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Review Article

Changes in airway dimensions following functional appliances in growing patients with skeletal class II malocclusion: A systematic review and meta-analysis

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ABSTRACT

Objectives: The purpose of the study was to evaluate the treatment effects of functional appliances (FAs) on upper airway dimensions in growing Class II patients with mandibular retrognathism.
Methods: Five databases and the references of identified articles were electronically searched for relevant studies that met our eligibility criteria. The quality of the included studies was assessed using the Newcastle-Ottawa Scale. The effects of FAs on airway dimensions were combined by meta-analysis using the RevMan and STATA software.
Results: Seven studies (177 treated patients with mean age: 11.48 years and 153 untreated controls with mean age: 11.20 years) were included in this review. Compared to the control group, the oropharyngeal dimensions in the treatment group subjects were significantly increased at the superior pharyngeal space (MD = 1.73 mm/year, 95% CI, 1.13–2.32 mm, $P < 0.00001$), middle pharyngeal space (MD = 1.68 mm/year, 95% CI, 1.13–2.23 mm, $P < 0.00001$) and inferior pharyngeal space (MD = 1.21 mm/year, 95% CI, 0.48–1.95 mm, $P = 0.001$). No significant differences were found in nasopharyngeal and hypopharyngeal dimensions and the position of hyoid bone ($P > 0.05$). Soft palate length and soft palate inclination were improved significantly in the treatment group ($P < 0.05$).
Conclusions: The results showed that FAs can enlarge the upper airway dimensions, specifically in the oropharyngeal region, in growing subjects with skeletal Class II malocclusion. The early intervention for mandibular retrognathism with FAs may help enlarge the airway dimensions and decrease potential risk of obstructive sleep apnea syndrome for growing patients in the future.

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1. Introduction

Class II malocclusion is a type of malocclusion in which the mandible is posterior to the maxilla and the relationship of the first permanent molar is distoclusion. Various factors contribute to Class II malocclusion, but mandibular retrognathism is the most common factors [1,2]. Skeletal Class II malocclusion with mandibular retrognathism have such an effect of varying intensities on facial appearance and masticatory function that it causes a large number of patients to seek orthodontic treatment.

Some studies have reported research on the relationship between airway space and different anteroposterior skeletal patterns and indicated that the sagittal skeletal pattern does have an influence on airway dimensions [3]. Compared to the children with skeletal Class I malocclusions, the children with skeletal Class II malocclusions had smaller airway dimensions and had a higher risk of future respiratory problems, such as snoring and obstructive sleep apnea syndrome (OSAS) [3–6]. OSAS, which is characterized by recurrent episodes of airway obstructions during sleep, is a common sleep-related breathing disorder that affect 3–7% of the population [7]. The sequelae of snoring may be mild, however, OSAS may degrade the health-related quality of life, induce systemic problems such as hypertension, cardiovascular disease and pathoglycemia, or even increase the risk of mortality [7–11].

There are various therapies for OSAS. When the symptoms of OSAS are milder, the treatment focuses on lifestyle modifications, such as weight loss, smoking cessation, limitation of wine, position management and sleep hygiene. For severe cases, Continuous Positive Airway Pressure (CPAP) or Mandibular Advancement Devices (MADs) are usually recommended [12]. The effect of CPAP will be limited by the patient's intolerance. MADs are an effective therapy for adult patients with mild to moderate OSAS, and they can prevent upper airway collapse and increase the airway dimensions [13]. If necessary, maxillomandibular advancement surgery, which is an invasive therapy, is also recommended to increase airway dimensions and improve respiratory function [14], but many patients refuse this option because of the operative risk and postoperative complications.

It is generally known that prevention is still the best medicine, so taking preventative or control measures as soon as possible for potential patients is the best means of treatment. Functional appliances (FAs) is a routine method for growing patients with retrusive mandibles [15–18], and it may help to increase the airway dimensions and decrease the risk of respiratory disorders [19]. Recently, many studies evaluated the effects of different FAs, such as the activator, bionator and twin-block, on the change in upper pharyngeal dimensions in growing skeletal Class II patients [20–26]. The majority of these studies showed a positive effect on the upper airway dimensions [22,23,27–31], but other showed the opposite conclusion [32–34]. In addition, most of the studies were designed without controls [21,23,27,28,32] or without proper controls [29,35,36] due to the ethical issues involved in not providing orthodontic treatment to growing patients with relevant malocclusions. Further, still other reports [37,38] assessed the effect of FAs and the followed-fixed appliances and could not exclude the influence of fixed appliances on airway dimensions.

Thus, the effect of FAs on airway dimensions remained uncertain, and the inconclusive evidence did not support the clinical application and promotion of FAs to prevent the occurrence of snoring and OSAS in growing patients with mandibular retrognathia. Therefore, we conducted this study to evaluate the changes in airway dimensions induced by FAs in growing patients with skeletal Class II malocclusion.

2. Methods

We conducted this review according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.

2.1. Search strategy

Multiple electronic databases were searched for relevant articles, including Medline (via PubMed), Embase, Cochrane Library, web of science, Science Direct (last search updated on Mar 14th, 2017). The main search terms include “functional appliances”, “malocclusion, angle classII” and “airway”. The search strategy was modified appropriately in each database. Additionally, the reference lists of the relevant studies were also scanned. Two authors (Mingli Xiang and Bo Hu) searched and selected the studies. We first excluded irrelevant articles by reviewing the titles and abstracts. Then we selected studies for inclusion among the remaining studies by evaluating the full texts according to the selection criteria. Any disagreements between the authors were resolved by discussion with the third author (Jinlin Song). Final decisions were made after consensus was reached.

2.2. Selection criteria

The PICOS (patient; intervention; comparison; outcome; study design) criteria were used to determine whether a study should be included or excluded.

Participant characteristics: Growing patients with skeletal class II malocclusion due to retrognathic mandible, no airway problems or abnormalities. At least two high-quality cephalograms or CBCTs existing, one at the pre-treatment phase and the other at the post-treatment phase.

Intervention: FAs only.

Comparison: Control group, with Class II malocclusion, matched for age, had pre-functional treatment only or no treatment. The pre-functional treatment included only sectional fixed orthodontic appliance to correct mild crowding and/or rotations.

Outcome: The primary outcomes included variables of the upper airway. Secondary outcomes included skeletal, hyoid bone and soft palate variables.

Study design: Randomized or non-randomized controlled trials, cohort studies.

2.3. Data collection

We extracted the following contents: Author and Publish date, Study design, Setting, Characteristics of patients, Interventions, Number of patients (M/F), Age, Treatment/Observation time and Outcomes, Image examination. Due to the variability of the terms used for identical variables among these included studies, all equivalent terms pertaining to the same variable were grouped and one term was used throughout the review. Similarly, although the measures of some variables differed slightly among the studies, these measures were combined due to the poor sensitivity of the small difference measured. If the same variable was reported in at least two of the included studies, the respective data were extracted and synthetized. In an effort to minimize the heterogeneity caused by prominent differences in the duration of treatment/observation among the included studies, annualized changes for all variables were used for meta-analysis [15]. If these data were not available directly from the articles, we calculated them according to the methods in the Cochrane Handbook for Systematic Reviews of Interventions (version5.1.0). In order to research only the effects of FAs, data concerning the followed-fixed appliances were excluded because fixed appliances may alter the effects caused by FAs.

2.4. Quality assessment

Two authors (Mingli Xiang and Bo Hu) independently assessed the quality of the studies according to the Newcastle-Ottawa Scale recommended by Cochrane handbook [39,40]. The scale uses the "star system", and the total number of stars reflects the level of quality. According to the number of stars, we graded these studies as either low (0–5) or High (6–9). Disagreements were resolved by discussion with the third author (Jinlin Song).

2.5. Statistical analysis

Data were considered suitable for pooling if the retrieved studies met to the selected criteria. The annualized mean differences and standard error were computed using RevMan 5.1 (Cochrane Collaboration, Copenhagen, Denmark). The statistical significance of the hypothesis test was set at $P < 0.05$ (2-tailed z tests). We chose a random-effects model to estimate all pooled data considering the inherent differences across primary studies. Heterogeneity was assessed using the I^2 index. I^2 index ranging from <25 to 50 and to 75% indicated low, moderate, and high heterogeneity, respectively. If high heterogeneity existed, sensitivity analyses were conducted using the 'metaninf' command in Stata 12.0 (StataCorp, College Station, TX) to evaluate the effect of individual studies on the overall mean difference. Funnel plots and the Begg's rank correlation test were conducted to detect publication bias if the number of included studies exceeded 10.

3. Results

The initial number of retrieved studies was 840, 839 of which were derived from electronic databases and 1 from the reference lists of relevant articles. After removing duplicates, 760 studies were remained. A total of 720 articles were excluded on the basis of title and abstract; for the remaining 40 articles, 33 were excluded after evaluating their full texts according to the selection criteria. Finally, 7 studies [41–47] were included in this review, and 6 of those articles [41–46] were included in this meta-analysis. Fig. 1 shows the flow diagram for the selection of the studies.

The characteristics of the included studies are summarized in Table 1. The participants included 330 growing subjects with Class II malocclusion, 177 of them were treated with FAs at a mean age of 11.48 years, and 153 were control individuals with a mean age of 11.20 years. All included studies investigated the change on pharyngeal airway after treatment with FAs, one [46] explored the effect after treatment with FAs and the followed-fixed appliance, and one [41] reported results after the long-term retention phase. For the control group, the majority of the patients were untreated individuals, whereas in the two studies [43,44], the participants were treated with only sectional fixed orthodontic appliance. All

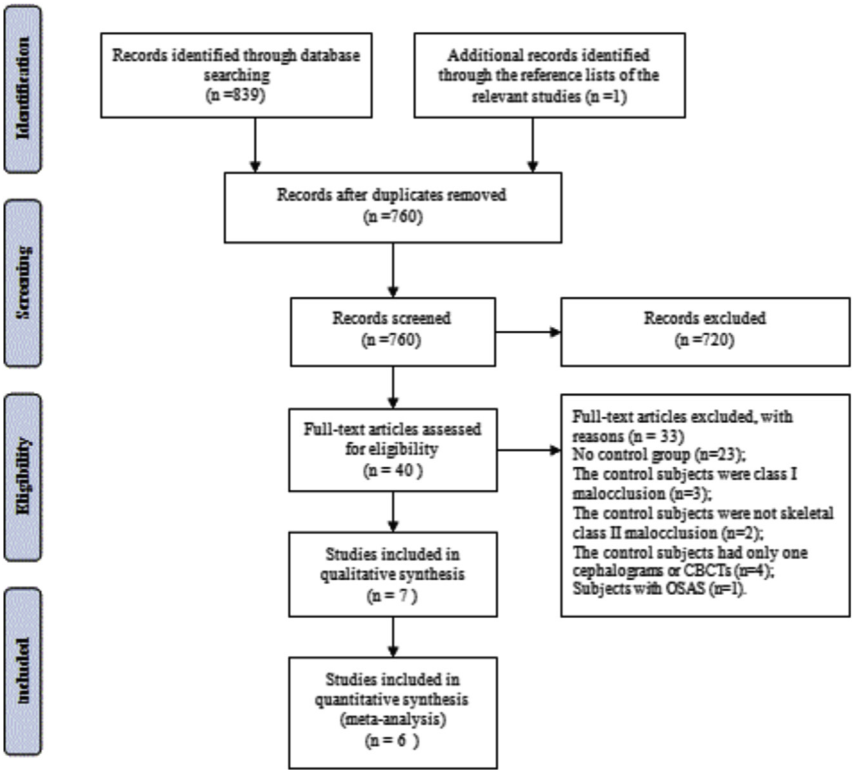


Fig. 1. Flow diagram of the search strategy (PRISMA).

Table 1
Characteristics of included studies in the review.

Study	Study design	Setting	Characteristics of patients	Interventions	No. of patients (M/F)	Age in years (SD)	Treatment/ Observation time	Image examination	Outcome
Bavbek 2015	Retrospective	Turkey	Skeletal and dental Class II malocclusion with mandibular retrusion, overjet >5 mm, Optimal mandibular plane angle (32 ± 6°).	Gt: FFRD Gc: untreated	Gt: 18(10/8) Gc: 19(8/11)	Gt: 13.62(1.92) Gc: 12.74(0.91)	Gt: 8.74 ± 3.46m Gc: 11.89 ± 1.37m	cephalogram	Compared to controls, treatment group showed increased airway dimensions at soft palate ($P < 0.05$) and more forward positioning of the hyoid bone ($P < 0.05$).
Ali 2015	Retrospective	Pakistan	Skeletal Class II malocclusion with mandibular deficiency, Angle's Class II malocclusion, normal vertical growth pattern.	Gt: twin-block Gc: untreated	Gt: 42(21/21) Gc: 32(16/16)	Gt: 10.40(1.27) Gc: 10.10(0.78)	Gt: TB, 8.14 ± 2.9m followed-fixed therapy, 28.3 ± 6.5m Gc: 3y	cephalogram	Superior pharyngeal space ($p < 0.001$) were significantly increased in twin-block groups, and the change in superior pharyngeal space remained stable after fixed mechano-therapy.
Elfeky 2015	Prospective	Egypt	Skeletal Class II malocclusion with mandibular deficiency, Class II molar and/or canine relationship, vertical growth pattern.	Gt: twin-block Gc: untreated	Gt: 18 F Gc: 18 F	Gt: 11.27(2.19) Gc: 11.89(1.85)	Gt: 8m Gc: 8m	CBCT	The mean change of oropharynx and nasopharynx in twin-block group was significantly higher than those in the control group
Ulusoy 2014	Retrospective	Turkey	Skeletal Class II malocclusion with mandibular retrusion, dental Class II malocclusion, overjet >5 mm, Optimal mandibular plane angle.	Gt: activator Gc: untreated	Gt: 16(8/8) Gc: 19(8/11)	Gt: 11.36(0.77) Gc: 12.14(0.65)	Gt: activator,11 ± 3.4m; retention time, 29.75 ± 5.17m, Gc: 11.37 ± 1.2m	cephalogram	The mean change of airway and skeletal parameters between control and treatment groups were no significant difference.
Ghodke 2014	Prospective	India	Skeletal class II malocclusion with normal maxilla and retrognathic mandible, Angle's class II molar relationship, FMA (20°–28°), minimal or no crowding or spacing in either arch, overjet (6–10 mm).	Gt: twin-block Gc: pre-functional therapy	Gt: 20(11/9) Gc: 18(9/9)	Gt: 10.90 (1.48) Gc: 10.94 (1.86)	Gt: 244.63 ± 35.58d Gc: 222.80 ± 32.91d	cephalogram	The oropharyngeal dimension was increased significantly in the treatment group subjects as compared to the control group subjects ($P < 0.05$).
Jena 2013	Prospective	India	skeletal class II malocclusion with normal maxilla and retrognathic mandible, Angle Class II molar relationship, FMA 20°–25°, overjet 6–10 mm, minimal or no crowding or spacing in either arch.	Gt1: twin-block Gt2: MPA-IV Gc: pre-functional therapy	Gt1: 21(11/10) Gt2: 16(9/7) Gc:16(9/7)	Gt1: 11.38(2.47) Gt2: 12.81 (0.85) Gc: 10.56(0.91)	Gt1: 9.38 ± 1.68m Gt2: 6.18 ± 1.20m Gc:9.86 ± 1.79m	cephalogram	The mean changes of soft palate morphology and oropharynx depth in twin-block groups were significantly higher than those of the control group.
Ozbek 1998	Retrospective	Turkey	Skeletal class II malocclusion with retrognathic mandible, Angle's class II molar relationship, overjet >5 mm.	Gt: activator with/without occipital high-pull headgear Gc: untreated	Gt: 26(11/15) Gc: 15(7/8)	Gt: 11.63(0.24) Gc: 11.29(0.25)	Gt: 1.45 ± 0.10y Gc: 1.92 ± 0.05y	cephalogram	Compared to the controls, the oropharyngeal airway dimensions increased significantly in treated patients.

Gt, treatment group; Gc, control group; m, month; y, year; F, female; M, male; FMA, Frankfort mandibular plane angle; pre-functional therapy, sectional fixed appliances for the correction of mild crowding and/or rotations; CBCT, cone beam computed technology; FFRD, forsus fatigue resistant device.

included studies provided data on upper airway, six showed skeletal changes, two additional reported cephalometric outcomes on hyoid bone position, another two offered cephalometric outcomes on soft palate morphology and only one study investigated dentoalveolar changes. The treatment with FAs in five studies [41–43,45,47] was not ended until an Angle Class I molar relationship and normal overjet were achieved, but no clear endpoint was stated in the other two studies [44,46]. The quality assessment using Newcastle-Ottawa scale is shown in Table 2. The scores of all included studies were ranged from 8 to 9, indicating a high quality.

Six of the included studies were included in this meta-analysis, and one study [47] can't be synthesized due to the different ways of measuring and parameters. Meta-analyses could be performed regarding the short-term effectiveness of FAs (i.e. from the time point of FAs placement to immediately after their removal) compared to control subjects for 20 cephalometric variables, which were summarized and listed in Table 3.

With regard to the changes of orophayngeal dimensions, there were four cephalometric variables to be pooled (Fig. 2). According to our results, the oropharyngeal dimensions were the most evidently effected by FAs compared to the nasopharyngx and hypopharyngx, and significant improvements were found at SPS (MD = 1.73 mm/year, 95% CI, 1.13–2.32 mm, $P < 0.00001$), MPS (MD = 1.68 mm/year, 95% CI, 1.13–2.23 mm, $P < 0.00001$) and IPS (MD = 1.21 mm/year, 95% CI, 0.48–1.95 mm, $P = 0.001$) with acceptable heterogeneity. Three studies [41,42,45] assessed the effect of FAs on oropharyngeal area, and one study [42] could not be pooled due to the difference in measuring methods. Although the three studies each indicated that the FAs could increase the oropharyngeal area, we found no significant differences (MD = 838.49 mm/year, 95% CI, -106.97–1783.94 mm, $P = 0.08$). Five studies examined the nasopharyngeal changes, and the five cephalometric variables could be pooled (Fig. 3). No significantly difference were found except in S-PNS, which was slightly decreased an average of 0.89°/year (95% CI,−1.48 to −0.31 mm, $P = 0.0003$) compared to the control group. As for the changes in hypopharyngeal dimensions [43,44], there were no statistically significant changes (Fig. 4, MD = 0.83 mm/year, 95% CI,−0.19 to

Table 2
Quality assessment of nonrandomized studies.

Quality evaluation	study						
	Bavbek 2015	Ali 2015	Elfeky 2015	Ulusoy 2014	Ghodke 2014	Jena 2013	Ozbek 1998
Representativeness of the treatment groups	*	*	*	*	*	*	*
Selection of the control group	*	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study			*		*	*	
Comparability of participants in treatment groups and control groups	**	**	**	**	**	**	**
Assessment of outcome with independent blinding	*	*	*	*	*	*	*
Adequacy of follow-up	*	*	*	*	*	*	*
Lost to follow-up acceptable (<10% and reported>)	*	*		*	*	*	*
Total quality (score)	High (8)	High (8)	High (8)	High (8)	High (9)	High (9)	High (8)

This table shows the quality assessment of each study. Each item received 1 star (*), except for comparability, which can receive 2 stars. The total number of stars represents the score, which demonstrates the quality of the study. The quality of each study was graded as either low (0–5) or High (6–9).

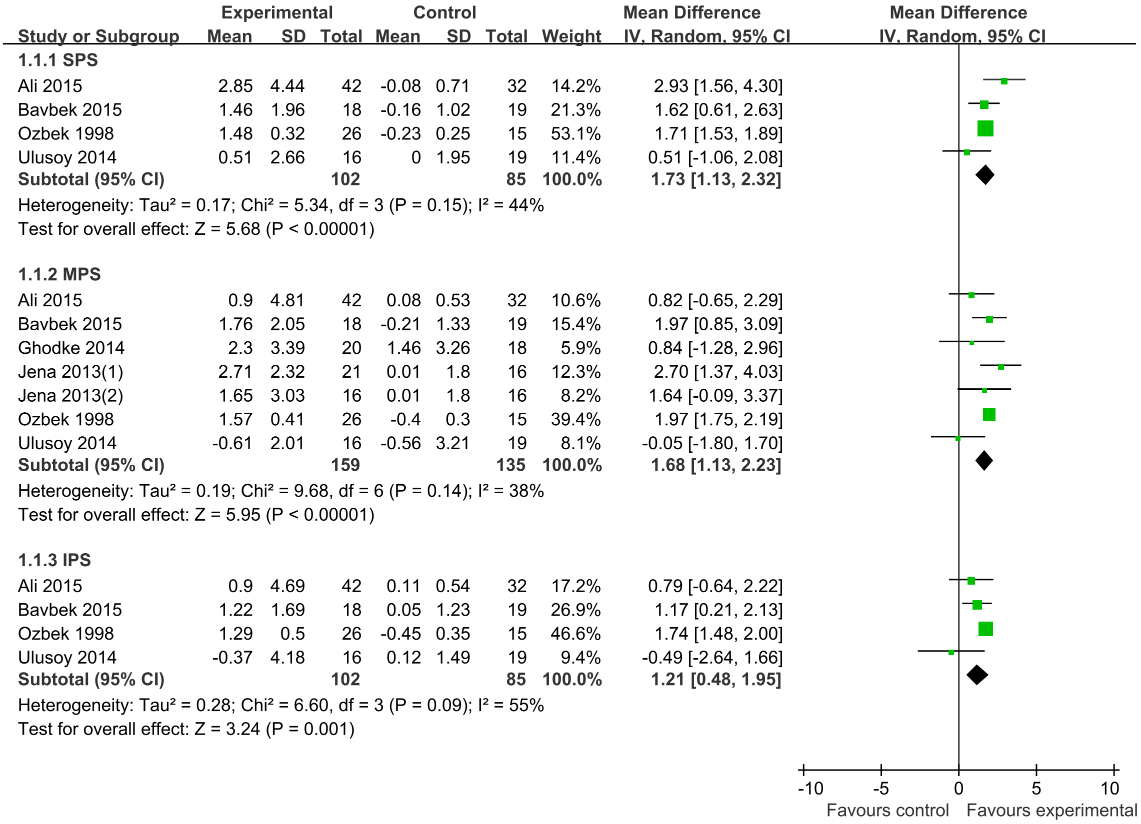
Table 3
Summary of variables.

Variable	Measurement
airway	
nasopharynx	
nasopharyngeal height	S-PNS
height of nasopharynx (HNP)	shortest distance from PNS to Ba-N plane.
upper airway thickness (UAT)	the distance from PNS to the adenoid tissue along the line from PNS to the mid-point of the line intersecting Ba to S
lower airway thickness (LAT)	the distance from PNS to the adenoid tissue along the line from PNS to the pharyngeal wall along the line from Ba to PNS;
depth of nasopharynx (DNP)	Ptm–UPW
oropharynx	
superior pharyngeal space (SPS)	the distance of the SP to the posterior pharyngeal wall along the parallel line to FH plane or the smallest distance between the posterior border of the soft palate and the PPW.
middle pharyngeal space (MPS)	the distance of the T to the posterior pharyngeal wall along the parallel line to FH plane, the distance of the T to the MPW, or the smallest distance between the posterior border of the tongue and the PPW through the T.
inferior pharyngeal space (IPS)	the distance of the intersection points on anterior and posterior pharyngeal wall through Cv2ai or U along the parallel line to FH plane or the smallest distance between the posterior border of the tongue and the PPW.
oropharyngeal area	The area between palatal line and the base of the epiglottis.
hypopharynx	
depth of hypopharynx (DHP)	V-LPW.
skeletal	
maxillary sagittal position	SNA, the angle between ‘S’, ‘N’ and ‘A’
mandibular sagittal position	SNB, the angle between ‘S’, ‘N’ and ‘B’
maxillary length	CoA, the distance of Co to A.
mandibular length	CoGn, the distance of Co to Gn.
mandibular plane angle	FMA, angle between FH plane and mandibular plane; or SN-CoGn, angle between SN and CoGn.
hyoid bone	
H-SN	the perpendicular distance from hyoid bone to SN plane.
C3-H	the distance from the anterio-inferior point of the third cervical vertebra to hyoid bone.
soft palate	
Length of soft palate (SPL)	the distance of T to PNS.
Thickness of soft palate (SPT)	the maximum thickness of the soft palate.
Inclination of soft palate (SPI)	the angle between Ptm perpendicular and the soft palate (PNS-T).

A, The deepest point between anterior nasal spine and prosthion; B, The deepest point between infradentale and pogonion; S, sella; N, nasion; Po, porion; Or, orbitale; Go, gonion; Po, pogonion; Gn, gnathion; Me, menton; ANS, anterior nasal spine; PNS, posterior nasal spine; Ptm, pterygomaxillary fissure; Ba, basion; Co, condylion; PNS, Posterior nasal spin; T, Tip of soft palate; SP, Mid-point of soft palate; U, Point of intersection of posterior border of tongue and lower border of mandible; V, vallecula; SN plane, the line joining ‘S’ and ‘N’; FH plane, the line joining Po and Or; Cv2ai, C2 vertebra; C3, C3 vertebra; UPW (upper pharyngeal wall), the intersection of line Ptm-Ba and posterior pharyngeal wall; MPW (middle pharyngeal wall), the intersection of perpendicular line on Ptm perpendicular from ‘T’ with posterior pharyngeal wall; LPW (lower pharyngeal wall), the intersection of perpendicular line on Ptm perpendicular from ‘V’ with posterior pharyngeal wall.

1.86 mm, $P = 0.11$).

With regard to the skeletal changes, we found that FAs can force mandibular advancement with an annual increase in SNB angles by 1.79°/year (Fig. 5, 95% CI, 0.89–2.69 mm, $P < 0.0001$). The effective length of the mandible was not significantly different between the treatment group and the control group because only two studies were included. Therefore, our meta-analysis was not able to establish that FAs can increase in mandibular length but concluded that FAs can reposition the mandible forward. In addition, we also found no significant change in the maxilla (SNA, $MD = -0.34$ mm/year, 95% CI,−0.86 to 0.18 mm, $P = 0.2$; CoA, $MD = -0.58$ mm/year, 95% CI,−3.21 to 2.05 mm, $P = 0.67$). For the effect of FAs on the mandibular plane angle, significant change was found on SN-GoGn ($MD = 1.19$ mm/year, 95% CI, 0.50–1.89 mm, $P = 0.0007$) but FMA



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 SPS								
Ali 2015	2.85	4.44	42	-0.08	0.71	32	14.2%	2.93 [1.56, 4.30]
Bavbek 2015	1.46	1.96	18	-0.16	1.02	19	21.3%	1.62 [0.61, 2.63]
Ozbek 1998	1.48	0.32	26	-0.23	0.25	15	53.1%	1.71 [1.53, 1.89]
Ulusoy 2014	0.51	2.66	16	0	1.95	19	11.4%	0.51 [-1.06, 2.08]
Subtotal (95% CI)			**102**			**85**	**100.0%**	**1.73 [1.13, 2.32]**
Heterogeneity: Tau² = 0.17; Chi² = 5.34, df = 3 (P = 0.15); I² = 44%								
Test for overall effect: Z = 5.68 (P < 0.00001)								
1.1.2 MPS								
Ali 2015	0.9	4.81	42	0.08	0.53	32	10.6%	0.82 [-0.65, 2.29]
Bavbek 2015	1.76	2.05	18	-0.21	1.33	19	15.4%	1.97 [0.85, 3.09]
Ghodke 2014	2.3	3.39	20	1.46	3.26	18	5.9%	0.84 [-1.28, 2.96]
Jena 2013(1)	2.71	2.32	21	0.01	1.8	16	12.3%	2.70 [1.37, 4.03]
Jena 2013(2)	1.65	3.03	16	0.01	1.8	16	8.2%	1.64 [-0.09, 3.37]
Ozbek 1998	1.57	0.41	26	-0.4	0.3	15	39.4%	1.97 [1.75, 2.19]
Ulusoy 2014	-0.61	2.01	16	-0.56	3.21	19	8.1%	-0.05 [-1.80, 1.70]
Subtotal (95% CI)			**159**			**135**	**100.0%**	**1.68 [1.13, 2.23]**
Heterogeneity: Tau² = 0.19; Chi² = 9.68, df = 6 (P = 0.14); I² = 38%								
Test for overall effect: Z = 5.95 (P < 0.00001)								
1.1.3 IPS								
Ali 2015	0.9	4.69	42	0.11	0.54	32	17.2%	0.79 [-0.64, 2.22]
Bavbek 2015	1.22	1.69	18	0.05	1.23	19	26.9%	1.17 [0.21, 2.13]
Ozbek 1998	1.29	0.5	26	-0.45	0.35	15	46.6%	1.74 [1.48, 2.00]
Ulusoy 2014	-0.37	4.18	16	0.12	1.49	19	9.4%	-0.49 [-2.64, 1.66]
Subtotal (95% CI)			**102**			**85**	**100.0%**	**1.21 [0.48, 1.95]**
Heterogeneity: Tau² = 0.28; Chi² = 6.60, df = 3 (P = 0.09); I² = 55%								
Test for overall effect: Z = 3.24 (P = 0.001)								

Fig. 2. Forest plot representing quantitative data synthesis relative to the effect of FAs on the oropharyngeal dimensions.

(MD = 0.62 mm/year, 95% CI,-1.66 to 2.90 mm, P = 0.59), and the inconsistency may due to the limited number of primary studies. There was no statistically significant effect in the vertical and sagittal direction of hyoid bone (Fig. 6, H-SN, MD = −1.44 mm/year, 95% CI,-2.95 to 0.08 mm, P = 0.06; C3-H, MD = 0.92 mm/year, 95% CI, 0.3–2.14 mm, P = 0.14). Finally, for the soft palate morphology, SPL and SPI were significantly decreased with little heterogeneity (SPL, MD = −2.01 mm/year, 95% CI,-2.93 to −1.09 mm, P < 0.0001; SPI, MD = −5.08 mm/year, 95% CI,-7.49 to −2.67 mm,P < 0.0001), and the change of SPT was unapparent compared to the control group (MD = 0.36 mm/year, 95% CI,-0.55–1.26 mm,P = 0.44) (Fig. 7).

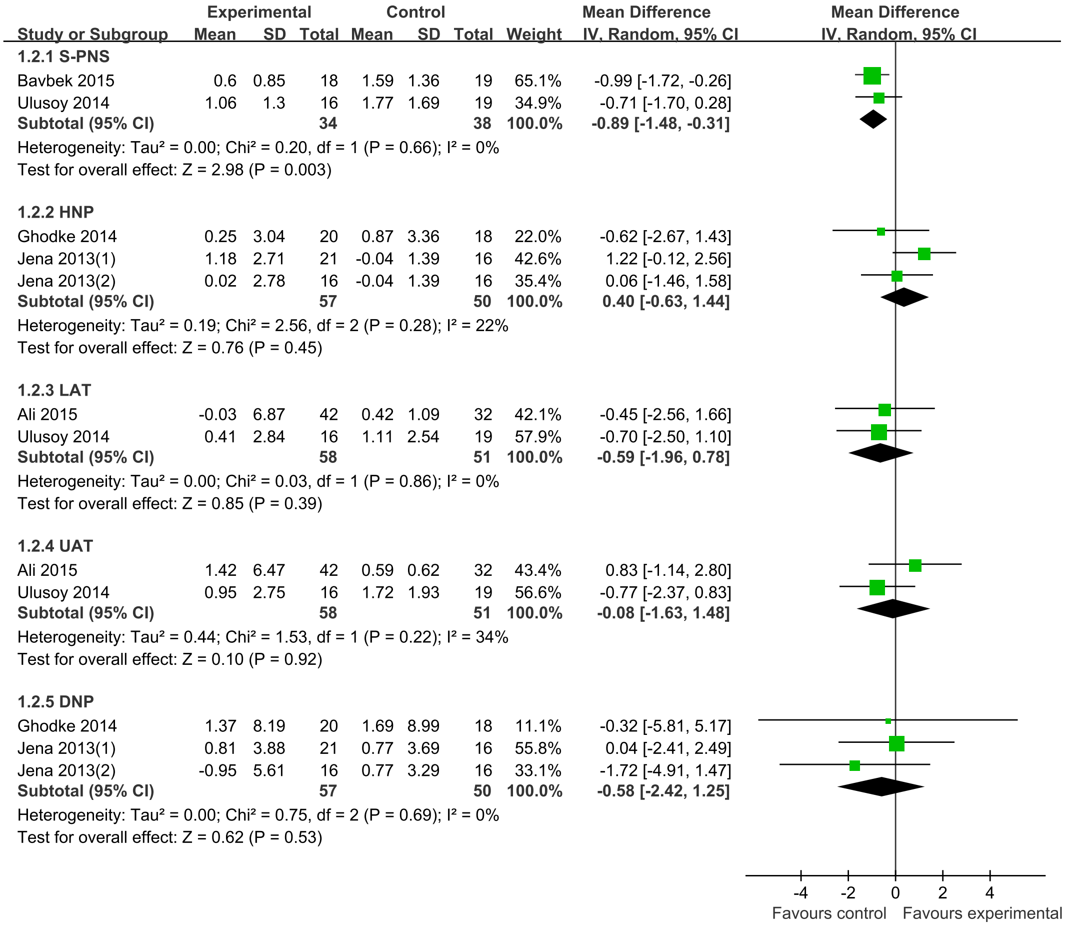
According to our results, the heterogeneity of the primary outcomes was acceptable. We did not conduct a sensitivity analysis to evaluate the impact of the individual studies on the overall MDs and 95% CIs. We also did not conduct a publication bias analysis because there are only six studies were synthesized.

4. Discussion

Recently, the pharyngeal airway has always been an interesting area for orthodontists not only because of the relationship between the respiratory function and the craniofacial growth and development but also due to the effect of orthodontic treatment on narrow airway dimensions. Numerous studies indicate that FAs can be a promising treatment method for growing skeletal Class II patients to improve airway dimensions [21,23,27,35,36,38,48]. Nonetheless, the effect of FAs on airway dimensions remains controversial. Therefore, we performed the meta-analysis based on primary studies to determine the effect of FAs on upper airway dimensions in growing patients with skeletal Class II malocclusion.

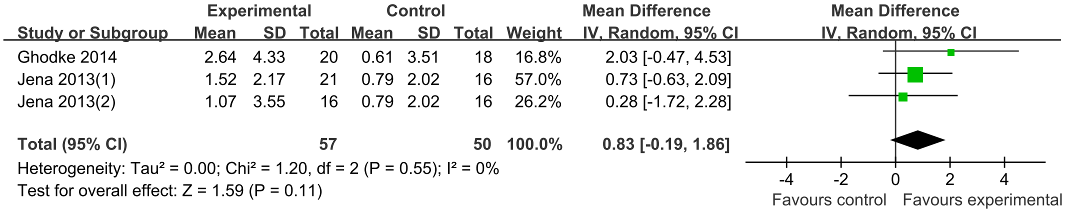
The present study demonstrated that FAs could increase the airway dimensions, specifically in the oropharyngeal region, which in line with many previous trials [23,29,30,35–38]. FAs effectively correct skeletal Class II malocclusion may depend on skeletal and/or dentoalveolar changes. The previous literature suggested that FAs could stimulate mandibular growth with a more anterior repositioning of the mandible [16,49,50]. However, recently systematic reviews reported that the skeletal changes were minimal and that dentoalveolar changes mainly contribute to the correction of skeletal class II malocclusion [15,17,51]. Although no significant change was found in the mandible length, a significant increase was observed in SNB, which has a positive effect on the oropharyngeal space. In addition, we found an obvious forward repositioning of the hyoid bone after treated with FAs but no significant difference as compared to control data. The hyoid bone showed a consistent forward movement with the anterior displacement of the mandible due to the direct soft tissue connections between them, and growth development plays a more prominent role than functional treatment. Similarly, we found that the SPL and SPI were significantly reduced, which contribute to the enlargement of upper airway. We did not research the dentoalveolar changes due to lack of data. The dentoalveolar effects, like the mesial movement of the lower dentition and the labial flaring of the lower incisors, could cause anterior traction on the tongue and hyoid bone, thereby causing the adaptive changes of the soft palate and leading to an increase in pharyngeal airway dimensions [45,52].

Six included studies [41–46] were measured using lateral cephalometrics, which is a routine method in orthodontic practice and provides only two-dimensional radiographs [53,54]. The pharyngeal airway area on lateral cephalograms is strongly correlated with its true volumetric size from cone beam computed technology (CBCT) [55], and the measurements acquired from both are reliable and reproducible [56,57]. However, CBCT would be



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 S-PNS								
Bavbek 2015	0.6	0.85	18	1.59	1.36	19	65.1%	-0.99 [-1.72, -0.26]
Ulusoy 2014	1.06	1.3	16	1.77	1.69	19	34.9%	-0.71 [-1.70, 0.28]
Subtotal (95% CI)			**34**			**38**	**100.0%**	**-0.89 [-1.48, -0.31]**
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%								
Test for overall effect: Z = 2.98 (P = 0.003)								
1.2.2 HNP								
Ghodke 2014	0.25	3.04	20	0.87	3.36	18	22.0%	-0.62 [-2.67, 1.43]
Jena 2013(1)	1.18	2.71	21	-0.04	1.39	16	42.6%	1.22 [-0.12, 2.56]
Jena 2013(2)	0.02	2.78	16	-0.04	1.39	16	35.4%	0.06 [-1.46, 1.58]
Subtotal (95% CI)			**57**			**50**	**100.0%**	**0.40 [-0.63, 1.44]**
Heterogeneity: Tau² = 0.19; Chi² = 2.56, df = 2 (P = 0.28); I² = 22%								
Test for overall effect: Z = 0.76 (P = 0.45)								
1.2.3 LAT								
Ali 2015	-0.03	6.87	42	0.42	1.09	32	42.1%	-0.45 [-2.56, 1.66]
Ulusoy 2014	0.41	2.84	16	1.11	2.54	19	57.9%	-0.70 [-2.50, 1.10]
Subtotal (95% CI)			**58**			**51**	**100.0%**	**-0.59 [-1.96, 0.78]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 0.85 (P = 0.39)								
1.2.4 UAT								
Ali 2015	1.42	6.47	42	0.59	0.62	32	43.4%	0.83 [-1.14, 2.80]
Ulusoy 2014	0.95	2.75	16	1.72	1.93	19	56.6%	-0.77 [-2.37, 0.83]
Subtotal (95% CI)			**58**			**51**	**100.0%**	**-0.08 [-1.63, 1.48]**
Heterogeneity: Tau² = 0.44; Chi² = 1.53, df = 1 (P = 0.22); I² = 34%								
Test for overall effect: Z = 0.10 (P = 0.92)								
1.2.5 DNP								
Ghodke 2014	1.37	8.19	20	1.69	8.99	18	11.1%	-0.32 [-5.81, 5.17]
Jena 2013(1)	0.81	3.88	21	0.77	3.69	16	55.8%	0.04 [-2.41, 2.49]
Jena 2013(2)	-0.95	5.61	16	0.77	3.29	16	33.1%	-1.72 [-4.91, 1.47]
Subtotal (95% CI)			**57**			**50**	**100.0%**	**-0.58 [-2.42, 1.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 2 (P = 0.69); I² = 0%								
Test for overall effect: Z = 0.62 (P = 0.53)								

Fig. 3. Forest plot representing quantitative data synthesis relative to the effect of FAs on the nasopharyngeal dimensions.

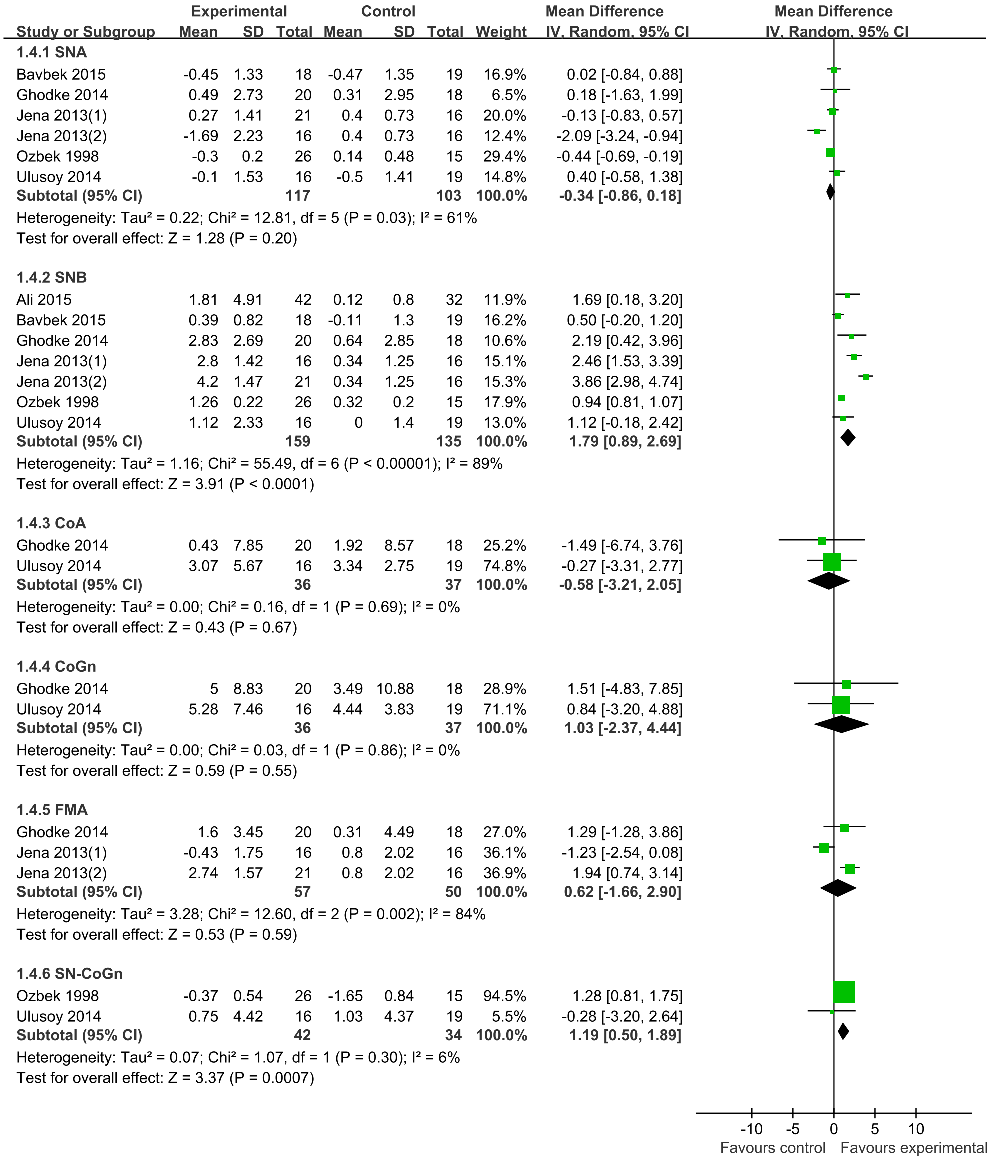


Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ghodke 2014	2.64	4.33	20	0.61	3.51	18	16.8%	2.03 [-0.47, 4.53]
Jena 2013(1)	1.52	2.17	21	0.79	2.02	16	57.0%	0.73 [-0.63, 2.09]
Jena 2013(2)	1.07	3.55	16	0.79	2.02	16	26.2%	0.28 [-1.72, 2.28]
Total (95% CI)			**57**			**50**	**100.0%**	**0.83 [-0.19, 1.86]**
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%								
Test for overall effect: Z = 1.59 (P = 0.11)								

Fig. 4. Forest plot representing quantitative data synthesis relative to the effect of FAs on the hypopharyngeal dimensions.

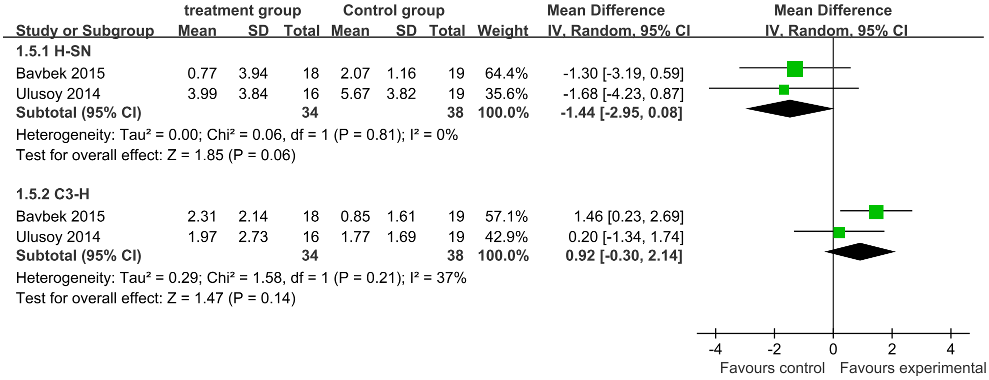
superior because it reveals the 3-dimensional imaging of all craniofacial structures with a greater spatial resolution [58,59]. Recently, many studies [21,23,28,30,35,37,47] have used CBCT to assess the change in the upper airway, and they all indicated a significant enlargement in oropharyngeal airway volume and/or dimensions after treatment with FAs. Elfeky et al. [47] evaluated the effect on pharyngeal airway using CBCT and concluded that the mean change of oropharynx and nasopharynx in twin-block group was significantly higher than those in the control group. An early study conducted by our team also assessed the upper airway changes after treatment with Twin-block, and significant differences were found in the volumetric increase in the oropharynx and hypopharynx compared to control data [30]. In addition, the followed research indicated that pharyngeal airflow characteristics were improved with mandibular advancement and upper airway volume enlargement [22]. FAs could increase oropharyngeal airway dimensions with the improvement of the skeletal, hyoid bone and soft palate [23] and improved the symptoms, such as mouth breathing and persistent snoring, for skeletal Class II patients with OSAS [23,48]. Additionally, some authors researched the long term effect of FAs combined with the followed-fixed appliances on growing Class II subjects, and they indicated that the enlargement of the upper dimensions was stable and maintained [29,38,41].

On the other hand, the results of our meta-analysis demonstrated that FAs cause little improvement of the nasopharynx and hypopharynx. Hypopharyngeal dimensions are affected by the mandible and surrounding structures. If the skeletal or dentoalveolar changes are not sufficiently large, the change in pharyngeal dimensions will be small. If the subjects in treatment group have poor growth potential, the enlargement in the airway dimensions will also be small. The design of FAs determines the effect on maxillary growth, which may affect the nasopharyngeal dimensions. Some studies noted that FAs restrained the maxillary growth [16,60]. However, other studies did not find significant



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 SNA								
Bavbek 2015	-0.45	1.33	18	-0.47	1.35	19	16.9%	0.02 [-0.84, 0.88]
Ghodke 2014	0.49	2.73	20	0.31	2.95	18	6.5%	0.18 [-1.63, 1.99]
Jena 2013(1)	0.27	1.41	21	0.4	0.73	16	20.0%	-0.13 [-0.83, 0.57]
Jena 2013(2)	-1.69	2.23	16	0.4	0.73	16	12.4%	-2.09 [-3.24, -0.94]
Ozbek 1998	-0.3	0.2	26	0.14	0.48	15	29.4%	-0.44 [-0.69, -0.19]
Ulusoy 2014	-0.1	1.53	16	-0.5	1.41	19	14.8%	0.40 [-0.58, 1.38]
Subtotal (95% CI)			**117**			**103**	**100.0%**	**-0.34 [-0.86, 0.18]**
Heterogeneity: Tau² = 0.22; Chi² = 12.81, df = 5 (P = 0.03); I² = 61%								
Test for overall effect: Z = 1.28 (P = 0.20)								
1.4.2 SNB								
Ali 2015	1.81	4.91	42	0.12	0.8	32	11.9%	1.69 [0.18, 3.20]
Bavbek 2015	0.39	0.82	18	-0.11	1.3	19	16.2%	0.50 [-0.20, 1.20]
Ghodke 2014	2.83	2.69	20	0.64	2.85	18	10.6%	2.19 [0.42, 3.96]
Jena 2013(1)	2.8	1.42	16	0.34	1.25	16	15.1%	2.46 [1.53, 3.39]
Jena 2013(2)	4.2	1.47	21	0.34	1.25	16	15.3%	3.86 [2.98, 4.74]
Ozbek 1998	1.26	0.22	26	0.32	0.2	15	17.9%	0.94 [0.81, 1.07]
Ulusoy 2014	1.12	2.33	16	0	1.4	19	13.0%	1.12 [-0.18, 2.42]
Subtotal (95% CI)			**159**			**135**	**100.0%**	**1.79 [0.89, 2.69]**
Heterogeneity: Tau² = 1.16; Chi² = 55.49, df = 6 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 3.91 (P < 0.0001)								
1.4.3 CoA								
Ghodke 2014	0.43	7.85	20	1.92	8.57	18	25.2%	-1.49 [-6.74, 3.76]
Ulusoy 2014	3.07	5.67	16	3.34	2.75	19	74.8%	-0.27 [-3.31, 2.77]
Subtotal (95% CI)			**36**			**37**	**100.0%**	**-0.58 [-3.21, 2.05]**
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%								
Test for overall effect: Z = 0.43 (P = 0.67)								
1.4.4 CoGn								
Ghodke 2014	5	8.83	20	3.49	10.88	18	28.9%	1.51 [-4.83, 7.85]
Ulusoy 2014	5.28	7.46	16	4.44	3.83	19	71.1%	0.84 [-3.20, 4.88]
Subtotal (95% CI)			**36**			**37**	**100.0%**	**1.03 [-2.37, 4.44]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 0.59 (P = 0.55)								
1.4.5 FMA								
Ghodke 2014	1.6	3.45	20	0.31	4.49	18	27.0%	1.29 [-1.28, 3.86]
Jena 2013(1)	-0.43	1.75	16	0.8	2.02	16	36.1%	-1.23 [-2.54, 0.08]
Jena 2013(2)	2.74	1.57	21	0.8	2.02	16	36.9%	1.94 [0.74, 3.14]
Subtotal (95% CI)			**57**			**50**	**100.0%**	**0.62 [-1.66, 2.90]**
Heterogeneity: Tau² = 3.28; Chi² = 12.60, df = 2 (P = 0.002); I² = 84%								
Test for overall effect: Z = 0.53 (P = 0.59)								
1.4.6 SN-CoGn								
Ozbek 1998	-0.37	0.54	26	-1.65	0.84	15	94.5%	1.28 [0.81, 1.75]
Ulusoy 2014	0.75	4.42	16	1.03	4.37	19	5.5%	-0.28 [-3.20, 2.64]
Subtotal (95% CI)			**42**			**34**	**100.0%**	**1.19 [0.50, 1.89]**
Heterogeneity: Tau² = 0.07; Chi² = 1.07, df = 1 (P = 0.30); I² = 6%								
Test for overall effect: Z = 3.37 (P = 0.0007)								

Fig. 5. Forest plot representing quantitative data synthesis relative to the effect of FAs on the skeletal change.

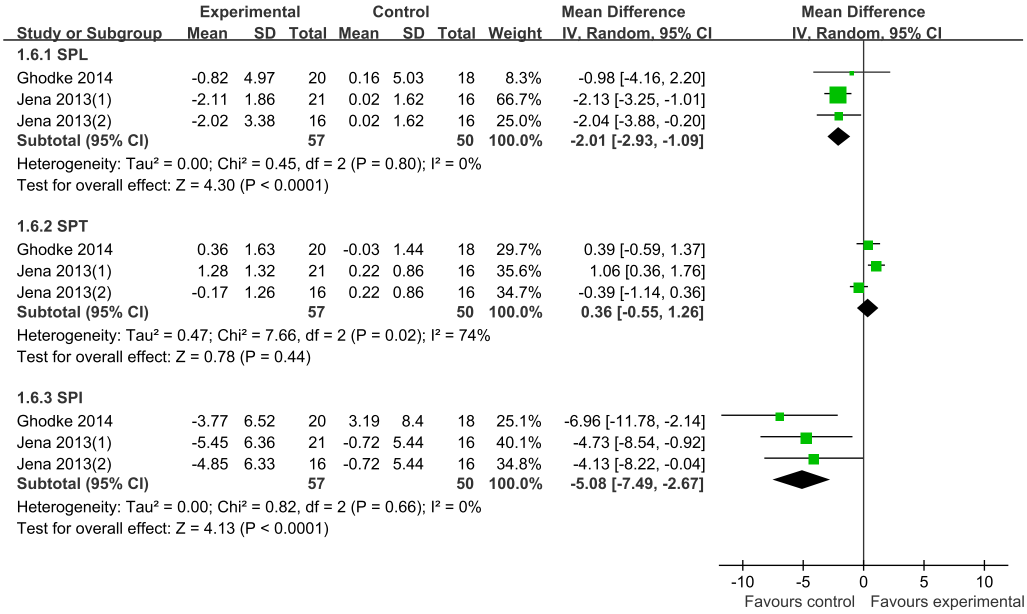


Study or Subgroup	treatment group Mean	treatment group SD	treatment group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 H-SN								
Bavbek 2015	0.77	3.94	18	2.07	1.16	19	64.4%	-1.30 [-3.19, 0.59]
Ulusoy 2014	3.99	3.84	16	5.67	3.82	19	35.6%	-1.68 [-4.23, 0.87]
Subtotal (95% CI)			**34**			**38**	**100.0%**	**-1.44 [-2.95, 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%								
Test for overall effect: Z = 1.85 (P = 0.06)								
1.5.2 C3-H								
Bavbek 2015	2.31	2.14	18	0.85	1.61	19	57.1%	1.46 [0.23, 2.69]
Ulusoy 2014	1.97	2.73	16	1.77	1.69	19	42.9%	0.20 [-1.34, 1.74]
Subtotal (95% CI)			**34**			**38**	**100.0%**	**0.92 [-0.30, 2.14]**
Heterogeneity: Tau² = 0.29; Chi² = 1.58, df = 1 (P = 0.21); I² = 37%								
Test for overall effect: Z = 1.47 (P = 0.14)								

Fig. 6. Forest plot representing quantitative data synthesis relative to the effect of FAs on the position of hyoid bone.

restraint in maxillary growth [49,61], which is consistent with our results. Additionally, some studies suggested that the nasopharyngeal dimensions are more correlated with the size of adenoids than with the effect of FAs [29,46].

Many factors may affect the results of FAs. First, growth potential has a great influence on the effect of FAs [60], and the patient's



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 SPL								
Ghodke 2014	-0.82	4.97	20	0.16	5.03	18	8.3%	-0.98 [-4.16, 2.20]
Jena 2013(1)	-2.11	1.86	21	0.02	1.62	16	66.7%	-2.13 [-3.25, -1.01]
Jena 2013(2)	-2.02	3.38	16	0.02	1.62	16	25.0%	-2.04 [-3.88, -0.20]
Subtotal (95% CI)			**57**			**50**	**100.0%**	**-2.01 [-2.93, -1.09]**
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%								
Test for overall effect: Z = 4.30 (P < 0.0001)								
1.6.2 SPT								
Ghodke 2014	0.36	1.63	20	-0.03	1.44	18	29.7%	0.39 [-0.59, 1.37]
Jena 2013(1)	1.28	1.32	21	0.22	0.86	16	35.6%	1.06 [0.36, 1.76]
Jena 2013(2)	-0.17	1.26	16	0.22	0.86	16	34.7%	-0.39 [-1.14, 0.36]
Subtotal (95% CI)			**57**			**50**	**100.0%**	**0.36 [-0.55, 1.26]**
Heterogeneity: Tau² = 0.47; Chi² = 7.66, df = 2 (P = 0.02); I² = 74%								
Test for overall effect: Z = 0.78 (P = 0.44)								
1.6.3 SPI								
Ghodke 2014	-3.77	6.52	20	3.19	8.4	18	25.1%	-6.96 [-11.78, -2.14]
Jena 2013(1)	-5.45	6.36	21	-0.72	5.44	16	40.1%	-4.73 [-8.54, -0.92]
Jena 2013(2)	-4.85	6.33	16	-0.72	5.44	16	34.8%	-4.13 [-8.22, -0.04]
Subtotal (95% CI)			**57**			**50**	**100.0%**	**-5.08 [-7.49, -2.67]**
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%								
Test for overall effect: Z = 4.13 (P < 0.0001)								

Fig. 7. Forest plot representing quantitative data synthesis relative to the effect of FAs on the soft palate morphology.

age and gender are the main factors affecting the growth potential. According to previous studies, skeletal effects seem to be more pronounced in patients treated during the growth peak [16,49], whereas dentoalveolar effects seem to increase in post-pubertal patients [16]. Although the average ages of the treatment group and control group were matched at the beginning of treatment or observation periods, using age as the sole indicator of growth potential is problematic [42]. Second, growth patterns also affect the results of treatment with FAs, and among the patients with skeletal class II malocclusion, those with vertical growth patterns had dramatically narrower upper airway dimensions than did patients with normal growth patterns [3]. Third, the patient's compliance plays an important role in removable FAs treatment but is difficult to control. In addition, the different durations of treatment/observation may also have been a factor in the results obtained for the FAs.

As far as we know, this is the first meta-analysis to assess the effect of FAs on the upper airway. It is known to that randomized controlled trials (RCTs) are the gold standard for interventional research. However, it is unreasonable to design RCTs for early function therapy because the age is very important in the correction of skeletal malocclusion and because it is unethical to not treat patients during the ideal treatment time. In our study, we employed a broad search strategy and used several key databases to ensure a full search. All included studies were not RCTs but were well designed and of high quality. In addition, a high degree of heterogeneity was only found in a few secondary outcomes, but a significant increase in oropharyngeal dimensions was confirmed with small heterogeneity.

Although we conducted this meta-analysis carefully, there still were some limitations. Firstly, despite a widely and accurate search, we found only seven eligible studies, the sample size of some included studies was small. Selection bias could not be entirely avoided due to lack of a manual search. There is a need for similar studies with higher-quality and larger sample size to obtain more reliable conclusions. Further, we only discussed the short-term effect of FAs because the studies that assessed the long-term effects on growing skeletal ClassIIpatients did not meet the inclusion criteria. In general, functional treatment was followed by fixed mechano-therapy, and it's hard to assess the influence of fixed appliances on airway dimensions. Additionally, the landmarks for measuring the airway dimensions had a few differences among the studies, and this discrepancy may have affected the pooled results. It is essential to establish a standard landmark to assess the pharyngeal airway in the future. Finally, although it is possible to use lateral cephalograms to evaluate the changes in the sagittal plane, there is a need for more studies using CBCT to investigate the three-dimensional upper changes in the future.

5. Conclusions

According to this meta-analysis we concluded that early treatment with FAs had positive effects on the upper airway, especially on oropharyngeal dimensions, in growing skeletal Class II patients. FAs cause the forward reposition of the mandible and the adaptive changes of the soft palate, thereby increasing the airway dimensions, which may help decrease the airway resistance and the potential risk of OSAS in the future.

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Conflict of interest

The authors declare that they have no conflict of interest.

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