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Effect of orthopedic and functional orthodontic treatment in children with obstructive sleep apnea: A systematic review and meta-analysis

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A B S T R A C T

Orthodontic treatment is suggested in growing individuals to correct transverse maxillary deficiency and mandibular retrusion. Since, as a secondary effect, these orthodontic procedures may improve pediatric obstructive sleep apnea (OSA), this systematic review assessed their effects on apnea-hypopnea index (AHI) and oxygen saturation (SaO2). Twenty-five (25) manuscripts were included for qualitative synthesis, 19 were selected for quantitative synthesis. Five interventions were analyzed: rapid maxillary expansion (RME, 15 studies), mandibular advancement (MAA, five studies), myofunctional therapy (MT, four studies), and RME combined with MAA (one study). RME produced a significant AHI reduction and minimum SaO2 increase immediately after active treatment, at six and 12 months from baseline. A significant AHI reduction was also observed six and 12 months after the beginning of MAA treatment. MT showed positive effects, with different protocols. In this systematic review and meta-analysis of data from mainly uncontrolled studies, interceptive orthodontic treatments showed overall favorable effects on respiratory outcomes in pediatric OSA. However, due to the low to very low level of the body evidence, this treatment cannot be suggested as elective for OSA treatment. An orthodontic indication is needed to support this therapy and a careful monitoring is required to ensure positive improvement in OSA parameters.

1. Introduction

Obstructive sleep apnea (OSA) is a common disease belonging to the sleep-disordered breathing (SDB), and characterized by repetitive episodes of complete and/or incomplete obstruction of the upper airways which occur during sleep [1,2]. Due to the hypoxemia associated with obstruction episodes, untreated OSA is a potentially life-threatening disorder [3]; furthermore, as for in adults, OSA in children presents several metabolic, and cardiovascular consequences, detrimental behavioral effects, neurocognitive impairments and academic underperformance [4]. Common symptoms associated with pediatric OSA are fragmented sleep, mouth breathing, snoring, nocturnal enuresis, headaches, and systemic inflammation [5–8]. The estimated prevalence of OSA among children ranges between 1% and 4%, depending on the different diagnostic method adopted, which could include nocturnal sleep laboratory–based polysomnography (PSG) and in-home sleep study, and different cut-offs [9]. Furthermore, numerous previous researches have adopted different patient-reported and parent-reported questionnaires to determine the presence of OSA in children [9], but studies have shown that questionnaires and clinical history alone are not adequate in clinical practice to distinguish primary snoring from OSA in children [10] and therefore nocturnal sleep laboratory–based PSG should be used as gold standard for the diagnosis of OSA through the assessment of apnea-hypopnea index (AHI) [11]. However, the high economical costs, the limited availability of sleep centers, the complexity of the equipment, and the need of specialized expertise for diagnosing children, limit the use of PSG in children for routine purposes [12]. Furthermore, the unfamiliar laboratory setting and

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Acronyms

AHI: apnea-hypopnea index
AT: adenotonsillectomy
MAA: mandibular advancement
OSA: obstructive sleep apnea
MT: myofunctional therapy
PRISMA: preferred reporting items for systematic reviews and meta-analysis
PROSPERO: prospective register of systematic reviews
PSG: polysomnography
RCT: randomized controlled trial
RME: rapid maxillary expansion
SDB: sleep-disordered breathing
SO2: oxygen saturation level
SR: systematic review

the placement of sensors and electrodes by a stranger can represent stressful events for the young patient. In turn, this emotional status can affect the compliance and the quality of sleep [13]. Portable and home sleep tests have been suggested as an alternative option to PSG for the screening of OSA in children, especially whenever PSG is not feasible (for instance, in low income countries or rural areas) [14].

The pathophysiology of OSA in children is complex and presents a multifactorial etiology. Major risk factors are adenotonsillar hypertrophy, obesity, neuromuscular disorders and craniofacial anomalies [15]. Since enlarged tonsils and adenoids remain the main anatomical condition that reduces the caliber of the upper airways, it has been shown that the peak of OSA in children can be observed around 10 years of age when the lymphatic system shows its maximum development [6]. Craniofacial features that have been linked with higher risk of OSA symptoms in children include macroglossia and incorrect tongue posture, retrognathic mandible, transversal maxillary deficiency, high palatal vault, increased total and lower anterior facial heights, and a more anterior and inferior position of the hyoid bone [15–19]. Interestingly, a recent epidemiological study pointed out doubled SDB risk prevalence in the pediatric orthodontic population compared with a healthy pediatric population (10.8% vs. 5%, respectively), supporting the idea that orthodontic practitioners should routinely screen SDB in their clinical practice [20,21]. On the other hand, inconsistent findings are reported in the literature regarding the prevalence of malocclusion in children with OSA. In particular, authors reported higher prevalence of posterior crossbite, and abnormal overjet and overbite in children with OSA compared to a control group [22], while other researches pointed out that prevalence of malocclusion in children with suspected sleep-disordered breathing was not greater than what has been reported for the general population [23].

The treatment strategy of OSA in children depends on several factors, including the severity of the syndrome and the etiology of the obstruction. Adenotonsillectomy (AT) is recognized as first-line treatment in case of adenotonsillar hypertrophy, which is supported by evidences of reduced symptoms and improved PSG outcomes after surgery [24]. However, it has been reported that in approximately half of the cases, surgical approach does not completely treat pediatric OSA, and up to 68% of patients can show post-surgical relapse [25], especially when underlying skeletal disharmonies, increased soft tissue crowding of the oropharynx or increased body mass index are present [26–28]. Functional and orthopedic orthodontic treatment (such as mandibular advancement, MAA, or rapid maxillary expansion, RME) have recently been proposed as a part of comprehensive treatment for pediatric OSA patients with craniofacial alterations. A recent systematic review (SR) reported evidence that AT and orthodontic treatment are more effective together rather than separately to cure OSA in pediatric patients [29]. A previous SR with meta-analysis examined the effects MAA on pediatric OSA, pointing out significant reduction in the mean AHI in the treatment group, compared to untreated controls [30]. However, the diagnosis of OSA was not based on PSG in all primary studies included. Other recent SRs investigated the efficacy of single orthodontic approaches (MAA or RME) in the treatment of pediatric OSA [30,31]. Favorable results were observed in both reviews, but the literature searches are currently out of date (search limit 2018 and 2017 respectively), and numerous studies could have been published in the following years considering the growing interest in the topic. Finally, in 2019 authors provided an overview on the effects and a comparison of the outcomes of various treatments in the management of pediatric OSA with adenotonsillar hypertrophy [32]. The authors concluded that, irrespective of the intervention used, complete resolution of OSA was not achieved in most included trials. However, the results of this review are limited to OSA patients presenting with specific adenotonsillary characteristics and cannot be extended to the general population. Furthermore, different type of surgical, pharmacological, and functional/orthodontic treatments were included.

The current study aimed to summaries the evidence on the effects orthodontic treatments on respiratory outcomes in OSA pediatric patients. The goal was to provide an overview of all types of orthodontic/orthopedic approaches available in the literature for the management of OSA pediatric patients. The question to be answered was as follows: ‘Is there any improvement in the polysomnographic parameters of OSA growing patients after orthopedic/functional orthodontic treatment?’

2. Methods

In accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [33], the protocol for the SR was registered (PROSPERO ID: CRD42020180164).

2.1. Selection criteria

According to the PICO approach, the inclusion criteria were the following:

- Population: children and adolescents (less than 18 years old in age), without craniofacial syndromes and with a polygraphic diagnosis of OSA
- Intervention: all kind of orthopedic/functional orthodontic interventions
- Comparison: no treatment, waiting list, placebo or other therapies
- Outcome: primary outcome was AHI; secondary outcome was oxygen saturation level (SaO2; minimum and mean).

The exclusion criteria were: multi-bracket orthodontic therapy and extractive orthodontic therapy; systematic reviews, reviews, opinion articles, letters to the editor, case series, case report, animal studies; studies including; sample size ≤10 patients studies including syndromic patients and/or patients affected by cleft lip and palate; dual publications; studies in which OSA diagnosis was performed by means of questionnaires, self-report, symptoms, clinical examination, and/or pulseoxymetry.

2.2. Literature search

Four electronic databases were investigated from their inception, up to January 2020: Medline (via PubMed), Scientific Electronic Library Online (SciELO), Cochrane Central Register of Controlled Trials, and Scopus. The key words *obstructive sleep apnea* AND *orthodontic** were adopted, and search strings were adapted to each database, according to the appropriate database-specific indexing terms and syntax (Table S1). An update of the search was conducted on January 2021. In addition, Google Scholar was explored for grey literature search, and a hand-search of the reference lists of the included studies was carried out. No restrictions on language or publication year were applied for the electronic searches. Full-texts in Chinese and Japanese languages were excluded.

2.3. Study selection

Two reviewers (BZ and RB) independently screened the articles by title and abstract, using the software Rayyan (http://rayyan.qcri.org) [34]. In case of disagreements, a third reviewer (VD) was contacted. In case of uncertainty, all potentially eligible studies were retrieved in full texts for further evaluation.

2.4. Data extraction

The following data were collected from each included study: author and year of publication, country, sample characteristics (sample size, gender, age), drop out, study design, description of treatment and control group, interventions, orthodontic diagnosis, OSA diagnosis, follow-up periods, success endpoint, outcome data (limited to the respiratory function) and general conclusion. Whenever relevant information was not available, the authors were privately contacted by email. Data extraction was performed independently by two reviewers (BZ and RB) using a preformed, standardized spreadsheet that was developed and agreed upon by the review team. A third reviewer (VD) was contacted to solve residual disagreements.

2.5. Risk of bias (quality assessment) of the studies

A methodological quality assessment of each study was performed by BZ and SIP independently, and any discrepancies were resolved through discussions with RB.

To evaluate the risk of bias of randomized controlled trials (RCT), the Cochrane Collaboration "risk of bias" (RoB-2) tool was used [35]. Similarly, to evaluate the risk of bias of non-randomized studies, the Cochrane Collaboration "risk of bias in non-randomized studies – of interventions" (ROBINS-I) tool was applied [36]. In particular, reporting of previous AT, measurement body mass index, and reporting of ear, nose and throat assessment were considered as confounders. Also, age ranges and orthodontic diagnosis at the baseline were evaluated in the selection of participants.

2.6. Certainty of the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to judge the quality of the evidence, using GRADEpro software [37]. Each outcome could obtain a high, moderate, low, or very low evidence value depending on the study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias [38]. The downgrading of evidence was based on the following criteria: (1) for study limitation if the majority of studies (>50%) were rated as high risk of bias; (2) for inconsistency if heterogeneity was considerable ($I2>75\%$) [39]; (3) for indirectness if the baseline orthodontic diagnosis or the device used for treatment were extremely diverse among studies or not clearly described; and (4) for imprecision if meta-analysis had a small sample size ($n<300$) or large CI.

2.7. Data synthesis

Statistical heterogeneity was explored using a the I2 statistics, and the level of significance was set at $P < 0.05$. To analyze changes in AHI and SaO2, a random-effects model was chosen, and a moderator analysis was performed. Data collected for the moderator analysis were the following: study design of primary studies, risk of bias, % of males, age, type of appliance, activation protocol, previous AT, OSA diagnosis (PSG or polygraph), and baseline OSA severity.

Quantitative data were computed as post-treatment minus pre-treatment and different meta-analysis were performed according to different follow-up times. The pooled estimate of the standardized mean difference (SMD) for each outcome and respective 95% Confidence Intervals (CIs) were computed. The statistical significance of the hypothesis test was set at $P < 0.05$ (two-tailed Z tests). Studies with incomplete statistical reporting (e.g. absence of standard deviation values, different number of patients between time points) or non-comparable assessments were excluded from the meta-analysis. The meta-analysis was performed with ProMeta software (Internovi, Cesena, Italy). Publication bias was evaluated through a visual inspection of funnel plots, in case more than 10 studies per outcome could be retrieved.

3. Results

3.1. Study selection

A total number of 764 records were identified through electronic search, and 36 additional records were identified through hand search. One-hundred and eight (108) full-text were read, and 84 articles were excluded (references and reasons for exclusion are listed in Table S2). Finally, 25 manuscripts were included in the review for qualitative synthesis [40–64]. Nineteen (19) articles were included in the quantitative synthesis. PRISMA flow diagram of study identification, screening, eligibility and inclusion phases is shown in Fig. 1.

3.2. Study characteristics

Summaries of study characteristics and results of the included studies, divided according to the different orthodontic therapy, are shown in Table 2 to 4 In particular, five interventions were collected: RME (15 studies, Table 1), MAA (five studies, Table 2), myofunctional therapy (MT) (four studies, Table 3), and RME in combination with MAA (one study, Table 4). Furthermore, different appliances and protocol were adopted. RME was performed with fixed tooth-anchored appliances, supported either by two- or four-bands, or by dental acrylic segments. MAA was performed with Twin-Block, modified monobloc, modified Planas appliance, or acrylic resin personalized oral appliance. MT included both active and passive approaches: passive approaches involve the use of custom-made adjustable oral devices, while active approaches rely solely on isometric and isotonic exercises which involves tongue, soft palate, and lateral pharyngeal wall designed in order to improve suction, swallowing, chewing, breathing, and speech functions. The largest sample included 110 patients [47], while the smallest included 11 patients [40]. In the vast majority of studies (20) the OSA diagnosis was performed with laboratory PSG; three

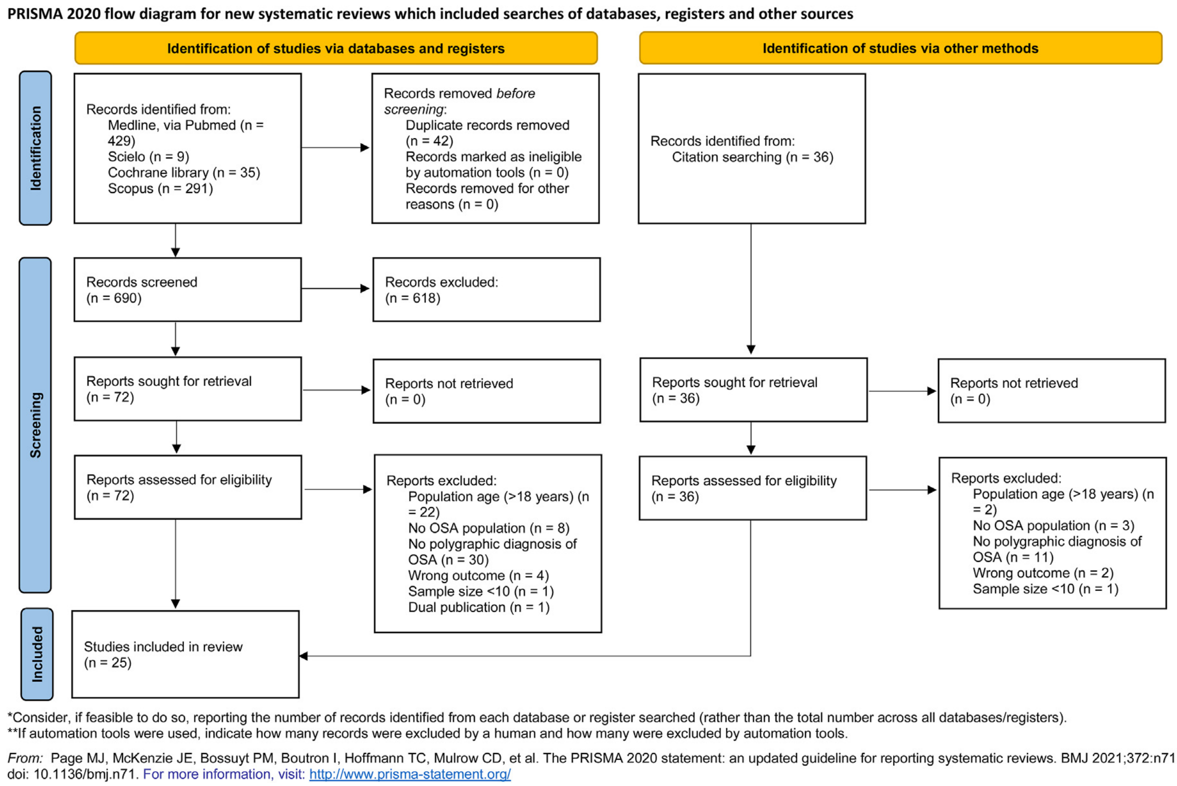

Fig. 1. PRISMA Flow chart of the study selection.
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. https://doi.org/10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

studies adopted portable home cardiorespiratory monitoring type 3 devices [46,49,53], one study employed a portable polygraph [57], and another study adopted an ambulatory polygraph [40]. Participants' age ranged from 5.03 ± 2.03 years [61] to 12.27 ± 1.93 [46]. The timing of the post-intervention assessments varied widely (from three week to six years follow-up).

Of the 25 included records, six articles were RCTs while 19 were non-randomized studies (five retrospective and 14 prospective). Most of the prospective studies were uncontrolled before-after studies (ten studies). Among the four remaining prospective non-randomized studies with a control group, two compared different therapies (AT vs. RME [53,61]), one adopted a control group of non-OSA untreated patients [42], and one compared full-birth and premature birth children [41]. With regards to the RCTs, three compared different therapies or combination of therapies (AT + RME vs. RME + AT [43], active MT vs. passive MT [47], and MT + nasal wash vs. nasal wash only [63]), while three adopted an untreated control group [46,48,58].

Some of the data collected for the meta-analsysis (activation protocol, and previous AT) were not included among moderators since information were not consistently reported across studies (frequently non reported or not clearly described). In addition, "type of appliance" was not included as a moderator in the RME meta-analysis since all the devices analyzed in the included primary studies were fixed expanders. Finally, publication bias was not explored since none of the assessed outcomes included more than 10 studies.

3.3. RME

- AHI

Eight studies evaluated AHI changes within six months from the end of active RME, of which six reported a significant reduction of the AHI compared to baseline values, while the remaining two also reported a reduction of the AHI, but no statistical analysis was performed. The only study with an untreated control group [46] reported reduction of the AHI also among controls, and non-significant differences between treated and untreated individuals in the short-term were observed.

Between six months and one-year follow up, 11 studies reported significant reduction of the AHI compared to baseline values, and 1 study pointed stable results (non-significant changes) compared to the immediate post-expansion findings. In addition, another study reported reduction of the AHI after one year compared to baseline values, but no statistical analysis was performed. The only study reporting non-significant changes in the AHI one year after RME [43] supported the need of treatment combination with AT, since significant AHI reduction was observed following RME + AT, despite treatment sequence.

Only one study [44] reported a very long-term follow-up assessment after RME, pointing out recurrence of the pathology in some individuals during adolescence.

Immediately after RME, the meta-analysis showed significant reduction in the AHI values, with considerable heterogeneity (SMD:

Table 1
Characteristics of the included studies addressing the effects of Rapid Maxillary Expansion.

Author, year,reference	Sample	Dropout	Orthodontic diagnosis	Study design	Groups	Treatment	Activation Protocol	OSA diagnosis	Other diagnostic instrumenta	Follow-up	Treatment success endpoint	Respiratory Outcomes	Results
Buccheri et al, 2017 [40]	11 (8 males, 3 females) 6.9 ± 1.04 years	none	crossbite high ogival palate mandibular retrusion	Cohort prospective	Group 1: RME	fixed 2-bands expander	3 turns chairside + 2 turns/day	Ambulatory Polygraphy (AHI>1)	snoring, apnea and nocturnal awakenings (as reported by the parents)	T0: baseline T1: 1 year	NR	AHI SaO2%	Significant reduction of AHI. Significant increase of SaO2%. Improvement of clinical symptoms.
Guilleminault et al., 2011 [43]	31 (14 males, 17 females) 6.5 ± 0.2 years	1 (from Group 2)* *normalized PSG values and clinical symptoms after first treatment*	narrow maxilla, high palate	RCT	Group 1: AT + RME Group 2: RME + AT	Upper jaw: fixed expand *Lower jaw: fixed or removable expander (4 participants)*	0.25 mm/day	In-lab PSG	- ENT examination: Tonsil scale, Tongue scale, Mallampati scale, inferior nasal turbinates assessment, nasal septum deviation assessment - Pediatric sleep questionnaire - Clinical symptoms reported by parents	T0: baseline T1: 4 weeks after AT, or 3 months after the end of the RME T2: 4 weeks after AT, or 3 months after the end of the RME	NR	AHI Min SaO2% RDI REM% TST	Significant increase of TST, REM and SaO2% and significant reduction of AHI and RDI after both treatments. No significant improvement after a single treatment (either AT or RME). No effect of treatment sequence.
Guilleminault et al., 2013 [44]	29 (20 males, 9 females) 7.6 ± 1.7 years	NA	Need for ortho treatment assessed by a specialist	Retrospective	Group 1: AT + RME	Upper jaw: fixed expand *Lower jaw: fixed or removable expander (4 participants)*	NR	In-lab PSG	- Clinical symptoms reported by parents -Clinical assessment -ENT examination -Pediatric sleep questionnaire -Cephalometric analysis	T0: Baseline T1: approximately 1 year after AT + RME T2: Prepubertal (around 11 years of age) * T3: Pubertal (around 16 years of age) **orthodontic records only*	NR	AHI Min SaO2% RDI	Reduction of AHI and RDI and increase of SaO2% after AT + RME (no statistical analysis). Recurrence of clinical complaints in 20 patients during adolescence.
Hoxha et al., 2018 [46]	30 (16 male and 14 female) -Group 1 (15): 12.27 ± 1.93 years -Group 2: 11.46 ± 2.06 years	none	maxillary transverse deficiency (high, narrow palate associated with deep bite, retrusive bite, or cross-bite)	RCT	Group 1: SRME Group 2: no treatment	modified McNamara RME with Hyrax type screw	2 turns/day for 7 days, then 1 turn/ day	Portable device – level III (ApneaLinkTM Plus) (AHI>1)	- ENT examination -Clinical symptoms reported by parents -Cephalometric analysis -Dental measurements on dental cast -Blood sample -Urine sample	T0: baseline T1: 5 months	Contact of the palatal cusp of the upper molar with the buccal cusp of the lower molar	AHI Mean SaO2% Min SaO2% ODI	Significant reduction of AHI both in Group 1 and 2. No significant difference between groups. Non-significant changes of ODI and SaO2.
Pirelli et al., 2004 [50]	31 (19 males, 12 females) 8.68 years (range 6–12)	none	maxillary constriction	Cohort prospective	Group 1: RME	fixed 4-bands expander	6 turns (3 + 3) at day 0, 2 turns/day	In-lab PSG	- ENT examination (active anterior rhinomanometry, nasal fibroscopy) -Pediatric sleep questionnaire -Clinical and radiographical	T0: baseline T1: 4–6 weeks (with the device in situ) T2: 4 months after the end of RME (that lasted 6–12 months)	total expansion 10–20 days	AHI Min SaO2% Duration of longest obstructive apnea Duration of desaturation SE%	Significant reduction of AHI both at T1 and T2, Reduction of the duration of the longest apnea, duration of desaturation and increase of SaO2%

(*continued on next page*)

Table 1 (*continued*)

Author, year,reference	Sample	Dropout	Orthodontic diagnosis	Study design	Groups	Treatment	Activation Protocol	OSA diagnosis	Other diagnostic instrumenta	Follow-up	Treatment success endpoint	Respiratory Outcomes	Results
									orthodontic examination				and SE (no dedicated statistics)
Pirelli et al., 2005 [51]	42 (26 males, 16 females) 7.3 years (range 6–13)	none	maxillary constriction	Cohort prospective	Group 1: RME	fixed 4-bands expander	6 turns (3 + 3) at day 0, 2 turns/day	In-lab PSG	- ENT examination (audiometry, tympanometry with tubaric functionality maneuvers, active anterior rhino-manometry, nasal fibroscopy) -Daytime sleepness questionnaire -Clinical and radiographical orthodontic examination	T0: baseline T1: 4–6 weeks (with the device in situ) T2: 4 months after the end of RME (that lasted 6–12 months)	total expansion 10–20 days	AHI Min SaO2% Duration of longest obstructive apnea Duration of desaturation SE%	Significant reduction of AHI both at T1 and T2, Reduction of the duration of the longest apnea, duration of desaturation and increase of SaO2% and SE (no dedicated statistics)
Pirelli et al., 2010 [52]	60 (38 males, 22 females) 7.3 years (range 6–13)	none	maxillary constriction	Cohort prospective	Group 1: RME	fixed 4-bands expander	6 turns (3 + 3) at day 0, 2 turns/day	In-lab PSG	- ENT examination (audiometry, tympanometry with tubaric functionality maneuvers, active anterior rhinomanometry, nasal fibroscopy) -Daytime sleepness questionnaire -Clinical and radiographical orthodontic examination -CT	T0: baseline T1: 4–6 weeks (with the device in situ) T2: 4 months after the end of RME (that lasted 6–12 months)	total expansion 10–20 days	AHI Min SaO2% Duration of longest obstructive apnea Duration of desaturation SE%	Significant reduction of AHI both at T1 and T2, Reduction of the duration of the longest apnea, duration of desaturation and increase of SaO2% and SE (no dedicated statistics)
Pirelli et al., 2012 [53]	80 (43 males, 37 females) 7.3 years -Group 1: 40 participants -Group 2: 40 participants	21 completely cured after Treatment 1 (6 from Group 1 and 15 from Group 2); 17 from Group 2 with incomplete improvement after Treatment 1 presented too mild SDB problem and were dropped out	maxillary constriction	Case control prospective	Group 1: AT (+RME)* Group 2: RME (+AT)* *according to the finding at T1 is was decided whether patient should undergo Treatment 2 or not	fixed 4-bands expander	6 turns (3 + 3) at day 0, 2 turns/day	Portable PG (AHI>1)	- Clinical and radiographical orthodontic examination - CT - ENT evaluation (visual examination of upper airway including rhinopalatoscopy)	T0: baseline T1: 4 months after the end Treatment 1 T2: 1 year* *only participants who underwent Treatment 2	total expansion about 3 weeks	AHI Min SaO2%	At T1 15 subjects treated with RME were considered as cured compared to 6 patients after AT. At T2, AHI and SaO2% were normalized in 39 out of 42 patients (belonging to both Group 1 and Group 2). 3 patients (2 belonging to Group 2 and 1 belonging to Group 1) showed incomplete improvement.
Pirelli et al., 2015 [54]	31 (19 males, 12 females) 8.68 years (range 6–12)	8 (lost at T2)	maxillary constriction (narrow hard palates with	Cohort prospective	Group 1: RME	NR	NR	In-lab PSG	- Pediatric Daytime Sleepiness Scale or Epworth Sleepiness Scale	T0: baseline T1: after RME T2: 1 year	NR	AHI Min SaO2% SE	No significant difference for all outcomes between the results

			unilateral or bilateral cross-bite)						-Pediatric Sleep Questionnaire -ENT examination -CT				obtained at the completion of RME and at the end of long-term follow-up
Pirelli et al., 2019 [55]	14 (5 males, 9 females) 10.5 years (range 9–12)	NR	maxillary constriction	Retrospective	Group 1: RME	NR	NR	In-lab PSG	- Clinical symptoms -CT	T0: baseline T1: after the end of active expansion (device in situ)	NR	AHI Min SaO2%	Reduction of AHI and increase of SaO2 (no dedicated statistics)
Quo et al., 2017 [56]	45 (32 males, 13 females) 7.58 ± 2.82 years (range 3–14)	NA	NR	Retrospective	Group 1: bimaxillary expansion	Upper jaw: fixed 2-bands expander on second deciduous molars or 4-bands expander on first molars and first premolars Lower jaw: fixed 2 bands expander on first molars or second deciduous molars	- <13 years of age: 1 turn/day - >13 years of age: 2 turns/day upper +1 turn/day lower	In-lab PSG	Lateral cephalogram	T0:baseline T1: 3 months	NR	AHI Mean SaO2% SE TST Sleep onset latency	Significant reduction of AHI and TST. Non-significant changes of SaO2%, SE and Sleep onset latency
Villa et al., 2007 [59]	16 (9 males, 7 females) 6.6 ± 2.0 years (range 4–11)	2 (lost at T2)	high, narrow palate associated with deep or retrusive bite or crossbite	Cohort prospective	Group 1: RME	fixed 2-bands expander on second deciduous molars	2 turns/day	In-lab PSG (AHI>1)	-Clinical symptoms reported by the parents (Broullette questionnaire) -ENT examination -Dental measurements on dental casts	T0:baseline T1: 6 months T2: 1 year	Contact of the palatal cusp of the upper molar with the buccal cusp of the lower molar	AHI Mean SaO2% OAI OHI REM NREM ArI	After 12 months, significant reduction of AHI, OHI and ArI, as compared to T0. Non-significant changes of OAI, REM, NREM and mean SaO2.
Villa et al., 2011 [60]	10 (5 males, 5 females) 6.6 ± 2.1 years (range 4–8)	0* **follow up study of Villa 2007 – 4 subjects were lost to follow-up, authors reported baseline and T1 data of 10 participants only*	high, narrow palate associated with deep or retrusive bite or crossbite	Cohort prospective	Group 1: RME	fixed 2-bands expander on second deciduous molars	2 turns/day	In-lab PSG (AHI>1)	- Clinical symptoms reported by the parents (Broullette questionnaire) -ENT examination -Orthodontic examination	T0: baseline T1: 1 year T2: 2 years	Contact of the palatal cusp of the upper molar with the buccal cusp of the lower molar	AHI SaO2% REM TST SE S1/S2 SWS	Significant reduction of AHI at T1, and non-significant changes between T1 and T2. Significant increase of SaO2% at T1, and non-significant changes between T1 and T2. Short-term increase of REM and TST, but non-significant differences between T0 and T2.
Villa et al., 2014 [61]	47 (34 males, 13 females)	none	high-arched palate and/or	Case-control prospective	Group 1: AT Group 2:	fixed 2-bands	2 turns/day	In-lab PSG (AHI ≥1)		T0: baseline T1: 1 year	Contact of the palatal	AHI Mean SaO2%	Group 1: significant reduction of AHI

(continued on next page)

Table 1 (*continued*)

Author, year,reference	Sample	Dropout	Orthodontic diagnosis	Study design	Groups	Treatment	Activation Protocol	OSA diagnosis	Other diagnostic instrumenta	Follow-up	Treatment success endpoint	Respiratory Outcomes	Results
	5.03 ± 2.03 years -Group 1: 25 participants -Group 2: 22 participants		malocclusion (only Group 2)		RME *Group 3: AT + RME or RME + AT (5 participants)* *- separate statistics*	expander on second deciduous molars			- Clinical symptoms reported by the parents -ENT examination - Orthodontic examination		cusp of the upper molar with the buccal cusp of the lower molar	TST SE ArI	and ArI, and significant increase of SaO2%. Non-significant changes of SE and TST. Group 2: Significant reduction of AHI, and significant increase of TST and SaO2%. Non-significant changes of ArI and SE. Group 3: significant reduction of AHI and non-significant change of SaO2%.
Villa et al., 2015 [62]	40 (23 males, 17 females) 6.3 ± 1.6 years	none	high, narrow palate associated with deep or retrusive bite or crossbite	Cohort prospective	Group 1: RME	fixed 2-bands expander on second deciduous molars	2 turns/day	In-lab PSG (AHI>1)	- Clinical symptoms reported by the parents (Brouillette questionnaire) -ENT examination - Clinical and radiographical orthodontic examination	T0:baseline T1: 1 year	Contact of the palatal cusp of the upper molar with the buccal cusp of the lower molar	AHI Mean SaO2% REM TST SE S1/S2 SWS	Significant reduction of AHI and ArI. Significant increase of TST and SaO2%. Non-significant change of SE, S1, S2, SWS and REM

AHI: Apnea Hypopnea Index; ArI: Arousal Index; AT: Adenotonsillectomy; CT: Computed Tomography; ENT: ears, nose and throat; Min: Minimum; NA: Not Applicable; NR: Not Reported; OAI: Obstructive Apnea Index; ODI: Oxygen Desaturation Index; OHI: Obstructive Hypopnea Index; PG: Polygraph; PSG: Polysomnography; RCT: Randomized Clinical Trial; RDI: Respiratory Disturbance Index; REM: Rapid Eye Movement sleep; RME: Rapid Maxillary Expansion; S1: Sleep Stage 1; S2: Sleep Stage 2; SaO2: oxygen saturation; SDB: Sleep Disordered Breathing; SE: Sleep Efficiency; SRME: Semi-Rapid Maxillary Expansion; SWS: Slow-wave sleep; TST: total sleep time.

Table 2
Characteristics of the included studies addressing the effects of Mandibular Advancement.

Author, year,reference	Sample	Dropout	Orthodontic diagnosis	Study design	Groups	Treatment	Activation Protocol	OSA diagnosis	Other diagnostic instrumenta	Follow-up	Treatment success endpoint	Respiratory Outcomes	Results
Cozza et al., 2004 [42]	-Group 1: 20 (10 males, 10 females) 5.91 ± 1.14 years (range 4–8) -Group 2: 20 (10 males, 10 females) 6.0 ± 0.71 years (range 5–7)	none	NR	Case-control prospective	Group 1: mandibular advancement Group 2: no-OSA untreated* *only for orthodontic comparison	Modified monobloc (full occlusal coverage, maxillary expansion screw, lingual arch, Tucat's pearl) + class II elastics at night	Construction bite: EtoE position (3 mm shorter than maximum protrusion) Wearing time: Full time wear for 7 days, then at night only	In-lab PSG (only in Group 1)	-Epworth sleepiness scale -Lateral cephalogram -Dental measurements on casts	T0: baseline T1: 6 months (with appliance in situ)	NR	AHI Min SaO2% ArI	Significant reduction of AHI. Non-significant change of ArI and SaO2.
Machado-Junior et al., 2016 [48]	16 Group 1: 8, 8.39 ± 1.31 years Group 2: 8, 8.13 ± 0.99 years	2 (from Group 2)	mandibular retrusion	RCT	Group 1: mandibular advancement Group 2: untreated	Modified Planas appliance: two separate acrylic plate (occlusal tracks in advancement), telescopic tube, upper Cofen spring and lower anti-labial device	Construction bite: NR Wearing time: full time	In-lab PSG (AHI≥1)	NR	T0: baseline T1: 1 year	Correct the mandibular position and dental occlusion	AHI	Significant reduction of AHI in Group 1. Significant increase of AHI in Group 2. Significant difference between the 2 Groups.
Modesti-Vedolin et al., 2018 [49]	18 (10 males, 8 females) 8.39 years (range 5 −12)	2 (initial sample of 20 patients)	NR	Cohort prospective	Group 1: Mandibular advancement	Two soft, 3 mm thick, translucent thermoplastic bite splints fused in the preregistered position	Construction bite: 75% of mandibular maximum protrusive movement (8 mm advancement + 5 −7 mm interincisal opening) Wearing time: NR	Portable device – level III (ApneaLinkTM Plus) (RDI≥1.5)	-Clinical symptoms reported by the parents -Sleep disturbance scale for children -EMG- RDC/TMD	T0: baseline T1: 2 months	NR	ODI Mean SaO2% Min SaO2% Snoring events RDI	Significant reduction of ODI, RDI, Snoring events. Significant increase of Mean and Min SaO2%.
Villa et al., 2002 [58]	32 (20 males, 12 females) 7.1 ± 2.6 years (range 4 -7) -Group 1 (19): 10 males, 9 females, 6.86 ± 2.34 years -Group 2 (13): 10 males, 3 females, 7.34 ± 3.10 years	9 (5 from Group 1 and 4 from Group 2)	NR	RCT	Group 1: Mandibular advancement Group 2: Untreated	Acrylic resin personalized oral appliance for mandibular repositioning	Construction bite: Receding bite was advanced, deep bite was raised, and cross-bite was recentered Wearing time: full time, except for mealtime	In-lab PSG (AI>1)	-Clinical symptoms reported by the parents (Brouillette questionnaire) -ENT examination -Orthodontic examination	T0: baseline T1: 6 months	Solve the SDB and correct the orthodontic defect	AHI AI DI	Significant reduction of AHI and AI in Group 1. Non-significant changes in Group 2. Non-significant change of DI.

(*continued on next page*)

Table 2 (*continued*)

Author, year,reference	Sample	Dropout	Orthodontic diagnosis	Study design	Groups	Treatment	Activation Protocol	OSA diagnosis	Other diagnostic instrumenta	Follow-up	Treatment success endpoint	Respiratory Outcomes	Results
Zhang et al., 2013 [64]	46 (31 males, 15 females) 9.7 ± 1.5 years	none	ANB° > 3 SNB° < 80 OVJ> 3 mm CVMM 2-3	Cohort prospective	Group 1: mandibular advancement	Twin-block appliance	Construction bite: Maximum mandible protrusion within the patient's comfort (edge-to-edge) Wearing time: full time except for mealtime	In-lab PSG (AHI>1)	-Clinical symptoms reported by the parents -Lateral cephalogram	T0: baseline T1: immediately after the end of treatment	1 month after mandible reached the designed position	AHI Min SaO2% Mean SaO2%	Significant reduction of AHI. Significant increase of Min SaO2%. Non-significant change of mean SaO2%.

AHI: Apnea Hypopnea Index; AI: Apnea Index; ArI: Arousal Index; CVMM: Cervical Vertebrae Maturation Method; DI: Desaturation Index; EMG: Electromyography; Min: Minimum; NR: Not Reported; ODI: Oxygen Desaturation Index; OSA: Obstructive Sleep Apnea; PSG: Polysomnography; RCT: Randomized Clinical Trial; RDC/TMD: Research Diagnostic Criteria for Temporomandibular Disorders; RDI: Respiratory Disturbance Index; SaO2: oxygen saturation; SDB: Sleep Disordered Breathing.

-4.70, CI: -7.81, -1.58, P<0.005; $I^2 = 83.46\%$, Figs. 2 and 3), and the level of evidence supporting this finding was very low (Table S3). The risk of bias the primary studies was a significant moderator, pointing out that higher effects were reported by studies presenting higher risk of bias ("serious risk" SMD: -6.54 vs "moderate risk" SMD: -3.32).

In the short (within six months) and in the medium term (within 12 months) follow up, significant reduction of AHI following RME was found in the meta-analysis (SMD: -2.97, CI: -4.35, -1.59, P<0.001, and SMD: -1.08, CI: -1.56, -0.61, P<0.001, respectively, Figs. 2 and 3). Concerning both time-points, high rate of heterogeneity was observed (I^2: 95.03%, and I^2: 80.04%, respectively) and the quality of the body evidence was very low (Table S3). At six months follow-up, risk of bias, OSA diagnosis and baseline AHI were significant moderators. In particular, the two RCTs with some concern of risk of bias and the non-randomized study with moderate risk of bias showed higher effects, as compared to the two non-randomized studies with serious risk of bias ("some concern of risk of bias" SMD: -5.54; "moderate risk of bias" SMD: -5.22; "serious risk of bias" SMD: -0.35). In addition, five studies adopting PSG as diagnostic method present a pooled SMD (SMD: -3.85) higher than those using polygraphic recording (SMD: -0.65). Finally, studies including sample presenting severe AHI index (AHI >10) at the baseline, showed the highest findings (SMD: -6.65).

At 12 months of follow-up, the only significant moderator was the baseline AHI index, supporting highest effect in individuals presenting with severe AHI before treatment (SMD: -4.10).

Finally, non-significant findings were observed in the long-term meta-analysis (>12 months), with high heterogeneity (SMD: -4.04, CI: -10.10, 2.02, P = 0.192, $I^2 = 98.46\%$, Figs. 2 and 3). Also, this finding was supported by very low evidence (Table S3).

- SaO2

Few studies evaluated the changes in the mean and minimum SaO2 within six months following RME, and the results pointed mainly toward lack of changes. On the other hand, the majority of the studies reported results considering one-year of follow-up pointing out significant increase in both minimum and mean SaO2, compared to baseline values. As for AHI, the only study reporting long-term data [44] showed recurrence of the pathology during adolescence also with regards to SaO2 values.

Immediately after RME, the meta-analysis pointed out significant increase of the minimum SaO2, with moderate heterogeneity (SMD: 2.03, CI: 1.06, 3.00, P<0.001, $I^2 = 65.17\ \%$, Figs. 2 and 4). This finding was provided with low quality of evidence (Table S3) and none of the studied moderators was significant. Similarly, also in the short (within six months) and in the medium term (within 12 months), significant increase of minimum SaO2 was found after RME (SMD: 4.54, CI: 2.12, 6.96, P<0.001, and SMD: 2.60, CI: 0.41, 4.79, P<0.001, Figs. 2 and 4). High rate of heterogeneity was observed both in the short term (I^2: 95.20%), and in the medium term (I^2: 91.74%). These findings present with low and very low quality of evidence, respectively (Table S3). At six months follow-up, OSA diagnosis was a significant moderator, showing increased effects from the three studies using the PSG (SMD: 7.17), as compared to the only study adopting polygraphic recordings (SMD: 0.43). At 12 months, baseline AHI severity was found as significant moderator, showing enhanced effects in individuals presenting with severe AHI before treatment (SMD: 3.78).

3.4. MMA

- AHI

Table 3
Characteristics of the included studies addressing the effects of Myofunctional Therapy.

Author, year,reference	Sample	Dropout	Orthodontic diagnosis	Study design	Groups	Treatment	Protocol	OSA diagnosis	Other diagnostic instrumenta	Follow-up	Treatment success endpoint	Respiratory Outcomes	Results
Chuang et al., 2017 [41]	29 (23 males, 6 females) 9.76 ± 3.54 years (range 3–15) -Group 1 (18): 10.44 ± 3.18 years -Group 2 (11): 8.64 ± 3.96 years	none	NR	Case-control prospective	-Group 1: full-term birth -Group 2: premature birth (<37 weeks)	One-piece, custom-made adjustable oral device for advancing the mandible during sleep with a bead mounted on the lower part of the frame for the tip of the tongue to roll	Construction bite: 50% of maximum mandibular advancement Wearing time: at night	In-lab PSG ($AHI \geq 1$; $RDI \geq 5$)	-Clinical symptoms	T0: baseline T1: 1 week after the end of 6-month treatment	NR	AHI Mean SaO2% AI HI DI RDI SE % Awake % REM S1, S2, S3 % TST Sleep latency ArI	Overall significant reduction of AHI, HI and Awake%. Non-significant differences between groups.
Guilleminault et al., 2013 [45]	24 (14 males, 10 females) 5.5 ± 1.2 years -Group 1: 11 -Group 2: 13	NA	NR	Retrospective	-Group 1: Reeducation -Group 2: No reeducation	Orthodontics: RME or Bimaxillary expansion Reeducation: strengthening of the tongue and orofacial muscles	NR	In-lab PSG	-Pediatric sleep questionnaire -ENT examination (Friedman classification tonsil size; modified Mallampati score, nasal turbinates, nasal valve, septum) -Orthodontic clinical examination	T0:baseline T1: post AT T2: post ortho T3: 38–50 months	Reeducation programs were completed after 2 years	AHI Min SaO2%	In the long-term follow up, significant reduction of AHI, and significant increase of Min SaO2% in Group 1 compared to Group 2
Huang et al., 2019 [47]	110 -Group 1: 54, 7.02 ± 2.44 years; -Group 2: 56, 7.97 ± 3.08 years	Group 1: 31 at T1, 23 at T2 (total: 54) Group 2: 4 at T1, 4 at T2 (total: 8)	NR	RCT	-Group 1: active MFT -Group 2: passive MFT	-active MFT: isotonic and isometric exercises (20 min/day) that target oral (lip, tongue) and oropharyngeal structures (soft palate, lateral pharyngeal wall) -passive MFT: One-piece, custom-made adjustable oral device for advancing the mandible during sleep with a bead mounted on the lower part of the frame for the tip of the tongue to roll	Construction bite: 50% of maximum mandibular advancement* Wearing time: at night* **only passive MFT group*	In-lab PSG ($AHI>1$, $RDI>5$)	Lateral cephalogram	T0: baseline T1: 6 months T2: 1 year	NR	AHI Mean SaO2% AI HI DI RDI SE % Awake % S1, S2, S3 % REM TST Sleep latency ArI RERA Hypopnea	Significant reduction of RDI, RERA and Sleep latency in Group 1 at T1. Significant reduction of AHI, HI, and Hypopnea, and significant increase of SE both at T1 and T2 in Group 2. At T1 AHI in sleep, HI, hypopnea count, and Awake % showed significantly more improvement in Group 2 compared to Group 1. No between-groups comparison at T2 due to loss to follow-up.
Villa et al., 2017 [63]	54 (29 males, 25 females) 7.1 ± 2.5 years	none	NR	RCT	-Group 1: MFT + nasal wash	Isometric and isotonic exercises for tongue, soft palate and lateral pharyngeal wall (nasal breathing rehabilitation, labial seal and	NA	In-lab PSG ($AHI>1$)	-ENT examination -Clinical symptoms reported by the	T0: baseline T1: 2 months	NR	AHI Mean SaO2% Min SaO2% TST	Significant reduction of ODI and increase in mean SaO2% in Group 1. Non-significant changes in Groups 2.

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Table 3 (*continued*)

Author, year,reference	Sample	Dropout	Orthodontic diagnosis	Study design	Groups	Treatment	Protocol	OSA diagnosis	Other diagnostic instrumenta	Follow-up	Treatment success endpoint	Respiratory Outcomes	Results
	-Group 1 (36): 6.7 ± 2.3 years -Group 2 (18): 6.7 ± 2.8 years Healthy controls (28): 25 males, 3 females, 7.8 ± 2.2 years				-Group 2: Nasal wash only -Group 3: healthy untreated* **only for tongue tone comparison*	lip tone exercises, and tongue posture exercises) every day, at least three times a day, doing 10–20 repetitions each time.			parents (Broullette questionnaire) -IOPI (tongue and lip strength)			N1, N2, N3% REM% ArI ODI	

AHI: Apnea Hypopnea Index; AI: Apnea Index; ArI: Arousal Index; AT: Adenotonsillectomy; DI: Desaturation Index; ENT: ears, nose and throat; HI: Hypopnea Index; IOPI: Iowa Oral Performance Instrument; MFT: Myofunctional Therapy; N1: Non REM Sleep Stage 1; N2: Non REM Sleep Stage 2; N3: Non REM Sleep Stage 3; NA: Not Applicable; NR: Not Reported; Min: Minimum; ODI: Oxygen Desaturation Index; PSG: Polysomnography; RCT: Randomized Clinical Trial; RDI: Respiratory Disturbance Index; REM: Rapid Eye Movement sleep; RERA: Respiratory Effort Related Arousal; RME: Rapid Maxillary Expansion; S1: Sleep Stage 1; S2: Sleep Stage 2; S3: Sleep Stage 3; SaO2: oxygen saturation; SE: Sleep Efficiency; TST: total sleep time.

In the pre-post treatment assessment, both at six and at 12 months from the beginning of the treatment, all included studies assessing this outcome (four studies) reported significant reduction of AHI. Also, these results were significantly different from those obtained from the untreated groups that showed non-significant changes or even increase of the AHI [48,58].

Significant changes in the AHI values (SMD: -1.33, CI: -2.18, -0.47, P<0.005, Figs. 2 and 5) with considerable heterogeneity (I^2 = 84.18%) were observed in the meta-analysis considering the data within six months after treatment. This finding was supported by very low quality of evidence (Table S4). The type of appliance was found as significant moderator, with the best results showed by the modified monobloc (SMD: -2.40).

Significant reduction of AHI, with moderate heterogeneity, was observed also in the long-term meta-analysis (>12 months; SMD: -3.71, CI: -5.91, −1.51, P< 0.005, I^2 = 64.74 %, Figs. 2 and 5), and supported by moderate evidence (Table S4). None of the studied moderators was significant.

- SaO2

Three studies evaluated SaO2 following MMA: two of them reported non-significant changes in the mean SaO2, while one study supported a significant increase of minimum value only and one study reported significant increase of both mean and minimum values following treatment. The meta-analysis showed non-significant changes in the minimum SaO2 within six months of treatment (SMD:0.13, CI: -1.46, 1.73, P = 0.869, Figs. 2 and 6) with high heterogeneity (I^2 = 94.63%). This result was supported by very low evidence (Table S4). The moderator analysis showed significant findings with regards to the type of appliance and OSA diagnosis. In particular, the device made by two thermoplastic bite splints showed some positive effects (SMD: 0.95), while the modified monobloc showed negative findings (SMD: -0.67). Similarly, the study using PSG for OSA diagnosis presented favorable effects, while the study adopting polygraphic recordings showed unfavorable results.

3.5. *MT*

- AHI

Significant reduction in the AHI was observed at six months follow-up with passive MT. Also, passive MT showed significantly better results with regards to AHI reduction, compared to active MT. In the long-term follow-up (more than three years), significant effect of MT following orthodontic treatment was observed, compared to individuals who did not performed any reeducation.

No meta-analysis was performed regarding this outcome since different therapeutic approaches were found.

- SaO2

Two studies supported non-significant changes of the mean SaO2, following both passive and active MT. On the other hand, one study underlined that nasal washes in combination with MT provided significant improvement of mean SaO2. Finally, in the long-term follow up, minimum SaO2 was significantly increased in individuals performing regular MT, compared to those not following any reeducation program.

3.6. *RME + MAA*

- AHI

Table 4
Characteristics of the included studies addressing the effects of Rapid Maxillary Expansion + Mandibular Advancement.

Author, year,reference	Sample	Dropout	Orthodontic diagnosis	Study design	Groups	Treatment	Protocol	OSA diagnosis	Other diagnostic instrumenta	Follow-up	Treatment success endpoint	Respiratory Outcomes	Results
Remy et al., 2021 [57]	103, 7.0 ± 1.8 years (range 3–12)	NA	Class II malocclusion	Retrospective	Group 1: fixed maxillary expansion + mandibular advancement	Upper jaw: Hyrax-type expander with embedded tube Lower jaw: removable acrylic plate connected with a 0.045 wire	Upper Jaw: 1 turn/day for 20 days; 2 turn/day x 10 days Lower Jaw: - Construction bite: mandibular maximal jumping -Wearing time: night time only (after upper expansion)	Portable polygraph (SOMNOlab) AHI≥1	Pediatric sleep questionnaire	T0:baseline T1: 9 months	Expansion >10 mm, Class I	AHI ODR AI ArI	Significant decrease of AHI and ArI. Non-significant changes of ODR and AI

AHI: Apnea Hypopnea Index, AI: Apnea Index; ArI: Arousal Index; ODR: Oxygen Desaturation Rate; NA: Not Applicable.

Treatment combination supported significant decrease of AHI after 9 months of therapy.

- SaO2

None of the included studies assessed SaO2 changes following combined treatment.

3.7. Risk of bias (quality assessment) of the included studies

- RCT

Two RCTs on RME were rated with some concern of bias (Table S5), while of the two RCTs on MAA, one was rated with some concern and one with high risk of bias (Table S5). Finally, both RCTs (two out of two) on the MT were rated with high risk of bias (Table S5).

- Non-randomized studies

Eight studies on RME presented serious risk of bias, while the remaining five studies presented moderate risk of bias (Table S6). With regards to MAA, two studies presented serious risk of bias and only one study presented moderate risk of bias (Table S6). Finally, the only study on MAA + RME (Table S6) and the two studies on MT (Table S6) presented with serious risk of bias. Common reasons for loosing points in the quality assessment were: poor description and evaluation of the sample characteristics, variability in the age range of the sample, absence of the uniform orthodontic diagnosis at baseline, lack of appliance description (type of appliance, design, screw, anchorage teeth), lack of description of activation protocol.

4. Discussion

The aim of this SR was to assess the effects of different types of orthopedic and functional treatment on the respiratory outcomes in OSA children and adolescents. Overall, within one year from the baseline, favorable respiratory outcomes have been found following different types of orthodontic treatments, suggesting that interceptive orthodontics might play a role in the multidisciplinary therapeutic approach of pediatric OSA in children. However, the level of the body evidence supporting those findings ranged between very low and low for the majority of the outcomes of the studies, thus limiting the applicability of the findings. In addition, in the longer distance, few data and mainly non-significant findings have been found.

4.1. RME

RME is an effective procedure for the correction of maxillary transverse deficiency, with the primary treatment goal to increase the widths of the maxilla through the opening of the mid-palatal and peri-maxillary sutures [65]. In turn, in growing patients, this treatment can significantly affect the dimension of the nasal vault and increase the tridimensional volume of the nasal cavity [66–68] resulting in decreased nasal resistance and increased nasal flow [69–71]. These secondary effects may improve OSA [72] and support the significant improvements observed in the current SR, concerning respiratory outcomes (both AHI and SaO2%) at different time-points. Furthermore, the augmented maxillary width provides increased space available for a more forward and upward positioning of tongue, thus indirectly enhancing the oropharyngeal/retrolingual air space [73]. The results of the meta-analysis on the effects of RME showed substantial heterogeneity in all the studied timepoints. That could be explained by several factors

Orthodontic treatment	Outcome	Follow up	n. of Studies (n. of patients)	Result
RME	AHI	Immediately after (≤1 month)	2 (74)	↓
		>1 month; ≤6 months	5 (136)	↓
		>6months; ≤12 months	7 (150)	↓
		>12 months	2 (70)	↓
	Lowest SaO2	Immediately after (≤1 month)	2 (74)	↑
		>1 month; ≤6 months	3 (77)	↑
		>6months; ≤12 months	2 (53)	↑
		>12 months	*No Meta-analysis*	-
MAA	AHI	Immediately after (≤1 month)	*No Meta-analysis*	-
		>1 month; ≤6 months	3 (68)	↓
		>6months; ≤12 months	*No Meta-analysis*	-
		>12 months	2 (54)	↓
	Lowest SaO2	Immediately after (≤1 month)	*No Meta-analysis*	-
		>1 month; ≤6 months	2 (38)	↑
		>6months; ≤12 months	*No Meta-analysis*	-
		>12 months	*No Meta-analysis*	-

Fig. 2. Summary of the results of the meta-analysis. The arrows show the direction (reduction or increase) of the effect for each variable (Apnea-Hypopnea Index, AHI and lowest Oxygen Saturation, SaO2), considering the two studied orthodontic treatments (Rapid Maxillary Expansion and Mandibular Advancement). In green are reported statistically significant results, in red are reported non significant results.

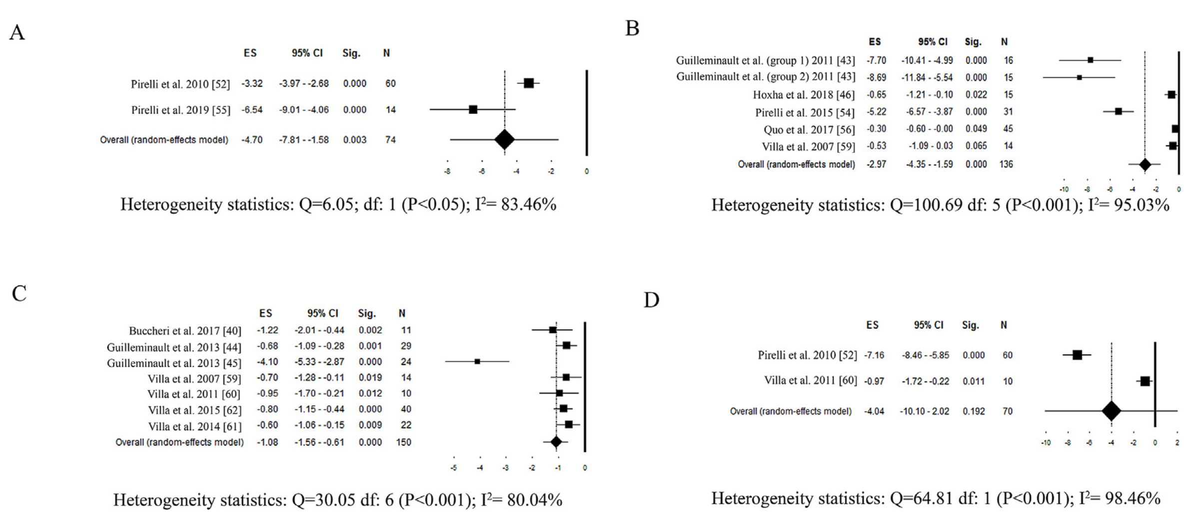

Fig. 3. Meta-analyses of AHI changes following Rapid Maxillary Expansion. Forest plot including source studies, effect sizes (ES) with 95% confidence intervals (CI), significance (Sig), number of participants (N) and assessments of heterogeneity. A: Immediately after; B: < six months; C: <12 months; D: >12 months.

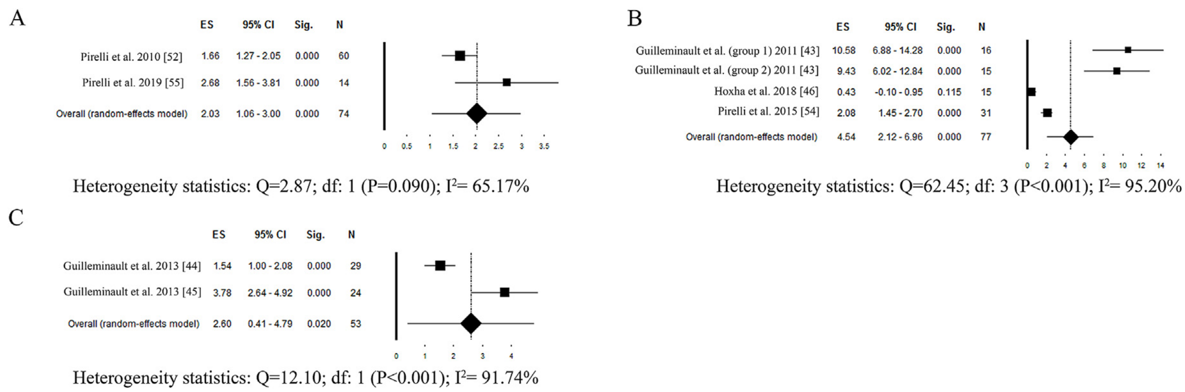

Fig. 4. Meta-analyses of SaO2 changes following Rapid Maxillary Expansion. Forest plot including source studies, effect sizes (ES) with 95% confidence intervals (CI), significance (Sig), number of participants (N) and assessments of heterogeneity. A: Immediately after; B: < six months; C: <12 months.

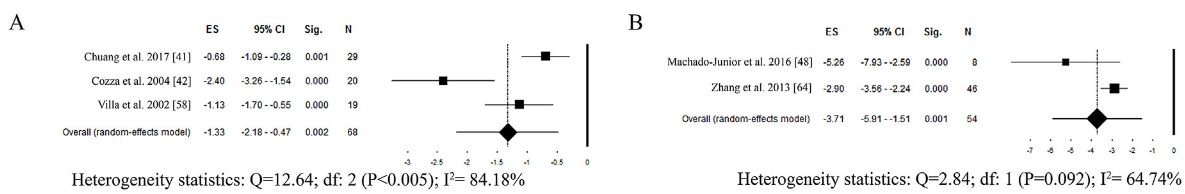

Fig. 5. Meta-analyses of AHI changes following Mandibular Advancement. Forest plot including source studies, effect sizes (ES) with 95% confidence intervals (CI), significance (Sig), number of participants (N) and assessments of heterogeneity. A: < six months; B: >12 months.

related to patients' characteristics and treatment modalities. Some factors were included in the statistical analysis as moderators, but still several confounders were not addressed due to the lack of transparency in reporting sample characteristics across studies. In particular, despite the multifactorial etiology of the OSA, few studies considered the body mass index of the participants. For instance, in one of the included primary studies published by Quo and colleagues [56], the authors retrospectively observed, albeit not significant, an increase in the AHI in one third of the sample following expansion of the upper and lower jaw. Moreover, those patients who had a positive response to therapy did show residual OSA. These findings could be explained by the lack of control of confounding factors that might have contributed to the worsening of the symptoms during the follow-up period and could also be ascribed to the lack of an adequate diagnosis at baseline.

Furthermore, the assessment of adenotonsillar hypertrophy as either inclusion or exclusion criteria was not consistently reported among studies, and presence or absence previous adenotonsillectomy was also extremely diverse among studies. The type of appliance was not considered a potential confounder as all included studies measured the effects of tooth-anchored fixed expanders. However, the devices presented different designs (2-bands, 4-bands, acrylic supported, or not reported) and different anchor teeth (second deciduous molars, first permanent molars, or not reported). In addition, although the majority of the studies reported a screw activation protocol of 2 turns/day (approximately 0.50 mm/day), other studies applied slower expansion rates [43,46], or adapted the expansion protocol according to participants' age [56]. Moreover, few studies included also participants performing transversal expansion at the lower jaw [43,44,56].

Interestingly, most of the included studies on the effects of RME reported a subjective diagnosis of maxillary constriction, narrow maxilla, cross bite or ogival palate at the baseline, thus supporting an indication for an orthodontic treatment of maxillary expansion, independently from the OSA management. Therefore, the results of the current meta-analysis can be extended only to those patients presenting with transversal discrepancies, but there is still no indication for RME in OSA patients in absence of maxillary constriction, in accordance with the recommendations of the American Association of Orthodontists white paper which support the use of RME only when there is an appropriate underlying skeletal condition [72]. Furthermore, the vast majority of the RME studies were uncontrolled studies (11 studies), or compared different therapies (3 studies); only 1 study included an untreated

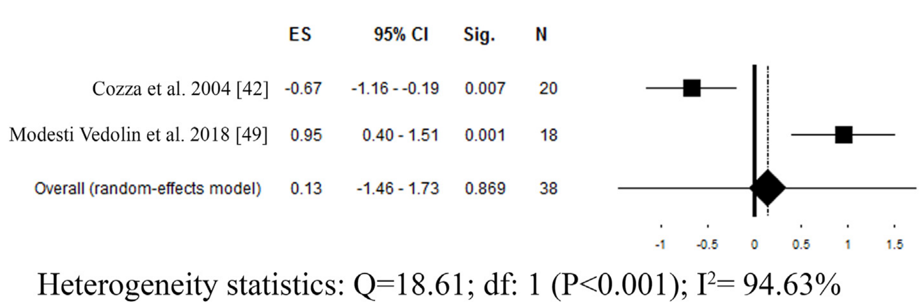

Fig. 6. Meta-analyses of SaO2 changes following Mandibular Advancement (< six months). Forest plot including source studies, effect sizes (ES) with 95% confidence intervals (CI), significance (Sig), number of participants (N) and assessments of heterogeneity.

control group composed by individuals with the same malocclusion pointing out reduction of the AHI also among controls and non-significant differences between treatment arms after 5 months of follow-up [46]. Similarly, a large, randomized, controlled trial of therapy for the pediatric OSA comparing the efficacy of early AT versus watchful waiting with supportive care, showed a significant reduction of the AHI in both groups after 7 months of follow-up [74]. These results could be explained by a trend of natural remission of OSA in children. A longitudinal study of objectively measured OSA in a community-based child cohort examined OSA's natural history from middle childhood to adolescence. A very small percentage (approximately 4%) of children and adolescents presented an objective OSA diagnosis at each time point, thus suggesting that OSA rarely persists from middle childhood through late adolescence [75]. However, both studies were conducted without taking into account the craniofacial morphology of the children included in the study sample, therefore it is still to be elucidated whether in diagnosed OSA patients with a dentofacial deformities (either transversal maxillary deficiency or Class II due to mandibular retrusion) the natural course of OSA presents a favorable prognosis with spontaneous improvement in absence of treatment. Notwithstanding, in order to clearly elucidate the role of growth in the changes of respiratory variables, controlled studies are critically needed, although ethical concerns of not treating children with OSA make it extremely difficult to recruit such control group.

4.2. MAA

The retruded position of the mandible is considered, as well as the narrow dental arches, a common feature in pediatric OSA [16]. In fact, anterior jaw-positioning was the second most studied therapy for the treatment of childhood OSA in the current SR (five studies). The primary goal of this treatment modality is to correct the dento-skeletal class II discrepancy. As a secondary effect, the anterior displacement of the mandible and of the hyoid bone leads to anterior repositioning of the tongue, thus widening the available space in the upper airways and consequently potentially improving OSA [76]. In adulthood, mandibular advancement devices are recognized as an effective, non-invasive and safe approach for mild or moderate OSA [77,78]. While for adult patients mandibular advancement devices therapy is to date a symptomatic treatment, in growing patients MAA, unlike adults, could act as a causal treatment, aiming at eliminating the retruded position of the lower jaw. According to the results of the current SR, different appliances have been used to attempt forward positioning the mandible in growing patients, but interestingly only two studied [48,64] adopted devices (Twin Block and Planas appliance) which are specifically designed to correct dentoskeletal malocclusion in patients clearly diagnosed with a Class II and/or mandibular retrusion at the baseline [79]. The remaining studies adopted devices which resemble more the concept of the adult mandibular advancement device, thus providing a more forward position of the mandible with the main purpose of increasing the airway patency, rather than an orthopedic functional treatment. Furthermore, in those studies, the baseline diagnosis of Class II and/or mandibular retrusion was not clearly stated, thus limiting the external validity of the current findings. Interestingly, in the short-term follow up meta-analysis (< six months), the appliances used in the three studies were all monobloc devices. The study by Cozza and co-workers [42] provided the highest results, probably due to the fact that the PSG was performed with the appliance “in-situ”. On the other hand, in the meta-analysis performed in the longer term (<12 months) the appliances compared were both composed by two separate acrylic plates, and no difference was observed between the two devices.

4.3. MT

Even though RME and MAA in children might be useful in achieving normal upper airway size, these treatments do not ensure correct tongue posture and function and normal orofacial and pharyngeal muscle tonicity, which are crucial factors in the maintenances of upper airway patency [45]. In this context, MT may implement the correct function of oral muscles in order to avoid OSA residues and recurrence of symptoms [44,45]. One previous SR on the role of MT, pointed out a reduction in the AHI by approximately 50% in adults and 62% in children affected by OSA [80]. Extremely diverse MT protocols have been found in the current SR, including active and passive therapies, and combination of both. Hence, it was not possible to perform a meta-analysis due to the observed heterogeneity in outcomes, protocols and timing. Notwithstanding, the analyzed MT protocols supported positive effects on the PSG outcomes, with slightly more favorable results observed with passive MT as compared to active MT. It has to be mentioned that the efficacy of MT is strongly influenced by patients' compliance and adherence to the exercise protocol, which seem to be lower in younger children, and largely related to parental cooperation [41]. Furthermore, reported compliance for active MT seem to be lower than passive MT [81].

As pointed out by several authors, the primary focus of the OSA therapy should be to identify the cause of airways obstruction: the pathophysiology of pediatric OSA is complex and the respiratory disorders could be induced by a combination of factors [82]. The major confounding factors emerged from the current scientific literature on pediatric OSA patients are the lack of accuracy in the baseline ENT assessment, and the unclear exclusion/inclusion of subjects with adenotonsillar hypertrophy, or those who have previously undergone AT surgery, although it is widely recognized that tonsils dimensions and nasal flow are critical element for the prognosis of OSA patients [83].

Following the PRISMA statements, the present SR was based on strict inclusion and exclusion criteria. Assuming PSG findings as primary outcomes dramatically restricted the search results, as numerous studies evaluated treatment efficacy based only on anatomical changes of nasal cavity volume and pharyngeal space, measured from radiographic images and not on respiratory outcomes.

Although differences in the anatomy of the upper airways can be encountered [84], the radiographic assessment does not allow to directly relate changes in the respiratory function and the reliability of the radiographic assessment in OSA is questionable since it is a static measurement performed in wakefulness and in upright position, to evaluate a pathology that is dynamically expressed during sleep and in clinostatism.

Moreover, instrumental diagnosis of OSA at the baseline by means of PSG diagnosis as an inclusion criterion also limited the retrieved results; numerous studies include diagnoses based on self-reported or parental-reported questionnaires, and/or anamnestic findings.

5. Conclusion

RME shows significant improvement of the analyzed PSG parameters within one-year from the beginning of the therapy, but further studies are needed to determine whether these effects are stable in the longer term. MAA provides positive effects on AHI after six months of therapy, but studies lack of a clear definition of the study population. MT might be a valid adjunct to other OSA treatments, and combination of treatments should be investigated.

However, due to the overall low-very low quality of the body evidence, supported mainly by uncontrolled clinical trials, the current scientific literature does not support orthodontic interceptive treatment as the elective treatment for OSA growing patients.

Practice Points.

1. Growing patients with obstructive sleep apnoea should perform regular consultation with an orthodontic specialist
2. In growing patients with constricted maxilla and obstructive sleep apnoea, rapid maxillary expansion may provide positive short-term effects on polysomnographic outcomes
3. No indications regarding orthodontic treatment to manage obstructive sleep apnoea in absence of malocclusion can be drawn

Research Agenda.

1. Controlled studies with untreated controls to rule out the contribution of growth in the resolution of obstructive sleep apnoea
2. Clear reporting of previous ENT examination and transparent criteria concerning inclusion/exclusion of patients with enlarged tonsils and adenoids, or previous adenotonsillectomy surgery
3. Mandibular advancement studies in patients diagnosed with Skeletal Class II, based on cephalometric assessment
4. Standardised protocol of myofunctional therapy
5. Longitudinal tracking to assess recurrence of obstructive sleep apnoea in adulthood

Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101730.

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