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CLINICAL REVIEW

Orthodontics treatments for managing obstructive sleep apnea syndrome in children: A systematic review and meta-analysis

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SUMMARY

A small maxilla and/or mandible may predispose children to sleep-disordered breathing, which is a continuum of severity from snoring to obstructive sleep apnea. Preliminary studies have suggested that orthodontic treatments, such as orthopedic mandibular advancement or rapid maxillary expansion, may be effective treatments.

The aim is to investigate the efficacy of orthopedic mandibular advancement and/or rapid maxillary expansion in the treatment of pediatric obstructive sleep apnea. Pubmed, Medline, Embase, and Internet were searched for eligible studies published until April 2014. Articles with adequate data were selected for the meta-analysis; other articles were reported in the qualitative assessment. Data extraction was conducted by two independent authors. A total of 58 studies were identified. Only eight studies were included in the review; of these, six were included in the meta-analysis. The research yielded only a small number of studies. Consequently, any conclusions from the pooled diagnostic parameters and their interpretation should be treated carefully. Although the included studies were limited, these orthodontic treatments may be effective in managing pediatric snoring and obstructive sleep apnea. Other related health outcomes, such as neurocognitive and cardiovascular functions have not yet been systematically addressed. More studies are needed with larger sample size, specific inclusion and exclusion criteria and standardized data reporting to help establish guidelines for the orthodontic treatment of pediatric obstructive sleep apnea.

Introduction

Description of the condition

Craniofacial growth influenced by genetic inheritance and functional factors can have an impact on general health. Predominant mouth breathing, often caused by increased nasal breathing resistance or adenoid and tonsil hypertrophy, leads to altered muscle recruitment in the nasal and oral cavities, impacting craniofacial growth in a developing child [1,2] altering tongue position [3] and oropharyngeal volume, thereby increasing the risk of developing a significant malocclusion. In other words, a small maxilla and/or mandible may predispose children to sleep-disordered breathing (SDB), which is a continuum of severity from snoring to obstructive sleep apnea (OSA).

OSA is a breathing problem occurring during sleep; it is a common chronic disorder in children and adolescents, with a dramatic impact on systemic health [4] and development [5,6]. Among children and adolescents, the reported prevalence of snoring and OSA is 3–27% and 1–10%, respectively [7–11]. Snoring/OSA is a disorder of upper airway obstruction with multisystem implications and associated complications [11]. Snoring/OSA is often underdiagnosed in children and youth when the primary complaint is a behavioral problem. The American Academy of Sleep Medicine (AASM) states that other problems associated with untreated OSA in children include aggressive behavior [12], attention-deficit/hyperactivity disorder (ADHD) [13] and delays in development [14]. An 11-y longitudinal study on early childhood (4 y old) showed that early sleep problems predicted behavioral and emotional problems in adolescence [15]. If left untreated, OSA can

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Abbreviations

AASM	American Academy of Sleep Medicine
ADHD	attention-deficit/hyperactivity disorder
AHI	apnea-hypopnea index
ANOVA	analysis of variance
ARRIVE	animal research: reporting in vivo experiments
CI	confidence interval
CONSORT	consolidated standards of reporting trials
ICC	intraclass correlation coefficient
NRCT	non-randomized controlled trial
OMA	orthopedic mandibular advancement
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
PRISMA	preferred reported items for systematic reviews and meta-analyses
RCT	randomized controlled trial
RDI	respiratory disturbance index
RME	rapid maxillary expansion
SaO_2	oxygen saturation level
SDB	sleep-disordered breathing
SQ	sleep quality

negatively affect a child for the rest of his or her life. There are few proven treatments currently available, and most children are managed with tonsillectomy and adenoidectomy, which have not been demonstrated to fully abolish apnea in all patients, and/or positive airway pressure devices, which have a very poor compliance and are not ideal for all children [16–19]. Preliminary studies [1–3,15,20–23] have suggested that orthodontic treatments, such as maxillary expansion or mandibular advancement with functional appliances, may be effective in handling pediatric snoring and OSA. Accordingly, these preliminary results suggest that the correction of craniofacial structure imbalances during growth may reduce snoring and OSA in children and young adolescents.

Description of the interventions

This systematic review and meta-analysis focused on two main orthodontic interventions. The first intervention involves an orthopedic mandibular advancement (OMA) that aims to correct dental and skeletal retrognathia by re-directing mandibular growth into a more forward and downward position. This could potentially increase the opening of the oropharyngeal airway during wake and sleep. The second intervention involves rapid maxillary expansion (RME) which is used when the patient is diagnosed with a narrow upper jaw. RME decreases nasal resistance and allows tongue repositioning; as a result, it may reduce the risk of obstruction which contributes to sleep apnea. As a consequence, both interventions hold a probability of becoming valuable alternative treatments for patients who have known craniofacial risk factors, but who are not surgical candidates or are not able to tolerate the standard therapy for OSA or who failed either first-line treatments, i.e. adenotonsillectomy or nocturnal application of positive airway pressure.

How the interventions might work

Radiological studies indicate that a long and narrow face, a transverse deficiency, and retrognathia are craniofacial morphological factors associated with a narrow upper airway and SDB in children [24–27]. A recent study found that, compared to obesity, craniofacial morphology was a stronger risk factor for pediatric SDB [28]. Correction of craniofacial risk factors, with orthodontic treatments such as OMA and RME, in optimal conditions afforded by childhood growth may reduce snoring and OSA in children and young adolescents.

In 1860, RME therapy was first published as an orthodontic correction of maxillary constriction [29]. Thus, there is a great body of literature on RME in the fields of orthodontics and dental medicine. However, this therapy was first linked to SDB, when it was shown to decrease nocturnal enuresis in children, a sign and symptom associated to SDB [30–32]. RME is currently performed most often using a fixed intra-oral orthodontic appliance, which will be adjusted and worn at all times during the treatment. An expansion of 5–8 mm will be obtained over 30 d, with the expansion screw activated daily by parents (active phase). Following this active phase, the expansion screw will be locked into place for a retention phase of 2–6 mo to allow re-calcification of the palatine suture (retention phase).

OMA was first introduced by Dr Kingley with the "bite-jumping" appliance in 1879 [33]. The OMA encourages mandibular growth in a passive or active manner, while being fixed or removable (worn at night, from 21:00 h to 08:00 h). There are many different types of functional appliances, such as monobloc, activator, Frankel, Herbst, bionator and Twin-block [33]. Expected advancement will be of half cusp to full cusp (Class II; 3–6 mm). The mandibular advancement phase of OMA lasts up to 6–9 mo (depending on patient compliance with the removable appliance) followed by approximately 6 mo of retention. Moreover, some of the OMA appliances can be combined with RME appliances.

Why it is important to do this systematic review and meta-analysis

Following the *Pediatric Dental Sleep Apnea* strategic planning meeting in 2012 supported by the Canadian Institutes of Health Research, it was recognized that the level of evidence on orthodontic treatments to manage OSA is unknown. More specifically, the number and quality of non-randomized controlled trials (NRCT), and/or controlled before and after studies involving children and adolescents is undefined. There is a need to create a systematic review that includes meta-analysis components to synthesize the data from several studies. This estimation could overcome the barriers faced by clinicians [34] in applying evidence-based medicine and dentistry. To our knowledge, few systematic reviews and/or meta-analyses about craniofacial pediatric OSA have been published [11,35–39]. None has yet reviewed and synthesized the available orthodontic treatments for managing OSA in children and young adolescents (i.e. 18 y old or younger). Therefore, there is a need to create a systematic review and meta-analysis of all the available literature regarding orthodontic treatments, such as OMA and RME, for managing OSA in children and young adolescents.

Objectives

Our aims were to investigate the efficacy of the use of OMA (aim 1) and RME (aim 2) in the treatment of OSA in children and young adolescents.

Methods

Methods of analysis and inclusion criteria were specified in advance and documented in a protocol following Cochrane guidelines [40].

Electronic searches

For the identification of potential studies to include in the review and meta-analysis, detailed search strategies were developed for each

database searched. An electronic literature search was performed in PubMed & MEDLINE (1946–April 2014), and Embase (1974–April 2014). Moreover, Internet was searched (Google and Google scholar searches) for eligible studies published until April 2014.

All available titles and abstracts were read and those related to either OMA or RME, or involving both interventions, were chosen by two reviewers (Nelly Huynh and Eve Desplats). When the information provided by the titles and abstracts was incomplete, the full texts were also carefully read and examined to determine whether they were to be included for future analysis. Only English language papers were evaluated.

Selection of studies

The collected articles were assessed by two reviewers (Nelly Huynh and Eve Desplats) independently for eligibility, and any possible disagreement was solved through discussion with a third reviewer (Fernanda Almeida). The inclusion and exclusion criteria are listed in Table 1. Studies that did not fulfill the inclusion criteria were excluded (see Appendix I-III). References from original papers and review articles were cross-checked to identify additional trials. In addition, to avoid data that were published multiple times, only the original articles were included in the review and meta-analysis.

Types of studies

The search attempted to identify all relevant studies that met the inclusion criteria, independently of source of information. In most studies, a control group was not considered since it is deemed unethical to withhold treatment for children and young adolescents with specific diagnoses. Consequently, NRCT designs and controlled studies (containing before and after treatment data) were considered. In addition, randomized controlled trials (RCTs) were also considered as potential studies; however, only the treatment group data were considered.

Types of participants

Children and adolescents (18 y old or younger) who received OMA and/or RME functional orthopedic appliances in order to treat OSA without craniofacial syndromes were considered. There was no gender restriction.

Data extraction and management

Studies that fulfilled the inclusion criteria were put into a digital electronic database (Excel). The following information was extracted by each unblinded reviewer in their respective database: author, year of publication, title, study design, patients, methods, outcomes, results, conclusion, full-text extracted (yes or no), and included (yes or no). Then a qualitative assessment of the retrieved articles in this report was discussed among the authors to come up with a consensus. The outcome data were extracted by the two reviewers (Nelly Huynh and Eve Desplats) to validate and control the data.

Table 1
Inclusion and exclusion criteria for the studies.

Inclusion criteria	Exclusion criteria
Snoring	Adults (18 y old age and above)
Obstructive sleep apnea symptoms	Surgery
Obstructive sleep apnea with polysomnography diagnosis	Case report
Orthodontic mandibular advancement	Short commentaries
Maxillary expansion	Review articles
Malocclusion (class I and II)	Meta-analysis
Orthodontic appliance (functional or oral)	Animal studies
Upper airway resistance	Duplicate data
Original article	Craniofacial syndromes

Dealing with duplicate data

Data published multiple times were considered as duplicates [3,15,21,41], which was sometimes confirmed by authors [42], and a short commentary [43]. In case of any doubt or ambiguity, the original article was always considered as the final choice for the analyses; by doing so, any overestimation of intervention efficacy was reduced, since there was exclusion of duplicated data.

Dealing with missing or incomplete data

Strategies for missing and/or incomplete information in included studies were as follows: i) contacted the corresponding author, whenever possible; ii) analyzed only the available data (i.e. ignoring the missing data); and finally, iii) addressed the potential impact of missing data on the findings of the review in the Discussion section.

Types of interventions

All types of treatments using OMA (aim 1) or RME (aim 2), or both in order to treat OSA in children and adolescents were compared. The list of characteristics of included studies is summarized in Table 2a–c.

Types of outcome measures

The primary and secondary outcomes reported are summarized in Table 3.

Quality assessment of the studies

Quality assessment scoring of the final selected articles was conducted by the three reviewers (Nelly Huynh, Fernanda Almeida and Eve Desplats) independently. The grading followed the modified criteria provided by the animal research: reporting in vivo experiments (ARRIVE) [44] guidelines for human experimental studies [45]. An intraclass correlation coefficient (ICC) evaluated the agreement between the three reviewers.

Statistical procedures

Data synthesis

The participants, interventions and outcomes were judged to be sufficiently similar to ensure meaningful findings; therefore, a meta-analysis for each aim was undertaken for the primary outcome. Pooled data for post-treatment results were used for Pirelli et al., 2012 [46], since they presented results separated between responders and non-responders. Qualitative syntheses regarding the secondary outcomes are summarized in the Results section. As the true effect size varied from study to study, a random-effects model should have been used. However, because there were too few studies to obtain an accurate estimate of the between-studies variances [47], a fixed-effect model was implemented instead with the assumption that the studies considered for each aim had enough in common.

Investigation of heterogeneity and subgroup analysis

Since no two studies will be absolutely identical, clinical and/or methodological heterogeneity across studies should be assessed to

Table 2a
Characteristics of included studies.

Orthopedic mandibular advancement (OMA)										
Author	Study design	Country	Subjects M/F[c]	Age ± SD (y)[b]	Interventions	Wearing time	Follow-up (mo)	Drop-out	Outcomes	Adenoids or Tonsils[c]
Villa et al., 2002 [20].	RCT	Italy	10/9	6.86 ± 2.34	Personalized acrylic resin oral bite plate	Continuous, except mealtimes	6	5	AHI, SQ	Assess presence of tonsillar hypertrophy
Cozza et al., 2004 [49].	NRS	Italy	10/10	5.91 ± 1.14	MM	Full-time 1st wk; after at night only	6	none	AHI, AI, minSaO_2	Not mentioned

Abbreviations: AHI = apnea and hypopnea index; AI = arousal index; F = female; M = male; OMA = orthopedic mandibular advancement; MM = modified monobloc; NRS = non-randomized study; RCT = randomized controlled trial; SaO_2 = arterial oxygen saturation; SD = standard deviation; SQ = sleep quality.
[a] Experimental subjects presented only.
[b] Mean age at the baseline of the treatment.
[c] Clinical inclusion criteria evaluated.

Table 2b
Characteristics of included studies.

Rapid maxillary expansion (RME)										
Author	Study design	Country	Subjects M/F	Age ± SD (y)	Interventions	Expansion (or active) phase	Follow-up (mo)	Drop-out	Outcomes	Adenoids or tonsils
Villa et al., 2007 [1].	NRS	Italy	9/7	6.9 ± 2.2	Endo-oral	10 d (2 turns of screw/d)	6 mo[c] 12 mo[d]	2	AHI, AI, mean SaO_2, SQ	Presence of adenotonsillar hypertrophy; underwent adeno/or tonsillectomy before study.
Pirelli et al., 2004 [2].	NRS	Italy	19/12	8.68 (6–12)	Fixed appliance with expansion screw	10–20 d (1 mm/d)	1 mo[c] 10–16 mo[d]	none	AHI, total SaO_2, SQ	Absence of adenotonsillar hypertrophy.
Guilleminault et al., 2011 [22].	RCT	US	14/17[a]	6.5 ± 0.2	ME (n=27); Bi-ME (n=4) Fixed or removal appliances	[e]d (0.25mm/turn)	≤4[c]	1	AHI, RDI, min SaO2,	Group 2: orthodontic treatment followed by adeno-tonsillectomy.
Marino et al., 2012 [23].	RCT	Italy	11/14	5.94 ± 1.64	2 bands type	11.2 d (2 turns/d; 0.25mm/turn)	12 mo[c] 18 mo[d]	?	RDI	Not evaluated.
Pirelli et al., 2012 [46].	NRS	Italy	43/37[b]	(6–13)	Fixed appliance with expansion screw	21 d (2 turns/d; 0.25mm/turn)	≤4[c]	none	AHI	Presence of adenotonsillar hypertrophy (2+ or 3+) as inclusion criteria; no clear presence of chronic adenotonsillar inflammatory problems at baseline.

Abbreviations: AHI = apnea and hypopnea index; AI = arousal index; F = female; M = male; ME = maxillary expansion; NRS = non-randomized study; RCT = randomized controlled trial; RDI = respiratory disturbance index; RME = rapid maxillary expansion; SaO_2 = arterial oxygen saturation; SD = standard deviation; SQ = sleep quality; US = United States of America.
[a] Total of 31 individuals; although only Group 2 orthodontic data considered (surgery performed post-orthodontic treatment); $n = 16$.
[b] Total of 80 individuals; although only Group 1 orthodontic data considered (surgery performed post-orthodontic treatment); $n = 40$.
[c] Device *in situ*.
[d] Device *ex situ*.
[e] Not specified.

Table 2c
Characteristics of included studies.

Myofunctional appliances (MA) and rapid maxillary expansion (RME)										
Author	Study design	Country	Subjects M/F	Age ± SD (mo)	Intervention	Expansion (or active) phase	Follow-up (mo)	Drop-out	Outcomes	Adenoids or tonsils
Schütz et al., 2011 [10].	PS	Brazil	16[a]	12.6 ± 11.5	Acrylic-splint Herbst appliance	Advanced anterior mandible by 6.0 mm; followed 15 d posterior RME	12	none	AHI, AI, mean SaO_2, airway space (angle and volume)	No adenontonsillar hypertrophy (Exclusion criteria)

Abbreviations: AHI = apnea and hypopnea index; AI = arousal index; F = female; M = male; MA = myofunctional appliance; PS = prospective study; RME = rapid maxillary expansion; SaO_2 = arterial oxygen saturation; SD = standard deviation.
[a] Ratio M/F not specified.

look at the variability across studies in order to make sensible decisions about pooling data or making particular comparisons [48] in the meta-analysis. With respect to aim 1 (OMA), studies were 'similar', even though the studies' designs differed (NRCT [49] vs. RCT [20]). Only the treatment data were considered in Villa et al., 2002 [20] for the analysis. On the other hand, once the extraction of the data from the studies was done for aim 2 (RME), the four studies [1,2,22,46] had differences in the length of the intervention, as well as in whether the device was *in situ* (intra-oral) or *ex situ* (removed from the upper jaw), as detailed in Table 2b. In Guilleminault et al., 2011 [22], data from Group 2 and in Pirelli et al., 2012 [46], data from Group 1, who underwent RME before adenotonsillectomy, were considered for the analysis. As heterogeneity was encountered, post-hoc subgroup analyses were performed following Cochrane guidelines [40] to assess whether or not the intervention effects vary in relation to specific clinical characteristics of the included studies. Otherwise, the effects were described in the qualitative summary of the Results section.

Data extraction

For both aims, the generic inverse variance was performed when extracting data. The software package used to conduct the possible analyses was Review Manager (RevMan) 5.2. The ICC was

Table 3
Outcomes (for aims 1 and 2).

Primary Outcome
1) Apnea-hypopnea index: number of events per hour of sleep measured by standard polysomnography
Secondary Outcomes
1) Oxygen saturation level: expressed as a percentage (%)
2) Arousal index: number of arousals per hour of sleep
3) Increase of the upper airway volume or structures
4) Sleep quality (%)
5) Drop outs and withdrawals (*n*).

calculated using a commercially available software package (IBM SPSS Statistics, Version 21.0.0 for Windows; SPSS, Chicago, IL).

Results

Search and study selection

A flow diagram of the study identification, screening, eligibility and inclusion is shown in Fig. 1 [50]. A total of 58 articles were identified by using the search strategy and sources listed previously. Seven articles [3,15,21,41,42,51,52] were excluded due to identified duplicate data. After the titles and abstracts had been screened, a total of 21 articles [37,38,53–71] were excluded based on the criteria in Table 1 (see Appendices I–III). The remaining 30 articles were read for a complete evaluation of the text, and 22 of these articles [31,43,72–91] were excluded (see Appendices I–III). Finally, eight studies [1–3,10,22,23,46,49] were included in the review. Six of those articles [1,2,20,22,46,49] were included in the meta-analysis according to the aim.

Quality assessment of the studies

Quality assessment scoring of the final selected articles had an ICC of 0.85. This suggests that there was “almost a perfect” agreement among the three reviewers concerning the designated articles.

Meta-analysis (quantitative summary)

OMA (aim 1)

Both studies [20,49] were sufficiently ‘similar’ (Table 2a) to be pooled. However, due to the small number of studies considered, a fixed-effect model was the only viable option [47]. There were 39 treated patients in total, with a mean of 9.75 patients per study (range: 9, 10 patients) with equal sex ratio. The value of the test for heterogeneity is 0% ($p = 0.57$), suggesting that all variability in effect size estimates is due to sampling error within studies. Moreover, the test for overall effect suggests that the proportion of the variation in studies' estimates is not due to heterogeneity ($p < 0.001$). The pooled mean difference in change

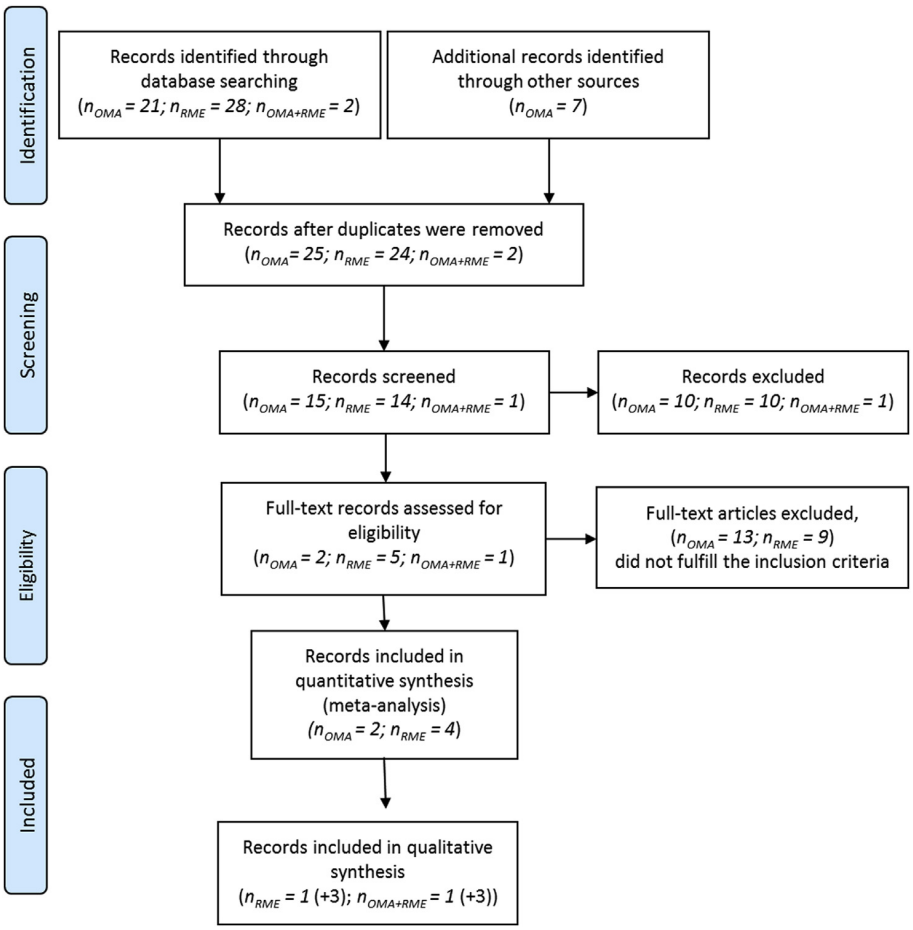

Fig. 1. Flow diagram on the screening of study. Six of the studies were meta-analyzed with respect to aims one and two, respectively. Abbreviations: OMA = obstructive mandibular advancement; RME = rapid maxillary expansion.

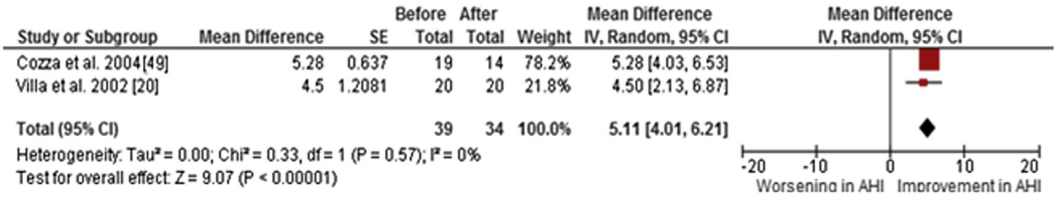

Fig. 2. Forest plot of the OMA comparison in a fixed-effect model using the generic inverse variance (IV) method with the mean difference described for AHI as events per hour. Abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; df = degree of freedom; IV = inverse variance; OMA = obstructive mandibular advancement; SE = standard error.

in the apnea-hypopnea index (AHI) for both studies, represented by the black diamond at the bottom of Fig. 2, was 5.11 events per hour (95% confidence interval [CI]: 4.01–6.21), and suggests that AHI decreased after treatment. The study of Cozza et al., 2004 [49] contributes to the pooled effect, due to the 78.2% weight observed. In addition, the 95% CI for each individual studies had an acceptable overlap presenting a poor statistical heterogeneity.

RME (aim 2)

There was a total of 88 treated patients, with a mean of 22 patients per study (range: 16, 25 patients) with adequate sex ratio. The data with *in situ* devices were separated depending on the intervention's length, i.e. short intervention (4 wk) or long intervention (4–6 mo), in order to make comparisons between subgroups. In Pirelli et al., 2012 [46], pooled data from 25 of 40 patients were used since the remaining patients showed normal polygraphy results following RME treatment, but no data were shown. The analysis required a fixed-effect model due to the small number of studies [47]. The null hypothesis in the subgroup analysis was testing whether the treatment effect on AHI was homogeneous across subgroups or demonstrated a variation too large to be accounted for by chance alone [92]. Therefore, the subgroup analysis was no longer based on randomized comparisons due to clinical observations of varying intervention lengths. High heterogeneity for subgroup differences, $I^2 = 98.4\%$ ($p < 0.001$) was observed (Fig. 3); hence, it was reported in the qualitative summary of the Results section. Nonetheless, each presented study reduced AHI after treatment, even though this conclusion could not be statistically reached due to the considerable heterogeneity of pooled data. Similarly, the data with the *ex situ* devices (approximately 12 mo) were also reported in the qualitative summary, as only two studies [1,2] were considered appropriate; however, they presented a high level of heterogeneity (Fig. 4).

Systematic review (qualitative summary)

The main characteristics of the included studies are presented in Table 2a–c.

OMA (aim 1)

A lack of comparable secondary outcomes prevented the performance of an adequate meta-analysis of both studies [20,49] (Table 3). For example, Villa et al., 2002 [20] summarized sleep quality (SQ) data as daytime and nighttime symptoms, expressed as the percentage of positive reports among treated subjects. These administered questionnaires showed diminished symptoms following 6 mo of treatment. Conversely, Cozza et al., 2004 [49] discussed reduced daytime sleepiness following OMA, but without reporting any data. Missing outcomes that are measured but not reported can lead to a publication bias [93]. Similarly, Villa et al., 2002 [20] mentioned to have recorded oxygen saturation levels (SaO_2), but did not present any data, whereas Cozza et al., 2004 [49] reported mean SaO_2 data. As a consequence, this limited the meta-analysis *a posteriori*.

Each study presented modified or personalized OMA. Overall, the appliances were well tolerated: Cozza et al., 2004 [49] had 100% compliance observed among patients; whereas Villa et al., 2002 [20] reported that 26% (5 out 19) discontinued therapy. Different adverse effects were pointed out, such as lack of tolerability and simple inconvenience at school causing dropouts in Villa et al., 2002 [20], generating a potential bias from missing data. Finally, only this latter study assessed through clinical criteria and reported

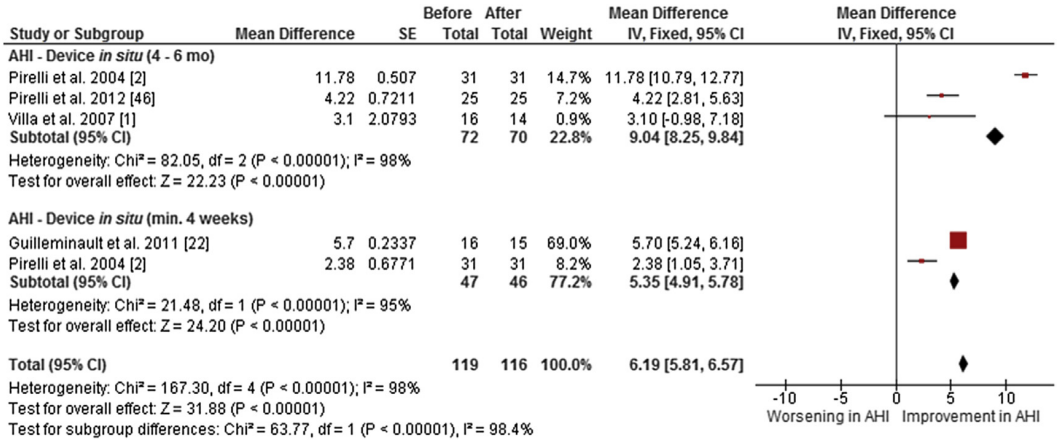

Fig. 3. Forest plot of the RME *in situ* comparison in a fixed-effect model using the generic inverse variance (IV) method with the mean difference described for AHI as events per hour. Abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; df = degree of freedom; IV = inverse variance; RME = rapid maxillary expansion; SE = standard error.

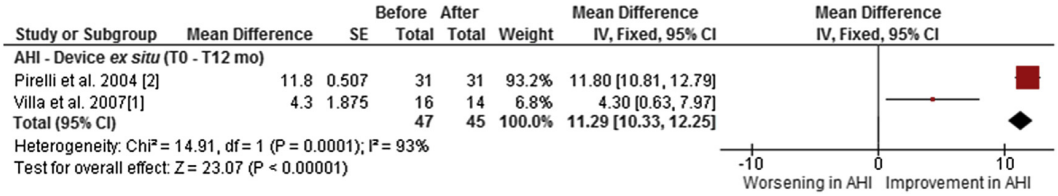

Fig. 4. Forest plot of the RME *ex situ* comparison in a fixed-effect model using the generic inverse variance (IV) method with the mean difference described for AHI as events per hour. Abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; df = degree of freedom; IV = inverse variance; RME = rapid maxillary expansion; SE = standard error.

the presence of tonsillar and/or adenoid hypertrophy, a major factor associated with OSA.

RME (aim 2)

The five articles [1,2,22,23,46] selected for eligibility present a total of 123 treated patients, with a mean of 16.33 patients per study (range: 16, 25 patients) with adequate sex ratio. There was high clinical heterogeneity for the primary outcome with the *in situ* devices in terms of intervention length among Villa et al., 2007 [1], Guilleminault et al., 2011 [22], Pirelli et al., 2004 [2] and Pirelli et al., 2012 [46] when comparing their follow-up, i.e. 4 wk or 4–6 mo. This clinical heterogeneity could be associated with differences in the interventions and presence/absence of tonsils and adenoids across the studies.

Two studies [1,2] presented data with *ex situ* devices. The high clinical heterogeneity could be explained by the small differences in the interventions and presence/absence of tonsils and adenoids across the studies. Overall, the AHI decreased from baseline to follow-ups at 6 and 12 mo (Friedman's analysis of variance [ANOVA], $p = 0.005$) in Villa et al., 2007 [1]. However, two of 14 subjects' AHI remained unchanged following the RME treatment. Similarly, the overall results by Pirelli et al., 2004 [2] for AHI showed a decrease from baseline to follow-ups at 10–16 mo (Wilcoxon $z = -2.0$, $p = 0.046$), for all children even though AHI subgroups were not evenly distributed. Marino et al., 2012 [23] published data with *ex situ* devices at 18-mo follow-up but reported respiratory disturbance index (RDI). They did not indicate whether or not there were drop-outs, and did not evaluate adenoids or tonsils size.

Once again, there was no consensus between the included studies to report adequately the information regarding the secondary outcomes. For example, Pirelli et al., 2004 [2] tabulated SaO_2 under 92% whereas mean SaO_2 was reported in Villa et al., 2007 [1]. Moreover, both studies administered different validated questionnaires on symptoms of OSA (pediatric sleep questionnaire [96] and Brouillette questionnaire [95]). As a result, this limited the possibility to realize a meta-analysis on OSA symptoms.

OMA & RME (aims 1 & 2)

There was only one article [10] that proposed a prospective study with both OMA and RME to examine modification in sleep and in craniofacial morphology. In this study, 16 patients underwent cephalometry, magnetic resonance imaging and four polysomnograms (including an adaptation night) throughout the 12-mo treatment. Treatment consisted of mandibular advancement using an acrylic-splint Herbst appliance continuously (24 h a d) and RME was performed by adapting a rapid maxillary expander to the appliance. Schütz et al., 2011 [10] pointed out that it was a difficult study to conduct due to the complexity of the examinations, which went beyond the orthodontic treatment period itself. Nevertheless, morphological and functional modifications were clinically significant with a progressive reduction in airway resistance during the treatment period suggesting that this might help to eliminate predisposing factors to OSA. There was no withdrawal reported. Therefore, this suggests that besides the complexity of the examinations after the treatment, overall treatment was well tolerated by the patients.

Discussion

OSA is one of the most common sleep disorders to have received attention in the pediatric population within the past decade. The present review and meta-analysis provide updated information on the efficacy of OMA and/or RME treatments for children and young adolescents diagnosed with OSA using AHI as the primary outcome measurement. It is well known that AHI, measured with a sleep study, is an essential criterion for the diagnosis of OSA, confirming signs and symptoms documented by pediatric sleep specialists.

Summary of evidence

The corollary of this review and meta-analysis underlines the paucity in quantity and in quality of studies evaluating the efficacy of orthodontic treatments for the management of pediatric OSA. A total of 58 articles were identified. About 30% and 21% of articles, with unspecific title and/or abstract, were ineligible due to the inclusion of adult participants and no mention of OSA, respectively. Only 10% were considered for quantitative and 14% for qualitative analyses. Yet, this is a relatively recent domain of clinical research in sleep medicine, with many research opportunities and unanswered questions.

Overall studies [20,49] evaluating OMA tended to suggest that it is an interesting and potential treatment for the management of OSA in children and young adolescents. Individual studies [1,2,22,46] assessing RME recommend this treatment to manage OSA in this population. Conversely, pooled data with *in situ* devices was clinically heterogeneous, thus preventing from extrapolating the overall treatment effect. Clinical heterogeneity could be explained by any differences in the interventions' and patients' criteria, such as the presence/absence of tonsils and adenoids across the studies. There were not enough studies with *ex situ* devices for the primary and secondary outcomes to perform a meta-analysis. The effect of the device (*in situ* vs. *ex situ*) was assessed only in Pirelli et al., 2004 [2], showing a further improvement of AHI when the device was removed, potentially allowing the tongue to regain its natural position, thus decreasing its posterior collapse. Moreover, there was only one study published by Schütz et al., 2011 [10] that combined both OMA and RME as an alternative treatment for managing OSA in children and young adolescents. Since there is extremely little evidence supporting these treatments, care must be taken regarding the interpretation of orthodontic treatments results in pediatric OSA.

Limitations

The total number of studies with evidence on the impact of orthodontic treatments was low and the sample sizes small. A fixed-effect model was the only viable solution due to the small number of studies considered; therefore, any conclusions from the

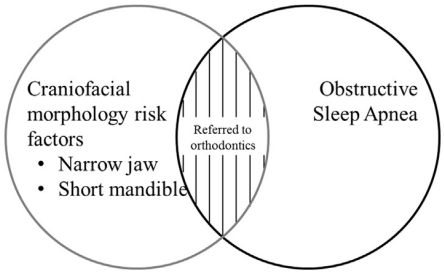

Fig. 5. Diagram of the possible relationship between craniofacial morphology risk factors and obstructive sleep apnea (OSA) in children. Children with OSA with concomitant craniofacial risk factors should be referred to an orthodontist involved in dental sleep medicine. It is important to note, that not all children with narrow and/or short jaws have sleep apnea. Moreover, not all children with OSA have craniofacial risk factors.

pooled diagnostic parameters and their interpretation, for each aim respectively, should be treated carefully.

In addition, the considerable heterogeneity of RME studies with *in situ* devices suggests that these studies were not entirely comparable based on variability between interventions or patient populations. Among the five considered studies [1,2,22,23,46], adenoids and tonsils size was not consistently evaluated and specified in the inclusion/exclusion criteria. This can introduce a potential bias of confounding factors due to possible previous adenotonsillectomy versus untreated adenotonsillar hypertrophy.

Susceptibility of publication bias is plausible because our protocol was not registered initially; even though, there was a protocol written *a priori*. However, the review and meta-analysis aimed for all the relevant studies (original articles). Studies with missing or incomplete data were only reported in the qualitative summary of the Results section. There was a lack of consistency among studies when reporting similar outcomes, for example, some studies presented only AHI or RDI. There was evidence that for some studies presented, the outcome was measured, but reported inadequately or not at all. Furthermore, great caution should be taken with data published multiple times, as they could overestimate and bias results, leading to improper audit for certain data as well as outcomes. In consequence, these are challenges to an accurate meta-analysis.

Conclusions

The last decade has been marked with pioneer studies resulting in an overall improvement of patient care and underlining the importance of multidisciplinary management of pediatric OSA. Considering the limited number of included studies [1–3,10,22,23,46,49], the presented orthodontic treatments may be effective in managing pediatric snoring and OSA (Fig. 5). Consequently, their respective results suggest that the correction of craniofacial structure imbalances in the optimal conditions afforded by childhood growth may diminish snoring and OSA. Other important health outcomes related to OSA, such as quality of life, neurocognitive function and cardiovascular health have not yet been systematically addressed and no conclusion on orthodontic treatments should be taken in this regard. Orthodontic treatment of pediatric OSA guidelines cannot be extrapolated and generalized from this systematic review and meta-analysis.

In the future, more studies should be conducted with larger sample size and with specific inclusion and exclusion criteria. The use of the preferred reported items for systematic reviews and meta-analyses (PRISMA) [93] or the consolidated standards of reporting trials (CONSORT) [94] guidelines depending on the study design could improve the quality of the publications. Moreover, there is room for improvement when reporting studies of both OMA and/or RME treatments for managing OSA in children and young adolescents through standardized data reporting. This will enhance the comparability of studies based on identical outcome measures, which will help to establish guidelines for orthodontic treatment of pediatric OSA.

Practice Points

Orthodontic treatments to correct craniofacial morphology, such as orthopedic mandibular advancement or rapid maxillary expansion, can be useful to:

1) correct craniofacial morphology, such as a smaller maxilla and/or mandible, which can be a risk factor of sleep-disordered breathing in children.
2) reduce pediatric snoring and obstructive sleep apnea, considering the paucity in quantity and in quality of studies;
3) help management pediatric snoring and obstructive sleep apnea, but one should be careful when interpreting orthodontic treatment results in pediatric obstructive sleep apnea, due to limited number of included studies.

Research Agenda

In the future we need further standardized studies assessing the efficacy of orthodontic treatments on obstructive sleep apnea, but also we also need:

1) to systematically address other important health outcomes related to OSA, such as quality of life, neurocognitive function and cardiovascular health;
2) to reduce clinical heterogeneity between studies, such as different patients' inclusion/exclusion criteria (presence/absence of tonsils and adenoids);
3) to explore long term efficacy of these treatments, further compounded with growth and development of children with obstructive sleep apnea;
4) to combine both orthopedic mandibular advancement and rapid maxillary expansion as an alternative treatment for managing pediatric sleep-disordered breathing.

Conflicts of interest

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

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Appendix I. OMA – Studies excluded from the systematic review and meta-analysis.

Study	Case report	Meta-analysis	Review	Abstract (no article)	Surgery	Adults	Animals	Duplicate data	Outcome	No OSA
Villa et al. *2012* [53]			X							
Yoshida et al. *1999* [72]						X				
Schessl et al. *2008* [54]	X									
Rose et al. *2006* [55]										
Nunes et al. *2009* [56]				X						
Anantanarayanan et al. *2006* [82]					X				X	
Nout et al. *2012* [76]					X	X				
Carvalho et al. *2007* [37]		X								
Miyao et al. *2007* [57]	X									
Cozza et al. *2004* [41]								X		
Maurer et al. *2007* [77]						X				
Pliska et al. *2012* [75]			X							
Hoekema et al. *2007* [79]						X				
Gagnadoux et al. *2009* [80]						X				
Trzepizur et al. *2009* [74]						X				
Aarab et al. *2011* [58]						X				
Aarab et al. *2011* [52]						X		X		
Holley et al. *2011* [78]						X				
Tsuiki et al. *2004* [73]						X				
Geraads et al. *2010* [59]						X				
Tomer et al.*1982* [60]							X			X
Fritsch et al. *2001* [81]						X				
Holty et al. *2010* [38]		X				X				
Restrepo et al. *2011* [89]									X	X
Hänggi et al. *2008* [91]										X

Abbreviations: OMA = orthopedic mandibular advancement; OSA = obstructive sleep apnea.

Appendix II. RME – Studies excluded from the systematic review and meta-analysis.

Study	Case report	Review	Short commentary	Surgery	Adults	Animals	Syndrome	Malocclusion class III	Duplicate data	No OSA
De Felippe et al.*2009* [42]									X	X
Bonetti et al.*2009* [64]	X			X						
Moura et al.*2008* [86]							X			
Miano et al.*2009* [51]									X	
Pirelli et al.*2010* [15]									X	
Pirelli et al.*2005* [21]									X	
Villa et al.*2011* [3]									X	
Monini et al.*2009* [85]								X		
Phoenix et al.*2011* [84]				X						X
Hiyama et al.*2002* [61]								X		X
Aurora et al.*2011* [65]		X								
Cistulli et al.*1998* [63]				X						
Foltan et al.*2011* [62]				X						X
Harvold et al.*1981* [66]						X				X
Palmisano et al.*1996* [68]	X									
Schütz-Fransson et al.*2008* [83]										X
Thickett et al.*2009* [67]					X					
Timms et al.*1990* [31]				X						X
Bach et al.*2013* [69]				X	X					
Zheng [43]			X							
Burstein et al.*1995* [70]				X			X			X
Fearon et al.*2004* [87]				X						
Guilleminaults et al.*2004* [88]				X	X					
De Felippe et al.*2008* [90]										X

Abbreviations: OSA = obstructive sleep apnea; RME = rapid maxillary expansion.

Appendix III. OMA & RME – Studies excluded from the systematic review and meta-analysis.

Study	Malocclusion class III
Singh et al.*2007* [71]	X

Abbreviations: OMA = orthopedic mandibular advancement; RME = rapid maxillary expansion.

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