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CLINICAL REVIEW

Dental and skeletal changes associated with long-term oral appliance use for obstructive sleep apnea: A systematic review and meta-analysis

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SUMMARY

An oral appliance (OA) is an effective treatment option for patients with obstructive sleep apnea (OSA), but dental and skeletal changes have been detected by many studies after long-term OA use. Better understanding of the long-term side effects may decrease discontinuation of OA use and assist clinicians to make informed decisions. Accordingly, a systematic review and meta-analysis were performed to evaluate the dental and skeletal changes associated with OAs designed to advance the mandible. The quality of the studies was determined by using the risk of bias assessment tool for non-randomized studies (RoBANS), and 12 studies were included in the meta-analysis. OA use was associated with a significant decrease of overjet (OJ) and overbite (OB), and it was suggested that both parameters decreased along with the duration of treatment. Meta-analysis also demonstrated a significant increase of L1-MP. However, there were no significant changes of skeletal modifications or mandibular rotation. Changes of incisor inclination were suggested to make a contribution to reduction of OJ and OB. In conclusion, long-term OA use was associated with dental changes. The results of this study provide information for clinicians about the long-term effects of OAs.

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Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by recurrent episodes of partial or complete upper airway obstruction while sleeping, which result in fragmentation of sleep and oxygen desaturation [1,2]. Continuous positive airway pressure (CPAP) is the most effective treatment for OSA, while oral appliance (OAs) designed to advance the mandible represent the main non-CPAP option for this chronic disease [3]. Other treatments that have been suggested for OSA include weight loss, positional therapy, and surgery [3]. OAs are often well accepted by patients, and are therefore widely used [3–6].

OA therapy is not curative for OSA because the appliance simply acts by shifting the mandible forward and downward to relieve upper airway obstruction [7]. Therefore, OA therapy needs to be continued indefinitely [8]. The most common reasons for discontinuing OA use are lack of efficacy and side effects of the appliance [6]. Some studies have found that 40–50% of patients discontinue OA use because of side effects [9,10]. Both short-term and long-term side effects of OA use have been reported. The most common short-term side effects are increased salivation, dry mouth, and discomfort of the teeth or temporomandibular joint [11–14]. These effects are reversible and tend to resolve in a short period.

In contrast to such short-term side effects, long-term use of OAs that advance the mandible has been shown to cause irreversible dental and skeletal changes in many studies, with the only exception being appliances that hold the tongue forward by suction [15–18]. Various studies have evaluated dental and skeletal changes by using different imaging techniques and outcome measures [19–21], with significant changes of overjet (OJ) and overbite (OB) usually being reported. OJ and OB are indicators of the extent of vertical and horizontal overlap of the incisors, respectively [22]. Improved knowledge about the long-term side effects of OA use may help to decrease the discontinuation rate and may assist clinicians to make more informed decisions during follow-up.

Accordingly, we conducted a meta-analysis of available studies to evaluate the dental and skeletal changes associated with OA use.

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Abbreviations

AHI	apnea hypopnea index
ANB	angle between the point A-nasion line and point B
CPAP	Continuous positive airway pressure
CI	confidence interval
L1-MP	lower incisor angle to mandibular plane
MAD	mandibular advancement device
MP-SN	angle between the SN and MP planes (mandibular plane angle)
OA	oral appliance
OJ	overjet
OB	overbite
OSA	obstructive sleep apnea
RCT	randomized controlled trial
RDI	respiratory disorder index
RoBANS	the Risk of Bias Assessment Tool for Nonrandomized Studies
SD	standard deviation
SEM	standard errors of mean
SNA	angle between the sella-nasion line and point A
SNB	angle between the sella-nasion line and point B
U1-L1	interincisor angle
U1-SN	upper incisor angle to SN plane
WMD	weighted mean difference

Methods

Eligibility criteria

This review included studies that assessed the changes of the entire dental arch after long-term OA use (defined as > 1 y) and only investigated adults (aged ≥ 18 y). Participants in each study were treated for snoring or OSA with an OA that advanced the mandible (mandibular advancement devices). Studies of appliances that hold the tongue forward by suction (tongue retaining devices) were specifically excluded because the mechanism of action of such devices was incompatible with the objectives of this review [7]. There were no restrictions on the materials used to make the OA or the method of fixation, in order to allow to comprehensive assessment of the effects of OAs.

Literature search and study selection

An electronic literature search of Pubmed was performed on 21 August 2016 using pre-specified search terms (Appendix 1). Manual searching of the reference lists of the studies identified and previous systematic reviews was also conducted to increase the comprehensiveness of the search process, which followed the PRISMA Statement (Preferred reporting items for systematic review and meta-analysis protocols) [23]. Three authors (T.A., K.O., and H.O.) independently screened the titles and abstracts, and then performed full-text review to determine the eligibility of articles identified by screening. All case reports, case series, review articles and studies published in languages other than English were excluded.

Data extraction

Data were independently extracted by three authors (T.A., K.O., and H.O.), including the author, year, study design, study population, OSA severity, appliance type, treatment duration, measurement methods, and measured outcomes. Both pre-treatment and post-treatment outcomes were recorded. The following parameters were investigated to assess dental and skeletal movements: OJ, OB, angle between the sella-nasion line and point A (SNA), angle between the sella-nasion line and point B (SNB), angle between the point A-nasion line and point B (ANB), upper incisor angle to SN plane (U1-SN), interincisor angle (U1-L1), lower incisor angle to mandibular plane, and angle between the SN and MP planes (MP-SN). Among these variables, OJ and OB are indices of bite changes, while SNA, SNB, and ANB are indices of skeletal changes, U1-L1, U1-SN, and L1-MP are indices of dental changes, and SN-MP is an index of mandibular rotation (Fig. 1). If the standard error of the mean (SEM) was reported for outcomes, the standard deviation (SD) was also calculated from the number of subjects in the study and the reported SEM.

Quality assessment

The methodological quality of the studies was assessed and scored with the risk of bias assessment tool for non-randomized studies (RoBANS) [24]. This tool was designed to rate the risk of bias for nonrandomized studies and it comprises six domains: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. Each domain is judged to be 'Low,' 'High,' or 'Unclear'. The validity and reliability of RoBANS have been established previously [24]. RoBANS ratings were conducted independently by three authors (T.A., K.O., and H.O.), with disagreements being resolved by consensus after discussion between all three authors.

Data synthesis and statistical analysis

Analyses were conducted by three authors (T.A., K.O., and H.O.) using Review Manager Version 5.3. Extracted studies were classified according to each target outcome. When multiple studies were combined, the weighted mean difference (WMD) was calculated. The extent of change in each study was evaluated from the WMD and its 95% confidence interval (CI). A forest plot was constructed by using the WMD of the target variable obtained by comparison between pre-treatment and post-treatment data. Meta-analysis was performed with the random effects models, because the measurement

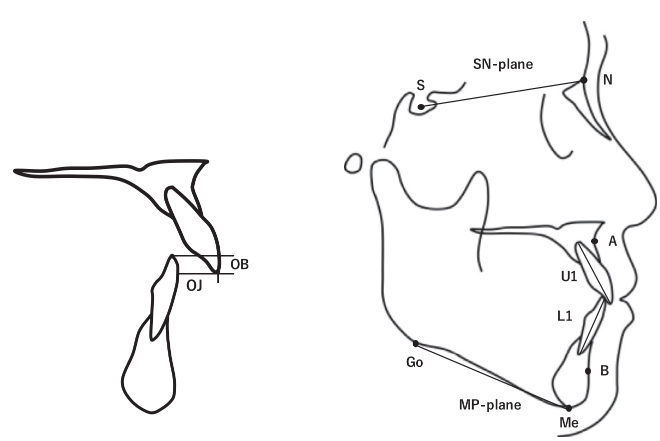


Fig. 1. Dental and skeletal measurements: landmarks, reference lines, and distances. Points: S, sella; N, nasion; A, innermost point on the anterior contour of the maxilla; B, innermost point on the contour of the mandible; Me, menton; Go, gonion; Plane: SN, anterior cranial base; MP, mandibular plane (Me-Go); U1, maxillary incisor axis (connects the incisor edge to root apex); L1, mandibular incisor axis (connects the incisor edge to root apex). Distance: OB, vertical overlap between the tips of the upper and lower incisors; OJ, horizontal distance between the labial surface of upper incisor and the lower incisor.

methods, participants, and duration of the studies were different. Heterogeneity was assessed with the I^2 index and the tau-squared test. If heterogeneity was identified, post-hoc subgroup analyses were performed based on the duration of OA use in the studies. To assess the risk of publication bias, funnel plots were constructed using the standard error and the difference of mean values.

Results

Description of the studies

The search identified 185 articles from the database and manual searches for relevant reviews. Fig. 2 presents a flowchart of the study selection process. After excluding irrelevant articles based on screening of the title and abstract, 56 articles were reassessed by full-text review. After the second eligibility check, 21 studies [13,15–21,25–37] were subjected to detailed analysis and quality assessment. Table 1 presents the characteristics of the studies undergoing quality assessment. The number of participants in each study ranged from 10 to 155 and the duration of follow-up was from 6 mo to 19.3 y. Methods of assessment and outcomes varied among the studies.

Nine studies [15,17,26,30–34,36] were excluded from meta-analysis because outcomes were only reported as differences or median values, and the findings of these studies are summarized in Table 2. The remaining 12 studies [13,16,18–21,25,27–29,35,37] were included in the meta-analysis.

Quality assessment

A total of 21 studies [13,15–21,25–37] were assessed and scored according to the RoBANS guideline [24]. Table 3 presents the results of this assessment. Patients were not recruited consecutively in two prospective studies [20,37], indicating a high risk of bias in relation to selection of participants. Multiple biases were evident in all of the studies [13,15–21,25–37], such as ignoring the effect of gender as a cofactor or differences of dentition and occlusal habits. Therefore, the risk of bias was high with respect to confounding variables. Twelve studies [13,20,21,26,28,29,31–35,37] were judged to have a high risk of bias in relation to measurement of exposure since there was insufficient description of daily OA use and the weekly use rate. In seven studies [21,25,29–31,34,37], adequate blinding of outcome measurements or statistical analysis was not conducted. Accordingly, we judged that the risk of bias was high in relation to blinding of outcome assessments. In two studies [18,28], some patients used an OA together with CPAP or Uvulopalatopharyngoplasty, leading to a high risk of bias for incomplete outcome data.

Meta-analysis

Fig. 3 shows the forest plot for each study, including the standardized mean difference and 95% CI. OA use had an influence on the bite, with changes of both OJ and OB. The mean change of OJ (total change) was −0.99 mm (95% CI: −1.30 to −0.68, $p < 0.00001$)

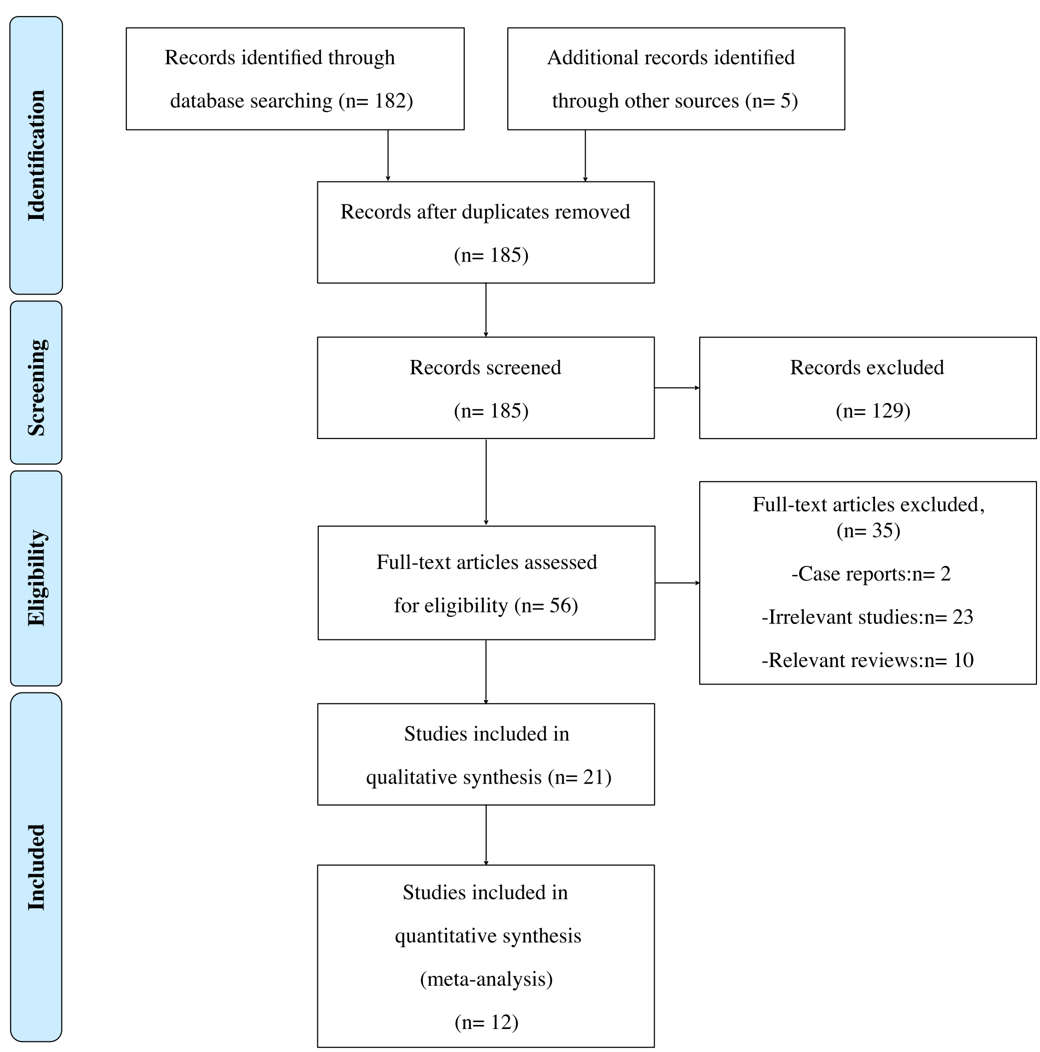


Fig. 2. Flow diagram of article management.

Table 1
Characteristics of the studies analyzed.

Authors, year	Study design	Population (Male, Female)	OSAS severity (AHI: mean ± SD)	Appliance type	Treatment duration (mean ± SD)	Measuring method	Measured outcomes
Wang et al., 2015 [19]	Prospective	42 (31M, 11F)	27 ± 19 (range: 5 to 74)	Silensor	4 ± 3 (range: 1 to 11) y	Cephalometry	OJ, OB, SNA, SNB, ANB, U1-L1, U1-SN, L1-MP, MP-SN
Pliska et al., 2014 [20]	Retrospective	77 (62M, 15F)	29.8 ± 16.9 (range: 2.4 to 77.4)	Klearway	11.1 ± 2.8 (range: 8 to 19.8) y	Dental study cast	OJ, OB
Gong et al., 2013 [37]	Retrospective	25	24.5 (short-term group) 25.6 (long-term group)	Mandibular repositioner	median 33 (range: 24 to 130) mo	Cephalometry	OJ, OB, SNA, SNB, ANB, U1- SN, U1-L1, L1-MP, MP-SN
Doff et al., 2010 [18]	Prospective	51	39 ± 31	Thornton adjustable positioner	2.3 ± 0.2 (range: 2.1 to 3.1) y	Cephalometry	OJ, OB, SNA, SNB, ANB, U1-L1, L1-MP, MP-SN
Maiklund et al., 2010 [36]	Prospective	10	10 (range: 1.6 to 19)	A monoblock elastomeric appliance	2.3 (range: 2.2 to 2.4) y	Denial study cast	OJ, OB, SNA, SNB
Martinez-Gomis et al., 2010 [21]	Prospective	15	AHE>10/h	The MAD consisted of two full-coverage acrylic splints connected by two lateral telescopic	4.8 (range: 3.6 to 5.8) y	Intraoral	OJ, OB
Ghazal et al., 2008 [35]	Retrospective	21 (17M, 4F)	not listed	Thornton anterior positioner	33 ± 9 mo	Dental study cast	OJ, OB
Chen et al., 2008 [17]	Retrospective	70 (62M,8F)	RDI = 28.0 (range: 0.0 to 68.0)	Klearway	7.4 (range: 88.4 ± 26.7 mo) y	Dental study cast	OJ, OB
Hammond et al., 2007 [34]	Retrospective	45 (33M, 12F)	25.3 ± 17.7 (range: 3 to 81)	A unique 2-piece acrylic design providing full occlusal coverage and a screw device to titrate advancement	25.1 ± 11.8 mo	Cephalometry, Dental study cast	OJ, OB, SNA, SNB, ANB, MP-SN
Hou et al., 2006 [33]	Prospective	67 (50M, 17F)	not listed	Modified Harvold monobloc type of functional appliance	1 year: n = 64 2 years: n = 43 3 years: n = 30	Cephalometry	OJ, OB, SNA, SNB, ANB, MP-SN
Maiklund, 2006 [32]	Prospective	155 (127M, 28F)	median 13 (range: Oto 76)	Soft elastomeric device and Hard acrylic device	5.4 ± 0.8 y	Dental study cast	OJ, OB
Almeida et al., 2006 [31]	Retrospective	71 (63M, 8F)	RDI = 28.9 ± 17	Klearway	7.3 ± 2.1 y	Cephalometry	OJ, OB, U1-SN, L1-MP, MP-SN
Battagel et al., 2005 [30]	Retrospective	30 (26M, 4F)	not listed	Herbst MAS	Median 3.6 (range: 2.2 to 6.1) y	Dental study cast	OJ, OB
Fransson et al., 2004 [29]	Prospective	65	not listed	Mandibular protruding device	2 y	Intraoral	OJ, OB
Ringqvist et al., 2003 [28]	Prospective	30	5 < AI<25	MAD	4.1 (range: 4.0 to 4.2) y	Cephalometry	OJ, OB
Rose et al., 2002 [8]	Retrospective	34	median 21.7 (range: 14.9 to 28.4)	The device consists of maxillary and mandibular plates that are made of hard acrylic and are joined by U-shaped clasps	29.6 ± 5.1 (range: 24.1 to 43.5) mo	Cephalometry, dental study cast	OJ, OB, SNA, SNB, ANB, U1-SN
Fritsch et al., 2001 [13]	Prospective	22	27.6 ± 3.5	Monoblock and Herbst	Median 14 (range: 12 to 30) mo	Cephalometry, dental study cast	OJ, OB, SNA, SNB, ANB, L1-MP
Marklund et al., 2001 [26]	Retrospective	75	46 patients = 5 ≤ AHI≤ 20 28 patients = 20 < AHI	MAD made of soft elastomer	2.5 ± 0.5 y	Dental study cast	OJ, OB
Robertson, 2001 [27]	Retrospective	100 (87M, 13F)	Not listed	Non-adjustable rigid splint	6, 12, 18, 24 or 30 mo	Cephalometry	OJ, OB, SNA, L1-MP
Bondemark et al., 2000 [25]	Prospective	32 (23M, 9F)	27 ± 19 (range: 5 to 74)	Monoblock	2 y	Dental study cast	OJ, OB
Bondemark, 1999 [15]	Prospective	30 (21M, 9F)	Not listed	Monoblock	2 y	Cephalometry	OJ, OB, SNA, SNB, ANB

AHI = apnea hypopnea index; ANB = angle between the point A-nasion line and point B; L1-MP = lower incisor angle to mandibular plane; MAD = mandibular advancement device; MP-SN = angle between the SN plane and MP plane (mandibular plane angle); OJ = overjet; OB = overbite; RDI = respiratory disorder index; SNA = angle between the sella-nasion and line point A; SNB = angle between the sella-nasion line and point B; U1-L1 = interincisor angle; U1-SN = upper incisor angle to SN plane.

Table 2
Characteristics of the studies excluded from meta-analysis because outcomes were only presented as the extent of change.

Authors, year	Study population (Male, Female)	Methodology	Findings
Marklund et al., 2010 [36]	10	Bite changes by long-term use of OA were evaluated on plaster casts and radiographs and by questionnaires. The mean treatment duration was 2.4 y (range: 2.2–2.7 y). Overjet, overbite, and degree of mandibular opening were measured by a digital sliding caliper on the upper right central incisor on the study casts.	The mean change of overjet was −0.2 mm.
Chen et al., 2008 [17]	70 (62M, 8F)	A MicroScribe-3DX dental study model analysis system was used to make 3D measurements on baseline and follow-up study model. The mean treatment duration was 7 y 4 mo (range: 88.4 ± 26.7 mo).	The mean change of OB was larger for the anterior teeth (range: 1.25–1.69 mm) than for the posterior teeth (range: 0.09–1.06 mm). Similar to OB, the mean change of OJ wa larger for the anterior teeth (range: 1.15–1.55 mm) than the posterior teeth (range: 0.14–1.03 mm).
Hammond et al., 2007 [34]	45 (33M, 12F)	Cephalometric analyses and dental cast measurements were conducted to identify objectively dental and skeletal changes caused by MAS over time. Patients had been using MAS on average for 25.1 ± 11.8 mo range: 10.7–64.5 mo).	Reductions in overbite (−0.3 ± 0.08 mm, $P < 0.01$) and overjet (−0.2 ± 0.06 mm, $P < 0.05$) were found, and cephalometric analysis showed statistically significant but clinically unimportant changes limited to anterior movement of the mandibular incisors (0.5 ± 0.12 mm, $P < 0.01$).
Hou et al., 2006 [33]	67 (50M, 17F)	The cephalograms were obtained at start of treatment (T0), after 1 y (T1), 2 y (T2), and 3 y (T3) of treatment. The lateral cephalograms were digitized twice, and the average two readings was used for statistical analyses.	Statistically significant dental changes were observed during the first year of follow-up only. Both overjet and the overbite showed statistically significant reduction, but the mean values were small: 0.3 mm ($P < 0.01$) and 0.2 mm ($P < 0.05$), respectively. Over the 3- y follow-up period (T0-T3), the mean total reductions of overjet and overbite were 0.8 and 0.6 mm, respectively.
Marklund, 2006 [32]	155 (127M, 28F)	Plaster casts in centric occlusion were before the start of treatment and at the 5-y follow-up. A sliding caliper to the nearest 0.05 mm or transparent graph paper to the nearest 0.5 mm were used for measurements casts of each jaw separately, casts in centric occlusion or directly on the patient's teeth.	The MAD induced a median overjet change of −0.6 mm (range: −3.5 to 1.3) ($P < 0.001$) and a median overbite change of −0.6 mm (range: −5.0 to 1.3) ($P < 0.001$) in the 155 frequent users.
Almeida et al., 2006 [31]	71 (63M, 8F)	Upright lateral cephalometric radiographs in centric occlusion taken before treatment and after a mean of 7.3 ± 2.1 y of OA use were compared.	The relationship between maxillary and mandibular incisors significantly changed, with decreases in OB (2.8 mm), OJ (2.6 mm), interincisor angle (4.1°), and an increase in basal bone relationship (0.5°).
Battagel et al., 2005 [30]	30 (26M, 4F)	Dental casts were obtained and BMI and Epworth Sleepiness Scale scores recorded. These data were compared with those collected when the subject was first referred. The median duration of appliance wear was 3.6 y with a range of 2.2–6.1 y.	Small, statistically significant reduction in both vertical (−0.4 mm) and horizontal (−0.5 mm) overlap of the incisor teeth were found.
Marklund et al., 2001 [26]	75	Plaster casts in centric occlusion taken before the start of treatment and after a treatment time of 2.5 ± 0.5 y (mean ± SD) were used to measure tooth movement.	The treatment induced a change in overjet of −0.4 ± 0.8 mm (mean ± SD) and a change in overbite of −0.4 ± 0.7 mm (mean ± SD).
Bondemark, 1999 [15]	30 (21M, 9F)	For each patient, two lateral head radiographs were taken in centric occlusion, one before and one after 2 y of treatment.	The forward and downward movement of the mandible was accomplished by a statistically significant increase in mandibular length (0.4 ± 0.62 (mean ± SD), $P < 0.1$) and a significant decrease in overjet (−0.4 ± 0.53 mm (mean ± SD), $P < 0.001$) and overbite (−0.1 ± 0.26 (mean ± SD), $P < 0.05$).

ANB = point A-nasion to point B; MAD = mandibular advancement device; MAS = mandibular advancement splint; OA = oral appliance.

(Fig. 3.1) and that of OB (total change) was −1.00 mm (95% CI: −1.34 to −0.66, $p < 0.00001$) (Fig. 3.2). The I^2 indices for OJ (total change) and OB (total change) were 25% and 41%, respectively. These data suggested moderate to severe heterogeneity. The studies included in this analysis had differences in the duration of intervention. Therefore, subgroup analyses were conducted for OJ and OB to assess the influence of treatment duration using the following categories: 12M-24M (treatment duration of more than 1 y and less than 2 y), 24M-36M (treatment duration of more than 2 y and less than 3 y), 36M- (treatment duration of more than 3 y). These analyses revealed a gradual decrease of OJ and OB with continued OA use. The mean change of OJ (12-24M), OJ (24-36M), and OJ (36M-) in each study was −0.70 mm (95% CI: −1.29 to −0.1), −0.89 mm (95% CI: −1.29 to −0.50), and −1.22 mm (95% CI: −1.89 to −0.54), respectively (Fig. 3.1). In addition, the mean change of OB (12-24M), OB (24-36M), and OB (36M-) in each study was −0.60 mm (95% CI: −1.29 to 0.09), −0.92 mm (95% CI: −1.29 to-0.56), and −1.25 mm (95% CI: −2.14 to −0.37), respectively (Fig. 3.2).

Among the skeletal indices, the pooled SNA value demonstrated no significant change, being −0.28° (95% CI: −1.10 to 0.54, $p = 0.50$) (Fig. 4.1). The mean change of SNB was −0.11° (95% CI: −0.98 to 0.76, $p = 0.81$) (Fig. 4.2) and that of ANB was −0.12° (95% CI: −0.60 to 0.35, $p = 0.61$) (Fig. 4.3). Among the dental indices, the pooled U1-L1 value showed no significant change, being −0.28° (95% CI: −3.04 to 2.47, $p = 0.84$) (Fig. 5.1). The mean change of U1-SN was −1.90° (95% CI: −3.95 to 0.15, $p = 0.07$) (Fig. 5.2). However, the mean change of L1-MP was significant at 2.07° (95% CI: 0.37 to 3.77, $p = 0.02$) (Fig. 5.3). There was no significant long-term change of the mandibular rotation index (MP-SN), with the change being only 0.79° (95% CI: −1.84 to 3.42, $p = 0.56$) (Fig. 6). In short, there were only significant dental changes (L1-MP), and there were no significant changes of skeletal parameters or mandibular rotation. The I^2 indices for SNA, SNB, ANB, U1-L1, U1-SN, L1-MP, and MP-SN were all 0%, suggesting no heterogeneity.

Risk of publication bias

Appendixes 2.1 and 2.2 present funnel plots of the standard error for OJ and OB data, respectively. Both plots are symmetrical, indicating no publication bias. As the number of eligible articles

Table 3
Quality assessment score (RoBANS).

Author, year	Risk of bias					
	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessment	Incomplete outcome data	Selective outcome data
Wang et al., 2015 [19]	Low	High[b]	Low	Low	Low	Low
Pliska et al., 2014 [20]	High[a]	High[b]	High[c]	Low	Low	Low
Gong et al., 2013 [37]	High[a]	High[b]	High[c]	High[d]	Low	Low
Doff et al., 2010 [18]	Low	High[b]	Low	Low	High[e]	Low
Marklund et al., 2010 [36]	Low	High[b]	Low	Low	Low	Low
Martinez-Gomis et al., 2010 [21]	Low	High[b]	High[c]	High[d]	Low	Low
Ghazal et al., 2008 [35]	High[a]	High[b]	High[c]	Low	Low	Low
Chen et al., 2008 [17]	High[a]	High[b]	Low	Low	Low	Low
Hammond et al., 2007 [34]	High[a]	High[b]	High[c]	High[d]	Low	Low
Hou et al., 2006 [33]	Low	High[b]	High[c]	Low	Low	Low
Marklund, 2006 [32]	Low	High[b]	High[c]	Low	Low	Low
Almeida et al., 2006 [31]	High[a]	High[b]	High[c]	High[d]	Low	Low
Battagel et al., 2005 [30]	High[a]	High[b]	Low	High[d]	Low	Low
Fransson et al., 2004 [29]	Low	High[b]	High[c]	High[d]	Low	Low
Ringqvist et al., 2003 [28]	Low	High[b]	High[c]	Low	High[e]	Low
Rose et al., 2002 [8]	High[a]	High[b]	Low	Low	Low	Low
Fritsch et al., 2001 [13]	High[a]	High[b]	High[c]	Low	Low	Low
Marklund et al., 2001 [26]	High[a]	High[b]	High[c]	Low	Low	Low
Robertson, 2001 [27]	Low	High[b]	Low	Low	Low	Low
Bondemark et al., 2000 [25]	Low	High[b]	Low	High[d]	Low	Low
Bondemark, 1999 [15]	High[a]	High[b]	Low	Low	Low	Low

RoBANS = the Risk of Bias Assessment Tool for Nonrandomized Studies.
[a] Retrospective study or patients not consecutively recruited.
[b] Multiple biases such as ignoring gender, dentition differences, and occlusal habits.
[c] Insufficient description of OA use time per day and use rate per week.
[d] Inadequate blinding for assessment of outcome measurement or inadequate statistical analysis.
[e] Data were included for patients who used OAs together with other treatment methods.

was <10, funnel plots were not used to assess publication bias for SNA, SNB, ANB, U1-L1, U1-SN, L1-MP, and MP-SN.

Discussion

We conducted a systematic review and meta-analysis to quantify the dental and skeletal changes associated with long-term OA use in OSA patients. Meta-analysis of 12 studies was performed to assess dental and skeletal changes, and the results revealed a significant decrease of bite indices (OJ and OB) with long-term OA use. Moreover, subgroup analyses showed that the decrease of OJ and OB progressed with the duration of treatment. Furthermore, meta-analysis demonstrated a significant increase of L1-MP, which is one of the dental indices. On the other hand, there were no significant changes of the other dental indices (U1-L1 and U1-SN), the skeletal indices (SNA, SNB, and ANB), or the mandibular rotation index (SN-MP) with OA use.

OJ and OB are measured in the oral cavity as indices of the bite that are convenient to use in daily clinical practice [22,38]. Significant decreases of OJ and OB after long-term OA use have been reported by many authors, and this review obtained the same findings [15–18]. However, it has not been clarified which factors are associated with the changes of bite. To obtain more information about the pathology of dental and skeletal changes, we investigated the following outcomes that were common to the studies included in this meta-analysis: dental changes (U1-L1, U1-SN, and L1-MP), skeletal changes (SNA, SNB, and ANB) and mandibular rotation (SN-MP). Because “long-term” was defined as at least 1 y in most of the studies, we defined OA use for more than 1 y as long-term use. We used RoBANS, which is designed to evaluate bias in systematic reviews of non-randomized trials, because all of the studies included in this review were observational studies [24].

To the best of our knowledge, this is the first meta-analysis of the dental and skeletal changes associated with long-term OA use. As expected, significant reduction of OJ and OB occurred over time in the patients using OAs. In addition, we found that the decrease of OJ and OB was progressive as the duration of OA use became longer. It is understood that dental movement can be induced by a small force with a magnitude from 0.9 to 2.5N [39]. In general, OAs with dental arch coverage impose force on the teeth to hold the mandible in a forward position [3,40]. Because the mandible tends to return to its natural position, palatal force is applied to the maxilla and a labial force is applied to the mandible. Even if a force is only applied for several hours at night, movement of teeth may occur [41]. Our results suggested that the continued OA use contributed to greater changes of OJ and OB over time. The mean change of OJ was −0.70 mm at 12–24M, −0.89 mm at 24–36M, and −1.22 mm at 36M-, while the mean change of OB was −0.60 mm at 12–24M, −0.92 mm at 24–36M, and −1.25 mm at 36M-. Several dental and skeletal changes associated with OA use that could affect OJ and OB have been described, including skeletal variations [13], inclination of the incisors [19] and an increase of anterior facial height induced by mandibular rotation [37]. This systematic review demonstrated a significant increase of L1-MP and a tendency of U1-SN to decrease. On the other hand, the indices of skeletal change and mandibular rotation showed no significant changes according to our review. Patients using OAs that only cover the bilateral posterior teeth were reported to show smaller reductions of OJ and OB compared to those using OAs with full-arch coverage [28]. This suggests that inclination of the incisors may be a more important contributor to the significant reduction of OJ and OB than skeletal changes or mandibular rotation.

We investigated similarity between the results of this meta-analysis and the results of each of the studies that were excluded from our analysis. Five studies showed similar results to the present meta-analysis. In brief, Chen et al. [34] reported a decrease of OJ (range: 1.15–1.55 mm) and OB (range: 1.25–1.69 mm), Hou et al. [32] reported a mean decrease of OJ by 0.8 mm and OB by 0.6 mm, Marklund et al. [31] reported a mean decrease of OJ and OB by 0.6 mm each, Battagel et al. [29] reported a mean decrease of OJ by 0.5 mm and OB by 0.4 mm, and Bondemark [15] reported a mean decrease of OJ by 0.4 mm and OB by 0.1 mm. However, four studies obtained outcomes that were not within the 95% CI for our meta-analysis. In brief, Marklund et al. [35] reported a mean decrease of

Figure 3.1. Forest plot for mean difference in OJ and corresponding 95% Cl.

Study or Subgroup	post-treatment Mean	post-treatment SD	post-treatment Total	pre-treatment Mean	pre-treatment SD	pre-treatment Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.1.1 treatment (12M-24M)									
Fritsch et al., 2001 [13]	3.1	1.8	22	3.3	1.8	22	6.5%	−0.20 [−1.26, 0.86]	2001
Robertson, 2001 [27]	3.3	1.62	20	4.36	1.97	20	6.0%	−1.06 [−2.18, 0.06]	2001
Martinez-Gomis et al., 2010 [21]	1.99	2	35	2.82	2	35	7.9%	−0.83 [−1.77, 0.11]	2010
Subtotal (95% CI)			**77**			**77**	**20.4%**	**−0.70 [−1.29, −0.10]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 2 (P = 0.52); I² = 0%									
Test for overall effect: Z = 2.30 (P = 0.02)									
1.1.2 treatment (24M-36M)									
Bondemark et al., 2000 [25]	4.1	2.59	32	4.5	2.66	32	4.8%	−0.40 [−1.69, 0.89]	2000
Robertson, 2001 [27]	3.08	2	40	4.32	2.72	40	6.7%	−1.24 [−2.29, −0.19]	2001
Rose et al., 2002 [8]	3.1	2.4	34	4.4	2.3	34	6.0%	−1.30 [−2.42, −0.18]	2002
Fransson et al., 2004 [29]	3.2	2.5	65	3.7	2.4	65	9.2%	−0.50 [−1.34, 0.34]	2004
Ghazal et al., 2008 [35]	2.3	1.8	21	2.5	2	21	5.7%	−0.20 [−1.35, 0.95]	2008
Doff et al., 2010 [18]	2.8	2.6	31	4.4	2.2	31	5.4%	−1.60 [−2.80, −0.40]	2010
Gong et al., 2013 [37]	3.26	1.85	25	4.38	1.58	25	7.7%	−1.12 [−2.07, −0.17]	2013
Subtotal (95% CI)			**248**			**248**	**45.4%**	**−0.89 [−1.29, −0.50]**	
Heterogeneity: Tau² = 0.00; Chi² = 5.28, df = 6 (P = 0.51); I² = 0%									
Test for overall effect: Z = 4.39 (P < 0.0001)									
1.1.3 treatment (36M-)									
Ringqvist et al., 2003 [28]	3.1	2.2	30	3.5	2.4	30	5.6%	−0.40 [−1.57, 0.77]	2003
Martinez-Gomis et al., 2010 [21]	1.97	2	15	3.07	2	15	4.0%	−1.10 [−2.53, 0.33]	2010
Pliska et al., 2014 [20]	1.4	2.1	77	3.3	1.7	77	13.8%	−1.90 [−2.50, −1.30]	2014
Wang et al., 2015 [19]	3.29	1.75	42	4.32	1.73	42	10.8%	−1.03 [−1.77, −0.29]	2015
Subtotal (95% CI)			**164**			**164**	**34.2%**	**−1.22 [−1.89, −0.54]**	
Heterogeneity: Tau² = 0.25; Chi² = 6.56, df = 3 (P = 0.09); I² = 54%									
Test for overall effect: Z = 3.54 (P = 0.0004)									
Total (95% CI)			**489**			**489**	**100.0%**	**−0.99 [−1.30, −0.68]**	
Heterogeneity: Tau² = 0.08; Chi² = 17.35, df = 13 (P = 0.18); I² = 25%									
Test for overall effect: Z = 6.32 (P < 0.00001)									
Test for subgroup differences: Chi² = 1.30, df = 2 (P = 0.52), I² = 0%									

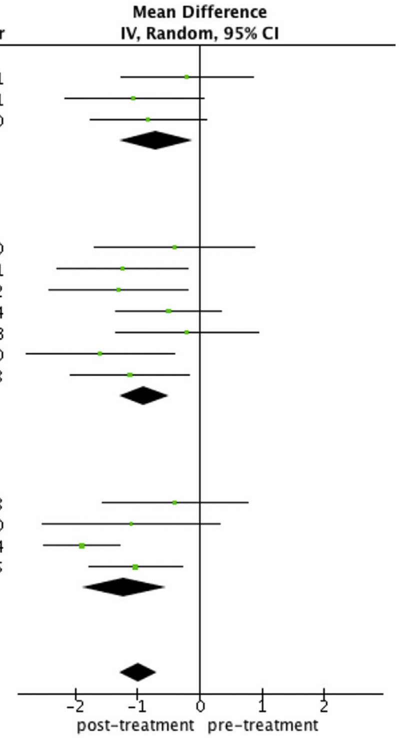


Figure 3.2. Forest plot for mean difference in OB and corresponding 95% Cl.

Study or Subgroup	post-treatment Mean	post-treatment SD	post-treatment Total	pre-treatment Mean	pre-treatment SD	pre-treatment Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.2.1 treatment (12M-24M)									
Robertson, 2001 [27]	2.93	1.74	20	3.83	2.45	20	4.9%	−0.90 [−2.22, 0.42]	2001
Fritsch et al., 2001 [13]	3.6	2.8	22	4	2.8	22	3.5%	−0.40 [−2.05, 1.25]	2001
Martinez-Gomis et al., 2010 [21]	2.2	2	35	2.71	2	35	7.7%	−0.51 [−1.45, 0.43]	2010
Subtotal (95% CI)			**77**			**77**	**16.1%**	**−0.60 [−1.29, 0.09]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.86); I² = 0%									
Test for overall effect: Z = 1.69 (P = 0.09)									
1.2.2 tretment (24M-36M)									
Bondemark et al., 2000 [25]	3.5	2.13	32	3.6	2.14	32	6.7%	−0.10 [−1.15, 0.95]	2000
Robertson, 2001 [27]	2.88	1.78	40	4.47	2.4	40	7.8%	−1.59 [−2.52, −0.66]	2001
Rose et al., 2002 [8]	2.5	1.2	34	3.6	2.1	34	9.0%	−1.10 [−1.91, −0.29]	2002
Fransson et al., 2004 [29]	2.6	2.1	65	3.2	2	65	10.3%	−0.60 [−1.31, 0.11]	2004
Ghazal et al., 2008 [35]	2.5	2.1	21	3.2	1.9	21	5.6%	−0.70 [−1.91, 0.51]	2008
Doff et al., 2010 [18]	1.4	2.4	31	2.4	1.4	31	7.3%	−1.00 [−1.98, −0.02]	2010
Gong et al., 2013 [37]	2.58	2.34	25	4.04	1.74	25	6.0%	−1.46 [−2.60, −0.32]	2013
Subtotal (95% CI)			**248**			**248**	**52.8%**	**−0.92 [−1.29, −0.56]**	
Heterogeneity: Tau² = 0.01; Chi² = 6.36, df = 6 (P = 0.38); I² = 6%									
Test for overall effect: Z = 4.98 (P < 0.00001)									
1.2.3 treatment (36M-)									
Ringqvist et al., 2003 [28]	3.8	2.3	30	4.3	2.1	30	6.2%	−0.50 [−1.61, 0.61]	2003
Martinez-Gomis et al., 2010 [21]	2.54	3	15	3.35	2	15	2.9%	−0.81 [−2.63, 1.01]	2010
Pliska et al., 2014 [20]	1.1	2.1	77	3.4	2.3	77	10.4%	−2.30 [−3.00, −1.60]	2014
Wang et al., 2015 [19]	2.27	1.46	42	3.28	1.4	42	11.6%	−1.01 [−1.62, −0.40]	2015
Subtotal (95% CI)			**164**			**164**	**31.1%**	**−1.25 [−2.14, −0.37]**	
Heterogeneity: Tau² = 0.55; Chi² = 10.89, df = 3 (P = 0.01); I² = 72%									
Test for overall effect: Z = 2.77 (P = 0.006)									
Total (95% CI)			**489**			**489**	**100.0%**	**−1.00 [−1.34, −0.66]**	
Heterogeneity: Tau² = 0.17; Chi² = 22.22, df = 13 (P = 0.05); I² = 41%									
Test for overall effect: Z = 5.74 (P < 0.00001)									
Test for subgroup differences: Chi² = 1.35, df = 2 (P = 0.51), I² = 0%									

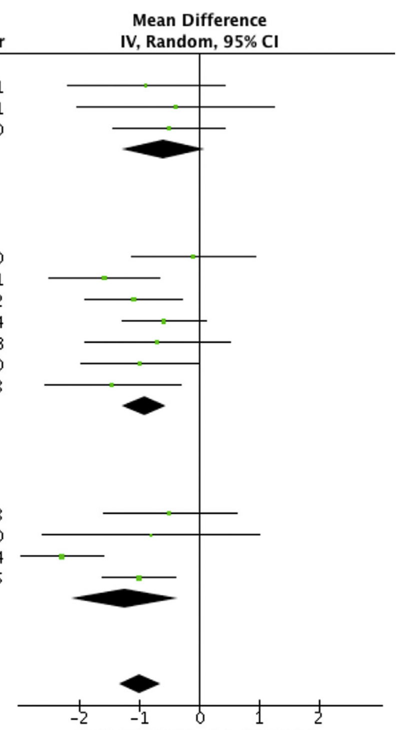


Fig. 3. Forest plots of the mean differences in OJ and OB with the corresponding 95% CIs. 12M-24M: treatment duration of more than 1 y and less than 2 y; 24M-36M: treatment duration of more than 2 y and less than 3 y; 36M-: treatment duration of more than 3 y. OJ = overjet; OB = overbite; CI = confidence interval; SD = standard deviation; df = degrees of freedom.

Figure 4.1. Forest plot for mean difference in SNA and corresponding 95% CI.

Study or Subgroup	post-treatment Mean	SD	Total	pre-treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Robertson, 2001 [27]	81.95	4.09	20	81.25	4.48	20	9.5%	0.70 [−1.96, 3.36]	2001
Fritsch et al., 2001 [13]	81.5	2.55	18	81.9	2.55	18	24.1%	−0.40 [−2.07, 1.27]	2001
Rose et al., 2002 [8]	82.5	4	34	83.5	5.3	34	13.4%	−1.00 [−3.23, 1.23]	2002
Doff et al., 2010 [18]	79.2	4.3	31	79.2	4.2	31	14.9%	0.00 [−2.12, 2.12]	2010
Gong et al., 2013 [37]	81.96	4.07	25	82.52	4	25	13.4%	−0.56 [−2.80, 1.68]	2013
Wang et al., 2015 [19]	80.64	3.84	45	80.8	4.1	45	24.8%	−0.16 [−1.80, 1.48]	2015
Total (95% CI)			**173**			**173**	**100.0%**	**−0.28 [−1.10, 0.54]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.09$, df = 5 (P = 0.96); $I^2 = 0\%$
Test for overall effect: Z = 0.67 (P = 0.50)

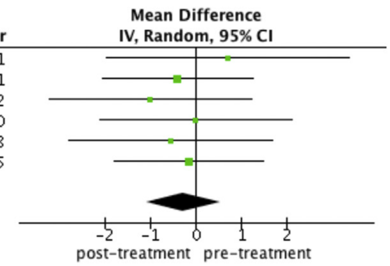


Figure 4.2. Forest plot for mean difference in SNB and corresponding 95% CI.

Study or Subgroup	post-treatment Mean	SD	Total	pre-treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Fritsch et al., 2001 [13]	77.3	2.55	18	77.7	2.97	18	23.0%	−0.40 [−2.21, 1.41]	2001
Rose et al., 2002 [8]	79.8	4.5	34	79.2	4.9	34	15.1%	0.60 [−1.64, 2.84]	2002
Doff et al., 2010 [18]	74.8	4.2	31	75.2	3.9	31	18.5%	−0.40 [−2.42, 1.62]	2010
Gong et al., 2013 [37]	75.76	3.87	25	76.28	4.26	25	14.8%	−0.52 [−2.78, 1.74]	2013
Wang et al., 2015 [19]	75.69	3.93	45	75.53	3.93	45	28.6%	0.16 [−1.46, 1.78]	2015
Total (95% CI)			**153**			**153**	**100.0%**	**−0.11 [−0.98, 0.76]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.80$, df = 4 (P = 0.94); $I^2 = 0\%$
Test for overall effect: Z = 0.24 (P = 0.81)

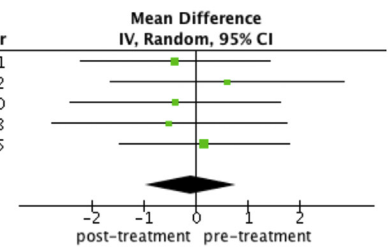


Figure 4.3. Forest plot for mean difference in ANB and corresponding 95% CI.

Study or Subgroup	post-treatment Mean	SD	Total	pre-treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Fritsch et al., 2001 [13]	4.1	1.7	19	4.2	2.2	19	14.3%	−0.10 [−1.35, 1.15]	2001
Rose et al., 2002 [8]	4	2.6	34	4.3	3	34	12.6%	−0.30 [−1.63, 1.03]	2002
Doff et al., 2010 [18]	4.3	2.2	31	4	1.9	31	21.3%	0.30 [−0.72, 1.32]	2010
Gong et al., 2013 [37]	6.2	2.03	25	6.36	1.75	25	20.3%	−0.16 [−1.21, 0.89]	2013
Wang et al., 2015 [19]	4.94	2.13	45	5.27	1.94	45	31.5%	−0.33 [−1.17, 0.51]	2015
Total (95% CI)			**154**			**154**	**100.0%**	**−0.12 [−0.60, 0.35]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.96$, df = 4 (P = 0.92); $I^2 = 0\%$
Test for overall effect: Z = 0.52 (P = 0.61)

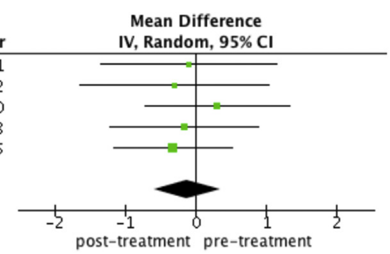


Fig. 4. Forest plots of the mean difference in SNA, SNB, and ANB with the corresponding 95% CIs. SNA = angle between the sella-nasion line and point A; SNB = angle between the sella-nasion line and point B; ANB = angle between the point A-nasion line and point B; CI = confidence interval; SD = standard deviation; df = degrees of freedom.

OJ by 0.2 mm, Hammond et al. [33] reported a mean decrease of OJ by 0.2 mm and OB by 0.3 mm, Almeida et al. [30] reported a mean decrease of OJ by 2.6 mm and OB by 2.8 mm, and Marklund et al. [26] reported a mean decrease of OJ and OB by 0.4 mm each [26,31,34,36]. In three of these studies [26,34,36], results were below the lower limit of the CI, while the results of one study [31] were above the upper limit. A possible cause for the discrepancies reported by Marklund et al. [26,35] is the use soft elastic OA material, unlike the other studies. This idea is consistent with the report by Marklund et al. [26] that bite changes are smaller with OAs made of soft elastic compared to OAs made of hard elastic. The frequency of OA use affects the extent of the bite change, but there was little description of OA use in the report by Hammond et al. [33] Poor adherence to OA use may also be related to deviation of study results from the 95% CI. Almeida et al. [30] reported a larger bite change than we found in our meta-analysis, presumably because the duration of OA use was 7.3 ± 2.1 y and was longer than in the other studies.

Furthermore, RoBANS showed that all of the studies included in this meta-analysis had a high risk of bias in relation to confounders. This is probably because they were all observational studies, making it difficult to unify patient factors such as sex, dental status, and the occlusal force of the OA. Regarding publication bias, there was no asymmetry of the funnel plot, indicating that the studies were chosen without bias.

Several limitations of this investigation should be acknowledged. First, all of the studies included in our systematic review were observational studies. However, to assess the side effects due to long-term OA use for OSA, observational studies seem to be more suitable than randomized controlled trials [42]. Second, we did not correct any factors that may have affected the results, such as the amount of mandibular protrusion, the occlusal state before treatment, or the type of OA used. Finally, a potential weakness of this meta-analysis was inclusion of studies with different treatment durations in the subgroup analysis (36M-), since the duration of follow-up ranged from 3 to 19.3 y [19–21,28]. It may be not appropriate to interpret the results uniformity because OA use is lifelong. In fact, long-term studies have found larger bite changes than in our results. We found a mean decrease of OJ by 1.22 mm and OB by 1.25 mm in subgroup (36M-). In contrast, Pliska et al. [20] (treatment duration: 11.1 ± 2.8 y) reported a mean decrease of OJ by 1.9 mm and OB by 2.3 mm, while Almeida et al. [31] (treatment duration: 7.3 ± 2.1 y) reported a mean decrease of OJ by 2.6 mm and OB by 2.8 mm. As our results suggested that bite changes continue to progress with longer OA use, the influence of very long-term use for periods such as 10 or 20 y should be considered in the future. Use of OAs to treat OSA has become widespread, and multiple kinds of OAs are employed by many people [3,40]. Despite the

Figure 5.1. Forest plot for mean difference in U1-L1 and corresponding 95% CI.

Study or Subgroup	post-treatment Mean	SD	Total	pre-treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Doff et al., 2010 [18]	122.5	10.9	31	124.8	10.8	31	26.0%	-2.30 [-7.70, 3.10]	2010
Gong et al., 2013 [37]	125.8	10.38	25	124.86	10.62	25	22.4%	0.94 [-4.88, 6.76]	2013
Wang et al., 2015 [19]	122.57	9.2	45	122.37	9.38	45	51.5%	0.20 [-3.64, 4.04]	2015
Total (95% CI)			**101**			**101**	**100.0%**	**-0.28 [-3.04, 2.47]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

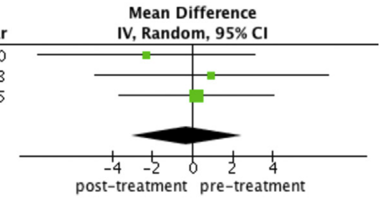


Figure 5.2. Forest plot for mean difference in U1-SN and corresponding 95% CI.

Study or Subgroup	post-treatment Mean	SD	Total	pre-treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Rose et al., 2002 [8]	98.7	9.4	34	100.1	9.5	34	20.8%	-1.40 [-5.89, 3.09]	2002
Gong et al., 2013 [37]	96.92	7.82	25	100.26	7.49	25	23.2%	-3.34 [-7.58, 0.90]	2013
Wang et al., 2015 [19]	99.02	6.86	45	100.51	6.37	45	56.0%	-1.49 [-4.23, 1.25]	2015
Total (95% CI)			**104**			**104**	**100.0%**	**-1.90 [-3.95, 0.15]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.82 (P = 0.07)

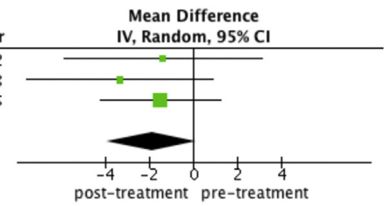


Figure 5.3. Forest plot for mean difference in L1-MP and corresponding 95% CI.

Study or Subgroup	post-treatment Mean	SD	Total	pre-treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Robertson, 2001 [27]	88.95	8.53	40	85.39	8.97	40	19.7%	3.56 [-0.28, 7.40]	2001
Fritsch et al., 2001 [13]	90.1	7.5	22	89.3	7	22	15.8%	0.80 [-3.49, 5.09]	2001
Doff et al., 2010 [18]	105.9	8.2	31	102.2	7.4	31	19.1%	3.70 [-0.19, 7.59]	2010
Gong et al., 2013 [37]	102.54	8.84	25	100.76	8.06	25	13.2%	1.78 [-2.91, 6.47]	2013
Wang et al., 2015 [19]	100.1	7.24	45	99.16	7.26	45	32.3%	0.94 [-2.06, 3.94]	2015
Total (95% CI)			**163**			**163**	**100.0%**	**2.07 [0.37, 3.77]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.15, df = 4 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.39 (P = 0.02)

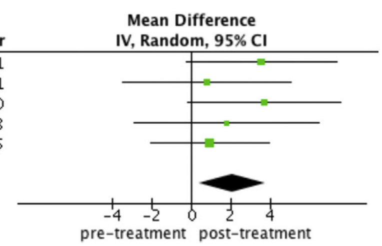


Fig. 5. Forest plots of the mean difference in U1-L1, U1-SN, and L1-MP with the corresponding 95% CIs. U1-L1 = interincisor angle; U1-SN = upper incisor angle to SN plane; L1-MP = lower incisor angle to mandibular plane; CI = confidence interval; SD = standard deviation; df = degrees of freedom.

Study or Subgroup	post-treatment Mean	SD	Total	pre-treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Doff et al., 2010 [18]	34.7	6.8	31	34.3	7.1	31	57.7%	0.40 [-3.06, 3.86]	2010
Gong et al., 2013 [37]	35.24	7.17	25	33.92	7.42	25	42.3%	1.32 [-2.72, 5.36]	2013
Total (95% CI)			**56**			**56**	**100.0%**	**0.79 [-1.84, 3.42]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)

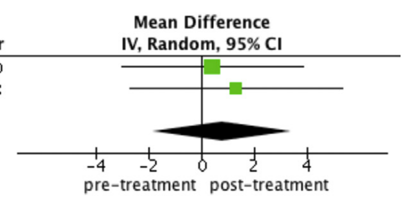


Fig. 6. Forest plot of the mean difference in MP-SN with corresponding 95% CI. MP-SN = angle between the SN plane and MP plane (mandibular plane angle); CI = confidence interval; SD = standard deviation; df = degrees of freedom.

above limitations, we believe that the results of this meta-analysis provide useful data concerning the dental and skeletal changes associated with long-term OA use.

Some studies reported the influence of bite change on OSA patients. It was reported that none of the patients with significant occlusal changes stopped OA use because of these changes [17]. Another study also showed that occlusal changes did not cause patients to discontinue OA use [33]. The authors of both studies concluded that changes of the bite do not influence compliance with OA use for OSA [17,33]. Some studies have shown that bite changes are minor based on follow-up in the actual clinical setting [28], and are tolerable in relation to the therapeutic benefits of OA use for OSA patients [34]. Interestingly, patients with long-term OA use are generally unaware of changes in occlusion [26], which means that it is essential for dentists to monitor these changes by regular follow-up and to explain the possibility of dental changes to the patient when consent is obtained prior to the start of therapy [20,28,34].

The incidence of bite changes was reported to range between 14% and 26% in patients with long-term OA use [16,26]. As bite changes do not occur in all patients, it will be important to develop methods for predicting which patients may develop changes after long-term OA use.

Conclusion

Significant change of OJ, OB, and L1-MP was observed in patients with long-term OA use, while there were no significant changes of skeletal indices or mandibular rotation. Our results suggested that inclination of the incisors may contribute to the decrease of OJ and OB, rather than skeletal change or mandibular rotation. Based on the results of this systematic review and meta-analysis, it may be possible to provide more detailed explanations to patients about the side effects of OA treatment.

Practice points

1. OJ and OB decreased significantly after long-term OA use in proportion to the duration of treatment. These changes were mainly associated with altered inclination of the incisors, rather than skeletal modifications or mandibular rotation.
2. Most of the studies analyzed had a high risk of bias in relation to selection of participants, confounders, and measurement of exposure.
3. Clinicians should appropriately explain the possible side effects of long-term OA use to patients and should provide adequate follow-up. Obtaining written informed consent is recommended.

Research agenda

In the future we need to:

1. Investigate how patient factors influence bite changes by performing studies with objective measures of OA adherence.
2. Find methods to reduce or eliminate bite changes in patients using OAs for OSA.

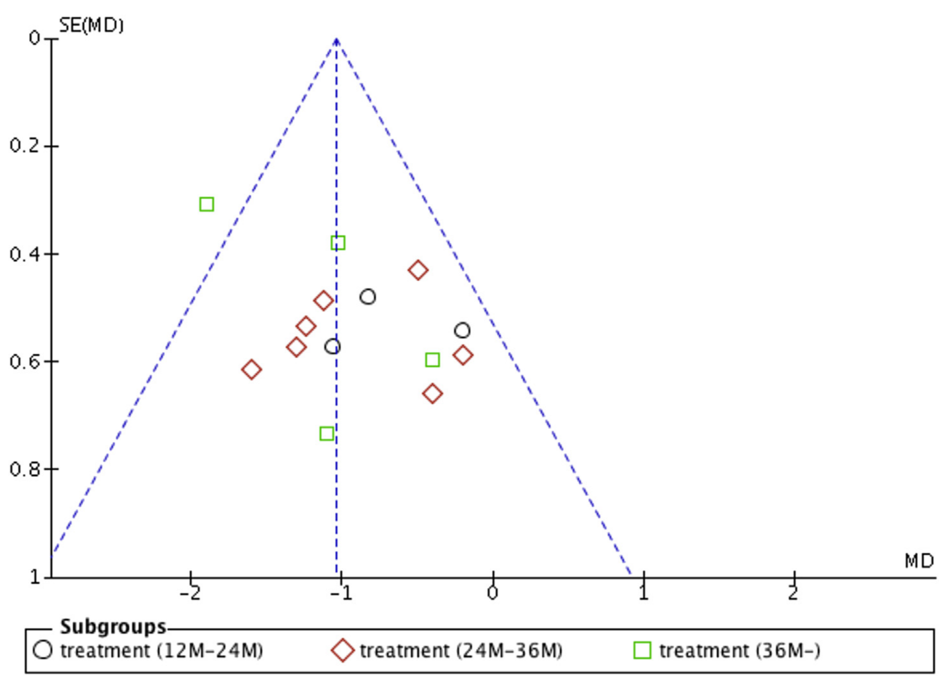
Conflicts of interest

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

Appendix 1. Search terms for Pubmed.

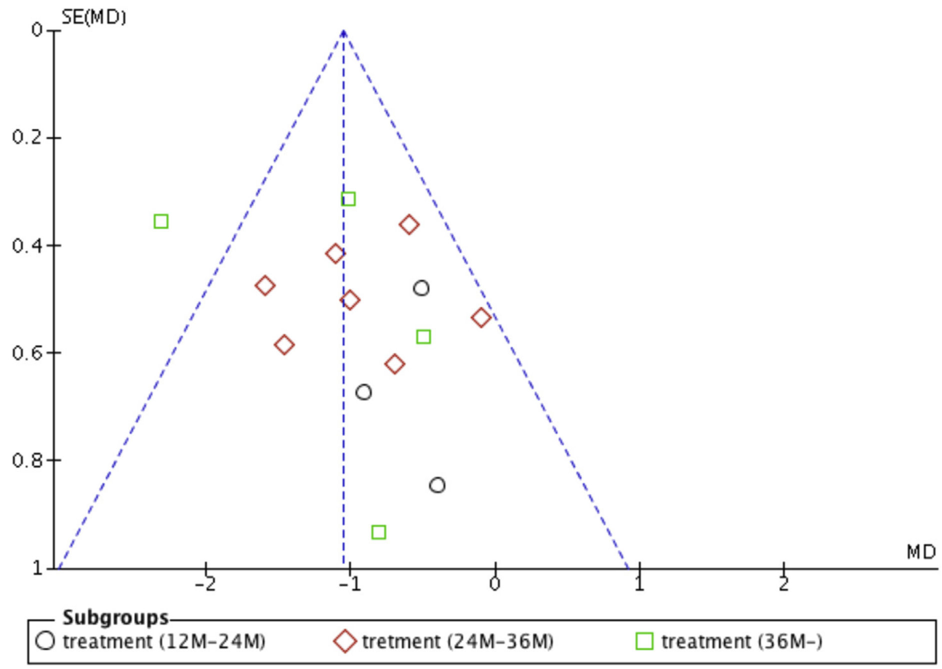
((((((sleep apnea[Mesh]) OR (breathing disorder*[TIAB] OR respiratory disorder*[TIAB]))) AND (((orthodontic appliance[Mesh]) OR (advancement*[TIAB] OR repositioning[TIAB])) OR (device* [TIAB] OR appliance*[TIAB] OR splint*[TIAB]))) AND ((((over jet [TIAB] OR over bite[TIAB])) OR (dental[Mesh] OR occlusal[TIAB])) OR (side effect*[TIAB] OR change*[TIAB]))) AND (retrospective [TIAB] OR retrospectively[TIAB] OR follow-up[TIAB] OR sequellae [TIAB] OR long-term[TIAB]))

Appendix 2.1. Funnel plot of OJ data.



The funnel plot of the OJ data is symmetrical.

Appendix 2.2. Funnel plot of OB data.



The funnel plot of OB data is symmetrical.

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