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CLINICAL REVIEW

Rapid maxillary expansion versus watchful waiting in pediatric OSA: A systematic review

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SUMMARY

Spontaneous resolution of pediatric obstructive sleep apnea (OSA) may stand behind the observed benefit of rapid maxillary expansion (RME), mainly supported by uncontrolled case series. We aimed to review the controlled, ideally randomized, evidence on the effectiveness of RME as compared to watchful waiting or alternative treatment of pediatric OSA. We only found one randomized clinical trial comparing RME with watchful waiting. The other four studies compared RME with the gold-standard treatment adenotonsillectomy, three of them in a non-randomized fashion. The results of the RCT showed no statistically significant differences in the enhancement of main (apnea hypopnea index, AHI) and secondary outcomes between RME and watchful waiting. Furthermore, reproducibility of the published studies was limited by insufficient description of their patients' inclusion criteria. We could not find convincing evidence of the benefit of RME over watchful waiting in patients with pediatric OSA. RCTs with reproducible inclusion criteria comparing RME with watchful waiting are still critically needed to support this intervention for the treatment of pediatric OSA. In the absence of solid evidence with RCT, RME should not be recommended for the treatment of pediatric OSA.

Prospero registration number: CRD42021249261.

Running summary: This systematic review explores the benefits of rapid maxillary expansion compared to spontaneous resolution of pediatric obstructive sleep apnea.

Introduction

Obstructive sleep apnea (OSA) is the most severe form of sleep-related disordered breathing (SRDB) [1]. Diagnostic criteria for pediatric OSA are not standardized [2], but Apnea Hypopnea Index (AHI) is frequently used for disease severity stratification and treatment indication [3–6] Pediatric OSA prevalence (.69–2.9%) [7,8] and cure rate (25–79%) [9,10] vary depending on the AHI threshold [6,10–13]. Although polysomnography (PSG) provides gold standard diagnosis of pediatric OSA [3,5,14], home sleep apnea tests (HSAT) are increasingly accepted, especially when PSG is not available [5,6].

Unlike adult OSA [15], in which a relentless disease progression is expected [16–19], pediatric OSA often spontaneously remits (69–100%) [20–23]. AHI reduction after gold-standard treatment with adenotonsillectomy (T&A) prevails [9,20,21], but recent randomized controlled trials reveal short-term small differences between T&A and watchful waiting [22–26]. Additionally, AHI normalization occurs in almost 50% of untreated patients [10]. Such findings have set the ground for a discussion on which patients may be spared of T&A [20,27–31].

Rapid maxillary expansion (RME), a non-invasive orthodontic treatment of maxillary constriction [32] usually performed for aesthetic and functional orofacial improvement, has been proposed as an alternative treatment for pediatric OSA, based on alleged upper airway positive effects [33–39]. However, current pediatric OSA treatment guidelines differ in their recommendation. Spanish [13] and European [6] guidelines recommend RME in children with OSA and "selected craniofacial alterations" or

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Glossary of terms (in alphabetical order)

AAP	American Academy of Pediatrics
AHI	Apnea hypopnea index
BMI	Body mass index
ERS	European Respiratory Society
HSAT	Home sleep apnea test
JBI	Joanna Briggs Institute
OSA	Obstructive sleep apnea
MSAT	Mean oxygen saturation
LSAT	Lowest oxygen saturation
PSG	Polysomnography
RCT	Randomized controlled trial
RDI	Respiratory disturbance index
RME	Rapid maxillary expansion
SES	Sociedad Española del Sueño
T_0	Pre-treatment assessment
T_1	Post-treatment assessment
T&A	Adenotonsillectomy

"maxillary constriction"; conversely, American [5] guidelines warn "data is insufficient to recommend maxillary expansion", due to the absence of controls in published case series and urge for "a randomized controlled trial to assess the efficacy of rapid maxillary expansion in the treatment of OSA in children". Previous systematic and narrative reviews have not stressed enough on the importance of appropriate controls to offset the unpredictable prospects of pediatric OSA, nor have they included the only randomized clinical trial comparing RME with watchful waiting [40] published to date.

Therefore, the objective of this systematic review is to answer the following question: In children (<18 years-old) with OSA, does RME improve sleep study outcomes as compared to watchful waiting or alternative treatment? Hereby we aim to highlight the importance of appropriate controls in pediatric OSA treatment.

Methods

The design of the current study matched the PRISMA 2020 guidelines [41] and was registered in PROSPERO (CRD42021249261) on June 18th, 2021.

Eligibility criteria

The inclusion criteria were: experimental (randomized clinical trials) or quasi-experimental (longitudinal prospective non-randomized studies) controlled studies. The exclusion criteria were: 1) Studies with adult patients, surgically assisted techniques or concomitant treatment in the intervention group, no diagnosis of OSA, no sleep study (PSG or HSAT), no data on the primary outcome (pre and post-treatment AHI); 2) Studies with patients with craniofacial, cardiorespiratory or neurological syndromes, or healthy non-OSA control patients; 3) Case reports, reviews, opinions, etc.; and 4) *in vitro* and *in vivo* studies.

PICO question was: Children diagnosed with OSA by means of PSG or HSAT (Population), Orthodontic maxillary expansion by means of an intraoral device (Intervention), watchful waiting or alternative treatment (Comparison) and Difference between pre and post-treatment AHI as measured in a sleep study (PSG or HSAT) (Outcome).

Information sources

An electronic bibliographic search was performed in the following databases: PubMed, Web of Science, Embase, Cochrane Library and Scopus. References from original papers and review articles were cross-checked to identify additional trials. No limitation on language or date of publication was considered. Authors were contacted if data was missing or incomplete.

Search strategy

Search was performed for articles published until 1st May 2021, and updated 1st Dec 2021 (Supplementary Table 1).

Selection process

Two independent reviewers (MFB, ILIM) systematically and independently assessed both the titles and abstracts of all identified records for inclusion and exclusion criteria. If an abstract failed to provide sufficient information to reach a decision, the full text was retrieved. In case of disagreement, a third reviewer was consulted (JMAU).

Data collection process

Extraction of qualitative and quantitative data was performed using a structured data extraction form (Excel datasheet) by one investigator (MFB) and double-checked by other (ILIM).

Data items

Data from pre- (T_0) and post-treatment (T_1) sleep study parameters in intervention (RME) and control groups were extracted: AHI (main outcome); obstructive AHI, lowest oxygen saturation, mean oxygen saturation (secondary outcomes). The percentage of change in AHI before and after treatment, the percentage of patients with residual disease after treatment and the time interval between initial and final sleep studies were also extracted. Other variables abstracted included demographic information, methodology, intervention details, and other known pediatric OSA risk factors as described in Supplementary Table 2.

Risk of bias

Two reviewers (MFB, ILIM) independently assessed the risk of bias using the modified Joanna Briggs Institute (JBI) critical appraisal checklist for randomized clinical trials and quasi-experimental studies [42]. In case of disagreement, a third reviewer was consulted (JMAU). Randomized and quasi-RCTs are considered together with 10 questions for critical appraisal, which are then incorporated into the analytical module of the JBI systematic review software.

Results

Study selection

The initial search yielded 1219 records, 604 unduplicated. From these, 581 met exclusion criteria and were excluded at the title (470) and abstract 116) screening, leaving 18 articles for full text review. At the end, 5 studies fulfilled the inclusion criteria and were selected for qualitative analysis [40,43–46]. Details on the selection process are given in Fig. 1, and rejected articles, with reasons, can be found in Supplementary Table 3.

Study characteristics

Methodology of the studies was heterogeneous and included one parallel RCT [40], one cross-over RCT [43] and three non-randomized controlled longitudinal prospective studies [44–46] (see Table 1). Critical data was lacking in the study by Pirelli et al. [44], some of which were extracted from a systematic review coauthored by Pirelli [47].

Results of individual studies

Demography and risk factors

We analyzed 213 patients, 129 of which underwent RME. Four studies included patients in early childhood [43–46] and one in early puberty [40]. Male patients were overrepresented in one study [45]. Three studies reported BMI data, featuring non-overweight patients [44–46]. None of the articles reported on race, socioeconomic status or pre-term birth. One patient dropped out before treatment [43], and no patient was reported to be lost during follow-ups. History of previous treatment for OSA was an exclusion criterion from two prospective cohorts [45,46], and only one study reported tonsil stage at entry [43]. Another study [44] reported an adenoid assessment (rhinopalatoscopy and lateral cephalogram), but did not provide data in their sample.

Intervention and controls

All patients allocated to RME had both a medical diagnosis of pediatric OSA and a concurrent dentofacial exam subsidiary of RME treatment. They were treated with an endo-oral appliance as described in Supplementary Table 4. Absence of adverse effects in RME treated patients was reported in two studies [40,44]. Alternative treatment was T&A in four studies [43–46]. One study described the surgical technique as "cold dissection tonsillectomy and a curettage of the adenoid vegetations under direct vision via oral access" [46], and also included a medical therapy arm subgroup consisting of "nasal washes with 2.5% saline hypertonic solution and topical intranasal corticosteroids". The parallel RCT did not describe any intervention in the control group, though a watchful waiting policy was understood [40].

Outcomes

To facilitate comparisons, the crossover RCT [43] was split into a *primary treatment* cohort (RME *vs.* T&A) and a *salvage treatment* cohort (T&A after failed RME *vs.* RME after failed T&A). Meanwhile, the three-armed study was split into two parallel studies [46]: RME *vs* T&A and RME *vs* Medical therapy. AHI before (T_0) and after (T_1) treatment, cure rate and AHI change percentage in the selected studies are given in Table 2. Secondary outcomes (LSAT and MSAT) are shown in Table 3.

Dentofacial measures

Dentofacial inclusion criteria of patients were vaguely described in all studies: "narrow maxilla associated with a high and narrow hard palate, as determined by an orthodontist" [43], "high-arched palate and/or malocclusions, and dysgnathia, according to the orthodontist's evaluation" [45], "clinical signs of maxillary transverse

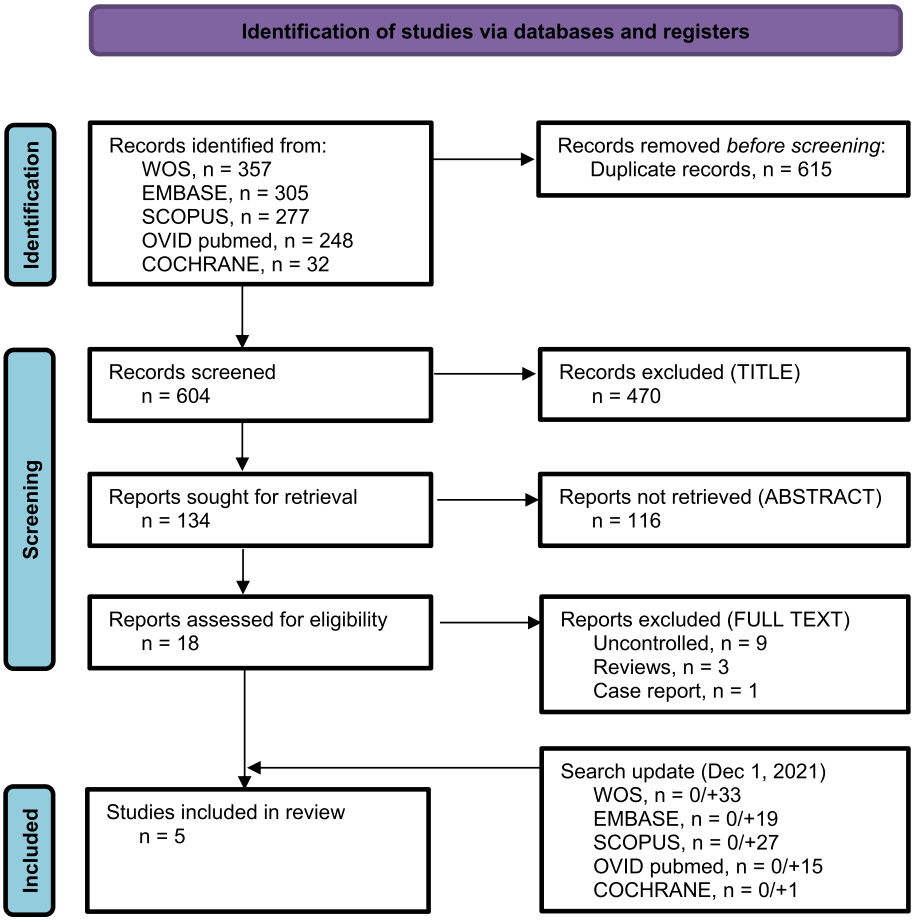

Fig. 1. PROSPERO flow diagram.

Table 1
General characteristics of included studies.

Authors, reference	Country	Study design	Sleep study	Control group	Gender (M/F)	RME (n)	Age mean (SD) (years)	Follow-up (months)	BMI mean (SD) (kg/m^2)
Guilleminault et al. 2011 [43]	France, Italy	Cross-over RCT	PSG	T&A	14/17	16 + 15	6.5 (.2)[a]	RME: 3 T&A: 1	–
Hoxha et al. 2018 [40]	Turkey	Parallel RCT	HSAT	WW	14/16	15	RME: 12.27 (1.93) OBS: 11.46 (2.06)	RME: 5.01 (.96) OBS: 5.38 (1.36)	–
Pirelli et al. 2012 [44]	Italy	NRC	HSAT	T&A	43/37	40	7.1 (.8)[a,b]	4	<24[b]
Villa et al. 2014 [45]	Italy	NRC	PSG	T&A	34/13	22	RME: 6.58 (1.83)[c] T&A: 3.7 (.92)[c]	12	RME: 18,82 (3.44)[c] T&A: 15,75 (1.82)[c]
Villa et al. 2016 [46]	Italy	NRC	PSG	T&A MT	44/32	21	RME: 6.16 (1.68) T&A: 4.54 (1.69) MT: 4.34 (1.08)	>6	RME: 19,91 (2.23) T&A: 16,98 (3.29) MT: 15,86 (1.53)

BMI: Body mass index; F: Female; HSAT: Home sleep apnea test; M: Male; MT: Medical treatment; NRC: Non-randomized controlled; PSG: Polysomnography; RCT: Randomized controlled trial; RME: Rapid maxillary expansion; SD: Standard deviation; T&A: Adenotonsillectomy; WW: Watchful waiting; -: Not reported.
[a] Mean age of full sample provided only.
[b] Not available in the original manuscript and not provided upon request. Extracted from the systematic review of *Camacho* et al. 2017 [48], coauthored by *Pirelli*.
[c] Statistically significant difference between T&A and RME cohorts.

Table 2
Sleep study primary outcomes: AHI pre- and post-intervention, percentage cured, AHI change percentage.

Authors, reference	Treatment arm	AHI at T_0 mean (SD)	*P*	AHI at T_1 mean (SD)	% cured at T_1, AHI<1	% ΔAHI mean (SD)
Guilleminault et al. *2011* [43] *(Primary)*	Intervention	11.1 (.7)	.00	5.4 (.6)	7% (1/15)	51%[a]
	P	.2	.53	.15	–	–
	Control (T&A)	12.5 (.8)	.00	4.9 (.6)	0% (0/16)	60%[a]
Guilleminault et al. *2011* [43] *(Salvage)*	Intervention	4.9 (.6)	.00	.9 (.3)	93% (13/14)[b]	81%[a]
	P	.15	.49	.16	–	–
	Control (T&A)	5.4 (.6)	.00	.9 (.3)	93% (15/16)[b]	83%[a]
Hoxha et al. *2018* [40]	Intervention	2.5 (1.12)	<.05	1.79 (1.05)	–	28%[a]
	P	–	n.s.	–	–	–
	Control (WW)	2.67 (1.23)	<.05	1.8 (1.08)	–	33%[a]
Pirelli et al., 2012 [44]	Intervention	12.1 (4.9)[c]	–	5.4 (5.4)[c]	37% (15/40)	55%[c]
	P	–	–	–	–	–
	Control (T&A)	–	–	–	15% (6/40)	–
Villa et al. *2014* [45]	Intervention	5.81 (6.05)	.005	2.64 (3.11)	37% (8/22)	36% (74.63)
	P	.000	–	.468	.408	.011
	Control (T&A)	17.25 (13.94)	.000	1.79 (1.82)	44% (11/25)	84% (17.79)
Villa et al. *2016* [46] *(RME vs. T&A)*	Intervention	5.6 (1.8–17.2)	<.005	1.9 (0–11.8)	38% (8/21)	66%[a]
	P	–	–	–	–	–
	Control (T&A)	16.3 (6–71.5)	<.005	1.3 (0–11.9)	31% (13/42)	92%[a]
Villa et al. *2016* [46] *(RME vs. MT)*	Intervention	5.6 (1.8–17.2)	<.005	1.9 (0–11.8)	38% (8/21)	66%[a]
	P	–	–	–	–	–
	Control (MT)	4.4 (.8–31.3)	n.s.	2.4 (.6–21.1)	15% (2/13)	45%[a]

MT: Medical treatment; n.s: Not significant; T&A: Adenotonsillectomy; WW: Watchful waiting; -: Not reported. % ΔAHI: Percentage of change in AHI between T_0 and T_1 assessments.
[a] % ΔAHI not reported, calculated as the percentage of the difference of pre and post-treatment AHI means= (AHI T_0 mean-AHI T_1 mean)/AHI T_0 mean*100.
[b] Study reports "persistence of abnormal PSG findings in two individuals" but does not specify to which group they belonged; we hypothesized one belonged to each group to give an estimate of the cure percentage, the plausible range would be 85,71%–100% success for the intervention group and 87,5%–100% in the control group.
[c] Data unavailable in the original manuscript and not provided upon request. Extracted from the systematic review of *Camacho* et al. *2017* [47], coauthored by Pirelli.

deficiency, malocclusion (high, narrow palate associated with deep bite, retrusive bite, or cross-bite)" [40]. Two studies described more thoroughly the features of a narrow maxilla [44,46], but did not provide data of their samples. The parallel RCT reported pre- (intercanine distance: 31.96 ± 2.69 mm; intermolar distance: 47.77 ± 4.07 mm) and post-treatment (intercanine distance: 36.39 ± 2.98 mm; intermolar distance: 54.4 ± 3.26) objective dentofacial measurements, but only of the patients assigned to RME [40]. Maxillary widening in patients treated with RME was measured from dental casts in one study (intermolar width change: 3.68 ± .53 mm) [43]. An anteroposterior radiographic measure of maxillary widening was reported in one longitudinal study (intermolar distance increase: 8.18 ± .3 mm) [44] while pre- (55.12 ± 6.50 mm) and post-treatment (59.15 ± 4.55 mm) measures were provided in another [40].

Quantitative synthesis

Quantitative synthesis of the results was not performed due to heterogeneity: asymmetric distribution of confounders between treatment arms [45,46], differences in duration of follow-up assessments [43], type of sleep study and scoring criteria [40,43,44,46], and treatment indication threshold [44]. Data was incomplete on primary [44] and secondary [40,43–46] outcomes. Furthermore, only one study compared treatment with watchful waiting [40].

Risk of bias in studies

After applying the JBI tool [42], we recognized some authors did not analyze important features regarding the randomization process, such as allocation concealment and blindness of the clinicians and outcome assessors [40,43]. Furthermore, it was not clearly

Table 3
Sleep study secondary outcomes: mean oxygen saturation (MSAT), lowest oxygen saturation (LSAT).

Authors, reference	Treatment arm	MSAT at T_0 mean (SD)	*p*	MSAT at T_1 mean (SD)	LSAT at T_0 mean (SD)	*P*	LSAT at T_1 mean (SD)
Guilleminault et al. *2011* [43]	Intervention	–	–	–	92.5 (.4)	.00	95.9 (.3)
Primary	*P*	–	–	–	.53	.15	.65
	Control (T&A)	–	–	–	92.1 (.5)	.00	95.2 (.3)
Guilleminault et al. *2011* [43]	Intervention	–	–	–	95.2 (.3)	.00	98 (.2)
Salvage	*P*	–	–	–	.65	.68	.004
	Control (T&A)	–	–	–	95.9 (.3)	.00	97.6 (.3)
Hoxha et al. *2018* [40]	Intervention	96.31 (.75)	n.s.	96.08 (.64)	88.08 (4.32)	n.s.	89.75
	P	–	–	–	–	n.s.	–
	Control (WW)	95.87 (1.36)	n.s.	95.8 (1.15)	89 (4.49)	n.s.	89.5 (3.63)
Pirelli et al. *2012* [44]	Intervention	–	–	–	84.6 (2.7)[a]	–	95.2 (3.5)[a]
	P	–	–	–	–	–	–
	Control (T&A)	–	–	–	–	–	–
Villa et al. *2014* [45]	Intervention	96.56 (.47)	.013	97.42 (1.84)	–	–	–
	P	n.s.	–	n.s.	–	–	–
	Control (T&A)	96.11 (2.7)	.013	97.5 (1.14)	–	–	–
Villa et al. *2016* [46]	Intervention	97.29 (1.49)	<.005	97.62 (.86)	–	–	–
(RME vs. T&A)	*P*	–	–	–	–	–	–
	Control (T&A)	96.47 (1.79)	<.005	98.03 (.79)	–	–	–
Villa et al. *2016* [46]	Intervention	97.29 (1.49)	<.005	97.62 (.86)	–	–	–
(RME vs. MT)	*P*	–	–	–	–	–	–
	Control (MT)	96.96 (1.16)	n.s.	97.37 (1.21)	–	–	–

LSAT: Lowest oxygen saturation; MSAT: Mean oxygen saturation; MT: Medical treatment; n.s: Not significant; T&A: Adenotonsillectomy; WW: Watchful waiting; -: Not reported.

[a] Data unavailable in the original manuscript and not provided upon request. Extracted from the systematic review of *Camacho* et al. *2017* [47], coauthored by Pirelli.

stated whether comparison groups were similar and outcome measurements reliable [44–46]. These results demonstrate that, although quality of some studies is good, overall risk of bias is significant (see Table 4).

Discussion

Given the ability of pediatric OSA for spontaneous resolution, treatment alternatives should outperform watchful waiting. Evidence supporting RME as a therapeutic option comes mainly from uncontrolled, short-term, small case series [5]. In this systematic review, we found five controlled studies that met the inclusion criteria, although only one compared RME therapy with watchful waiting [40]. This randomized clinical trial reported a 5-month AHI decrease from 2.5 to 1.79 (28% drop) in the RME arm ($p < 0.05$) and from 2.67 to 1.8 (33% drop) in the watchful waiting arm ($p < 0.05$). The difference between both treatment arms was not statistically significant, yet this pivotal fact was not clearly stated nor discussed. No difference in secondary outcomes (MSAT, LSAT) before and after treatment was found neither. According to their results, the orthodontic intervention would not be better than watchful waiting in terms of AHI, MSAT or LSAT enhancement.

Pediatric OSA risk factors (baseline AHI, age, BMI, disease duration, dentofacial and oropharyngeal features) were unevenly distributed in the treatment arms of two prospective non-randomized studies from one institution [45,46]. A third non-randomized study [44] lacked critical data that was not fulfilled upon request to the corresponding author. In this cross-over-like design, patients with similar degrees of residual OSA after RME were considered “too mild” to undergo salvage T&A after failed RME, but amenable for salvage RME after failed T&A. Such differences in the baseline characteristics and management of the treatment arms reflect the institutions’ preferences for treatment but preclude a genuine control of the results of RME in their studies.

The crossover RCT [43] reported distinct unmatched results. In the “primary treatment cohort”, cure rate was 0% for T&A and 7% for RME; this is an exceedingly low cure rate even for a concurrent dentofacial and oropharyngeal obstructive sample. In the residual OSA “salvage treatment cohort”, cure rate was 86–100% for T&A (after failed RME) and 87–100% for RME (after failed T&A) an exceedingly high cure rate after combined T&A and RME treatment. The same group [48] previously published a similar RCT that was first corrected and later retracted due to an “incomplete and inaccurate description of the methodology”. These results have supported the use of RME in patients with a narrow maxilla and residual OSA after T&A yet have never been replicated. The reason why AHI drops in self-resolving pediatric OSA remains unknown and unpredictable. Some studies on RME in pediatric OSA [44,49] have reported continuing improvement at intermediate and final controls. Multiple short-term assessments and asymmetric cross-over longitudinal studies [43,44] may magnify the efficacy of consecutive treatment regimens as compared to spontaneous AHI progressive fade-out. Although the results of RME in uncontrolled case series were stable at three [50] and 12 [51] year follow-ups, controlled long-term data demonstrating RME efficacy in growing pediatric OSA patients is lacking.

As in previously published uncontrolled case series [49,52–56], the sample size of the selected studies was low. The actual patient flow and recruitment pace has been rarely disclosed: a clinic pioneering this treatment modality recruited 80 pediatric OSA patients candidate for RME throughout 8 years, resulting in less than 10 patients per year [44]. Furthermore, duplicate and/or cumulative reporting of case series has been noted [47,57]. Finding pediatric OSA patients candidate for RME might be harder than suggested, therefore limiting its relevance within the pediatric OSA therapeutic algorithm [58].

Besides the adequacy of the control groups and study designs, reproducibility of these results is limited, because most articles relied dentofacial patient selection upon undisclosed expert opinion: “all children were felt to have maxillary involvement”, “the definition of narrow maxilla was made clinically by the experienced orthodontists” [43], “high-arched palate and/or malocclusions, and dysgnathia, according to the orthodontist's evaluation” [45]. Studies that described objective tools for the diagnosis of maxillary hypoplasia [44,46] did not report their samples' characteristics. Although orthodontic diagnosis and treatment often encompasses a significant amount of subjective/aesthetic observation, basic dentofacial measurements may be reported for the sake of reproducibility. The parallel RCT [40] was the only study to report pre- and post-intervention objective dentofacial exam

Table 4
JBI critical appraisal checklist for: a) randomized clinical trials, b) quasi-experimental designs (b).

#	a) JBI for RCTs	*Hoxha* et al. *2018* [40]	*Guilleminault* et al. *2011* [43]
1	Was true randomization used for assignment of participants to treatment groups?	NA	U
2	Was allocation to treatment groups concealed?	NA	U
3	Were treatment groups similar at the baseline?	Y	Y
4	Were participants blind to treatment assignment?	N	N
5	Were those delivering treatment blind to treatment assignment?	N	N
6	Were outcomes assessors blind to treatment assignment?	NA	U
7	Were treatment groups treated identically other than the intervention of interest?	NA	NA
8	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Y	Y
9	Were participants analyzed in the groups to which they were randomized?	Y	Y
10	Were outcomes measured in the same way for treatment groups?	Y	Y
11	Were outcomes measured in a reliable way?	Y	Y
12	Was appropriate statistical analysis used?	Y	Y
13	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Y	Y

#	b) JBI for Quasi-experimental designs	*Pirelli* et al. *2012* [44]	*Villa* et al. *2014* [45]	*Villa* et al. *2016* [46]
1	Is it clear in the study what is the 'cause' and what is the 'effect' (i.e., there is no confusion about which variable comes first)?	Y	Y	Y
2	Were the participants included in any comparisons similar?	Y	N	N
3	Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	N	U	U
4	Was there a control group?	Y	Y	Y
5	Were there multiple measurements of the outcome both pre and post the intervention/ exposure?	Y	N	N
6	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Y	Y	Y
7	Were the outcomes of participants included in any comparisons measured in the same way?	Y	Y	Y
8	Were outcomes measured in a reliable way?	U	Y	U
9	Was appropriate statistical analysis used?	Y	Y	Y

N: No; NA: not answered; U: Unclear.; Y: Yes.

data, but only of the patients treated with RME. They were not markedly constricted: the mean intercanine distance at entry was 32 mm in a 12 year-old cohort, similar to normal reference values for Caucasian 12-year-old patients (32.5 mm for boys and 31.5 for girls) [59]. A narrow maxilla is often considered a risk factor for pediatric OSA [60,61]. However, Marino et al. [62] recently found wider maxillary arches in 6-year-old late primary dentition patients with severe OSA (mean intercanine distance 29 mm) as compared to mild (27.6 mm; $p = 0.023$) and moderate (26.9 mm; $p = 0.003$) counterparts. Kim et al. [63] found no correlation between nasomaxillary complex widening and AHI reduction. The maxillary width gained in patients undergoing RME reported by Hoxha et al. [40] (6.63 mm) almost doubled that reported by Guilleminault et al. [43] (3.68 mm), despite the latter having significantly better AHI enhancement rates. These findings challenge the widespread belief in a linear correlation between maxillary width and pediatric OSA severity.

Previous systematic reviews have warned on the risk for publication bias within their selected studies [47,57]. A congress abstract [64], rejected in our systematic review for being uncontrolled, reported modest results of RME in maxillary constricted pediatric OSA patients recruited for a RCT registered in 2013 (NCT01837914). These negative results (baseline AHI 7.1 and mean AHI change after RME 1.2 IC95%:-2.1; 4.6), have not yet turned into a peer-reviewed indexed publication. Moreover, multiple publication bias resulting from cumulative reporting [47,57] may overestimate the effect of treatment and magnify the amount of evidence available [65].

The main limitation of this review is the exclusive use of three objective sleep study outcomes (AHI, LSAT, MSAT) to measure the efficacy of the intervention. Other sleep study outcomes have been used to assess treatment outcomes (i.e., oxygen desaturation index, arousal index, respiratory disturbance index, sleep efficiency). Although currently challenged, AHI remains the best studied and most used metric of OSA [66]. On the other hand, more than a hundred clinical tools for the screening of pediatric OSA have been proposed [67], but the absence of universally accepted questionnaires and the unreliability for the diagnosis of pediatric OSA [68] hinder their validity and comparability. The effect of the intervention on morbid conditions associated with pediatric OSA (i.e., snoring, behavioral and neurocognitive disorders, quality of life, growth impairment) would be another measure of effect of great interest; they might be the caregiver's main motive for RME indeed. Larger studies using consolidated treatment alternatives have struggled to prove clinically significant beneficial effects over blood pressure [69] and neurocognitive outcomes [10]. A recent RCT showed significant enhancement at 6 months in sleep-related quality of life of two- to 4-year-old patients undergoing T&A as compared to watchful waiting [20]. However, another study using the same clinical tool (OSA-18 questionnaire) found the advantage of T&A compared to watchful waiting at early follow-up (4 months) almost disappeared at late follow-up (8 months) [70]. The controversy on the boundaries of sleep-related disorders, their effect over children's health and quality of life and its response to treatment, is beyond the scope of this review, but conflicting evidence of a true causal relationship between pediatric OSA and its associated morbidity exists [71].

Another limitation of this review is the small amount of studies selected. Only one of them was indeed a RCT comparing RME with watchful waiting [40], and the critical appraisal tool used for quality assessment of the studies included in this systematic review identified several design flaws. We acknowledge that the evidence level of some of the included studies was low: class I for RCTs [40,43] and class III for observational studies [44–46]. Therefore,

the conclusions drawn from this study may be taken cautiously. This systematic review has some limitations [72].

The lack of randomized controlled evidence to support RME for the treatment of pediatric OSA was already noted in the 2012 American Academy of Pediatrics (AAP) guidelines [5] and has not yet been fulfilled. There are several limitations for the start-up of such RCTs. First, ethical concerns have been argued to justify the absence of controls in pediatric OSA and RME research: "it is ethically difficult to refrain from treating children with OSAS for 12 months" [50]. These ethical concerns were overcome in the CHAT RCT that kept over 200 hundred children from receiving the current gold-standard treatment (T&A) for 7 months arguing such waiting period "is not much beyond the range encountered in some clinical practices" and "appears small relative to the average time elapsed between the onset of significant symptoms and T&A" [10]. Ethical issues proposing an insufficiently proven or inefficient treatment may outweigh those of delaying treatment for a few months. Second, true patient blinding is precluded by the evident aesthetic effect (interincisal diastema) produced by RME activation, and placebo treatment is only feasible in very short-term cross over settings [73]. Third, the number of children with OSA screened to find one RME candidate has not been often disclosed and might be higher than anticipated [57]; validated easy-to-use dentofacial screening tools applicable to all OSA patients in a non-specialized setting would be of great interest.

Our search strategy found several registries of unpublished or ongoing RCTs on RME in pediatric OSA. Most of them intended to compare different treatment modalities (i.e., T&A [74–78], mandibular advancement [78–80], myofunctional therapy [79]) or RME regimens (i.e., tissue/tooth/bone-borne devices [81,82], different treatment sequences [74,80]), but without a watchful waiting arm. Such designs will not be able to distinguish a genuine treatment effect from the frequent spontaneous pediatric OSA alleviation. Therefore, the core question will remain unanswered. One RCT plans to compare RME with watchful waiting in terms of upper airway airflow in volumetric models, but no OSA assessment or sleep study is described [80]. Only one RCT plans to compare ERM with watchful waiting in pediatric OSA and assess outcomes in sleep studies [83]. Reluctance to confront wide-spread practice with well-designed RCTs in orthodontics, a field were "treatment success and failure are ill-defined" [32], has been previously discussed [32,84,85]. If pediatric OSA and its associated morbidities are to be summoned to indicate treatment with RME, current standards for evidence-based medicine apply. Almost 20 years after its first description, clinicians and researchers have not been able to overcome the limitations to start, or finish, such RCTs. If they were to start in the future, disclosure of reproducible inclusion criteria and patient flow would be strongly encouraged.

Conclusion

In summary, in this systematic review we were not able to find convincing evidence of a significant benefit of RME treatment over watchful waiting in patients with pediatric OSA. Comparisons with other treatment alternatives (T&A) were hindered by non-homogeneous distribution of confounders and suboptimal designs. Accordingly, in absence of solid evidence with RCT, RME should not be recommended for the treatment of pediatric OSA. This systematic review focused on objective diagnosis of pediatric OSA by means of validated sleep studies. Other conditions that have been associated with pediatric OSA (i.e., snoring, quality of life, neurocognitive, behavioral and growth impairment) were not specifically addressed. Regardless of the outcome assessed, future RCTs should compare results of treatment with RME with those of spontaneous enhancement of pediatric OSA and its associated morbidity. There are several limitations for the onset of such RCTs, of which the actual number of patients with pediatric OSA amenable for RME might be among the most significant.

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Registration number

The design of the current study matched the PRISMA 2020 guidelines and was registered in PROSPERO (CRD42021249261) on June 18th, 2021.

Practice points

- Pediatric obstructive sleep apnea (OSA) may spontaneously resolve in over half of the patients.
- Treatment alternatives should outperform watchful waiting to be considered effective.
- The association between a narrow maxilla and pediatric OSA might result from biased observations.

Research agenda

- Randomized clinical trials comparing rapid maxillary expansion (RME) with watchful waiting are critically needed to support treatment of pediatric obstructive sleep apnea (OSA).
- Randomized trials comparing different modalities of maxillary expansion (i.e., rapid vs. slow maxillary expansion, different intraoral devices, sequence order) are inadequate to answer the fundamental doubts upon RME effectivity for pediatric OSA.
- Disclosure of inclusion criteria is strongly advised to allow reproducibility of the results.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101609.

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