (the outcome measured was subjective once the frequency of nocturnal enuresis was assessed by asking to parent monthly; the measurement of nasal cavity width was performed in only 4 patients of the experimental group)	Serious risk of bias (there is a high risk of selective reporting once results of clinical and lateral headfilm examination was performed at the pre-expansion period; reporting of improvement on sleep, school performance, and alert feeling was performed for only 2 participants)	Serious risk of bias
Low risk of bias	Serious risk of bias (the outcome measured was subjective once the frequency of nocturnal enuresis was assessed by orphanage nurses monthly)	Low risk of bias	Moderate risk of bias
Low risk of bias	Serious risk of bias (the outcome measured was subjective once the frequency of nocturnal enuresis was assessed monthly by parents and by interviews with participants 10 y postexpansion)	Serious risk of bias (there is a high risk of selective reporting once description of frequency of nocturnal enuresis was not described in details in each month)	Serious risk of bias
Low risk of bias	Serious risk of bias (the outcome measured was subjective once the frequency of nocturnal enuresis was assessed weekly by parents)	Low risk of bias	Moderate risk of bias
Low risk of bias	Serious risk of bias (the outcome measured was subjective once the frequency of nocturnal enuresis was assessed by parents)	Serious risk of bias (there is a high risk of selective reporting once description of frequency of nocturnal enuresis was not described in details monthly)	Serious risk of bias
Low risk of bias	Serious risk of bias (the outcome measured was subjective once the frequency of nocturnal enuresis was assessed by parents)	Serious risk of bias (there is a high risk of selective reporting once description of frequency of nocturnal enuresis was not described in details)	Critical risk of bias
Low risk of bias	Serious risk of bias (the outcome measured was subjective once the frequency of nocturnal enuresis was assessed by parents)	Low risk of bias	Moderate risk of bias

Finally, the difficulty in quantifying the number of NE episodes must be recognized since there is no laboratory test that accurately evaluates the improvement of NE. Although the blood plasma osmolality test is a reliable method for analyzing the concentration of antidiuretic hormone,[12] the correlation between ADH secretion and NE is not yet a consensus in the literature. In addition, the improvement in NE should be carefully analyzed, especially in studies assessing the patient during a long follow-up period, since NE has a multifactorial etiology and growth, patient psychological maturation, spontaneous reduction of adenoids, and/or improvement of sleep hygiene might have influenced the reduction of the number of episodes.

Table 4. GRADE Evidence Profile About the Outcome Influence of Rapid Maxillary Expansion on Reduction of Nocturnal Enuresis Episodes

Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Impact	Overall Certainty of Evidence
Prospective study, randomized controlled trial	Serious	Serious	Not serious	Very serious	Serious	Rapid maxillary expansion reduces nocturnal enuresis episodes in children	Low

Limitations

Limitations are associated with the high risk of bias of the selected studies and the low level of certainty due to the lack of randomization and allocation concealment of participants, the lack of control groups, incomplete description of eligibility and exclusion criteria, the lack of blinding during outcome analysis, and reporting bias. In addition, these results should be generalized only for children with respiratory disorders in the mixed and early permanent dentitions who underwent conventional RME.

CONCLUSIONS

- Rapid maxillary expansion seems to promote an improvement of nocturnal enuresis in children. However, the low level of quality of the existing evidence weakens the recommendation.
- Further randomized controlled trials with standardized samples, control groups, and better reporting of results are necessary to answer the issues raised in this review.

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