



Original Article

Mandibular advancement appliances for the treatment of obstructive sleep apnea in children: a systematic review and meta-analysis



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ABSTRACT

The objective of this review was to evaluate the effect of mandibular advancement appliances (MAAs) for obstructive sleep apnea (OSA) in children. To this end, several electronic databases (PubMed, EMBASE, Cochrane Library) were systematically searched until 18 June 2018. Randomized and non-randomized clinical trials were included. Articles of high-quality were included for the meta-analysis. Data extraction and quality assessment were conducted by two independent reviewers. Four randomized controlled trials (RCTs) and three non-RCTs were finally included in the review; of these, two RCTs of high-quality were included in the meta-analysis. The mean difference in apnea–hypopnea index (AHI) change for mandibular advancement group compared with control group was -1.75 events/h (95% confidence interval (CI) $-2.07, -1.44$), $p < 0.00001$. Sensitivity analysis including the quasi-randomized RCT and non-RCTs showed stable favorable results for MAAs.

The meta-analysis showed supportive evidence for MAA treatment in pediatric OSA patients. Subgroup analysis suggested that MAA can be effective for mild to severe patients before the end of the pubertal peak. Long-term treatment (at least six months) may be more effective than short-term treatment.

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1. Introduction

Pediatric obstructive sleep apnea (OSA), with a prevalence of 1–5%, is a common and important disease affecting children's systemic health and development [1–5]. Significantly different from adult OSA [6], adenotonsillar hypertrophy and obesity are the main etiological factors [7–9], which may cause aggressive behavior, attention deficit, delays in development, emotional problems [10–12] and unfavorable craniofacial changes (including transverse maxillary deficiency, retrognathic mandibles, incorrect tongue position and incompetent lips) [13,14]. In return, deficiency of maxillary and mandible can also become the etiological factors of OSA due to airway size decreasing [15,16]. Adenotonsillectomy markedly improves but does not necessarily normalize polysomnographic findings in children with adenotonsillar hypertrophy and related sleep-disordered breathing, especially in those with underlying skeletal deformities [17–19]. Orthodontic treatments including functional orthopedic mandibular advancement and

other treatment options such as rapid palatal expansion (RPE) have been taken into consideration as a part of comprehensive treatment for pediatric OSA patients [20,21].

Mandibular advancement is widely used in adult OSA, while in the treatment of pediatric OSA, it aims to correct retrognathic mandible by re-directing its growth into a more forward position and stimulates mandibular growth in a passive or active manner [22], which may be accomplished by various functional appliances, such as twin-block, activator, Herbst, Frankel-II, and Bionator, etc. [23]. This could increase the dimensions of the upper airway and potentially eliminate risk factors for OSA in adulthood [24].

The use of mandibular advancement appliances (MAAs) for pediatric OSA has not been widely studied and an evidence-based review is needed. A Cochrane review published in 2016 investigated oral appliances and functional orthopedic appliances for OSA in children [25]. At that time, there was not enough high-quality evidence to affirm that oral appliances and functional orthopedic appliances are effective in the treatment of OSA in children [26]. A few articles about the effectiveness of MAAs for pediatric OSA have been published since then. Thus, the aim of this systematic review was to investigate the efficacy of mandibular advancement appliances in the treatment of pediatric OSA and update the previous conclusions.

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2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist was followed in this systematic review [27].

2.1. Inclusion criteria

The inclusion criteria were formulated according to the population, intervention, comparison, outcome, study design (PICOS) principle.

Population: Children and adolescents (18 years old or younger), diagnosed with OSA without craniofacial syndromes.

Intervention: Mandibular advancement appliances.

Comparison: With or without a control group.

Outcome: Primary outcome was the apnea–hypopnea index (AHI); secondary outcomes were (1) oxygen saturation level, (2) sleep quality (SQ), and (3) upper-airway space.

Study design: Randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs).

2.2. Search strategy

A systematic search was conducted in the following electronic databases: PubMed, EMBASE, Cochrane Library, from their inception to 18 June 2018. The search was performed using Medical Subject Headings (MeSH) ‘sleep apnea,’ ‘obstructive,’ and free text words ‘OSA,’ ‘upper airway resistance,’ ‘sleep-disordered breathing,’ ‘mandibular advancement,’ ‘oral appliance,’ ‘orthodontic treatment,’ ‘children,’ and ‘pediatric’ without language restrictions. Detailed search strategies were developed for each database.

In addition, Google Scholar searches and manual searches of the reference lists were completed for relevant studies.

2.3. Study selection

Two reviewers (M.Y. and Y.M.) independently selected the articles, and discrepancies were resolved by discussion with each other and consultation with a third reviewer (G.X.). Studies available as abstracts only were included if we could verify the inclusion and exclusion criteria, and at least one of the outcomes of interest was reported.

2.4. Data items and collection

The following data items were extracted from each study included by two reviewers independently: author, year of publication, study design, subjects, age, interventions, wearing time, drop out, AHI before and after MAA (only effects of MAA would be pooled if combined with other treatment), and secondary outcomes.

2.5. Quality assessment of the studies

To evaluate the risk of bias in individual studies, the Cochrane Collaboration’s tool for assessing the risk of bias in randomized trials was used [28]. The following aspects were evaluated: sequence generation, allocation sequence concealment, blinding of participants/personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Two reviewers (M.Y. and Y.M.) independently evaluated the quality of the studies; a third reviewer (G.X.) was consulted when there was disagreement.

2.6. Data synthesis

A meta-analysis was considered if there were enough studies of high quality included. The software package RevMan5.3 provided by Cochrane Collaboration was used to conduct the data synthesis. Heterogeneity between studies was represented by the I^2 statistic and the χ^2 test for heterogeneity [29]. A fixed-effects model would be used if $I^2 < 50\%$, otherwise a random-effects model would be implemented, and subgroup analysis or sensitivity analysis would be conducted according to the methodological and clinical heterogeneity.

3. Results

3.1. Search and study selection

The flow chart of the selection process is shown in Fig. 1. A total of 213 articles were identified, 99 in PubMed, 107 in Embase, five in Cochrane Library, two of additional records identified through other sources. One hundred and sixty-nine articles remained after duplicates were removed. Later, 129 articles were excluded after screening the titles and abstracts, leaving 40 articles of possible interest. Thirty-three articles were excluded after reading the full text, among which three systematic reviews were found of great reference value but they were not updated [22,25,30], and two records [31,32] were considered as duplicates because of the same author and data. One conference abstract [33] was also included in consideration of the secondary outcomes (pharyngeal size and sleep quality analysis) reported. Finally, seven original studies [26,32–37] were included in the review. Two RCTs [32,35] of these articles were included in the meta-analysis.

3.2. Summary of included studies

A summary of study characteristics and results of included studies is shown in Table 1. Three articles [34,36,37] were non-randomized prospective studies. Four RCTs [26,32,33,35] compared MAA against no treatment or sham MAA, one of which was a conference abstract and AHI was not tested [33].

3.3. Quality analysis

The results of the quality analysis are shown in Figs. 2 and 3. Two RCTs [32,35] were assessed as at low risk of bias considering that the blinding of participants/personnel was impossible if the control group underwent no treatment and the primary outcomes were objective indicators. One RCT study [33] published as a conference abstract only was assessed as at unclear risk bias because certain items were not available. And another RCT [26] was assessed as at high risk of bias because they used a quasi-random method of allocation (alphabetically by surname), and the percentage of dropouts was higher than 20%.

3.4. Data synthesis

According to the risk of bias assessments, a meta-analysis of change in AHI (Δ AHI) before and after treatment in MAA and control group was performed including two high-quality RCTs [32,35]. Thirty-four patients participated in total, 17 in MAA and 17 in the control group. The test for heterogeneity was $I^2 = 0\%$ ($p = 0.78$), and a fixed-effects model was used. The mean difference in Δ AHI for MAA compared with control was -1.75 events/h (95% confidence interval (CI) $-2.07, -1.44$), $p < 0.00001$ (see Fig. 4).

Qualitative syntheses of all included studies regarding the primary and secondary outcomes were summarized in Table 2.

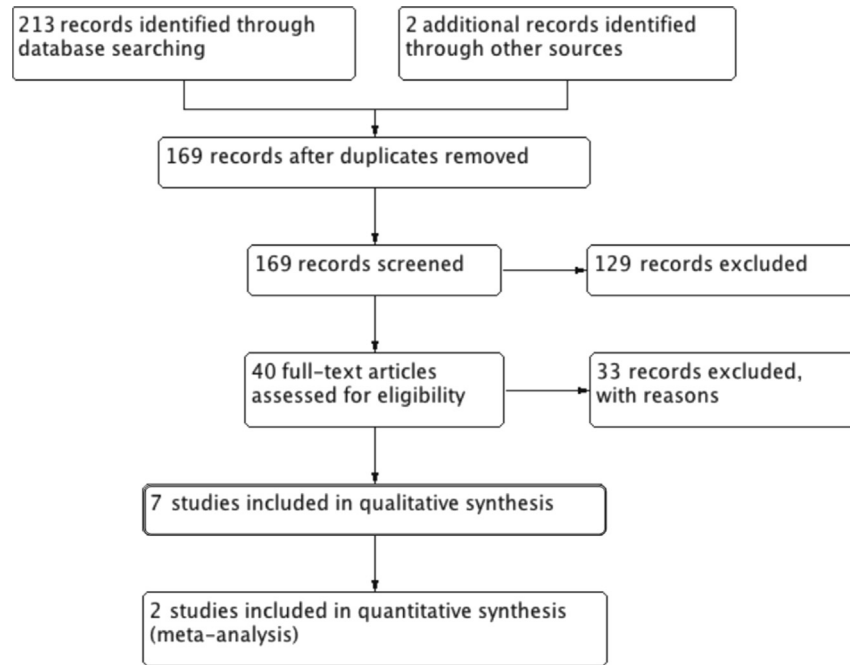


Fig. 1. Flow chart of the selection process.

Table 1

Characteristics of the included studies for systematic review.

Study	Study design	Subjects	Age	Interventions	Wearing time	Drop-out	Outcomes	
Villa et al., 2002 [26]	RCT	MAA Control	19 13	6.86 ± 2.34 years 7.34 ± 3.10 years	An acrylic plate No treatment	6 months (24 h) —	5 4	AI, AHI, ODI, SQ
Nunes et al., 2009 [33]	RCT	MAA Control	24 16	6–9 years No treatment	Bioajusta X appliance No treatment	6 months —	0 0	SQ, airway space
Machado-Junior et al., 2016 [35]	RCT	MAA Control	8 8	8.13 ± 0.99 years 8.39 ± 1.31 years	Two acrylic plates No treatment	12 months (24 h) —	0 2	AHI
Idris G. et al., 2018 [32]	Crossover -RCT	MAA Control	9 9	9.8 ± 1.1 years Twin-Block Sham MAA	3 weeks (overnight) 3 weeks (overnight)	3 0	AHI, minSaO ₂ , SQ	
Cozza et al., 2004 [34]	NRCT (prospective)	20	5.91 ± 1.14 years	Modified monobloc	6 months (overnight)	0	AHI, minSaO ₂ , SQ	
Schutz et al., 2011 [36]	NRCT (prospective)	16	12.6 years ± 11.5 months	Herbst + RPE	12 months (24 h)	0	AI, HI, RDI, SQ, airway space	
Zhang et al., 2013 [37]	NRCT (prospective)	46	9.7 ± 1.5 years	Twin block	10.8 months (24 h)	0	AHI, minSaO ₂ , airway space	

AHI, apnea–hypopnea index; AI, apnea index; HI, hypopnea index; MAA, mandibular advancement appliance; minSaO₂, lowest oxygen saturation; NRCT, non-randomized controlled trial; ODI, oxygen desaturation index; RCT, randomized controlled trial; RDI, respiratory disturbance index; RPE, rapid palatal expansion; SQ, sleep quality.

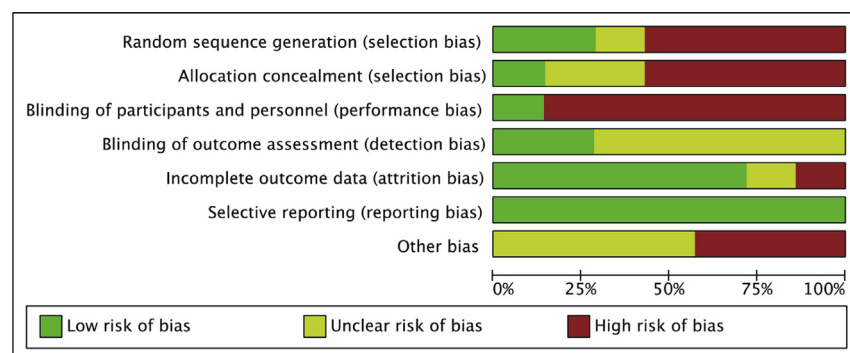


Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

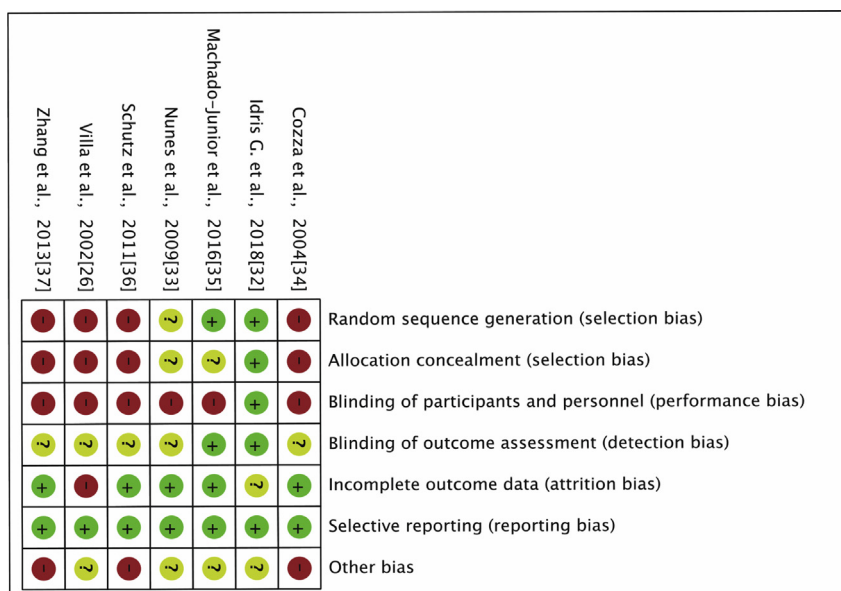


Fig. 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

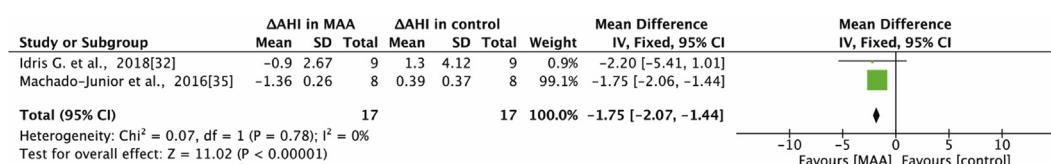


Fig. 4. Comparison of treatment effects (ΔAHI) of MAA and control group. CI, confidence interval; ΔAHI, change in apnea–hypopnea index; df, degrees of freedom; IV, inverse variance; MAA, mandibular advancement appliance; SD, standard deviation.

Table 2

The primary and secondary outcomes of all included studies.

Study	Group	AHI (events/h)		Secondary outcomes
		Pre-MAA	Post-MAA	
Villa et al., 2002 [26]	MAA	7.1 ± 4.6	2.6 ± 2.2	Desaturation index decreased in treated patients but was not significant; no significant difference in minSaO ₂ ; daytime and night-time symptoms in treated subjects diminished but in control subjects, remained unchanged
	Control	NA	unchanged	
Nunes et al., 2009 [33]	MAA	NA	NA	Improvements with respect to breathing and snoring confirmed by the questionnaire; a volumetric gain of 3.15 cm ³ for the treated group and reduction of -1.38 cm ³ for the untreated group (p < 0.001) measured by acoustic pharyngometry
	Control	NA	NA	
Machado-Junior et al., 2016 [35]	MAA	1.66 ± 0.28	0.30 ± 0.23	No secondary outcomes
	Control	1.58 ± 0.42	1.97 ± 0.30	
Idris G. et al., 2018 [32]	MAA	2.8 ± 3.0	1.9 ± 2.1	MinSaO ₂ showed a significant increase (+3.4%; 95% CI = 0.9–5.9; p = 0.007), whereas ODI did not show significant difference (p > 0.05); PSQ scores decreased (p = 0.012) and quality of life and behavior (p ≤ 0.028) improved.
	Control	2.4 ± 3.0	3.7 ± 4.7	
Cozza et al., 2004 [34]	MAA	7.88 ± 1.81	3.66 ± 1.70	No significant change in minSaO ₂ ; ESS decreased from 15.2 ± 4.9 to 7.1 ± 2.0
Schutz et al., 2011 [36]	MAA	4.8 ± 4.2	1.3 ± 1.8	
Zhang et al., 2013 [37]	MAA	14.08 ± 4.25	3.39 ± 1.86	Significant reduction in RDI from 7.3 ± 5.6 to 1.3 ± 1.8 (p < 0.05) due to a total increase in airway volume (p < 0.01); sleep architecture improved

AHI, apnea–hypopnea index; CI, confidence interval; ESS, Epworth sleepiness scale; MAA, mandibular advancement appliance; minSaO₂, lowest oxygen saturation; NA, not available; ODI, oxygen desaturation index; PSQ, pediatric sleep questionnaire; RDI, respiratory disturbance index.

Respiratory disturbance index (RDI) was extracted in the study of Schütz [36], considering that OSA in children may result in arousals and sleep fragmentation but little desaturation [4].

3.5. Sensitivity analysis

A sensitivity analysis was conducted to include the quasi-randomized study [26] considering the large sample size. The AHI

before and after treatment of the control group in this study was reported as 'unchanged' but the specific value was not available even though we contacted the author. According to the randomization principle, we assumed that the change in AHI (ΔAHI) of the control group was 0, and the standard deviation was as same as that of the MAA group. The results remained stable, and ΔAHI for MAA compared with control was -1.79 events/h, (95% CI -2.10, -1.48), p < 0.00001 (see Fig. 5).

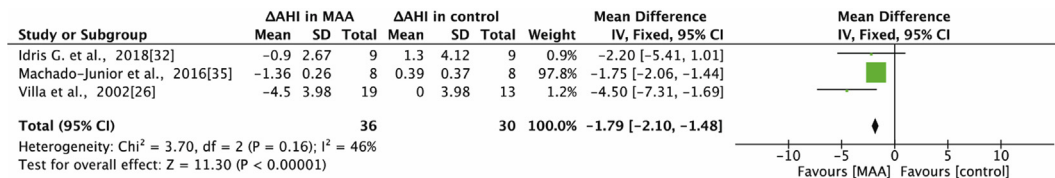


Fig. 5. Comparison of treatment effects (Δ AHI) of MAA and control group including the quasi-randomized study. CI, confidence interval; Δ AHI, change in apnea-hypopnea index; df, degree of freedom; IV, inverse variance; MAA, mandibular advancement appliance; SD, standard deviation.

Three NRCTs [34,36,37] did not consist of a control group because it was considered unethical to withhold treatment for children with retrognathic mandible in the growth period. Thus, we conducted a meta-analysis pooling only the treatment data in all studies, except for one abstract [33] without AHI tested. A random-effects model was used due to the high heterogeneity ($I^2 = 98\%$). Reduction of AHI after treatment was 4.23 events/h, (95% CI: 1.07, 7.38), which was stronger than the meta-analysis result of only RCTs (see Fig. 6).

3.6. Subgroup analysis

Considering the high heterogeneity ($I^2 = 98\%$) of the meta-analysis including NRCTs, subgroup analysis was conducted according to the severity of AHI, age, and treatment duration. High heterogeneity of subgroup differences was observed for severity, $I^2 = 98.0\%$ ($p < 0.00001$) (see Fig. 7). The reduction percentage of AHI was about 50% (1.72/3.5) for mild, 57% (4.27/7.5) for moderate, and 76% (10.69/14.08) for severe patients.

No significant subgroup difference existed as for age ($I^2 = 0\%$, $p = 0.59$), which indicated that MAA may be effective in different growth stages before 13 years old (see Fig. 8).

Subgroup difference of treatment duration (3 weeks, 6 months, 10–12 months) was also observed ($I^2 = 65.9\%$, $p = 0.05$) (see Fig. 9), suggesting that long-term treatment (6 months, 10–12 months) may be more effective.

4. Discussion

4.1. Summary of main results

Three systematic reviews [22,25,30] were previously published on the subject of MAA treatment for pediatric OSA but the included studies were scarce and of low quality. Two newly published RCTs [32,35] of high quality were included in our meta-analysis, and the result suggests that MAA reduces AHI for pediatric OSA patients compared to placebo or no treatment. Sensitivity analysis including the quasi-randomized study and NRCTs showed stable favorable results for MAA treatment in pediatric OSA, in spite of the fact that the effect may have been overestimated because of the absence of a control group.

Secondary outcomes including oxygen saturation, sleep quality, and airway space were summarized in a descriptive nature.

The change of oxygen saturation level was different among studies. The lowest oxygen saturation (minSaO_2) showed a significant increase in two studies [32,37] whereas there was no significant difference in another two [26,34]. Oxygen desaturation index (ODI) decreased but showed no significant difference in two RCTs [26,32].

Symptoms related to OSA were evaluated by variable questionnaires: daytime symptoms (sleepiness, irritability, tiredness, oral breathing, nasal stuffiness) and night-time symptoms (habitual snoring, restless sleep) in treated subjects diminished [26], Epworth sleepiness scale (ESS) and pediatric sleep questionnaire (PSQ) scores decreased [32,34]. Quality of life (OSA-18) and behavior (BASC-2 BESS questionnaire) improved [32]. As for sleep architecture, the number of respiratory effort-related arousals reduced, and a reduction in the relative proportions of stage 1 and stages 3–4 as well as an increase in the percentage of stage 2 after treatment were observed, which may be explained by brain maturation [36]. The latest study reported that growth hormone levels assessed by insulin-like growth factor 1 (IGF-1) increased after wearing an MAA but the difference was not significant ($p = 0.172$) [32]. Further investigation is needed to confirm its significance.

Airway volume increased measured by acoustic pharyngometry and magnetic resonance imaging [33,36]. Moreover, cephalometric measurements showed a significant increase in the superior posterior airway space, and middle airway space [37].

Subgroup analysis suggested that MAAs can be effective for mild to severe patients before 13 years of age, if they have growth potential. Long-term treatment (at least six months) would be necessary for obvious and stable mandible growth modification and may be more effective than short-term treatment, which should be interpreted with caution because only one short-term study was included [32].

4.2. Limitations

There were only two RCTs included in the primary meta-analysis and the sample size was small. More well-designed RCTs with large sample sizes are needed.

This meta-analysis was restricted to the most frequently used AHI value, and other important clinical outcomes, such as quality of life, sleep structure, and craniofacial development, were not always available or inconsistent in published studies, and meta-analysis of

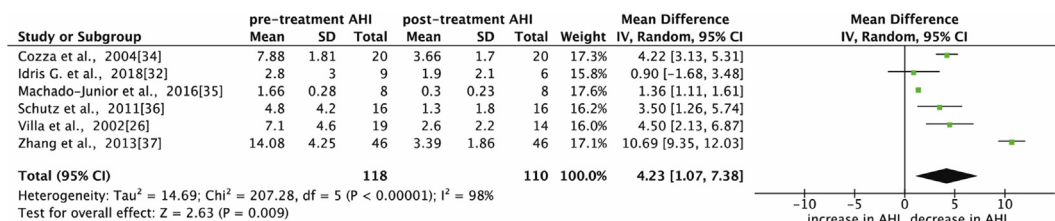


Fig. 6. Comparison of AHI before and after MAA treatment including both RCTs and NRCTs. AHI, apnea-hypopnea index; CI, confidence interval; df, degree of freedom; IV, inverse variance; MAA, mandibular advancement appliance; NRCT, non-randomized controlled trial; RCT, randomized controlled trial; SD, standard deviation.

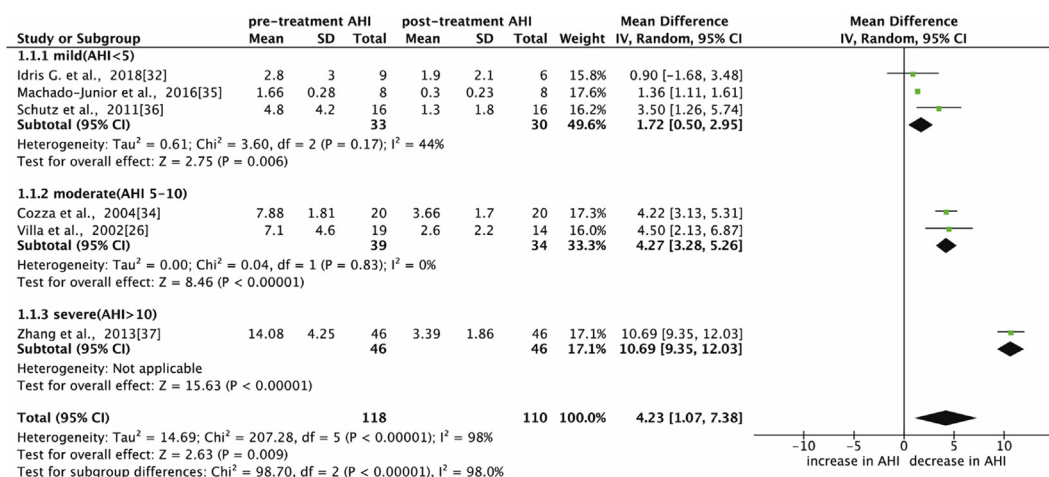


Fig. 7. Subgroup analysis according to severity of AHI. AHI, apnea-hypopnea index; CI, confidence interval; df, degree of freedom; IV, inverse variance; SD, standard deviation.

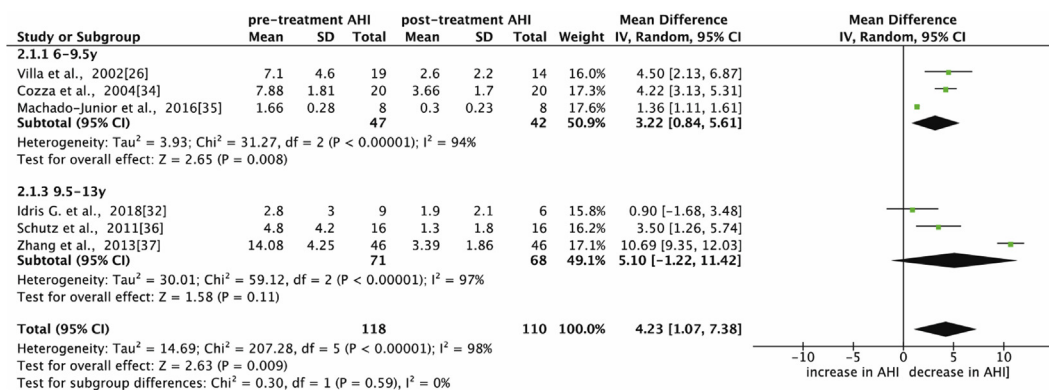


Fig. 8. Subgroup analysis according to age. AHI, apnea-hypopnea index; CI, confidence interval; df, degree of freedom; IV, inverse variance; SD, standard deviation.

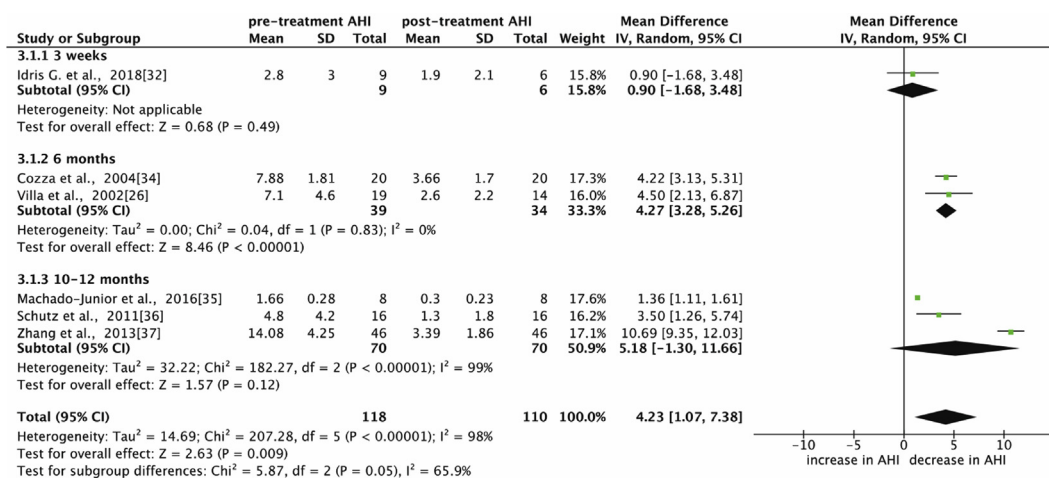


Fig. 9. Subgroup analysis according to treatment duration. AHI, apnea-hypopnea index; CI, confidence interval; df, degree of freedom; IV, inverse variance; SD, standard deviation.

these outcomes has not been possible. The varieties of appliances included in the review were also too divergent to be grouped.

4.3. Implications for practice

For further research, clinicians should pay more attention to treatment details, for instance, the skeletal pattern, the growth stage

(not only chronological age but also skeletal age), puberty burst time, patient compliance and its influences on the MMA therapy. There is no consensus on the wearing time per day and the total duration of MAA treatment. Twenty-four-hour or overnight usage of long-term (6–12 months) protocol and overnight usage of short-term (3 weeks) protocol were reported in the included studies. It was found that longer daily usage could advance the mandible faster

[35], and more wearing time might end up with a more stable and favorable muscle function against airway collapsibility [37]. For OSA children with dental and/or skeletal class II malocclusion, long-term use of MAA would be particularly suitable as it can increase the mandibular length and move the mandible and hyoid bone forward, thus increasing the posterior airway space. On the other hand, for patients with class I dental and skeletal relationship, prolonged wearing time may result in unfavorable dental and facial changes, therefore part-time usage only during sleep and close monitoring by the orthodontist should be recommended.

Different types of MMA appliance should be compared with each other and compared with other therapies or combined application (such as RPE). Moreover, other than AHI, studies on additional outcomes of MMA are also needed, especially growth amount and growth factor levels, cognitive function and emotion control ability.

5. Conclusions

The meta-analysis of two high-quality RCTs showed supportive evidence for MAA treatment in pediatric OSA patients. Subgroup analysis suggested that MAA can be effective for mild to severe patients before the end of the pubertal peak. Long-term treatment (at least 6 months) may be more effective than short-term treatment.

Conflicts of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2018.12.022>.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2018.12.022>.

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