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Long-term effects of functional appliances in treated versus untreated patients with Class II malocclusion: A systematic review and meta-analysis

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Abstract

Objective

To assess the cephalometric skeletal and soft-tissue of functional appliances in treated versus untreated Class II subjects in the long-term (primarily at the end of growth, secondarily at least 3 years after retention).

Search methods

Unrestricted electronic search of 24 databases and additional manual searches up to March 2018.

Selection criteria

Randomised and non-randomised controlled trials reporting on cephalometric skeletal and soft-tissue measurements of Class II patients (aged 16 years or under) treated with functional appliances, worn alone or in combination with multi-bracket therapy, compared to untreated Class II subjects.

Data collection and analysis

Mean differences (MDs) and 95% confidence intervals (95% CIs) were calculated with the random-effects model. Data were analysed at 2 primary time points (above 18 years of age, at the end of growth according to the Cervical Vertebral Maturation method) and a secondary time point (at least 3 years after retention). The risk of bias and quality of evidence were assessed according to the ROBINS tool and GRADE system, respectively.

Results

Eight non-randomised studies published in 12 papers were included. Functional appliances produced a significant improvement of the maxillo-mandibular relationship, at almost all time points (Wits appraisal at the end of growth, MD -3.52 mm, 95% CI -5.11 to -1.93, P < 0.0001). The greatest increase in mandibular length was recorded in patients aged 18 years and above (Co-Gn, MD 3.20 mm, 95% CI 1.32 to 5.08, P = 0.0009), although the improvement of the mandibular projection was negligible or not significant. The quality of evidence was 'very low' for most of the outcomes at both primary time points.

Conclusions

Functional appliances may be effective in correcting skeletal Class II malocclusion in the long-term, however the quality of the evidence was very low and the clinical significance was limited.

Systematic review registration

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Introduction

Rationale

Class II malocclusion is the most prevalent antero-posterior jaw problem in orthodontics, affecting one third of the population [1, 2]. The majority of Class II patients exhibit mandibular skeletal retrusion [3, 4]. Reduced mandibular size is also a major feature of Class II malocclusion patients [5]. As a result, there has been great interest in the use of 'functional appliances', designed primarily to influence the lower dentition and enhance the growth of the mandible [3]. These appliances promote forward posturing of the mandible, although their effects also impact on the upper jaw [6, 7].

The potential that functional appliances could modify skeletal growth is of great importance for patients and orthodontists alike. Improving facial aesthetics is one of the main reasons for seeking orthodontic treatment [8] and it is associated with a high level of patient and parent satisfaction [9]. Mandibular retrusion has a negative impact on perceived attractiveness [10], self-esteem and oral health-related quality of life [11]. The magnitude of the retrusion is also an important factor in treatment decision-making. Small skeletal discrepancies may only need multi-bracket therapy for the correction of malocclusion and refinement of teeth alignment. On the other hand, greater discrepancies may require a surgical treatment to modify the position and length of skeletal structures and to attain better aesthetic results [12].

Post-pubertal growth has been shown to produce dramatic alterations in skeletal and dental relationships [13]. There is no consensus on the age at which growth ends [14–18]. Overall, growth continues up to mid-adulthood, with different patterns in the two genders. Males show an anterior rotation of the mandible, whereas females demonstrate a posterior mandibular rotation [17, 18]. An alternative method to establish when growth comes to an end is through using indicators of the growth phase, such as the hand-and-wrist maturation method [19] or the cervical vertebral maturation method [20].

To fully understand the real effects of functional appliances on the growth of the jaws and profile, it is essential to study these effects at the completion of patient growth, when biases and confounding factors due to natural changes are negligible. The long-term stability of these changes is important too.

To date, most systematic reviews investigating the treatment effects of functional appliances in Class II malocclusion patients have synthesized studies evaluating the skeletal and soft-tissue changes at the end of the orthodontic treatment [6, 7, 21–26]. Only two reviews systematically searched for scientific evidence concerning the long-term stability of treatment results achieved by Class II functional appliance therapy [27, 28]. Another systematic review is ongoing [29]. No previous reviews determined the effects of removable and fixed functional appliances in patients with Class II malocclusion compared to untreated controls at growth completion.

Objective

The objective of this systematic review was therefore to assess the skeletal and soft-tissue effects measured on lateral cephalograms produced by functional appliances in treated versus untreated Class II subjects in the long-term (primarily at the end of growth, secondarily at least 3 years after retention).

Materials and methods

Protocol and registration

The present systematic review was performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [30], and is reported on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (S1 table [31]). The protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO) on 03 April 2018 (registration number CRD42018092139).

Information sources

The search strategy covered 11 bibliographic databases, 10 non-bibliographic databases and 3 unpublished studies sources, from their launch to March 2018 [32–35]. Hand-searching of the most common orthodontic journals was performed as well. The Cochrane Master List was consulted to facilitate the identification of these journals [30, 34, 36]. The reference lists of the trials eligible for inclusion and systematic reviews concerning Class II malocclusion treatment were also checked. Information concerning the name of the search source, the date range that were searched, and, for electronic databases, the search platform or provider are presented in S2 table.

Search

Search strategies were developed using medical subject headings (MeSH) and text words related to functional appliances. The search strategies of the preliminarily identified systematic reviews published between 2015 and 2018 were collected [6, 7, 21–26, 28]. As recommended by the Cochrane Collaboration [30], terms related to only three aspects of the review's question were selected: participants, interventions and timing.

Preliminary searches were conducted to screen the list of queries and define the MEDLINE and Google Scholar search strategies. After the MEDLINE strategy had been finalised, it was adapted to the syntax and subjects headings of the other databases. No restrictions based on

language, publication year, or publication status were applied to the search. The search strategy designed for each database is shown in S3 table.

Eligibility criteria

Randomised and non-randomised controlled trials reporting on cephalometric skeletal and soft-tissue measurements of Class II patients (aged 16 years or under) treated with functional appliances, worn alone or in combination with multi-bracket therapy, compared to untreated Class II subjects were included (Table 1). The rationale behind eligibility criteria is provided in S1 Appendix.

Study selection

Search results from those databases allowing for the export of valid file formats (MEDLINE, EMBASE, CENTRAL, LILACS, Web of Science, Scopus and ProQuest Dissertation & Theses) were uploaded to EndNote software. Results from Google Scholar, TRIP Database, British Library Direct, ISI proceedings, hand-searching, unpublished and ongoing studies were managed manually. A calibration exercise was undertaken to pilot and refine the screening questions, before initiating the formal screening process.

G.C. and A.U. independently screened the titles and abstracts to remove obviously irrelevant reports. After having retrieved full texts of potentially relevant and unclear reports, the reviewers examined if these met the eligibility criteria. Multiple reports of the same study were linked together at the end of the selection process [30]. G.C. sought additional information from study authors when it was deemed necessary to resolve questions about eligibility.

Table 1. Eligibility criteria used for the study selection.

Category	Inclusion	Exclusion
Study designs	Randomised controlled trials (RCTs), controlled (non-randomised) clinical trials (CCTs), controlled before-after (CBA) studies, and case-control or nested case-control studies	Prospective and retrospective cohort studies, cross-sectional studies, case series, and case reports
Participants	Children and adolescents (aged 16 years or under) receiving orthodontic treatment to correct Class II malocclusion	Participants with a cleft lip or palate or both, other craniofacial deformity/ syndrome (such as Apert, Crouzon, Hemifacial Microsomia/Goldenhar, Moebius, Pierre Robin, Treacher Collins syndromes or craniosynostosis), syndromes affecting the craniofacial structures or patients with temporo-mandibular joint disorders
	Active treatment with functional appliances had to be completed by the age of 16 years	
Interventions	Any type of functional appliance, defined as a removable or fixed orthodontic appliance that postures the mandible forward	Association with other Class II devices designed primarily to restrain the maxilla (e.g. headgear)
	Functional appliances worn alone or in combination with multi-bracket therapy. When functional appliances were worn alone, this therapy could also take place after the functional appliance treatment.	
	Functional appliances worn for 6 months or longer	
Comparators	Untreated Class II subjects	
	Groups with similar ages at the commencement of the observational period (age differences between the treated and untreated groups less than 18 months)	
Outcomes	Cephalometric skeletal measurements evaluating the antero-posterior position of the maxilla and mandible, the total mandibular length or length of its parts (ramus and corpus), the mutual relationship between the two jaws	
	Soft tissue changes of both lips and chin, measured on lateral cephalograms	
Timing	At the end of growth, defined by age or using indicators of the growth phase	
	Post-retention period of at least 3 years	

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Reviewers resolved disagreements by discussion, and an arbitrator (C.S.) adjudicated unresolved disagreements. Primary reasons for excluding trials were recorded.

Data collection process

G.C. and A.U. independently extracted data using a piloted data extraction form. This electronic form originated from those proposed by the Cochrane Collaboration [30] and a previous Cochrane review on Class II malocclusion [26]. To ensure consistency across reviewers, calibration exercises were conducted before starting the review. Disagreements were resolved through discussion.

Data items

Information was extracted from each included study on source and general information, methods, characteristics of participants and interventions, outcomes, data and analysis.

Risk of bias in individual studies

The risk of bias tool for non-randomised studies of interventions (ROBINS-I tool [37]) was used to ascertain the quality of the evidence of included trials.

Summary measures

Data were summarised and considered suitable for pooling only if the same cephalometric measurement was used for the same outcome. To circumvent the issue of the different follow-up periods of included studies, the overall treatment and post-treatment changes were analysed [30]. Mean differences (MDs) and 95% confidence intervals (95% CIs) between these changes were calculated. Whenever necessary, the enlargement of linear measurements due to the radiographic examination was adjusted at 0%. Studies in which the magnification was not reported for linear measurements were excluded from meta-analyses.

Skewed data and non-quantitative data were presented in narrative format.

Synthesis of results

The random-effects model proposed by DerSimonian and Laird [38] was chosen a priori to combine and compare data from included studies. The presence of statistical heterogeneity was assessed by inspecting the overlap of the confidence intervals in the forest plots and by using the chi-squared (Chi^2) test, while the impact of between-study heterogeneity on the meta-analysis was tested by calculating the τ^2 and the I^2 statistics [39].

Since variation applies as much within studies as across them, the choice to treat each independent subgroup as a separate study was preferred to computing a composite effect for each study and using it in the analysis [40].

As there is no consensus on the age at which growth ends, treatment effects were evaluated at 2 primary time points:

- Above 18 years of age. The age threshold of 18 years was chosen to maximise the data available [30];
- At the end of growth documented by the Cervical Vertebral Maturation (CVM) method (cervical vertebral maturation stage 5 or 6 [20]);

A secondary time point was established after a post-retention period of at least 3 years.

Additional analysis

Subgroup and sensitivity analyses were performed in order to explore the source of heterogeneity and test the overall robustness of the data, respectively. All subgroup and sensitivity analyses were pre-specified in the protocol.

For all outcomes, results were divided according to the type of functional appliance.

For the most clinically important outcomes, subgroup analyses were based on the following:

- Patient characteristics (gender);
- Beginning of the functional appliance therapy according to age (early treatments, commencing in children aged between 7 and 11 years; late treatments, beginning in adolescents aged between 12 and 16 years);
- Start of the treatment according to the cervical vertebral maturation method (early treatments, with patients presenting with Cervical Vertebral Maturation Stage [CVMS] 1 or 2 at the first observation; late treatments, with subjects presenting with CVMS 2 or 3);
- Post-retention period duration (3–4, 5–10 years after active treatment with functional appliances);

Sensitivity analysis was performed to examine the impact of the study quality assessment on the overall estimates of effect.

Risk of bias across studies

Outcome reporting bias and publication bias were evaluated. In order to determine whether reporting bias was present, the Clinical Trial Register was screened using the International Clinical Trials Registry Platform of the World Health Organisation (http://apps.who.int/trialssearch). When protocols were identified, discrepancies between the outcomes planned in the protocol and those reported in the final manuscript were assessed. The potential for reporting bias was explored by funnel plots if $\geq$10 studies were available [40].

The quality of evidence for all outcomes at both primary time points was judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology [41].

Results

Study selection

The results of the search are summarised in Fig 1. Among 3046 records, eight non-randomised studies published in 12 papers were identified for inclusion in this review [42–49]. Two authors were contacted to clarify whether duplicate data was used in their trials. Since the study by Pavoni et al. [43] contained partial data of previous studies [50–52] and has the greater sample size and subgroup analysis, it was considered the reference study of the other reports. The thesis by Wigal [47] with complete data of the subsequent published study [53] was included as well. Excluded studies with reasons are listed in supplementary files (S4 Table, S2 Appendix).

Study characteristics

The main characteristics of the 8 included studies are presented in Tables 2–3. All the studies were retrospective controlled clinical trials [42–49]. A wide range of eligibility criteria was found in the included studies. Class II malocclusion was defined by both skeletal and dental

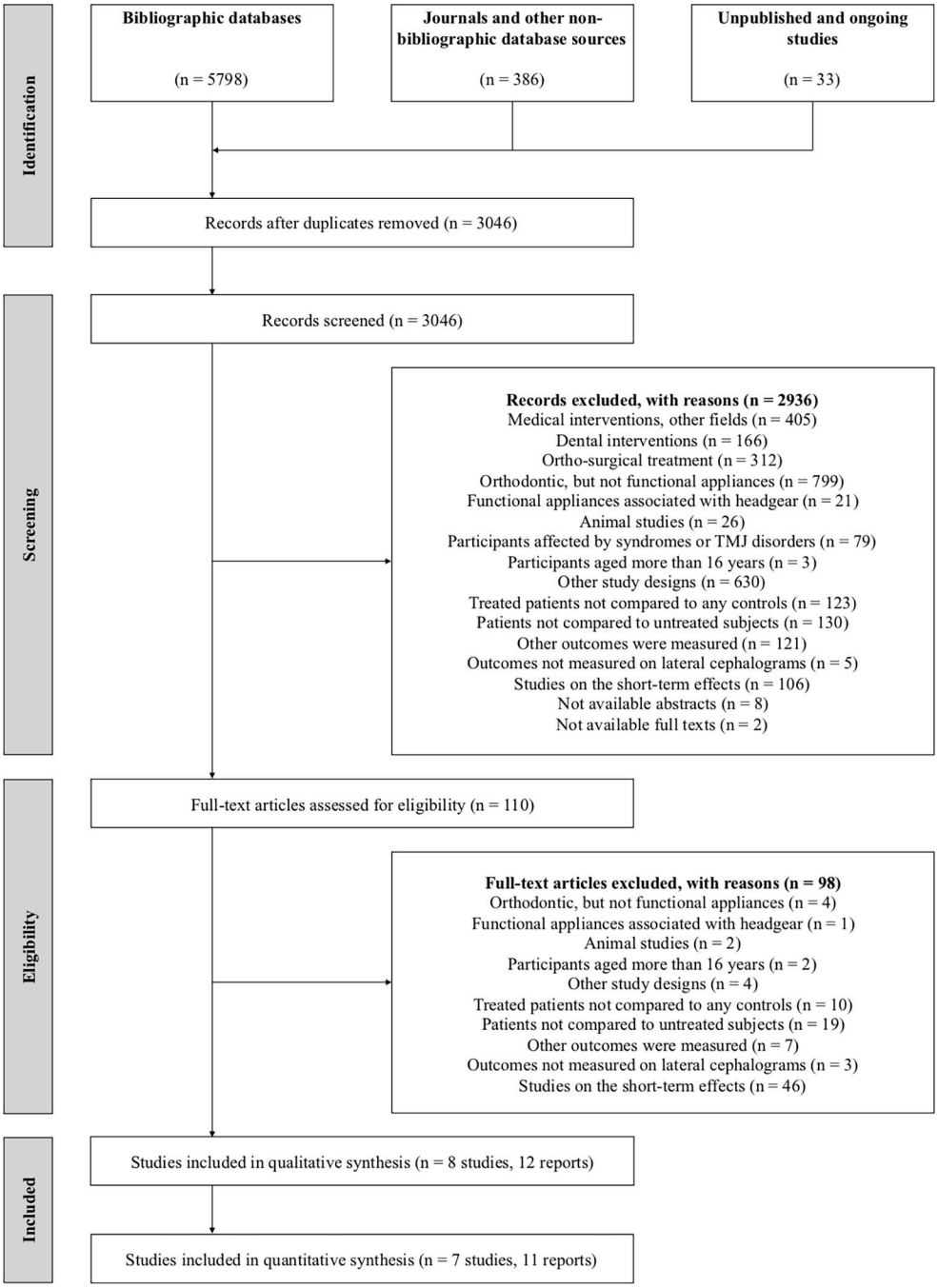

Fig 1. PRISMA flow diagram.

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parameters. Six trials used historical controls for the comparison with treated patients [43, 45, 46–49].

Five studies evaluated the treatment effects of three removable functional appliances as follows:

- Activator only [42];

Table 2. Characteristics of included studies (participants, interventions, outcomes).

Study	Groups (N)	Participants	Interventions		Outcomes		
			T1-T2	T2-T3	Mx skeletal	Md skeletal	Mx-Md skeletal
Wieslander 1979	TG (23)	ANB > 6 degrees, full Class II molar relationship, mixed dentition	Act	None	A to S perp	Pg to S perp, Co-Gn, Ar-Gn, Co to mand	ANB
	CG (23)	Matched according to gender, age, ethnicity, and socioeconomic background	None	None			
Pavoni 2017	TG (46)	ANB > 4 degrees, full Class II or end-to-end molar relationship, excessive overjet (greater than 5 mm)	Bio / Act	MBA	SNA	SNB, Pg to N perp, Co-Gn, Co-Go	ANB, Wits
	CG (31)	Matched according to age and skeletal maturation, and starting cephalometric characteristics	None	None			
Falck 1991	TG (50)	Class II division 1 malocclusion (no definition)	Fr2	-	Horiz. A to ORS	Horiz. B or Pg to ORS, Co-Gn	-
	CG (38)	Matched according to gender and age	None	None			
Freeman 2009	TG (30)	Full Class II molar relationship, excessive overjet (no definition)	Fr2	-	SNA, A to N perp, Co-A	SNB, Pg to N perp, Co-Gn	ANB, Wits, Co-Gn/Co-A diff
	CG (20)	Matched according to gender, age and skeletal maturation, and starting cephalometric characteristics	None	None			
Angelieri 2014	TG (17)	ANB > 2 degrees, full Class II or end-to-end molar relationship, excessive overjet (greater than 5 mm), late mixed dentition	Fr2	Fr2 / None	SNA, A to N perp, Co-A	SNB, Pg to N perp, Co-Gn	ANB, Wits, Co-Gn/Co-A diff
	CG (17)	Matched according to gender, age and skeletal maturation	None	None			
Wigal 2008	TG (22)	ANB > 4 degrees, mixed dentition	Hb	MBA	SNA, Co-A, Olp-A	SNB, Co-Gn, Olp-Pg, Olp-Co	ANB, Wits, Co-Gn/Co-A diff
	CG (22)	Matched according to gender, age, and starting cephalometric characteristics	None	None			
Drosen 2018	TG (13)	Class II malocclusion (no definition)	Hb +/- MBA	Act / None	SNA	SNB, Ar-Go	ANB, Wits
	CG (13)	Matched according to gender and age	None	None			
Alhoraibi 2017	TG (39)	ANB > 4 degrees, full Class II or end-to-end molar relationship, excessive overjet (greater than 10 mm)	FRD + MBA	None	SNA, A to N perp, Co-A	SNB, Pg to N perp, Co-Gn	ANB, Wits, Co-Gn/Co-A diff
	CG (39)	Matched according to gender, age and skeletal maturation, and starting cephalometric characteristics	None	None			

N, number of participants; TG, treated group; CG, control group

Act, Activator; Bio, Bionator; Fr2, Frankel-2; Hb, Herbst; FRD, Forsus; MBA, multi-bracket appliances

Mx skeletal, maxillary skeletal outcomes; SNA, SNA angle; A to N perp, A point to N perpendicular distance; A to S perp, A point to S perpendicular distance; Horiz. A to ORS, horizontal distance of A point to occipital reference system; Co-A, Co-A distance; Olp-A, distance of A point to occlusal line perpendicular

Md skeletal, mandibular skeletal outcomes; SNB, SNB angle; Pg to N perp, Pg point to N perpendicular distance; Pg to S perp, Pg point to S perpendicular distance; Horiz. B or Pg to ORS, horizontal distance of B point or Pg point to occipital reference system; Co-Gn, Co-Gn distance; Ar-Gn, Ar-Gn distance; Olp-Pg, distance of Pg point to occlusal line perpendicular; Olp-Co, distance of Co point to occlusal line perpendicular; Co to mand, distance of Co point to mandibular plane; Co-Go, Co-Go distance; Ar-Go, Ar-Go distance

Mx-md skeletal, maxillo-mandibular outcomes; ANB, ANB angle; Wits, Wits appraisal; Co-Gn/Co-A diff, Co-Gn/Co-A difference.

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- A mixed group of patients treated either with the Bionator or Activator [43];
- Frankel-2 appliance only [44–46].

Two trials evaluated respectively the effects of early treatment (mean age at start = 8.4 years [47]) and late treatment (mean age at start = 12.4 years [48]) of a fixed rigid appliance, the Herbst appliance. One study tested a fixed flexible appliance, the Forsus appliance [49]. Multi-bracket therapy was worn concurrently with functional appliance treatment in one study [49], and after functional appliance therapy in 3 trials [43, 47, 48]. A variety of appliances and retention protocols were used in the post-treatment period. All the studies compared Class II malocclusion patients treated with functional appliances to untreated Class II subjects [42–49].

Table 3. Characteristics of included studies (timing).

Study or subgroup	Groups (N)	Timing											
		T1			T2			T3			T1-T2	T2-T3	T1-T3
		Mean	SD	CVSM	Mean	SD	CVSM	Mean	SD	CVSM			
Wieslander 1979	TG (23)	~ 10	-	-	~ 13	-	-	~ 17	-	-	3.0	4.0	7.0
	CG (23)	~ 10	-	-	~ 13	-	-	~ 17	-	-	3.0	4.0	7.0
Pavoni 2017 (early)	TG (23)	9.5	1.2	1-2	11.4	1.2	1-3	17.9	2.3	5-6	1.9	6.5	8.4
	CG (16)	9.4	0.7	1-2	11.3	0.7	1-3	17.0	1.8	5-6	1.9	5.7	7.6
Pavoni 2017 (late)	TG (23)	10.2	1.3	2-3	12.5	1.2	4-5	18.5	2.1	5-6	2.3	6.0	8.3
	CG (15)	10.8	1.1	2-3	12.7	1.2	4-5	18.3	1.3	5-6	1.9	5.6	7.5
Falck 1991 (males)	TG (19)	7.3	-	-	-	-	-	17.5	-	-	-	-	10.2
	CG (18)	7.0	-	-	-	-	-	16.4	-	-	-	-	9.4
Falck 1991 (females)	TG (31)	7.3	-	-	-	-	-	17.2	-	-	-	-	9.9
	CG (20)	7.7	-	-	-	-	-	17.9	-	-	-	-	10.2
Freeman 2009	TG (30)	8.1	1.3	1-2	-	-	-	18.0	3.4	5-6	-	-	9.9
	CG (20)	8.5	1.2	1-2	-	-	-	18.2	3.7	5-6	-	-	9.7
Angelieri 2014	TG (17)	10.8	0.6	1-3	12.5	0.6	1-4	19.7	0.7	5-6	1.7	7.2	8.9
	CG (17)	11.3	0.6	1-3	12.7	0.6	2-4	18.9	2.0	5-6	1.4	6.2	7.6
Wigal 2008 (males)	TG (7)	8.7	1.3	-	9.6	1.2	-	15.2	1.5	-	0.9	5.6	6.5
	CG (7)	8.7	1.1	-	9.6	1.1	-	15.2	1.9	-	0.9	5.6	6.5
Wigal 2008 (females)	TG (15)	8.3	0.9	-	9.1	0.4	-	14.3	1.3	-	0.8	5.2	6.0
	CG (15)	8.3	1.1	-	9.2	0.3	-	14.4	1.3	-	0.9	5.2	6.1
Drosen 2018 (males)	TG (13)	12.4	0.9	-	14.2	1.2	-	20.2	1.0	-	1.8	6.0	7.8
	CG (13)	12.1	0.5	-	14.2	0.6	-	19.8	2.3	-	2.1	5.6	7.7
Alhoraibi 2017 (early)	TG (18)	11.5	0.8	1	13.1	0.8	-	16.4	1.1	-	1.6	3.3	4.9
	CG (18)	11.8	0.9	1	13.9	1.5	-	17.1	1.3	-	2.1	3.2	5.3
Alhoraibi 2017 (late)	TG (21)	13.3	0.6	2-3	15.3	0.8	-	18.4	1.0	-	2.0	3.1	5.1
	CG (21)	13.5	0.8	2-3	15.1	0.6	-	18.2	0.7	-	1.6	3.1	4.7

N, number of participants; TG, treated group; CG, control group

T1, at the start of the active phase of functional appliance therapy; T2, at the end of the active phase of functional appliance therapy; T3, long-term follow-up

SD, standard deviation; CVMS, cervical vertebral maturation stage.

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Only cephalometric skeletal measurements were recorded from the 8 studies included in this review [42–49]. Soft tissue changes of both lips and chin measured on lateral cephalograms were investigated only by a report [51] of an included study [43]. Cephalometric magnifications were set at 0% [47, 48], 8% [43, 45, 49], 10% adjusted to 0% [46]. In the rest of the studies, information was not provided [42, 44]. Outcomes were assessed above 18 years in age in 5 trials (5 subgroups [43, 45, 46, 48, 49]) and at the end of growth using the cervical vertebral maturation method in 3 trials (4 subgroups [43, 45, 46]). All the studies had a post-retention period of at least 3 years (Table 3 [42–49]).

Risk of bias within studies

The overall risk of bias ranged from moderate to critical in the included studies (Table 4). Most studies suffered bias in selection of participants and due to deviations from intended interventions [42–49]. The estimated effect can be predicted to be greater than the true effect estimate in studies with the observed selection bias [42, 43, 49]. Multi-bracket therapy, as well as retention appliances, could enhance the treatment effects of functional jaw orthopaedics or control their relapse [43, 47–49].

Table 4. Risk of bias for multiple outcomes within included studies, according to the risk of bias tool for non-randomised studies of interventions (ROBINS-I tool).

Bias domain	Signalling question	Wieslander and Lagerström, 1979	Pavoni et al., 2017	Falck, 1991	Freeman et al., 2009	Angelieri et al., 2014	Wigal, 2008	Drosen et al., 2018	Alhoraibi, 2017
1. Bias due to confounding	1.1	Y	Y	Y	Y	Y	Y	Y	Y
	1.2	N	N	N	N	N	N	N	N
	1.3	-	-	-	-	-	-	-	-
	1.4	PY	PY	PY	PY	PY	PY	PY	PY
	1.5	PY	PY	PY	PY	PY	PY	PY	PY
	1.6	PN	PN	PN	PN	PN	PN	PN	PN
	1.7	PY	Y	PY	PY	PY	PY	PY	PY
	1.8	PY	PY	PY	PY	PY	PY	PY	PY
Risk of bias judgement		Low	Low	Low	Low	Low	Low	Low	Low
2. Bias in selection of participants into the study	2.1	Y	PY	NI	NI	PY	NI	NI	PN
	2.2	Y	Y	-	-	Y	-	-	-
	2.3	Y	Y	-	-	Y	-	-	-
	2.4	Y	Y	Y	Y	Y	Y	Y	Y
	2.5	N	N	-	-	N	-	-	-
Risk of bias judgement		Crit	Ser	Low	Low	Ser	Low	Low	Low
3. Bias in classification of interventions	3.1	Y	Y	Y	Y	Y	Y	Y	Y
	3.2	Y	Y	Y	Y	Y	Y	Y	Y
	3.3	N	N	N	N	N	N	N	N
Risk of bias judgement		Low	Low	Low	Low	Low	Low	Low	Low
4. Bias due to deviations from intended interventions	4.1	PN	PN	N	N	N	PN	Y	PN
	4.2	-	-	-	-	-	-	Y	-
	4.3	NI	PN	Y	Y	Y	PN	PN	PN
	4.4	PY	PY	PY	PY	PY	PY	PY	PY
	4.5	PY	PY	PY	PY	PY	PY	PY	PY
	4.6	-	-	-	-	-	-	-	-
Risk of bias judgement		Low	Mod	Low	Low	Low	Mod	Ser	Mod
5. Bias due to missing data	5.1	N	Y	Y	Y	Y	N	Y	Y
	5.2	PN	PN	PN	PN	PN	PN	PN	PN
	5.3	Y	PN	PN	PN	PN	PN	PN	PN
	5.4	Y	-	-	-	-	Y	-	-
	5.5	PN	-	-	-	-	PN	-	-
Risk of bias judgement		Ser	Low	Low	Low	Low	Mod	Low	Low
6. Bias in measurement of outcomes	6.1	NI	NI	NI	NI	NI	NI	NI	NI
	6.2	NI	NI	NI	NI	NI	NI	NI	NI
	6.3	Y	Y	Y	Y	Y	Y	Y	Y
	6.4	PN	PN	PN	PN	PN	PN	PN	PN
Risk of bias judgement		Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod
7. Bias in selection of the reported result	7.1	PN	PN	PN	PN	PN	PN	PN	PN
	7.2	PY	PY	PY	PY	PY	PY	PY	PY
	7.3	N	N	N	N	N	N	N	N
Risk of bias judgement		Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod
Overall risk of bias		**Crit**	**Ser**	**Mod**	**Mod**	**Ser**	**Mod**	**Ser**	**Mod**

Y, yes; PY, probably yes; N, no; PN, probably no; NI, no information.

"-", not applicable or nothing to note

Mod, moderate; Ser, serious; Crit, critical.

https://doi.org/10.1371/journal.pone.0221624.t004

Results of individual studies

The main results of the included studies are reported in S5–S6 Tables.

Only one report [51] found that Bionator therapy was able to significantly alter the sagittal position of both the maxillary and mandibular soft tissue profile components. During the overall observation period, functional jaw orthopaedics with the Bionator, followed by multi-bracket appliances produced a restraining effect on the soft tissue A point (-1.8 mm, CI not reported) and a protrusive effect on the soft tissue Pg point (+2.6 mm, CI not reported).

Synthesis of results

Seven studies (10 subgroups [42, 43, 45–49]) were included in the meta-analyses of 9 outcomes at 3 time points (Table 5). Subgroup analyses according to the type of functional appliance are presented together with their overall effects (Tables 6–7). The forest plots concerning the most clinically relevant results are reported in the main text. Other findings are set out in S3 Appendix.

Maxillary/Upper jaw changes. It was found that functional appliances produced a statistically significant reduction in the angular position of the maxilla (SNA angle) at the end of growth according to the CVM method (MD -0.73˚, 95% CI -1.31 to -0.15, P = 0.01, I^2 = 0%, 4 studies [Fig 2]) and after a post-retention period of at least 3 years (MD -1.03˚, 95% CI -1.88 to -0.18, P = 0.02, I^2 = 84%, 9 studies [Table 5]).

The most clinically relevant maxillary effects were produced by fixed functional appliances: the Herbst appliance (Co-A distance at least 3 years after retention, MD -4.08 mm, 95% CI -6.03 to -2.12, P < 0.0001, I^2 = 0%, 2 studies [Table 7]) and the Forsus device, in combination with multi-bracket therapy (A to N perpendicular distance above 18 years of age, MD -6.30 mm, 95% CI -7.01 to -5.59, P < 0.00001, I^2 = Not applicable, 1 study [Table 7]).

Mandibular/Lower jaw changes. Treated patients showed a statistically significant increase in the mandibular length (Co-Gn distance) compared to untreated subjects, at both primary time points. The increase in the mandibular growth was 3.20 mm in patients aged 18 years and above (95% CI 1.32 to 5.08, P = 0.0009, I^2 = 75%, 4 studies [Fig 3]) and 2.87 mm at the end of growth according to the CVM method (95% CI 0.47 to 5.26, P = 0.02, I^2 = 74%, 4 studies [Fig 4]).

The angular improvement of the mandibular projection was significant above 18 years of age (SNB angle, MD 0.66˚, 95% CI 0.03 to 1.29, P = 0.04, I^2 = 43%, 5 studies [Table 5]), however the linear improvement of the same outcome was not significant at any time point (Pg to N perpendicular distance above 18 years of age, MD 1.42 mm, 95% CI 0.01 to 2.84, P = 0.05, I^2 = 70%, 4 studies [Table 5]).

Removable functional appliances produced greater treatment effects than fixed devices. The greatest significant increase in the mandibular growth (Co-Gn distance) above 18 years of age was observed in a single study [43], in which a mixed subgroup of patients was treated either with the Bionator or Activator during puberty (MD 5.10 mm, 95% CI 3.29 to 6.91, P < 0.00001, I^2 = Not applicable, 1 study [Table 6]). This group also showed a statistically significant improvement of the sagittal projection of the mandible (Pg to N perpendicular distance, MD 2.90 mm, 95% CI 1.11 to 4.69, P = 0.001, I^2 = Not applicable, 1 study [Table 6]), although the test for subgroup differences was not significant (P = 0.13, I^2 = 51.5%).

Maxillo-mandibular changes. Functional appliance therapy produced a statistically significant improvement of the mutual relationship between the maxilla and mandible, at almost all time points. The most clinically relevant maxillo-mandibular changes were recorded at the end of growth according to the CVM method, when treated patients exhibited an improvement in both angular and linear measurements relative to the controls (ANB angle, MD

Table 5. Details of the performed meta-analyses with tests on heterogeneity.

Outcome	Time point	Overall effect				Heterogeneity			
		N_s	MD	95% CI	P	Tau^2	Chi^2	P	I^2
Mx skeletal									
SNA (degrees)	Age 18 +	5	-0.31	-0.83, 0.21	0.24	0.05	4.62	0.33	13%
	CVMS 5-6	4	-0.73	-1.31, -0.15	0.01	0.00	0.02	1.00	0%
	3-years +	9	-1.03	-1.88, -0.18	0.02	1.28	50.87	0.00	84%
A to N perp (mm)	Age 18 +	3	-2.41	-6.45, 1.62	0.24	12.54	140.47	0.00	99%
	CVMS 5-6	2	-0.48	-2.74, 1.77	0.67	2.41	11.49	0.00	91%
	3-years +	4	-2.24	-4.79, 0.30	0.08	6.57	164.00	0.00	98%
Co-A (mm)	Age 18 +	3	0.53	0.00, 1.05	0.05	0.00	0.65	0.72	0%
	CVMS 5-6	2	0.15	-1.16, 1.46	0.82	0.00	0.27	0.60	0%
	3-years +	6	-0.96	-2.32, 0.40	0.17	2.04	39.60	0.00	87%
Md skeletal									
SNB (degrees)	Age 18 +	5	0.66	0.03, 1.29	0.04	0.22	7.05	0.13	43%
	CVMS 5-6	4	0.65	-0.45, 1.74	0.25	0.89	10.25	0.02	71%
	3-years +	9	0.14	-0.48, 0.76	0.67	0.52	21.67	0.01	63%
Pg to N perp (mm)	Age 18 +	4	1.42	0.01, 2.84	0.05	1.39	10.02	0.02	70%
	CVMS 5-6	4	1.54	-0.25, 3.32	0.09	2.22	9.30	0.03	68%
	3-years +	6	0.86	-0.41, 2.13	0.18	1.80	23.00	0.00	78%
Co-Gn (mm)	Age 18 +	4	3.20	1.32, 5.08	0.00	2.61	11.89	0.01	75%
	CVMS 5-6	4	2.87	0.47, 5.26	0.02	4.38	11.57	0.01	74%
	3-years +	8	1.79	-0.05, 3.64	0.06	5.73	57.49	0.00	88%
Mx-md skeletal									
ANB (degrees)	Age 18 +	5	-1.00	-2.15, 0.16	0.09	1.52	35.86	0.00	89%
	CVMS 5-6	4	-1.31	-2.37, -0.24	0.02	0.97	17.21	0.00	83%
	3-years +	10	-1.11	-1.82, -0.40	0.00	1.07	57.36	0.00	84%
Wits (mm)	Age 18 +	5	-3.40	-4.45, -2.35	0.00	0.87	11.10	0.03	64%
	CVMS 5-6	4	-3.52	-5.11, -1.93	0.00	1.85	10.71	0.01	72%
	3-years +	9	-2.89	-3.64, -2.14	0.00	0.78	23.26	0.00	66%
Co-Gn/Co-A diff (mm)	Age 18 +	3	2.07	0.79, 3.35	0.00	0.64	3.99	0.14	50%
	CVMS 5-6	2	2.69	1.51, 3.86	0.00	0.00	0.49	0.48	0%
	3-years +	6	2.56	1.07, 4.05	0.00	2.64	24.57	0.00	80%

Mx skeletal, maxillary skeletal outcomes; SNA, SNA angle; A to N perp, A point to N perpendicular distance; Co-A, Co-A distance

Md skeletal, mandibular skeletal outcomes; SNB, SNB angle; Pg to N perp, Pg point to N perpendicular distance; Co-Gn, Co-Gn distance

Mx-md skeletal, maxillo-mandibular outcomes; ANB, ANB angle; Wits, Wits appraisal; Co-Gn/Co-A diff, Co-Gn/Co-A difference

Age 18 +, above 18 years of age; CVMS 5–6, at the end of growth according to the cervical vertebral maturation method; 3-years +, after a post-retention period of at least 3 years

N_s, number of studies or subgroups; MD, mean differences; 95% CI, 95% confidence intervals; P, P value.

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-1.31˚, 95% CI -2.37 to -0.24, P = 0.02, I^2 = 83%, 4 studies [Fig 5]; Wits appraisal, MD -3.52 mm, 95% CI -5.11 to -1.93, P < 0.0001, I^2 = 72%, 4 studies [Fig 6]; Co-Gn/Co-A difference, MD 2.69 mm, 95% CI 1.51, 3.86, P < 0.0001, I^2 = 0%, 2 studies [Fig 7]).

The Frankel-2 appliance worn alone improved all skeletal maxillo-mandibular outcomes regardless of the time point chosen. The statistically significant improvement of the ANB angle, Wits appraisal and Co-Gn/Co-A difference were respectively -1.82˚ (95% CI -2.69 to -0.94, P < 0.0001, I^2 = 38%, 2 studies [Fig 5]), -3.64 mm (95% CI -5.59 to -1.68, P = 0.0003, I^2 = 75%, 2 studies [Fig 6), and 2.69 mm (95% CI 1.51 to 3.86, P < 0.00001, I^2 = 0%, 2 studies [Fig 7]).

Table 6. Details of the performed subgroup analysis according to the type of functional appliance (Bionator/Activator and multi-bracket appliances, Frankel-2 appliance).

Outcome	Time point	Bionator/Activator + multibracket appliances				Frankel-2 appliance			
		N_s	MD	95% CI	P	N_s	MD	95% CI	P
Mx skeletal									
SNA (degrees)	Age 18 +	1	-0.70	-2.20, 0.80	0.36	2	-0.70	-1.46, 0.06	0.07
	CVMS 5-6	2	-0.76	-1.67, 0.14	0.10	2	-0.70	-1.46, 0.06	0.07
	3-years +	2	-0.76	-1.67, 0.14	0.10	2	-0.70	-1.46, 0.06	0.07
A to N perp (mm)	Age 18 +	-	-	-	-	2	-0.48	-2.74, 1.77	0.67
	CVMS 5-6	-	-	-	-	2	-0.48	-2.74, 1.77	0.67
	3-years +	-	-	-	-	2	-0.48	-2.74, 1.77	0.67
Co-A (mm)	Age 18 +	-	-	-	-	2	0.15	-1.16, 1.46	0.82
	CVMS 5-6	-	-	-	-	2	0.15	-1.16, 1.46	0.82
	3-years +	-	-	-	-	2	0.15	-1.16, 1.46	0.82
Md skeletal									
SNB (degrees)	Age 18 +	1	1.10	-0.19, 2.39	0.09	2	1.19	0.11, 2.26	0.03
	CVMS 5-6	2	0.12	-1.74, 1.99	0.90	2	1.19	0.11, 2.26	0.03
	3-years +	2	0.12	-1.74, 1.99	0.90	2	1.19	0.11, 2.26	0.03
Pg to N perp (mm)	Age 18 +	1	2.90	1.11, 4.69	0.00	2	1.16	-2.26, 4.59	0.51
	CVMS 5-6	2	2.05	0.11, 3.99	0.04	2	1.16	-2.26, 4.59	0.51
	3-years +	2	2.05	0.11, 3.99	0.04	2	1.16	-2.26, 4.59	0.51
Co-Gn (mm)	Age 18 +	1	5.10	3.29, 6.91	0.00	2	3.18	1.31, 5.04	0.00
	CVMS 5-6	2	2.35	-3.23, 7.93	0.41	2	3.18	1.31, 5.04	0.00
	3-years +	2	2.35	-3.23, 7.93	0.41	2	3.18	1.31, 5.04	0.00
Mx-md skeletal									
ANB (degrees)	Age 18 +	1	-1.80	-2.74, -0.86	0.00	2	-1.82	-2.69, -0.94	0.00
	CVMS 5-6	2	-0.87	-2.64, 0.89	0.33	2	-1.82	-2.69, -0.94	0.00
	3-years +	3	-1.19	-2.41, 0.04	0.06	2	-1.82	-2.69, -0.94	0.00
Wits (mm)	Age 18 +	1	-5.40	-7.66, -3.14	0.00	2	-3.64	-5.59, -1.68	0.00
	CVMS 5-6	2	-3.45	-7.17, 0.27	0.07	2	-3.64	-5.59, -1.68	0.00
	3-years +	2	-3.45	-7.17, 0.27	0.07	2	-3.64	-5.59, -1.68	0.00
Co-Gn/Co-A diff (mm)	Age 18 +	-	-	-	-	2	2.69	1.51, 3.86	0.00
	CVMS 5-6	-	-	-	-	2	2.69	1.51, 3.86	0.00
	3-years +	-	-	-	-	2	2.69	1.51, 3.86	0.00

Mx skeletal, maxillary skeletal outcomes; SNA, SNA angle; A point to N perp, A to N perpendicular distance; Co-A, Co-A distance

Md skeletal, mandibular skeletal outcomes; SNB, SNB angle; Pg point to N perp, Pg to N perpendicular distance; Co-Gn, Co-Gn distance

Mx-md skeletal, maxillo-mandibular outcomes; ANB, ANB angle; Wits, Wits appraisal; Co-Gn/Co-A diff, Co-Gn/Co-A difference

Age 18 +, above 18 years of age; CVMS 5–6, at the end of growth according to the cervical vertebral maturation method; 3-years +, after a post-retention period of at least 3 years

N_s, number of studies or subgroups; MD, mean differences; 95% CI, 95% confidence intervals; P, P value

P_s, test for subgroup differences.

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Additional analysis

Few statistically significant differences were found among the subgroups analysed (Tables 8–9, S3 Appendix). Early treatment with functional appliances (commencing in children aged between 7 and 11 years) produced a greater improvement of the angular antero-posterior position of the maxilla (SNA angle) and the relationship between the two jaws (ANB angle) than late treatment (beginning in adolescents aged between 12 and 16 years).

Table 7. Details of the performed subgroup analysis according to the type of functional appliance (Herbst, Forsus and multi-bracket appliances).

Outcome	Time point	Herbst +/- multibracket appliances				Forsus + multibracket appliances				
		N_s	MD	95% CI	P	N_s	MD	95% CI	P	P_s
Mx skeletal										
SNA (degrees)	Age 18 +	1	-0.60	-1.91, 0.71	0.37	1	0.40	-0.38, 1.18	0.32	0.20
	CVMS 5-6	-	-	-	-	-	-	-	-	0.92
	3-years +	3	-1.62	-3.17, -0.07	0.04	2	-0.92	-3.47, 1.62	0.48	0.77
A to N perp (mm)	Age 18 +	-	-	-	-	1	-6.30	-7.01, -5.59	0.00	0.00
	CVMS 5-6	-	-	-	-	-	-	-	-	NA
	3-years +	-	-	-	-	2	-3.99	-8.50, 0.52	0.08	0.17
Co-A (mm)	Age 18 +	-	-	-	-	1	0.60	0.03, 1.17	0.04	0.54
	CVMS 5-6	-	-	-	-	-	-	-	-	NA
	3-years +	2	-4.08	-6.03, -2.12	0.00	2	-0.40	-2.36, 1.56	0.69	0.00
Md skeletal										
SNB (degrees)	Age 18 +	1	-0.30	-1.69, 1.09	0.67	1	0.30	-0.27, 0.87	0.31	0.25
	CVMS 5-6	-	-	-	-	-	-	-	-	0.33
	3-years +	3	-0.41	-1.35, 0.54	0.40	2	-0.21	-1.29, 0.87	0.70	0.15
Pg to N perp (mm)	Age 18 +	-	-	-	-	1	0.90	0.17, 1.63	0.02	0.13
	CVMS 5-6	-	-	-	-	-	-	-	-	0.66
	3-years +	-	-	-	-	2	-0.06	-2.02, 1.89	0.95	0.32
Co-Gn (mm)	Age 18 +	-	-	-	-	1	1.60	0.62, 2.58	0.00	0.00
	CVMS 5-6	-	-	-	-	-	-	-	-	0.78
	3-years +	2	-1.44	-6.09, 3.22	0.55	2	2.59	0.63, 4.55	0.01	0.35
Mx-md skeletal										
ANB (degrees)	Age 18 +	1	-0.40	-1.32, 0.52	0.40	1	0.60	-0.01, 1.21	0.05	0.00
	CVMS 5-6	-	-	-	-	-	-	-	-	0.35
	3-years +	3	-1.48	-2.72, -0.25	0.02	2	0.17	-0.80, 1.14	0.73	0.02
Wits (mm)	Age 18 +	1	-2.40	-4.11, -0.69	0.01	1	-2.70	-3.53, -1.87	0.00	0.13
	CVMS 5-6	-	-	-	-	-	-	-	-	0.93
	3-years +	3	-1.74	-2.66, -0.81	0.00	2	-3.10	-3.78, -2.42	0.00	0.09
Co-Gn/Co-A diff (mm)	Age 18 +	-	-	-	-	1	1.00	-0.32, 2.32	0.14	0.06
	CVMS 5-6	-	-	-	-	-	-	-	-	NA
	3-years +	2	1.63	-0.09, 3.34	0.06	2	2.97	-0.85, 6.79	0.13	0.58

Mx skeletal, maxillary skeletal outcomes; SNA, SNA angle; A point to N perp, A to N perpendicular distance; Co-A, Co-A distance

Md skeletal, mandibular skeletal outcomes; SNB, SNB angle; Pg point to N perp, Pg to N perpendicular distance; Co-Gn, Co-Gn distance

Mx-md skeletal, maxillo-mandibular outcomes; ANB, ANB angle; Wits, Wits appraisal; Co-Gn/Co-A diff, Co-Gn/Co-A difference

Age 18 +, above 18 years of age; CVMS 5–6, at the end of growth according to the cervical vertebral maturation method; 3-years +, after a post-retention period of at least 3 years

N_s, number of studies or subgroups; MD, mean differences; 95% CI, 95% confidence intervals; P, P value

P_s, test for subgroup differences.

https://doi.org/10.1371/journal.pone.0221624.t007

Sensitivity analyses revealed that, if only studies with low and moderate risk of bias were considered, differences in the most clinically important outcomes (SNA angle, Co-Gn distance, ANB angle) were not statistically significant (Table 9).

Risk of bias across studies

The protocol of the included studies was not retrieved in the Clinical Trial Register, thus outcome reporting bias could not be assessed. Due to the limited number of included studies, an

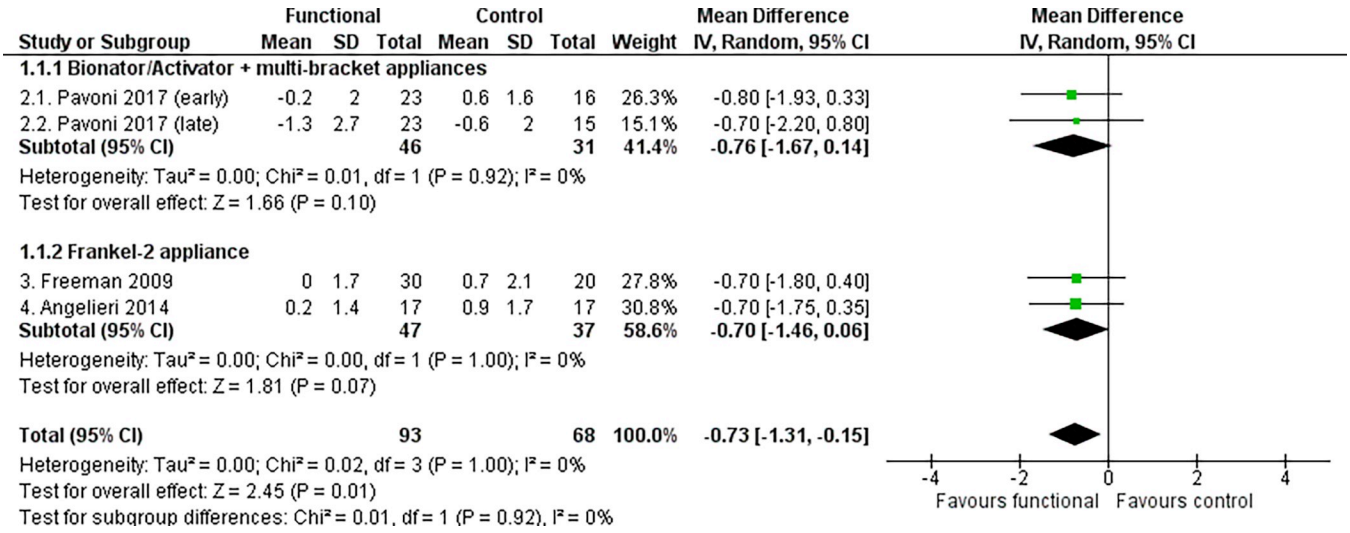

Fig 2. Meta-analysis; Outcome: SNA angle; Time point: End of growth according to the CVM method.

https://doi.org/10.1371/journal.pone.0221624.g002

evaluation for the existence of reporting bias (including publication bias) was not possible [40].

The GRADE assessment for all the outcomes at primary time points were rated as being 'very low' (Table 10), except for the Co-A distance when patients were 18 or older ('low'), and Co-Gn/Co-A difference above the age of 18 ('low') and at the end of growth ('moderate'). Since the included studies were observational, evidence supporting estimates of the intervention effects started to be rated as low-quality. The evidence was down rated for most of the outcomes, as a direct result of the risk of bias and inconsistency of included trials [41].

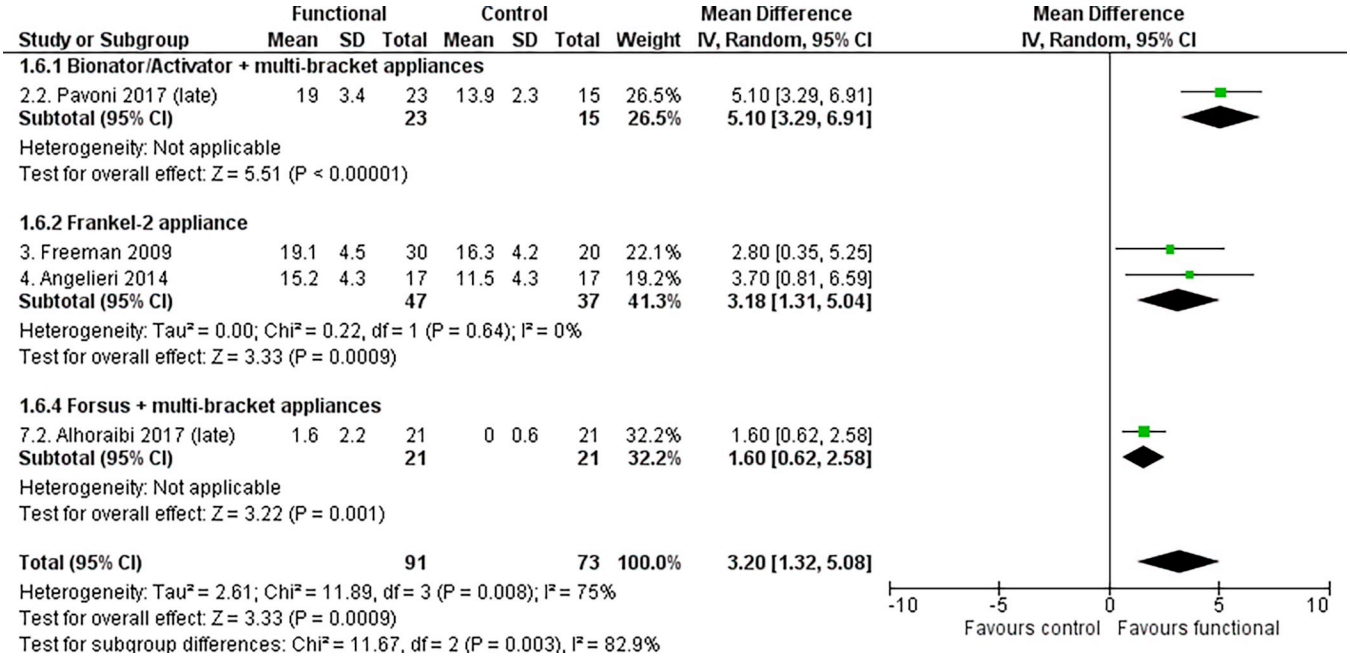

Fig 3. Meta-analysis; Outcome: Co-Gn distance; Time point: Above 18 years of age.

https://doi.org/10.1371/journal.pone.0221624.g003

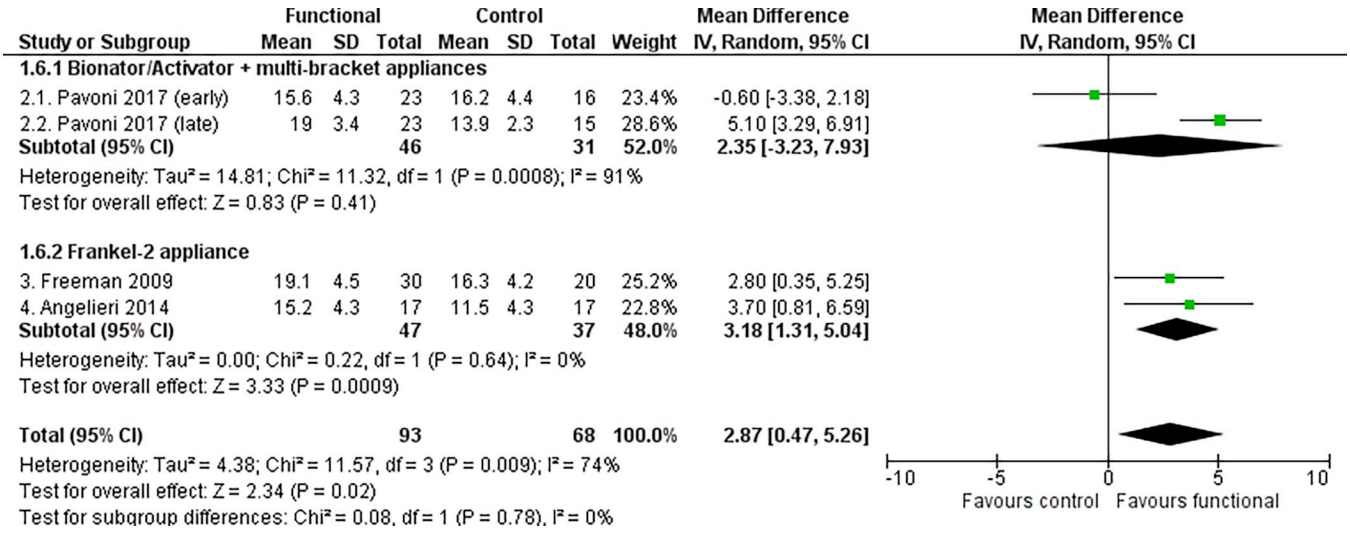

Fig 4. Meta-analysis; Outcome: Co-Gn distance; Time point: End of growth according to the CVM method.

https://doi.org/10.1371/journal.pone.0221624.g004

Discussion

Summary of evidence

The results demonstrated that functional appliances, worn alone or in combination with multi-bracket therapy, produced an improvement of the maxillo-mandibular relationship at almost all time points. The improvement was around -1 degree for the angular measurement (ANB angle) and between -3.5 and 2.5 mm for the linear outcomes (Wits appraisal, Co-Gn/Co-A difference). The decrease in the ANB angle and Wits appraisal was consistent with that reported in previous systematic reviews on the effects of functional appliances in the short- [6, 21, 22, 24, 26, 28] and long-term [28].

In agreement with previous reviews [7, 21, 24], a restraint of maxillary growth (SNA angle, -1 degree) was observed in included studies. Above 18 years of age or at the end of growth

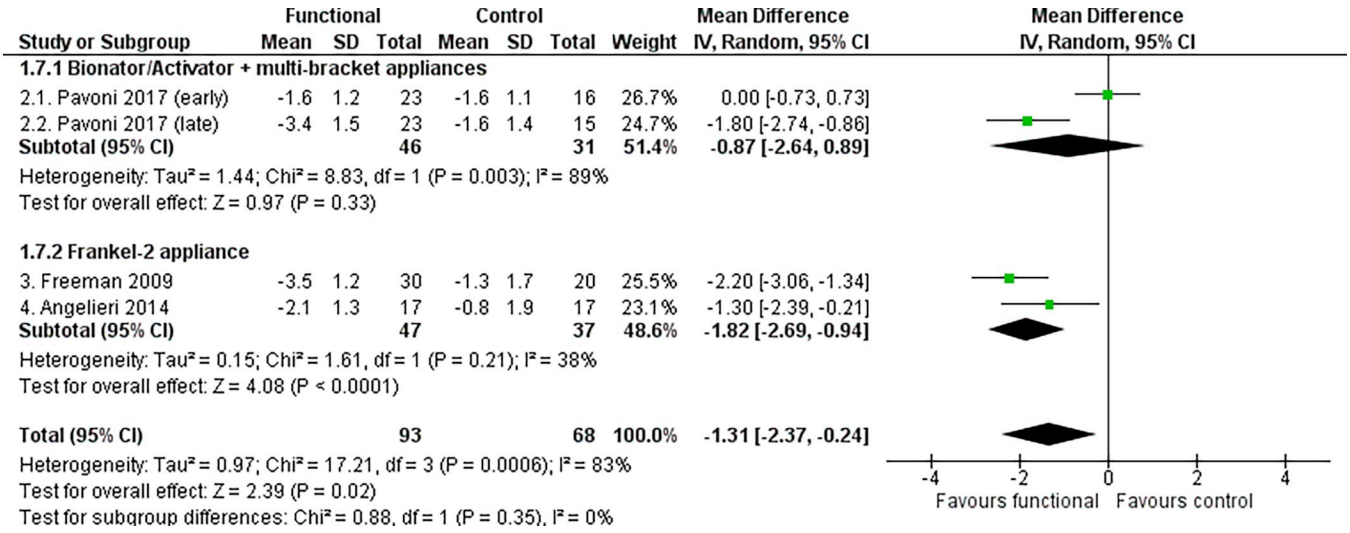

Fig 5. Meta-analysis; Outcome: ANB angle; Time point: End of growth according to the CVM method.

https://doi.org/10.1371/journal.pone.0221624.g005

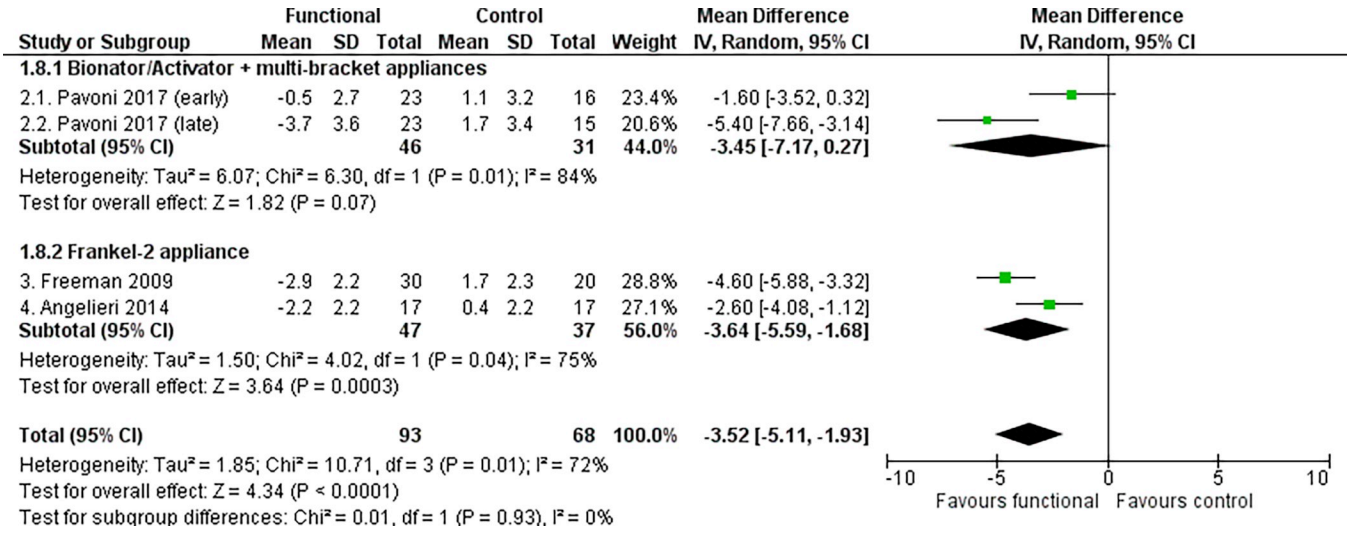

Fig 6. Meta-analysis; Outcome: Wits appraisal; Time point: End of growth according to the CVM method.

https://doi.org/10.1371/journal.pone.0221624.g006

according to the cervical vertebral maturation method [20], the increase in the mandibular length (Co-Gn distance) was approximately 3 mm greater in the treated patients compared to that in untreated subjects. Similar results were found in the subgroups of adolescents studied by Perinetti et al. [6, 22]. However, the improvement of the position of the mandible was negligible or not significant, as inferred from results of its measurements (SNB angle, Pg to N perpendicular). During growth, the mandible is translated downward and forward, while at the same time it increases in size by growing upward and backward [12, 14]. Vertical growth can reduce the effects of the increase in mandibular length on its projection.

According to the GRADE Working Group, the quality of evidence was 'very low' for most of the outcomes at both primary time points. Most of the studies received a very low rating, because of their risk of bias and inconsistency [41].

Overall, the clinical significance of these findings was limited. Several approaches were described to establish if the 'statistically significant' differences were also 'clinically important'. The small or minimal clinical important, moderate and large effects were conventionally defined as half, one, and two standard deviations of the normal values, respectively [54]. According to these thresholds, functional appliances produced only small clinically significant changes in the linear maxillo-mandibular measurements (Wits appraisal, Co-Gn/Co-A difference) and in the mandibular length (Co-Gn distance).

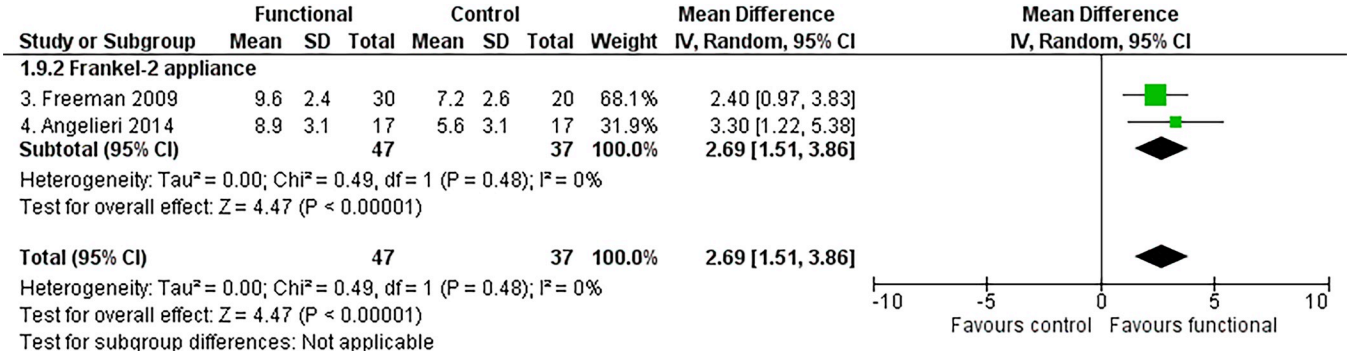

Fig 7. Meta-analysis; Outcome: Co-Gn/Co-A difference; Time point: End of growth according to the CVM method.

https://doi.org/10.1371/journal.pone.0221624.g007

Table 8. Details of the performed subgroup analyses, according to gender, beginning of the functional appliance therapy and post-retention period duration.

Outcome	Subgroups	Overall effect				Heterogeneity			
		N_s	MD	95% CI	P	Tau^2	Chi^2	P	I^2
Males Vs females									
SNA (degrees)	Males	2	-0.85	-1.96, 0.27	0.14	0.00	0.50	0.48	0%
	Females	1	-3.20	-5.25, -1.15	0.00	NA			
Total (95% CI)		3	-1.62	-3.17, -0.07	0.04	1.02	4.42	0.11	55%
Subgroup differences:							3.92	0.05	75%
Co-Gn (mm)	Males	1	1.30	-2.71, 5.31	0.52	NA			
	Females	1	-3.50	-5.41, -1.59	0.00	NA			
Total (95% CI)		2	-1.44	-6.09, 3.22	0.55	8.95	4.49	0.03	78%
Subgroup differences:							4.49	0.03	78%
ANB (degrees)	Males	2	-1.26	-3.11, 0.60	0.18	1.41	4.55	0.03	78%
	Females	1	-2.00	-3.11, -0.89	0.00	NA			
Total (95% CI)		3	-1.48	-2.72, -0.25	0.02	0.84	6.92	0.03	71%
Subgroup differences:							0.45	0.50	0%
Early Vs late treatments according to age									
SNA (degrees)	7 < age < 11	7	-1.34	-2.11, -0.57	0.00	0.66	20.39	0.00	71%
	12 < age < 16	2	0.04	-0.90, 0.98	0.93	0.20	1.66	0.20	40%
Total (95% CI)		9	-1.03	-1.88, -0.18	0.02	1.28	50.87	0.00	84%
Subgroup differences:							4.99	0.03	80%
Co-Gn (mm)	7 < age < 11	7	1.81	-0.61, 4.23	0.14	9.08	55.68	0.00	89%
	12 < age < 16	1	1.60	0.62, 2.58	0.00	NA			
Total (95% CI)		8	1.79	-0.05, 3.64	0.06	5.73	57.49	0.00	88%
Subgroup differences:							0.02	0.88	0%
ANB (degrees)	7 < age < 11	8	-1.43	-2.07, -0.79	0.00	0.61	26.11	0.00	73%
	12 < age < 16	2	0.16	-0.81, 1.13	0.74	0.34	3.13	0.08	68%
Total (95% CI)		10	-1.11	-1.82, -0.40	0.00	1.07	57.36	0.00	84%
Subgroup differences:							7.15	0.01	86%
Early Vs late treatments according to the cervical vertebral maturation method									
SNA (degrees)	CVSM 1-2	2	-1.61	-2.96, -0.25	0.02	0.80	5.40	0.02	81%
	CVSM 2-3	2	0.04	-0.97, 1.05	0.93	0.23	1.63	0.20	39%
Total (95% CI)		4	-0.85	-2.35, 0.64	0.26	2.06	40.60	0.00	93%
Subgroup differences:							3.67	0.06	73%
Co-Gn (mm)	CVSM 1-2	2	1.71	-2.39, 5.80	0.41	7.67	7.66	0.01	87%
	CVSM 2-3	2	3.26	-0.16, 6.69	0.06	5.57	11.11	0.00	91%
Total (95% CI)		4	2.61	0.76, 4.47	0.01	2.85	19.83	0.00	85%
Subgroup differences:							0.33	0.57	0%
ANB (degrees)	CVSM 1-2	2	-0.15	-0.73, 0.43	0.62	0.00	0.43	0.51	0%
	CVSM 2-3	2	-0.57	-2.92, 1.78	0.63	2.72	17.66	0.00	94%
Total (95% CI)		4	-0.36	-1.33, 0.61	0.47	0.81	18.10	0.00	83%
Subgroup differences:							0.12	0.73	0%
3-4 Vs 5-10 years after active functional appliance therapy									
SNA (degrees)	3-4 years	2	-0.92	-3.47, 1.62	0.48	3.29	36.06	0.00	97%
	5-10 years	7	-0.90	-1.40, -0.40	0.00	0.00	5.72	0.46	0%
Total (95% CI)		9	-1.03	-1.88, -0.18	0.02	1.28	50.87	0.00	84%
Subgroup differences:							0.00	0.98	0%
Co-Gn (mm)	3-4 years	2	2.59	0.63, 4.55	0.01	1.73	7.46	0.01	87%
	5-10 years	6	1.46	-1.63, 4.55	0.35	13.01	46.89	0.00	89%

(*Continued*)

Table 8. (Continued)

Outcome	Subgroups	Overall effect				Heterogeneity			
		N_s	MD	95% CI	P	Tau^2	Chi^2	P	I^2
Total (95% CI)		8	1.79	-0.05, 3.64	0.06	5.73	57.49	0.00	88%
Subgroup differences:							0.37	0.55	0%
ANB (degrees)	3-4 years	3	-0.53	-2.06, 1.00	0.50	1.67	25.46	0.00	92%
	5-10 years	7	-1.37	-2.11, -0.63	0.00	0.74	24.20	0.00	75%
Total (95% CI)		10	-1.11	-1.82, -0.40	0.00	1.07	57.36	0.00	84%
Subgroup differences:							0.94	0.33	0%

SNA, SNA angle; Co-Gn, Co-Gn distance; ANB, ANB angle

7 < age < 11; early treatments, commencing in children aged between 7 and 11 years; 12 < age < 16; late treatments, beginning in adolescents aged between 12 and 16 years

CVSM 1–2; early treatments, with patients presenting with Cervical Vertebral Maturation Stage (CVMS) 1 or 2 at the first observation; CVSM 2–3, late treatments, with subjects presenting with CVMS 2 or 3

N_s, number of studies or subgroups; MD, mean differences; 95% CI, 95% confidence intervals; P, P value.

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Strengths and limitations

Strengths of the present systematic review were in the efforts made to respect rigorous standards for quality and reduce risk of bias: original research question; unrestricted electronic search of 24 databases and additional manual searches; pre-defined and unambiguous eligibility criteria with rationale; adjustment for magnified linear measurements; 3 time points evaluated with rationale; pre-defined and broad additional analyses.

However, limitations occurred at some levels. Although both randomised and non-randomised controlled studies were sought, only retrospective controlled clinical trials were retrieved with negative consequences on the quality of evidence of the effect estimates. It needs to be noted that only long-term studies were considered eligible. The whole observational periods of included trials ranged from 4.7 to 10.2 years.

Participants were eligible regardless of their baseline disease severity. The antero-posterior relationship between the two arches or jaws affects the amount of advancement produced by functional appliances, therefore this could influence the treatment effects. The greater the space created between the upper and lower front teeth is, the more protruded position of the

Table 9. Details of the performed sensitivity analyses according to study quality assessment.

Outcome	Subgroups	Overall effect				Heterogeneity			
		N_s	MD	95% CI	P	Tau^2	Chi^2	P	I^2
SNA (degrees)	Low-mod	5	-1.34	-2.72, 0.05	0.06	2.03	41.62	0.00	90%
	Crit-ser	4	-0.71	-1.31, -0.10	0.02	0.00	0.05	1.00	0%
Co-Gn (mm)	Low-mod	5	1.19	-1.17, 3.54	0.32	5.99	41.55	0.00	90%
	Crit-ser	3	2.83	-0.57, 6.23	0.10	7.39	11.36	0.00	82%
ANB (degrees)	Low-mod	5	-1.20	-2.51, 0.11	0.07	1.96	39.09	0.00	90%
	Crit-ser	5	-1.05	-1.84, -0.26	0.01	0.61	16.90	0.00	76%

SNA, SNA angle; Co-Gn, Co-Gn distance; ANB, ANB angle

Mod, moderate; Ser, serious; Crit, critical.

N_s, number of studies or subgroups; MD, mean differences; 95% CI, 95% confidence intervals; P, P value.

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Table 10. Details for the GRADE assessment of the primary outcomes.

Outcome	RB	IC	IN	IM	Overall certainty of evidence	No. part. (studies)		Anticipated absolute effects	
						N_C	N_T	Risk with No treatment	Risk with Functional appliances
Above 18 years of age									
SNA	S	NS	NS	S	⊕○○○	190 (5)		The mean ranged from **-0.6 to 0.9** degrees	MD **0.31 degrees lower** (0.83 lower to 0.21 higher)
					VERY LOW	86	104		
A to N perp	NS	S	NS	S	⊕○○○	126 (3)		The mean ranged from **0.1 to 0.9** mm	MD **2.41 mm lower** (6.45 lower to 1.62 higher)
					VERY LOW	58	68		
Co-A	NS	NS	NS	NS	⊕⊕○○	126 (3)		The mean ranged from **0.6 to 9.6** mm	MD **0.53 mm higher** (0.00 higher to 1.05 higher)
					LOW	58	68		
SNB	S	NS	NS	NS	⊕○○○	190 (5)		The mean ranged from **1.0 to 2.2** degrees	MD **0.66 degrees higher** (0.03 higher to 1.29 higher)
					VERY LOW	86	104		
Pg to N perp	S	S	NS	NS	⊕○○○	164 (4)		The mean ranged from **0.9 to 3.6** mm	MD **1.42 mm higher** (0.01 higher to 2.84 higher)
					VERY LOW	73	91		
Co-Gn	S	S	NS	NS	⊕○○○	164 (4)		The mean ranged from **0.0 to 16.3** mm	MD **3.20 mm higher** (1.32 higher to 5.08 higher)
					VERY LOW	73	91		
ANB	S	S	NS	S	⊕○○○	190 (5)		The mean ranged from **-1.6 to -0.8** degrees	MD **1 degrees lower** (2.15 lower to 0.16 higher)
					VERY LOW	86	104		
Wits	S	S	NS	NS	⊕○○○	190 (5)		The mean ranged from **0.4 to 1.7** mm	MD **3.40 mm lower** (4.45 lower to 2.35 lower)
					VERY LOW	86	104		
Co-Gn/Co-A diff	NS	NS	NS	NS	⊕⊕⊕○	126 (3)		The mean ranged from **-0.6 to 7.2** mm	MD **2.07 mm higher** (0.79 higher to 3.35 higher)
					MODERATE	58	68		
At the end of growth according to the cervical vertebral maturation method									
SNA	S	NS	NS	NS	⊕○○○	161 (4)		The mean ranged from **-0.6 to 0.9** degrees	MD **0.73 degrees lower** (1.31 lower to 0.15 lower)
					VERY LOW	68	93		
A to N perp	S	S	NS	S	⊕○○○	84 (2)		The mean ranged from **0.1 to 0.9** mm	MD **0.48 mm lower** (2.74 lower to 1.77 higher)
					VERY LOW	37	47		
Co-A	S	NS	NS	S	⊕○○○	84 (2)		The mean ranged from **5.7 to 9.6** mm	MD **0.15 mm higher** (1.16 lower to 1.46 higher)
					VERY LOW	37	47		
SNB	S	S	NS	S	⊕○○○	161 (4)		The mean ranged from **1.0 to 2.2** degrees	MD **0.65 degrees higher** (0.45 lower to 1.74 higher)
					VERY LOW	68	93		
Pg to N perp	S	S	NS	S	⊕○○○	161 (4)		The mean ranged from **2.8 to 3.6** mm	MD **1.54 mm higher** (0.25 lower to 3.32 higher)
					VERY LOW	68	93		
Co-Gn	S	S	NS	NS	⊕○○○	161 (4)		The mean ranged from **11.5 to 16.3** mm	MD **2.87 mm higher** (0.47 higher to 5.26 higher)
					VERY LOW	68	93		
ANB	S	S	NS	NS	⊕○○○	161 (4)		The mean ranged from **-1.6 to -0.8** degrees	MD **1.31 degrees lower** (2.37 lower to 0.24 lower)
					VERY LOW	68	93		
Wits	S	S	NS	NS	⊕○○○	161 (4)		The mean ranged from **0.4 to 1.7** mm	MD **3.52 mm lower** (5.11 lower to 1.93 lower)
					VERY LOW	68	93		
Co-Gn/Co-A diff	S	NS	NS	NS	⊕⊕○○	84 (2)		The mean ranged from **5.6 to 7.2** mm	MD **2.69 mm higher** (1.51 higher to 3.86 higher)
					LOW	37	47		

SNA, SNA angle; A to N perp, A point to N perpendicular distance; Co-A, Co-A distance

SNB, SNB angle; Pg to N perp, Pg point to N perpendicular distance; Co-Gn, Co-Gn distance

ANB, ANB angle; Wits, Wits appraisal; Co-Gn/Co-A diff, Co-Gn/Co-A difference

RB, risk of bias; IC, inconsistency; IN, indirectness; IM, imprecision

No. part., number of participants; N_C, number of not treated subjects; N_T, number of treated patients.

S, serious; NS, not serious

All studies were observational studies.

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mandible can be achieved. Different classifications of malocclusion also bring into question the applicability of results.

Any type of functional appliance, worn alone or in combination with multi-bracket therapy, was included. As anticipated, multi-bracket therapy, as well as retention appliances, could enhance the treatment effects of functional jaw orthopaedics or control their relapse. Moreover, trials with historical untreated controls from growth studies showed larger treatment effects compared to trials with untreated controls from clinical archives [55].

Other limitations concerned the evaluated outcomes. The present systematic review mainly assessed cephalometric skeletal measurements which can be considered as 'clinically important outcomes'. The effects of functional appliances on the soft-tissue facial structures were searched, but few results were found. Multiple related outcomes were also analysed. In fact, the ANB angle is defined as the difference between the SNA and SNB angles, whilst the Co-Gn/Co-A difference is defined as the total mandibular length (Co-Gn) minus Co-A distance. The greater the number of outcomes, the higher the chance of finding a false positive result [56]. Cephalometric magnification was not reported or retrieved in 2 studies [42, 44]. Linear measurements of these studies were excluded from meta-analyses. The impact of dental movements on the skeletal measurements cannot be examined further, as the objective of this systematic review was to assess the skeletal effects produced by functional appliances in the long-term.

With regards to time points, two alternative methods were used to define the completion of growth. Each of these methods is affected by some limitations. The age threshold of 18 years, as reported in one included trial [48], was chosen to maximise the data available. In studies of long duration with several periods of follow-up, the Cochrane Collaboration recommends to select a single time point and analyse only data at this time [30]. Some investigations reported that growth continues up to 21 years of age [15] or more [16–18]. However, above 18 years of age, most changes in the mandibular growth (Co-Gn distance) appear to be as non-clinically significant (mean change = 0.1 mm per year [17, 18]). None of the included trials evaluated the treatment effects of functional appliances in patients aged at least 21 years old. The cervical vertebral maturation method was also employed. The accuracy of this method is questionable. No skeletal maturity indicator may be considered to have a full diagnostic reliability in the identification of the phases of mandibular growth [57]. All the studies had a post-retention period of at least 3 years, so that a sufficient post-retention period after the functional appliance therapy could be guaranteed [42–49].

Implications for practice

Based on results of this review, weak recommendations can be provided on the long-term effects of functional appliances in treated versus untreated Class II subjects. There is a very low quality evidence that functional appliance therapy produced an improvement of skeletal Class II malocclusion at the end of growth and at least 3 years after retention. Treated patients exhibited an increase in the mandibular length compared to untreated subjects, although with marginal clinical significance.

Implications for research

Further high quality primary studies are needed to confirm or reject the findings of this review. Randomised controlled trials comparing treated patients to untreated subjects (no historical controls) should be carried out. A consensus should be formed on the clinically important measurements to be used for the inclusion in the study and assessment of the effects. Few linear measurements for the position of the maxilla and mandible, the relationship between these

jaws, seem to be more appropriate because of their influence on the soft tissue measurements. Patient important outcomes, such as perceived attractiveness, self-esteem and oral health-related quality of life, should be assessed as well.

Conclusions

Functional appliances, worn alone or in combination with multi-bracket therapy, may be effective in correcting skeletal Class II malocclusion in the long-term. The increase in the mandibular length may contribute to the improvement of the maxillo-mandibular relationship, although it brought about a negligible or non-significant improvement of the mandibular projection. The quality of evidence was 'very low' for most of the outcomes at both primary time points; the clinical significance of these findings was limited. Further randomised controlled trials evaluating clinically and patient important outcomes are needed to confirm or reject the findings of this review.

Differences between protocol and review

The data extracted were not preliminarily annualised to minimize heterogeneity related to the observation period variability. Annualised changes (mean differences divided by the duration of the whole observational period) seemed to be inappropriate to evaluate the treatment effects in the long-term. If an appliance produced a certain amount of improvement in a given period (reported as degrees/year or mm/year), it does not mean that the device could cause the established improvement for each year of treatment.

An adjustment for magnified linear measurements was introduced to avoid distorted analyses.

Supporting information

S1 Table. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2009 Checklist.
(PDF)

S2 Table. Name of the search source, date range, search platform/provider and link of all databases that were used.
(PDF)

S3 Table. Search strategy and corresponding results for all databases.
(PDF)

S4 Table. Studies excluded with corresponding main reason of exclusion.
(PDF)

S5 Table. Results during the overall observational period for each outcome included in the meta-analysis.
(PDF)

S6 Table. Results during the overall observational period for each outcome excluded by the meta-analysis.
(PDF)

S1 Appendix. Eligibility criteria with rationale.
(PDF)

S2 Appendix. References to studies excluded from this review.
(PDF)

S3 Appendix. The forest plots concerning redundant or non-statistically significant results.
(PDF)

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S1 Table. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2009 Checklist.

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	26

S1 Table (continued). PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2009 Checklist.

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	26
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	32
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	33
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	36
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

Legend
NA, not applicable.

S2 Table. Name of the search source, date range, search platform/provider and link of all databases that were used.

Database	Search platform or provider; date range	Link
Bibliographic databases		
MEDLINE, EMBASE, CENTRAL		
MEDLINE	Pubmed; 1946 - 13th March 2018	https://www.ncbi.nlm.nih.gov/pubmed/advanced
EMBASE	OVID; 1974 - 15th March 2018	https://www.embase.com/search/advanced
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library; 1993 - 13th March 2018	http://onlinelibrary.wiley.com/cochranelibrary/search/
National and regional databases		
Latin America and the Caribbean (LILACS)	Biblioteca Regional de Medicina (BIREME), Pan American Health Organization (PAHO), WHO; 1982 - 13th March 2018	http://pesquisa.bvsalud.org/portal/advanced/?lang=en
General search engines		
Google Scholar	2004 - 14th March 2018	https://scholar.google.it/
Turning Research into Practice (TRIP) database	1997 - 14th March 2018	https://www.tripdatabase.com/
Citation indexes		
Web of Science Core Collection - Science Citation Index / Science Citation Index Expanded	Web of Science; 1945 - 15th March 2018	https://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch
Scopus	Elsevier; 2004 - 13th March 2018	https://www.scopus.com/
Dissertation and theses databases		
ProQuest Dissertations & Theses Global	1938 - 15th March 2018	https://search.proquest.com/pqdtglobal/advanced
ProQuest Dissertations and Theses – UK & Ireland	1950 - 15th March 2018	https://search.proquest.com/pqdtuk/advanced
Grey literature databases		
OpenGrey, formerly System for Information on Grey Literature (SIGLE)	1993 - 13th March 2018	http://www.opengrey.eu/
Journals and other non-bibliographic database sources		
Hand-searching		
American Journal of Orthodontics and Dentofacial Orthopaedics	1915 - 16th March 2018	https://www.ajodo.org/
Angle Orthodontist	1931 - 16th March 2018	https://www.angle.org/
Australian Journal of Orthodontics	2010 - 16th March 2018	https://www.aso.org.au/australasian-orthodontic-journal
European Journal of Orthodontics	1979 - 16th March 2018	https://academic.oup.com/ejo
Journal of Clinical Orthodontics	1967 - 16th March 2018	https://www.jco-online.com/
Journal of Orthodontics	1973 - 16th March 2018	https://www.tandfonline.com/loi/yjor20
Orthodontics & Craniofacial Research	1998 - 16th March 2018	https://onlinelibrary.wiley.com/journal/16016343
Progress in Orthodontics	2013 - 16th March 2018	https://progressinorthodontics.springeropen.com/
Seminars in Orthodontics	1995 - 16th March 2018	https://www.semortho.com/
Tables of contents		
British Library Direct	1930 - 16th March 2018	https://ondemand.bl.uk/onDemand/home
Current Contents Connect – Clinical Medicine	Web of Science; 1998 - 15th March 2018	https://apps.webofknowledge.com/CCC_GeneralSearch_input.do?product=CCC&search_mode=GeneralSearch
Scientific Electronic Library Online (SciELO) Citation Index	Web of Science; 1997 - 15th March 2018	https://apps.webofknowledge.com/SCIELO_GeneralSearch_input.do?product=SCIELO&search_mode=GeneralSearch

S2 Table (continued). Name of the search source, date range, search platform/provider and link of all databases that were used.

Database	Search platform or provider; date range	Link
Conference abstracts or proceedings		
BIOSIS Citation Index	Web of Science; 1969 - 15th March 2018	https://apps.webofknowledge.com/BCI_GeneralSearch_input.do?product=BCI&search_mode=GeneralSearch
Web of Science Core Collection – Conference Proceedings Citation Index – Science	Web of Science; 1990 - 15th March 2018	https://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch
ISI Proceedings	2004 - 16th March 2018	http://www.proceedings.com/
Other reviews, guidelines and reference lists as sources of studies		
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library; 1993 - 13th March 2018	http://onlinelibrary.wiley.com/cochranelibrary/search/
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library; 1993 - 13th March 2018	http://onlinelibrary.wiley.com/cochranelibrary/search/
Health Technology Assessment Database (HTA Database)	Cochrane Library; 1993 - 13th March 2018	http://onlinelibrary.wiley.com/cochranelibrary/search/
NHS Economic Evaluation Database (NHS EED)	Cochrane Library; 1993 - 13th March 2018	http://onlinelibrary.wiley.com/cochranelibrary/search/
Unpublished and ongoing studies		
ClinicalTrials.gov register	From inception - 16th March 2018	https://clinicaltrials.gov/
Current controlled trials metaRegister of Controlled Trials (mRCT) – active and archived registers	From inception - 16th March 2018	https://www.controlled-trials.com/mrct/
International prospective register of systematic reviews (PROSPERO)	From inception - 16th March 2018	https://www.crd.york.ac.uk/prospero/#searchadvanced

S3 Table. Search strategy and corresponding results for all databases.

Search	Query	Hits
MEDLINE		
#1	"Class II malocclusion" OR "Class II" OR Class II div* OR Class/*	68634
#2	"prominent upper front teeth" OR "prominent upper teeth" OR "prominent teeth"	107
#3	"increased overjet"	173
#4	Malocclusion, Angle Class II [Mesh]	5724
#5	#1 OR #2 OR #3 OR #4	69184
#6	Functional OR orthopedic OR orthopaedic OR interceptive OR preventive OR bite jump* OR (mandib* AND (advanc* OR enhanc* OR postur* OR protract* OR reposition*)) OR Activator OR Andresen OR Bass OR Bionator OR Bimler OR Frankel OR Fraenkel OR "Functional magnetic system" OR Harvold OR Monoblock OR "Twin block" OR Herbst OR "Mandibular anterior repositioning appliance" OR MARA OR "Eureka spring" OR Forsus OR "Jasper jumper" OR "Sabbagh spring" OR "Twin force"	1749977
#7	appliance OR device	1475369
#8	#6 AND #7	140521
#9	Mandibular advancement [Mesh] OR Orthodontic appliances [Mesh] OR Orthodontics [Mesh]	49535
#10	#8 OR #9	185661
#11	"End of growth" OR "completion of growth" OR long term OR longterm OR follow up OR post retention OR stability OR longitudinal	2251067
#12	#5 AND #10 AND #11	1623

Search	Query	Hits
EMBASE		
#1	("Class II malocclusion" or "Class II" or Class II div*).af.	65204
#2	("prominent upper front teeth" or "prominent upper teeth" or "prominent teeth").af.	11
#3	"increased overjet".af.	145
#4	Malocclusion, Angle Class II/	18774
#5	#1 OR #2 OR #3 OR #4	81885
#6	(Functional or orthopedic or orthopaedic or interceptive or preventive or bite jump* or (mandib* and (advanc* or enhanc* or postur* or protract* or reposition*)) or Activator or Andresen or Bass or Bionator or Bimler or Frankel or Fraenkel or "Functional magnetic system" or Harvold or Monoblock or "Twin block" or Herbst or "Mandibular anterior repositioning appliance" or MARA or "Eureka spring" or Forsus or "Jasper jumper" or "Sabbagh spring" or "Twin force").af.	2223341
#7	(appliance or device).af.	488726
#8	#6 AND #7	54578
#9	Mandibular advancement/	235
#10	Orthodontic appliances/	17679
#11	Orthodontics/	33049
#12	#8 OR #9 OR #10 OR #11	93445
#13	("End of growth" or "completion of growth" or long term or longterm or follow up or post retention or stability or longitudinal).af.	3051080
#14	#5 AND #12 AND #13	1613

Search	Query	Hits
Cochrane Library		
#1	"Class II malocclusion" OR "Class II"	3116
#2	"prominent upper front teeth" OR "prominent upper teeth" OR "prominent teeth"	6
#3	"increased overjet"	10
#4	Class II malocclusion explode all trees	11
#5	#1 OR #2 OR #3 OR #4	3121

S3 Table (continued). Search strategy and corresponding results for all databases.

Search	Query	Hits
Cochrane Library		
#6	Functional OR orthopedic OR orthopaedic OR interceptive OR preventive OR bite jump* OR (mandib* AND (advanc* OR enhanc* OR postur* OR protract* OR reposition*)) OR Activator OR Andresen OR Bass OR Bionator OR Bimler OR Frankel OR Fraenkel OR "Functional magnetic system" OR Harvold OR Monoblock OR "Twin block" OR Herbst OR "Mandibular anterior repositioning appliance" OR MARA OR "Eureka spring" OR Forsus OR "Jasper jumper" OR "Sabbagh spring" OR "Twin force"	84043
#7	appliance OR device	29577
#8	#6 AND #7	4554
#9	Mandibular advancement explode all trees or Orthodontic appliances explode all trees or Orthodontics explode all trees	34
#10	#8 OR #9	4565
#11	"End of growth" OR "completion of growth" OR long term OR longterm OR follow up OR post retention OR stability OR longitudinal	242883
#12	#5 AND #10 AND #11	144
	Cochrane Central Register of Controlled Trials (CENTRAL)	76
	Cochrane Database of Systematic Reviews (CDSR)	63
	Database of Abstracts of Reviews of Effects (DARE)	3
	Health Technology Assessment Database (HTA Database)	1
	NHS Economic Evaluation Database (NHS EED)	1

Search	Query	Hits
Latin America and the Caribbean (LILACS)		
	(tw:(("Class II malocclusion" OR "Class II" OR class ii div* OR class/*) OR ("prominent upper front teeth" OR "prominent upper teeth" OR "prominent teeth") OR "increased overjet")) AND (tw:((functional OR orthopedic OR orthopaedic OR interceptive OR preventive OR bite jump* OR (mandib* AND (advanc* OR enhanc* OR postur* OR protract* OR reposition*)) OR activator OR andresen OR bass OR bionator OR bimler OR frankel OR fraenkel OR "Functional magnetic system" OR harvold OR monoblock OR "Twin block" OR herbst OR "Mandibular anterior repositioning appliance" OR mara OR "Eureka spring" OR forsus OR "Jasper jumper" OR "Sabbagh spring" OR "Twin force") AND (appliance OR device))) AND (tw:("End of growth" OR "completion of growth" OR long term OR follow up OR post retention OR stability)) AND (instance:"regional") AND (db:("LILACS")) AND (instance:"regional") AND (db:("LILACS") AND jd:("ORTODONTIA" OR "ODONTOLOGIA" OR "MEDICINA"))	42

Search	Query	Hits
Google Scholar		
	"Class II malocclusion" AND "functional appliances" AND "long term"	1510

Search	Query	Hits
Turning Research into Practice (TRIP) database		
	"Class II malocclusion" AND "functional appliances" AND "long term"	14

Search	Query	Hits
Science Citation Index / Science Citation Index Expanded		
#1	TS=("Class II malocclusion" OR "Class II" OR Class II div*)	59008
#2	TS=("prominent upper front teeth" OR "prominent upper teeth" OR "prominent teeth")	15
#3	TS=("increased overjet")	104
#4	#1 OR #2 OR #3	59092

S3 Table (continued). Search strategy and corresponding results for all databases.

Search	Query	Hits
Science Citation Index / Science Citation Index Expanded		
#5	TS=(Functional OR orthopedic OR orthopaedic OR interceptive OR preventive OR bite jump* OR (mandib* AND (advanc* OR enhanc* OR postur* OR protract* OR reposition*)) OR Activator OR Andresen OR Bass OR Bionator OR Bimler OR Frankel OR Fraenkel OR "Functional magnetic system" OR Harvold OR Monoblock OR "Twin block" OR Herbst OR "Mandibular anterior repositioning appliance" OR MARA OR "Eureka spring" OR Forsus OR "Jasper jumper" OR "Sabbagh spring" OR "Twin force")	1725015
#6	TS=(appliance OR device)	815498
#7	#5 AND #6	42131
#8	TS=("End of growth" OR "completion of growth" OR long term OR longterm OR follow up OR post retention OR stability OR longitudinal)	3041564
#9	#4 AND #7 AND #8	296
	For all queries: Indexes=SCI-EXPANDED Timespan=All years	

Search	Query	Hits
Scopus		
	ALL ("Class II malocclusion" AND "functional appliances" AND "long term")	512

Search	Query	Hits
ProQuest Dissertation & Theses Global		
	"Class II malocclusion" AND "functional appliances" AND "long term"	112

Search	Query	Hits
ProQuest Dissertations and Theses — UK & Ireland / Index to Theses		
	"Class II malocclusion" AND "functional appliances" AND "long term"	0

Search	Query	Hits
OpenGrey - formerly System for Information on Grey Literature (SIGLE)		
	"Class II malocclusion" AND "functional appliances" AND "long term"	0

Search	Query	Hits
British Library Direct		
	"Class II malocclusion" AND "functional appliances" AND "long term"	9

Search	Query	Hits
Current Contents Connect - Clinical Medicine		
#1	TS=("Class II malocclusion" OR "Class II" OR Class II div*)	12168
#2	TS=("prominent upper front teeth" OR "prominent upper teeth" OR "prominent teeth")	4
#3	TS=("increased overjet")	68
#4	#1 OR #2 OR #3	12215
#5	TS=(Functional OR orthopedic OR orthopaedic OR interceptive OR preventive OR bite jump* OR (mandib* AND (advanc* OR enhanc* OR postur* OR protract* OR reposition*)) OR Activator OR Andresen OR Bass OR Bionator OR Bimler OR Frankel OR Fraenkel OR "Functional magnetic system" OR Harvold OR Monoblock OR "Twin block" OR Herbst OR "Mandibular anterior repositioning appliance" OR MARA OR "Eureka spring" OR Forsus OR "Jasper jumper" OR "Sabbagh spring" OR "Twin force")	321347
#6	TS=(appliance OR device)	115720
#7	#5 AND #6	10317

S3 Table (continued). Search strategy and corresponding results for all databases.

Search	Query	Hits
Current Contents Connect - Clinical Medicine		
#8	TS=("End of growth" OR "completion of growth" OR long term OR longterm OR follow up OR post retention OR stability OR longitudinal)	837413
#9	#4 AND #7 AND #8	222
	For all queries: Indexes=CM Timespan=All years	

Search	Query	Hits
Scientific Electronic Library Online (SciELO) Citation Index		
#1	TS=("Class II malocclusion" OR "Class II" OR Class II div*)	759
#2	TS=("prominent upper front teeth" OR "prominent upper teeth" OR "prominent teeth")	0
#3	TS=("increased overjet")	17
#4	#1 OR #2 OR #3	771
#5	TS=(Functional OR orthopedic OR orthopaedic OR interceptive OR preventive OR bite jump* OR (mandib* AND (advanc* OR enhanc* OR postur* OR protract* OR reposition*)) OR Activator OR Andresen OR Bass OR Bionator OR Bimler OR Frankel OR Fraenkel OR "Functional magnetic system" OR Harvold OR Monoblock OR "Twin block" OR Herbst OR "Mandibular anterior repositioning appliance" OR MARA OR "Eureka spring" OR Forsus OR "Jasper jumper" OR "Sabbagh spring" OR "Twin force")	19400
#6	TS=(appliance OR device)	7107
#7	#5 AND #6	520
#8	TS=("End of growth" OR "completion of growth" OR long term OR longterm OR follow up OR post retention OR stability OR longitudinal)	35213
#9	#4 AND #7 AND #8	14
	For all queries: Indexes=SCIELO Timespan=All years	

Search	Query	Hits
BIOSIS Citation Index		
#1	TS=("Class II malocclusion" OR "Class II" OR Class II div*)	55062
#2	TS=("prominent upper front teeth" OR "prominent upper teeth" OR "prominent teeth")	17
#3	TS=("increased overjet")	11
#4	#1 OR #2 OR #3	55088
#5	TS=(Functional OR orthopedic OR orthopaedic OR interceptive OR preventive OR bite jump* OR (mandib* AND (advanc* OR enhanc* OR postur* OR protract* OR reposition*)) OR Activator OR Andresen OR Bass OR Bionator OR Bimler OR Frankel OR Fraenkel OR "Functional magnetic system" OR Harvold OR Monoblock OR "Twin block" OR Herbst OR "Mandibular anterior repositioning appliance" OR MARA OR "Eureka spring" OR Forsus OR "Jasper jumper" OR "Sabbagh spring" OR "Twin force")	1162622
#6	TS=(appliance OR device)	681259
#7	#5 AND #6	24326
#8	TS=("End of growth" OR "completion of growth" OR long term OR longterm OR follow up OR post retention OR stability OR longitudinal)	1487148
#9	#4 AND #7 AND #8	53
	For all queries: Indexes=BCI Timespan=All years	

Search	Query	Hits
Conference Proceedings Citation Index - Science		
#1	TS=("Class II malocclusion" OR "Class II" OR Class II div*)	4205
#2	TS=("prominent upper front teeth" OR "prominent upper teeth" OR "prominent teeth")	0
#3	TS=("increased overjet")	2
#4	#1 OR #2 OR #3	4207

S3 Table (continued). Search strategy and corresponding results for all databases.

Search	Query	Hits
Conference Proceedings Citation Index - Science		
#5	TS=(Functional OR orthopedic OR orthopaedic OR interceptive OR preventive OR bite jump* OR (mandib* AND (advanc* OR enhanc* OR postur* OR protract* OR reposition*)) OR Activator OR Andresen OR Bass OR Bionator OR Bimler OR Frankel OR Fraenkel OR "Functional magnetic system" OR Harvold OR Monoblock OR "Twin block" OR Herbst OR "Mandibular anterior repositioning appliance" OR MARA OR "Eureka spring" OR Forsus OR "Jasper jumper" OR "Sabbagh spring" OR "Twin force")	197814
#6	TS=(appliance OR device)	412194
#7	#5 AND #6	10918
#8	TS=("End of growth" OR "completion of growth" OR long term OR longterm OR follow up OR post retention OR stability OR longitudinal)	498647
#9	#4 AND #7 AND #8	10
	For all queries: Indexes=CPCI-S Timespan=All years	

Search	Query	Hits
ISI Proceedings		
	"Class II malocclusion" AND "functional appliances" AND "long term"	10

Search	Query	Hits
ClinicalTrials.gov register		
	Condition: Class II malocclusion; Intervention: functional appliances	14

Search	Query	Hits
Current controlled trials metaRegister of Controlled Trials (mRCT) – active and archived registers		
	"Class II malocclusion" AND "functional appliances"	2

Search	Query	Hits
International prospective register of systematic reviews (PROSPERO)		
	Class II malocclusion AND functional appliances	17

S4 Table. Studies excluded with corresponding main reason of exclusion.

Study	Reference	Reason for exlusion
AAO COSA 2005	[1]	Other study design
Al-Jewair 2012	[2]	Study on the short-term effects
Al-Jewair 2013	[3]	Study on the short-term effects
Alió-Sanz 2012	[4]	Study on the short-term effects
Angelieri 2009	[5]	Patients not compared to untreated subjects
Baccetti 2010	[6]	Study on the short-term effects
Ball 1991	[7]	Study on the short-term effects
Barnett 2007	[8]	Study on the short-term effects
Bavbek 2016	[9]	Study on the short-term effects
Berg 1979	[10]	Treated patients not compared to any controls
Berg 1983	[11]	Orthodontic, but not functional appliances
Bigliazzi 2015	[12]	Outcomes not measured on lateral cephalograms
Bolmgren 1986	[13]	Study on the short-term effects
Bredy 1987	[14]	Not available abstract
Byloff-Clar 1970	[15]	Not available abstract
Cacciatore 2014	[16]	Study on the short-term effects
Casellas 2001	[17]	Study on the short-term effects
Chen 2011	[18]	Other outcomes were measured
Chhibber 2010	[19]	Other study design
Cozza 2003	[20]	Other study design
Craig 1977	[21]	Study on the short-term effects
Criswell 2011	[22]	Study on the short-term effects
Dalci 2014	[23]	Study on the short-term effects
DeVincenzo 1991	[24]	Patients not compared to untreated subjects
Dolce 2005	[25]	Outcomes not measured on lateral cephalograms
Dolce 2007	[26]	Patients not compared to untreated subjects
Dos Santos-Pinto 2013	[27]	Study on the short-term effects
Drage 1990	[28]	Study on the short-term effects
Ehmer 1990	[29]	Treated patients not compared to any controls
Falck 1983	[30]	Not available abstract
Faxén Sepanian 2014	[31]	Other outcomes were measured
Filip 1970	[32]	Not available abstract
Flores-Mir 2009	[33]	Study on the short-term effects
Foncatti 2017	[34]	Patients not compared to untreated subjects
Franchi 1999	[35]	Study on the short-term effects
Franchi 2006	[36]	Study on the short-term effects
Franchi 2011	[37]	Orthodontic, but not functional appliances
Franchi 2016	[38]	Outcomes not measured on lateral cephalograms
Frankel 1983	[39]	Other outcomes were measured
Fry 2006	[40]	Patients not compared to untreated subjects
Ghislanzoni 2011	[41]	Study on the short-term effects
Han 2014	[42]	Patients not compared to untreated subjects
Hansen 1992	[43]	Patients not compared to untreated subjects
Humphrey 2016	[44]	Study on the short-term effects
Jacob 2014	[45]	Functional appliances associated with headgear
Jakobsone 2013	[46]	Study on the short-term effects
Janson 2007	[47]	Patients not compared to untreated subjects
Johannesen 1972	[48]	Not available abstract
Karlowska 1971	[49]	Not available abstract
Keeling 1998	[50]	Study on the short-term effects
Keski-Nisula 2008	[51]	Study on the short-term effects
Knight 1988	[52]	Study on the short-term effects
Koroluk 2003	[53]	Other outcomes were measured
Lall 2011	[54]	Study on the short-term effects
Lima 2013	[55]	Study on the short-term effects
Livieratos 1995	[56]	Patients not compared to untreated subjects
Luder 1982	[57]	Study on the short-term effects
Lux 2001	[58]	Study on the short-term effects

S4 Table (continued). Studies excluded with corresponding main reason of exclusion.

Study		Reason for exlusion
Madone 1984a	[59]	Treated patients not compared to any controls
Madone 1984b	[60]	Not available abstract
Mills 2000	[61]	Study on the short-term effects
Mongini 1987	[62]	Orthodontic, but not functional appliances
Morris 1998	[63]	Study on the short-term effects
Morteson 2004	[64]	Participants aged more than16 years
Nelson 2007	[65]	Patients not compared to untreated subjects
O'Brien 2009	[66]	Study on the short-term effects
Omblus 1997	[67]	Patients not compared to untreated subjects
Pancherz 1977	[68]	Patients not compared to untreated subjects
Pancherz 1986	[69]	Treated patients not compared to any controls
Pancherz 1989	[70]	Not available full-text
Pancherz 1993	[71]	Patients not compared to untreated subjects
Pancherz 1994	[72]	Patients not compared to untreated subjects
Pancherz 1998	[73]	Patients not compared to untreated subjects
Pancherz 2003	[74]	Other outcomes were measured
Pancherz 2015	[75]	Treated patients not compared to any controls
Pancherz 2015	[76]	Treated patients not compared to any controls
Pangrazio 2012	[77]	Study on the short-term effects
Pavoni 2017	[78]	Other outcomes were measured
Perillo 1996	[79]	Patients not compared to untreated subjects
Perillo 2011	[80]	Treated patients not compared to any controls
Phelan 2012	[81]	Study on the short-term effects
Righellis 1983	[82]	Study on the short-term effects
Sander 1995	[83]	Study on the short-term effects
Sawrie 2007	[84]	Patients not compared to untreated subjects
Scalzone 2015	[85]	Study on the short-term effects
Schadlbauer 1984	[86]	Not available abstract
Schütz-Fransson 2006	[87]	Orthodontic, but not functional appliances
Siara-Olds 2010	[88]	Study on the short-term effects
Sivakumar 2005	[89]	Other study design
Stuber 1990	[90]	Not available full-text
Stuber 1990	[91]	Study on the short-term effects
Thompson 2001	[92]	Participants aged more than16 years
Tomblyn 2015	[93]	Study on the short-term effects
Tomblyn 2016	[94]	Study on the short-term effects
Tulloch 1998	[95]	Study on the short-term effects
Ulusoy 2014	[96]	Study on the short-term effects
Valant 1983	[97]	Study on the short-term effects
VanLaecken 2006	[98]	Study on the short-term effects
Vardimon 2001	[99]	Study on the short-term effects
Voudouris 2003	[100]	Animal study
Voudouris 2003	[101]	Animal study
Weschler 2005	[102]	Patients not compared to untreated subjects
Wheeler 2002	[103]	Study on the short-term effects
Wortham 2009	[104]	Other outcomes were measured
Yassaei 2012	[105]	Treated patients not compared to any controls
Yassaei 2014	[106]	Treated patients not compared to any controls
Yüksel 2010	[107]	Treated patients not compared to any controls
Zelderloo 2017	[108]	Patients not compared to untreated subjects

S5 Table. Results during the overall observational period for each outcome included in the meta-analysis.

Study	Intervention	Results								
		Treated			Control			Diff	95% CI	P
		Mean	SD	N	Mean	SD	N			
SNA (degrees)										
Pavoni 2017 (early)	Bio / Act + MBA	-0.2	2.0	23	0.6	1.6	16	-0.8	-2.0, 0.4	0.177
Pavoni 2017 (late)	Bio / Act + MBA	-1.3	2.7	23	-0.6	2.0	15	-0.7	-2.4, 1.0	0.391
Freeman 2009	Fr2	0.0	1.7	30	0.7	2.1	20	-0.7	-	-
Angelieri 2014	Fr2	0.2	1.4	17	0.9	1.7	17	-0.7	-	-
Wigal 2008 (males)	Hb + MBA	0.1	2.4	7	1.6	1.6	7	-1.5	-	0.172
Wigal 2008 (females)	Hb + MBA	-1.3	3.1	15	1.9	2.6	15	-3.2	-	0.005
Drosen 2018 (males)	Hb +/- MBA	0.1	1.7	13	0.7	1.7	13	-0.6	-	0.297
Alhoraibi 2017 (early)	FRD + MBA	-1.7	0.6	18	0.5	0.4	18	-2.2	-	0.000
Alhoraibi 2017 (late)	FRD + MBA	1.1	1.8	21	0.7	0.3	21	0.4	-	0.000
A to N perp (mm)										
Freeman 2009	Fr2	-1.6	1.4	30	0.1	1.5	20	-1.7	-	-
Angelieri 2014	Fr2	1.6	1.4	17	0.9	1.8	17	0.7	-	-
Alhoraibi 2017 (early)	FRD + MBA	-1.2	0.9	18	0.6	0.4	18	-1.8	-	0.000
Alhoraibi 2017 (late)	FRD + MBA	-6.3	1.7	21	0.5	0.4	21	-6.8	-	0.000
Co-A (mm)										
Freeman 2009	Fr2	10.2	3.4	30	10.4	3.7	20	-0.2	-	-
Angelieri 2014	Fr2	6.2	2.6	17	5.7	2.9	17	0.5	-	-
Wigal 2008 (males)	Hb + MBA	6.4	4.4	7	8.8	3.9	7	-2.4	-	-
Wigal 2008 (females)	Hb + MBA	4.0	3.2	15	8.5	2.9	15	-4.5	-	-
Alhoraibi 2017 (early)	FRD + MBA	0.9	1.1	18	2.4	0.7	18	-1.5	-	0.000
Alhoraibi 2017 (late)	FRD + MBA	1.3	1.3	21	0.6	0.6	21	0.7	-	0.000
SNB (degrees)										
Pavoni 2017 (early)	Bio / Act + MBA	1.4	2.0	23	2.2	1.6	16	-0.8	-2.0, 0.4	0.209
Pavoni 2017 (late)	Bio / Act + MBA	2.1	2.1	23	1.0	1.9	15	1.1	-0.2, 2.5	0.105
Freeman 2009	Fr2	3.5	1.7	30	1.8	2.1	20	1.7	-	-
Angelieri 2014	Fr2	2.3	1.9	17	1.7	1.8	17	0.6	-	-
Wigal 2008 (males)	Hb + MBA	2.1	2.2	7	1.4	1.8	7	0.7	-	0.525
Wigal 2008 (females)	Hb + MBA	1.0	2.4	15	2.2	2.1	15	-1.2	-	0.165
Drosen 2018 (males)	Hb +/- MBA	1.7	1.7	13	2.0	1.9	13	-0.3	-	0.878
Alhoraibi 2017 (early)	FRD + MBA	2.5	1.3	18	3.3	1.2	18	-0.8	-	0.050
Alhoraibi 2017 (late)	FRD + MBA	2.5	1.2	21	2.2	0.6	21	0.3	-	0.200
Pg to N perp (mm)										
Pavoni 2017 (early)	Bio / Act + MBA	4.3	3.8	23	3.4	4.1	16	0.9	-1.7, 3.5	0.479
Pavoni 2017 (late)	Bio / Act + MBA	6.8	2.3	23	3.7	3.4	15	3.1	1.3, 5.0	0.001
Freeman 2009	Fr2	2.5	3.6	30	3.0	3.1	20	-0.5	-	-
Angelieri 2014	Fr2	6.6	4.0	17	3.6	2.8	17	3.0	-	-
Alhoraibi 2017 (early)	FRD + MBA	0.4	0.9	18	1.6	2.3	18	-1.2	-	0.573
Alhoraibi 2017 (late)	FRD + MBA	1.9	0.9	21	1.0	1.6	21	0.9	-	0.570
Co-Gn (mm)										
Pavoni 2017 (early)	Bio / Act + MBA	16.8	4.6	23	17.5	4.7	16	-0.7	-3.8, 2.3	0.632
Pavoni 2017 (late)	Bio / Act + MBA	20.5	3.7	23	15.0	2.5	15	5.5	3.3, 7.7	0.000
Freeman 2009	Fr2	20.6	4.9	30	17.6	4.5	20	3.0	-	-
Angelieri 2014	Fr2	15.2	4.3	17	11.5	4.3	17	3.7	-	-
Wigal 2008 (males)	Hb + MBA	15.4	4.5	7	14.1	3.0	7	1.3	-	-
Wigal 2008 (females)	Hb + MBA	9.8	2.3	15	13.3	3.0	15	-3.5	-	-
Alhoraibi 2017 (early)	FRD + MBA	4.0	2.4	18	0.1	0.7	18	3.9	-	0.200
Alhoraibi 2017 (late)	FRD + MBA	1.7	2.4	21	0.0	0.7	21	1.7	-	0.772
ANB (degrees)										
Wieslander 1979	Act	-2.3	1.4	23	-0.5	1.0	23	-1.8	-	-
Pavoni 2017 (early)	Bio / Act + MBA	-1.6	1.2	23	-1.6	1.1	16	0.0	-0.8, 0.7	0.859
Pavoni 2017 (late)	Bio / Act + MBA	-3.4	1.5	23	-1.6	1.4	15	-1.8	-2.8, -0.8	0.001
Freeman 2009	Fr2	-3.5	1.2	30	-1.3	1.7	20	-2.2	-	-
Angelieri 2014	Fr2	-2.1	1.3	17	-0.8	1.9	17	-1.3	-	-
Wigal 2008 (males)	Hb + MBA	-2.1	1.6	7	0.2	1.2	7	-2.3	-	0.010
Wigal 2008 (females)	Hb + MBA	-2.3	1.7	15	-0.3	1.4	15	-2.0	-	0.002
Drosen 2018 (males)	Hb +/- MBA	-1.7	1.2	13	-1.3	1.2	13	-0.4	-	0.358

S5 Table (continued). Results during the overall observational period for each outcome included in the meta-analysis.

Study	Intervention	Results								
		Treated			Control			Diff	95% CI	P
		Mean	SD	N	Mean	SD	N			
Alhoraibi 2017 (early)	FRD + MBA	-3.3	1.6	18	-2.9	1.3	18	-0.4	-	0.537
Alhoraibi 2017 (late)	FRD + MBA	-0.9	1.3	21	-1.5	0.6	21	0.6	-	0.000
Wits (mm)										
Pavoni 2017 (early)	Bio / Act + MBA	-0.5	2.9	23	1.2	3.5	16	-1.7	-3.8, 0.3	0.098
Pavoni 2017 (late)	Bio / Act + MBA	-4.0	3.9	23	1.8	3.7	15	-5.8	-8.3, -3.2	0.000
Freeman 2009	Fr2	-3.1	2.4	30	1.8	2.5	20	-4.9	-	-
Angelieri 2014	Fr2	-2.2	2.2	17	0.4	2.2	17	-2.6	-	-
Wigal 2008 (males)	Hb + MBA	-2.2	2.1	7	0.1	2.2	7	-2.3	-	0.073
Wigal 2008 (females)	Hb + MBA	-1.3	1.9	15	-0.1	1.6	15	-1.2	-	0.072
Drosen 2018 (males)	Hb +/- MBA	-1.6	2.5	13	0.8	1.9	13	-2.4	-	0.006
Alhoraibi 2017 (early)	FRD + MBA	-2.9	1.3	18	0.8	0.9	18	-3.7	-	0.000
Alhoraibi 2017 (late)	FRD + MBA	-2.3	1.7	21	0.7	1.2	21	-3.0	-	0.000
Co-Gn/Co-A diff (mm)										
Freeman 2009	Fr2	10.4	2.6	30	7.8	2.8	20	2.6	-	-
Angelieri 2014	Fr2	8.9	3.1	17	5.6	3.1	17	3.3	-	-
Wigal 2008 (males)	Hb + MBA	7.7	1.8	7	5.4	2.8	7	2.3	-	0.090
Wigal 2008 (females)	Hb + MBA	5.8	4.0	15	4.8	2.5	15	1.0	-	0.404
Alhoraibi 2017 (early)	FRD + MBA	3.0	2.3	18	-2.3	1.1	18	5.3	-	0.000
Alhoraibi 2017 (late)	FRD + MBA	0.4	3.2	21	-0.6	0.8	21	1.0	-	0.004

Act, Activator; Bio, Bionator; Fr2, Frankel-2; Hb, Herbst; FRD, Forsus; MBA, multi-bracket appliances;
Mx skeletal, maxillary skeletal outcomes; SNA, SNA angle; A to N perp, A point to N perpendicular distance; Co-A, Co-A distance;

Md skeletal, mandibular skeletal outcomes; SNB, SNB angle; Pg to N perp, Pg point to N perpendicular distance; Co-Gn, Co-Gn distance;

Mx-md skeletal, maxillo-mandibular outcomes; ANB, ANB angle; Wits, Wits appraisal; Co-Gn/Co-A diff, Co-Gn/Co-A difference;

SD, standard deviation; N, number of participants;
Diff, difference; 95% CI, 95% confidence intervals; P, P value reported by the original study.

S6 Table. Results during the overall observational period for each outcome excluded by the meta-analysis.

Study	Outcome (mm)	Results								
		Treated			Control			Diff	95% CI	P
		Mean	SD	N	Mean	SD	N			
Wieslander 1979	A to S perp	2.8	2.7	23	4.1	2.1	23	-1.3	-	-
Falck 1991 (males)	Horiz. A to ORS	10.2	2.3	19	10.2	3.2	18	0.0	-	-
Falck 1991 (females)	Horiz. A to ORS	6.2	2.0	31	7.2	2.9	20	-0.9	-	-
Wigal 2008 (males)	Olp-A	6.2	2.2	7	8.1	2.4	7	-1.9	-	0.139
Wigal 2008 (females)	Olp-A	3.5	2.3	15	6.6	2.1	15	-3.1	-	0.001
Wieslander 1979	Pg to S perp	6.3	4.4	23	5.5	3.4	23	0.8	-	-
Falck 1991 (males)	Horiz. Pg to ORS	19.6	4.7	19	15.1	4.3	18	4.5	-	-
Falck 1991 (females)	Horiz. Pg to ORS	13.3	3.9	31	9.2	5.6	20	4.0	-	-
Falck 1991 (males)	Horiz. B to ORS	16.9	4.5	19	12.1	3.7	18	4.7	-	-
Falck 1991 (females)	Horiz. B to ORS	11.7	3.0	31	7.4	4.1	20	4.3	-	-
Wieslander 1979	Ar-Gn	11.8	5.1	23	11.2	4.5	23	0.7	-	-
Wieslander 1979	Co-Gn	13.2	5.7	23	11.8	5.7	23	1.5	-	-
Falck 1991 (males)	Co-Gn	23.2	3.7	19	20.3	3.8	18	2.9	-	-
Falck 1991 (females)	Co-Gn	18.1	3.1	31	14.5	3.6	20	3.6	-	-
Wigal 2008 (males)	Olp-Co	1.4	3.3	7	0.6	3.2	7	0.8	-	0.665
Wigal 2008 (females)	Olp-Co	0.5	2.1	15	1.8	1.8	15	-1.3	-	0.077
Wigal 2008 (males)	Olp-Pg	10.9	2.7	7	9.2	4.3	7	1.7	-	0.398
Wigal 2008 (females)	Olp-Pg	6.6	3.5	15	9.7	1.9	15	-3.1	-	0.005
Wieslander 1979	Co to mand	8.7	4.1	23	9.4	4.6	23	-0.6	-	-
Pavoni 2017 (early)	Co-Go	10.9	4.6	23	11.8	2.7	16	-0.9	-3.5, 1.7	0.482
Pavoni 2017 (late)	Co-Go	14.0	3.7	23	11.6	3.0	15	2.4	0.2, 4.8	0.036
Drosen 2018 (males)	Ar-Go	11.7	3.0	13	9.4	2.1	13	2.3	-	0.029

Mx skeletal, maxillary skeletal outcomes; A to S perp, A point to S perpendicular distance; Horiz. A to ORS, horizontal distance of A point to occipital reference system; Olp-A, distance of A point to occlusal line perpendicular;

Md skeletal, mandibular skeletal outcomes; Pg to S perp, Pg point to S perpendicular distance; Horiz. B or Pg to ORS, horizontal distance of B point or Pg point to occipital reference system; Ar-Gn, Ar-Gn distance; Olp-Co, distance of Co point to occlusal line perpendicular; Olp-Pg, distance of Pg point to occlusal line perpendicular; Co to mand, distance of Co point to mandibular plane; Co-Go, Co-Go distance; Ar-Go, Ar-Go distance;

Mx-md skeletal, maxillo-mandibular outcomes; ANB, ANB angle; Wits, Wits appraisal; Co-Gn/Co-A diff, Co-Gn/Co-A difference;

SD, standard deviation; N, number of participants;
Diff, difference; 95% CI, 95% confidence intervals; P, P value reported by the original study.

S1 Appendix. Eligibility criteria with rationale.

Study designs

The following study designs were included: randomised controlled trials (RCTs), controlled (non-randomised) clinical trials (CCTs), controlled before-after (CBA) studies, and case-control or nested case-control studies. Prospective and retrospective cohort studies, cross-sectional studies, case series, and case reports were excluded.

Since the aim of this review was to compare Class II malocclusion patients treated with functional appliances to untreated subjects, only experimental and observational studies with a comparison group were included [1]. The decision to evaluate both randomised and non-randomised controlled trials was made, in order to collect a wide range of studies. A limited number of trials assessing any type of outcome in the long-term was found in previous systematic reviews [2-5].

Participants

Children and adolescents (aged 16 years or under) receiving orthodontic treatment to correct Class II malocclusion were included. Active treatment with functional appliances had to be completed by the age of 16 years, to allow for a sufficient post-retention period at growth completion. Studies were considered eligible regardless of how the baseline disease was measured (e.g. dental casts, lateral cephalograms) and its severity (e.g. full or half Class II molar relationship, depending on whether the lower molars were placed in a completely or partially posterior position relative to the upper molars, respectively).

Given the potential of functional appliances in modifying the patient growth, they are commonly used in childhood and adolescence [6]. Thus, the analysis of the treatment effects of these appliances on adults was considered to be of minor relevance.

Although there is no agreement on the definitions of childhood and adolescence, in a recent

systematic review of the Cochrane Collaboration 'children' were defined as subjects aged from 7 to 11 years, whereas 'adolescents' were defined as subjects aged from 12 to 16 years [6]. This practical categorisation is also used in other systematic reviews [7], trials [8], and some national health services (e.g. United Kingdom and Italy). Alternative methods to establish the growth phase, such as the hand-and-wrist maturation method [9] or the cervical vertebral maturation method [10] were not chosen as inclusion criteria, due to them not being globally accepted [11].

Trials including participants with a cleft lip or palate or both, other craniofacial deformity/syndrome (such as Apert, Crouzon, Hemifacial Microsomia/Goldenhar, Moebius, Pierre Robin, Treacher Collins syndromes or craniosynostosis), syndromes affecting the craniofacial structures or patients with temporo-mandibular joint disorders were excluded.

Interventions

Any type of functional appliance, defined as a removable or fixed orthodontic appliance that postures the mandible forward [12]. Functional appliances had to be worn alone or in combination with multi-bracket therapy so as to be included. When functional appliances were worn alone, this therapy could also take place after the functional appliance treatment. A concurrent or subsequent phase with multi-bracket appliances to align teeth is the most common clinical pathway in Orthodontics [2, 13].

Conversely, association with other Class II devices designed primarily to restrain the maxilla (e.g. headgear) was set as an exclusion criterion. Mechanics opposite to those employed during the functional appliance therapy were kept out, so as to reduce co-intervention bias [14].

Only functional appliances worn for 6 months or longer were considered eligible. The duration of treatment with functional appliances is usually from 6 to 18 months, followed by night-time insertion of the appliance, or though the use of a stabilization plate [5, 6, 12, 13, 15, 16]. A wider spectrum of treatment period was considered to be valid, in order to include as many eligible

studies as possible.

Comparators

Class II malocclusion patients treated with functional appliances were compared only to untreated Class II subjects. No other type of orthodontic appliance or brace was considered as a comparator.

Patterns of mandibular growth in subjects with untreated Class II malocclusion differ from those of untreated subjects with normal occlusion (Class I). The deficiency in mandibular growth in Class II subjects is significant at the growth spurt, and it is maintained at the post-pubertal stage. Thus, the use of untreated Class II comparators in studies or reviews on the effectiveness of dentofacial orthopaedics on mandibular growth is recommended [17].

For this comparison, groups had to be of similar ages at the commencement of the observational period (age differences between the treated and untreated groups less than 18 months).

Outcomes

The following clinically important outcomes were recorded:

- Cephalometric skeletal measurements evaluating the antero-posterior position of the maxilla and mandible, the total mandibular length or length of its parts (ramus and corpus), the mutual relationship between the two jaws.

- Soft tissue changes of both lips and chin, measured on lateral cephalograms.

Measurements derived from any cephalometric analysis were included. Due to possible variation in outcome definitions over time, outcomes were collected as reported. Definitions of outcomes as reported in individual studies were extracted as well.

It is not possible to establish the true nature of a malocclusion without information on the underlying skeletal relationships. Cephalometric analysis still remains the most widespread, safest

and most precise method of measuring changes to skeletal structures [18]. The use of alternative methods, such as the cone-beam computer tomography (CBCT), should not be implemented for this purpose [19]. According to the 'Guidelines on CBCT for dental and maxillofacial radiology', large volume CBCT should not be used as a standard diagnosis method in Orthodontics. In comparison to conventional radiograph, CBCT has higher radiation doses and, having so stated, its use may be justified in treatment planning, solely for complex cases of skeletal abnormality, particularly those requiring combined orthodontic/surgical management [19].

Lateral cephalograms can also be useful for analysing soft-tissue changes. At this time, alternative methods, such as two-dimensional or three-dimensional photographs, are not widespread as much as lateral cephalograms in orthodontic practice and research.

Timing

Studies were selected for inclusion based on the duration of follow-up of outcomes. Studies should have measured outcomes at the end of growth, defined by age or using indicators of the growth phase. Otherwise, studies should have a post-retention period of at least 3 years.

Contrary to the age threshold established when selecting the inclusion of participants, no age criteria was used to define the end of growth. Literature disagrees on the completion of the maxillofacial unit growth [20-24].

Since the real and stable results produced by functional appliances are the areas of interest, a minimum post-retention period after functional jaw orthopaedics was imposed. There is no recognised duration for retainers to be worn after multi-bracket appliances. It has been shown that if patients stop wearing retainers for between 1 and 2 years after correction of teeth positions there is a risk of long-term relapse [25]. There is no definitive agreement on the retention protocol after functional appliance therapy either [15, 26, 27]. Nevertheless, it is clinically unlikely that a treatment initiated in adolescence and skeletally stable after a 3 year follow up could relapse. For

these reasons, a post-retention period of at least 3 years as eligibility criteria was set.

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S3 Appendix. The forest plots concerning redundant or non-statistically significant results.

Maxillary/upper jaw changes

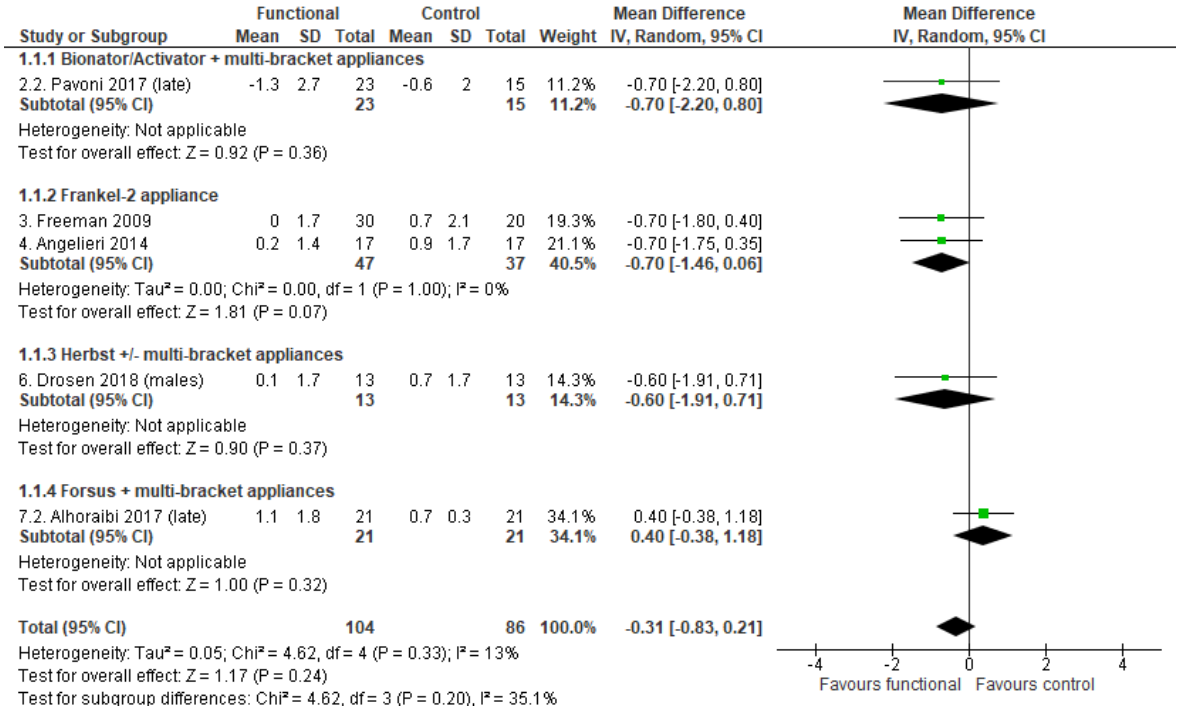

Figure 1. Meta-analysis; Outcome: SNA angle; Time point: above 18 years of age.

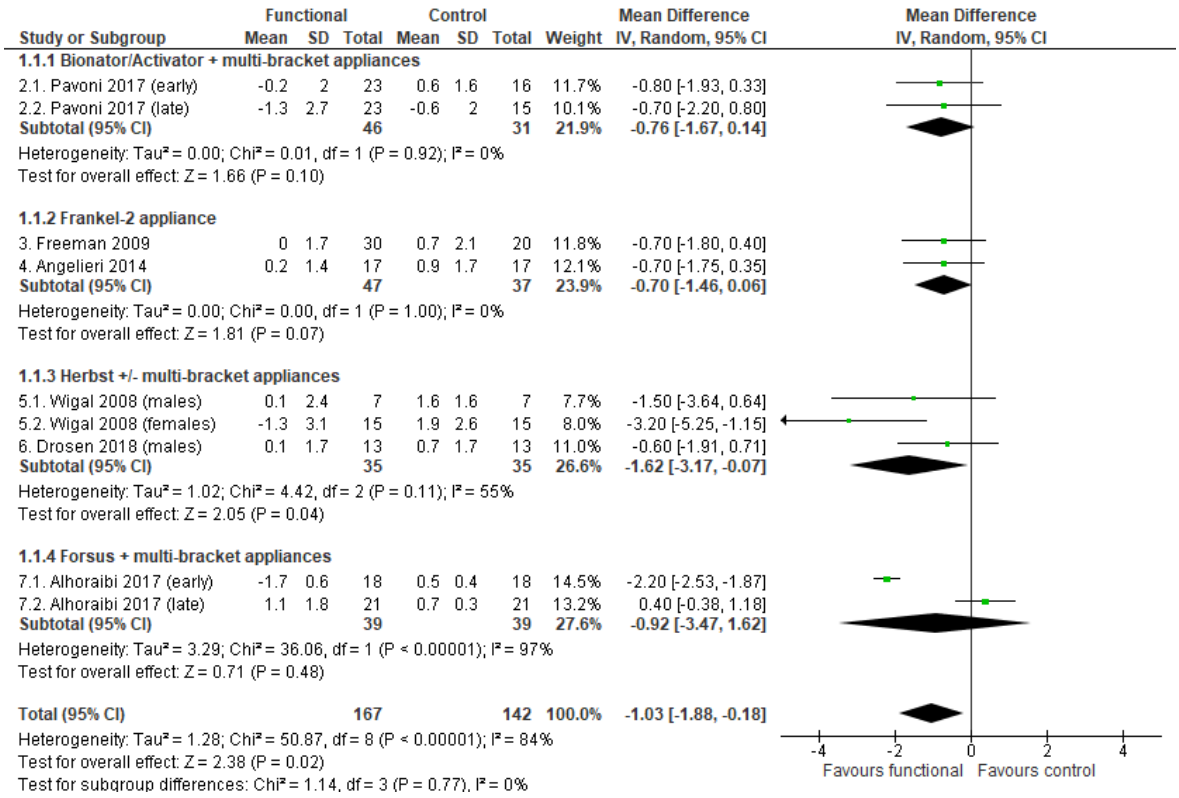

Figure 2. Meta-analysis; Outcome: SNA angle; Time point: After a post-retention period of at least 3 years.

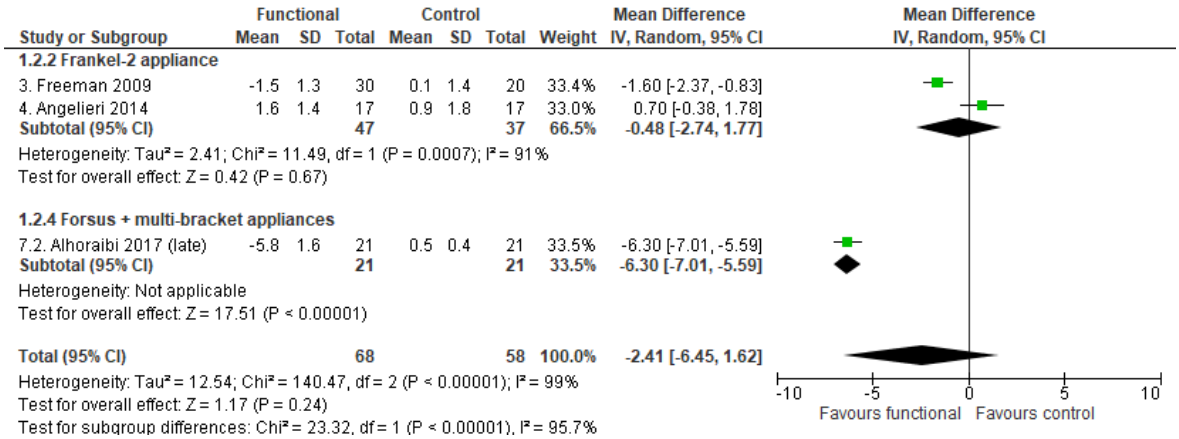

Figure 3. Meta-analysis; Outcome: A to N perpendicular distance; Time point: above 18 years of age.

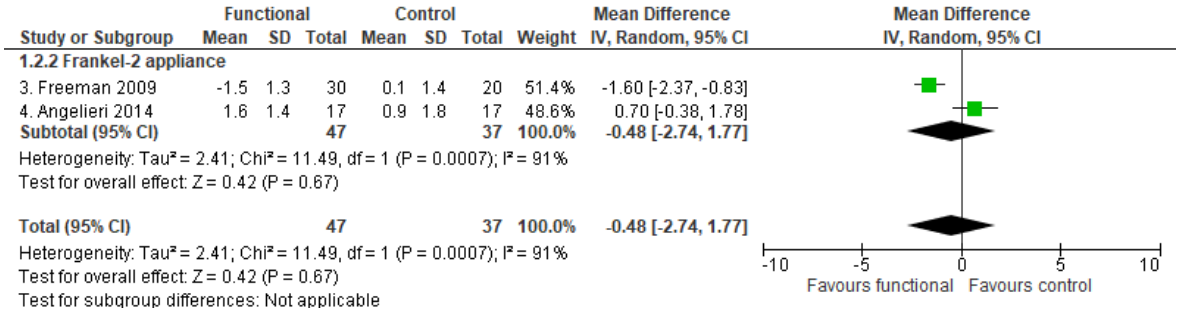

Figure 4. Meta-analysis; Outcome: A to N perpendicular distance; Time point: end of growth according to the CVM method.

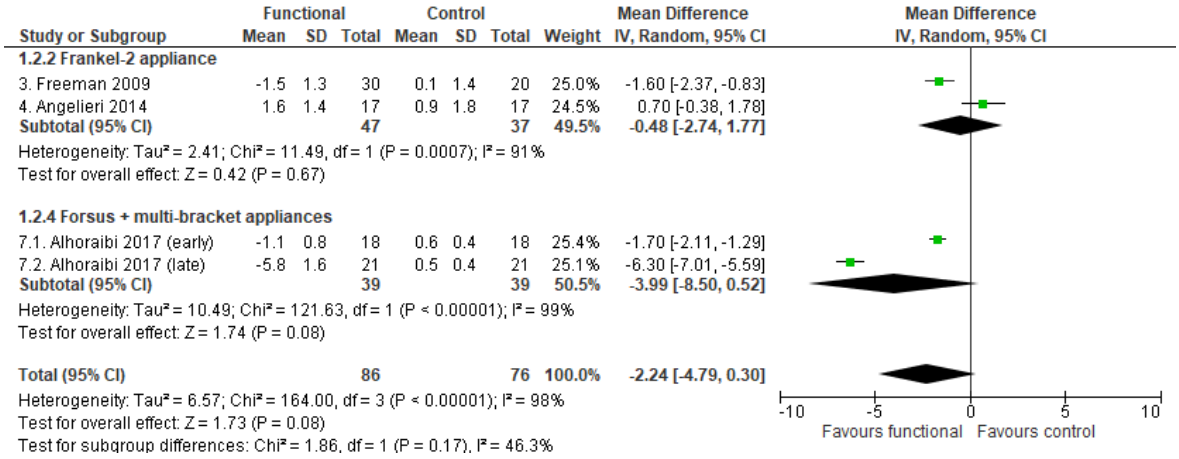

Figure 5. Meta-analysis; Outcome: A to N perpendicular distance; Time point: After a post-retention period of at least 3 years.

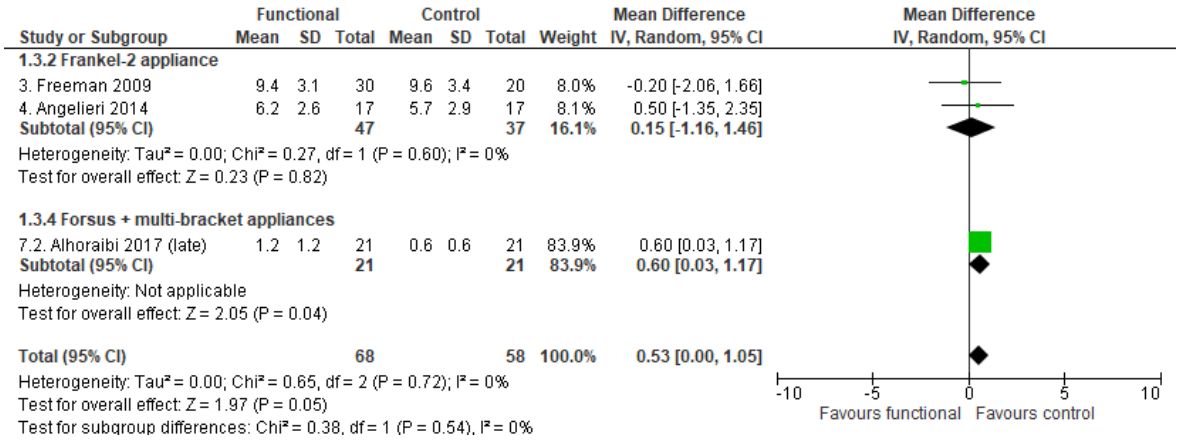

Figure 6. Meta-analysis; Outcome: Co-A distance; Time point: above 18 years of age.

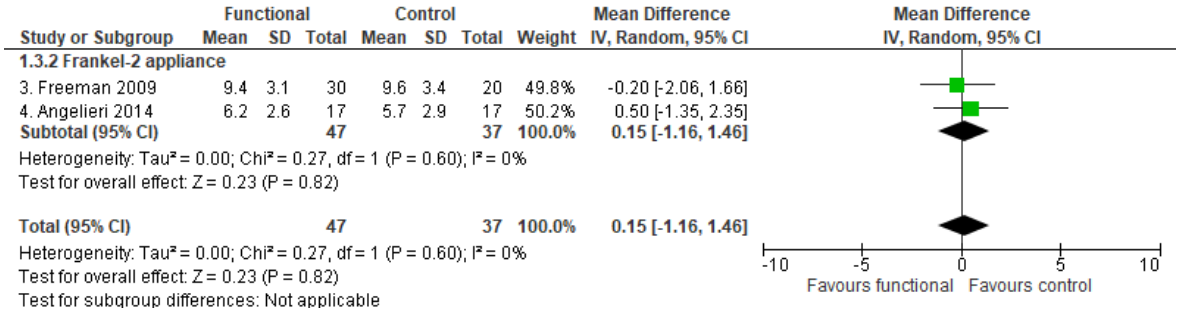

Figure 7. Meta-analysis; Outcome: Co-A distance; Time point: end of growth according to the CVM method.

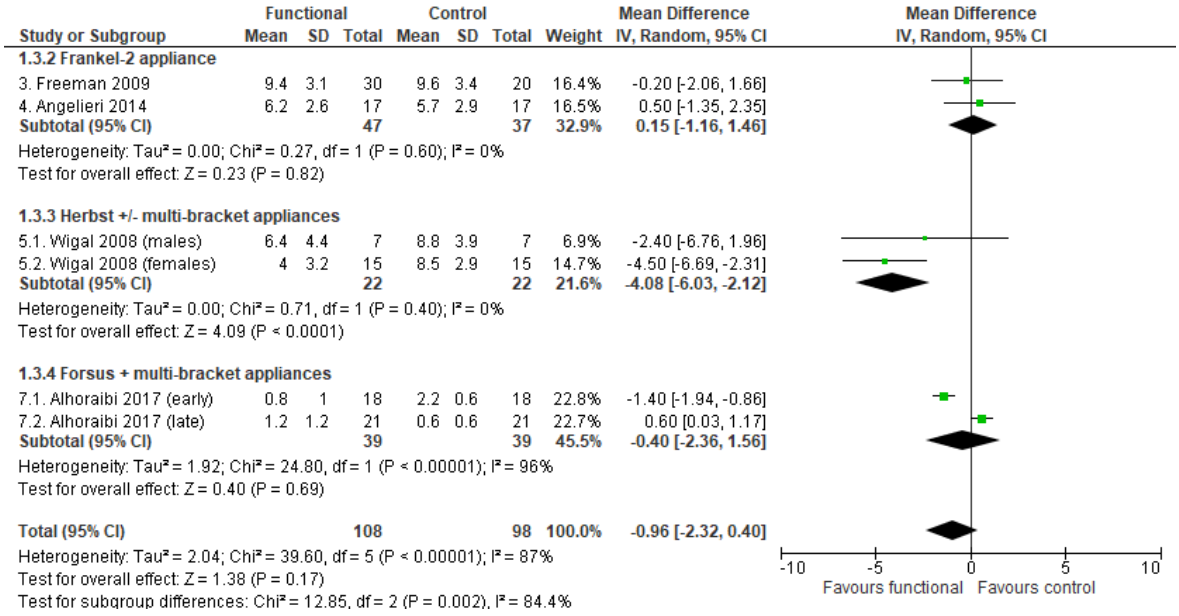

Figure 8. Meta-analysis; Outcome: Co-A distance; Time point: After a post-retention period of at least 3 years.

Mandibular/lower jaw changes

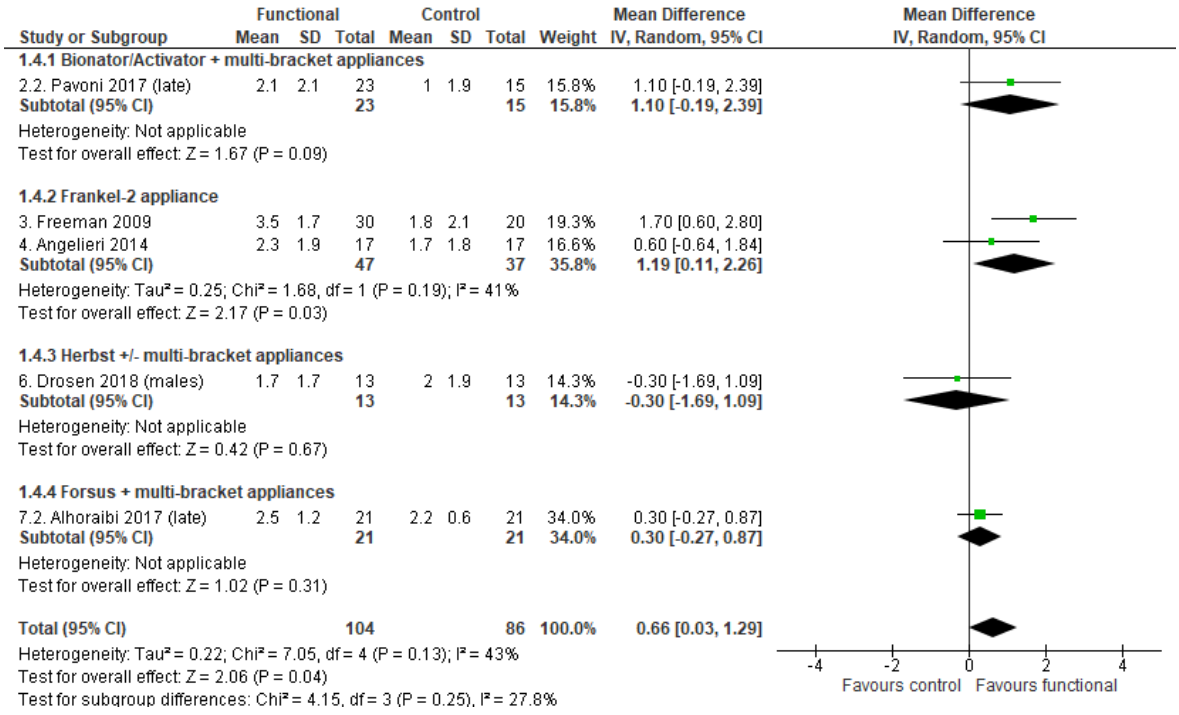

Figure 9. Meta-analysis; Outcome: SNB angle; Time point: above 18 years of age.

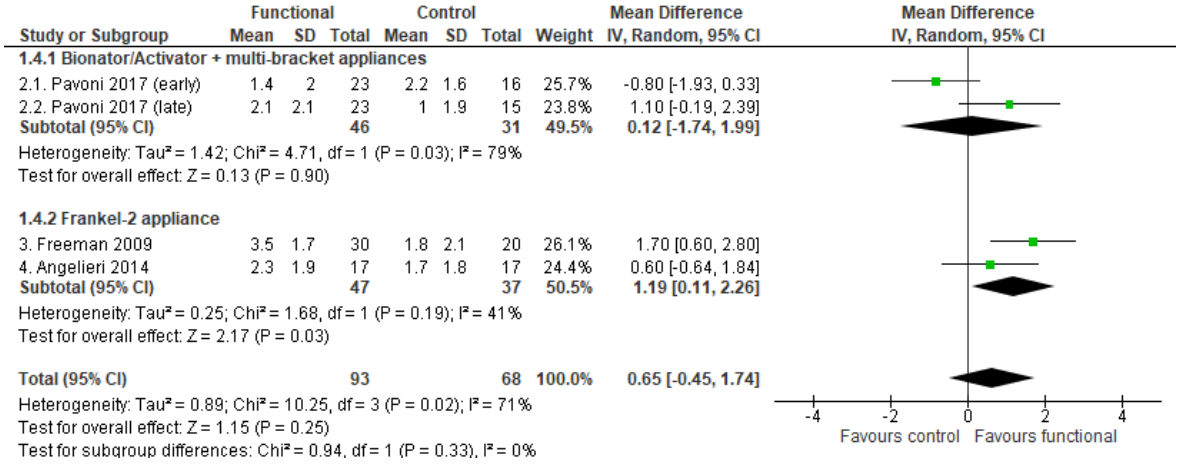

Figure 10. Meta-analysis; Outcome: SNB angle; Time point: end of growth according to the CVM method.

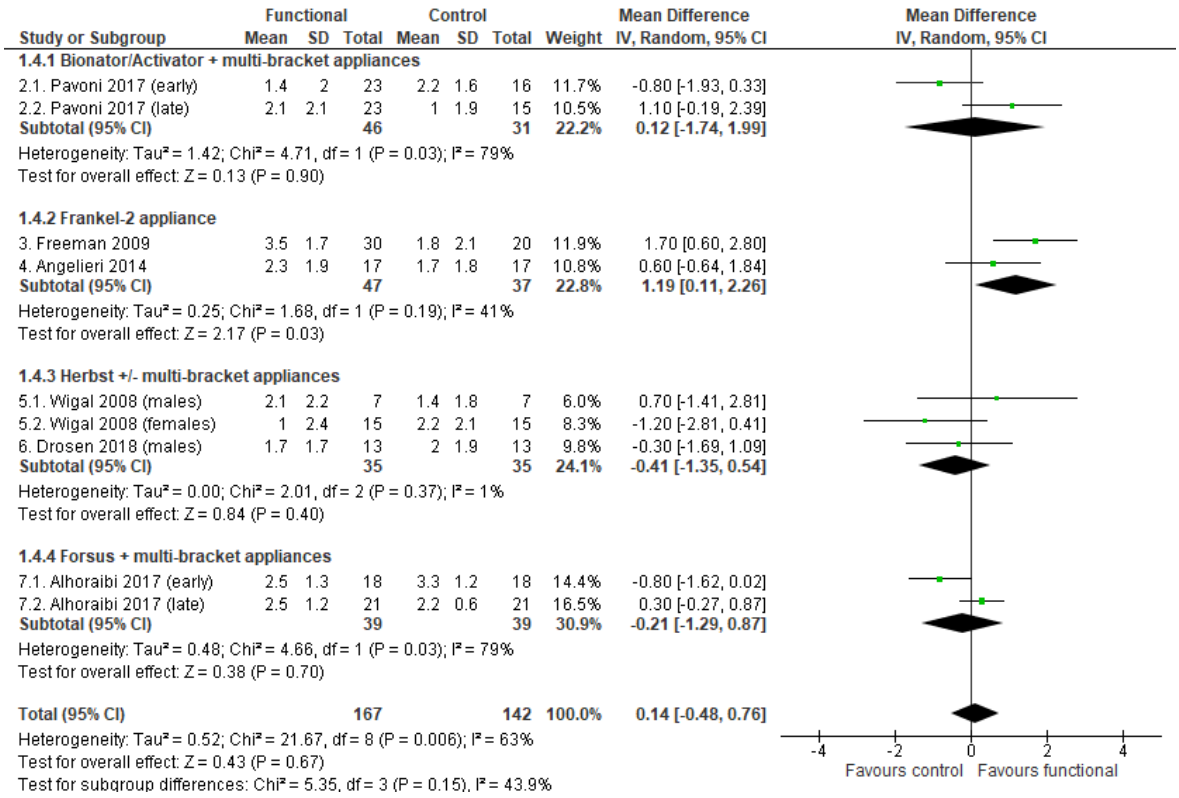

Figure 11. Meta-analysis; Outcome: SNB angle; Time point: After a post-retention period of at least 3 years.

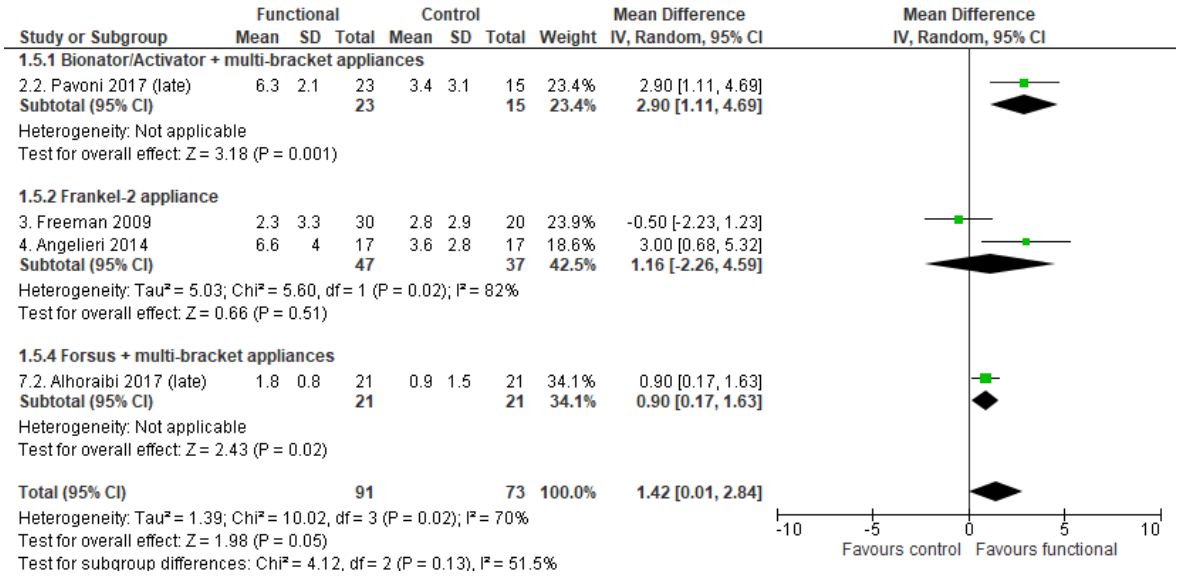

Figure 12. Meta-analysis; Outcome: Pg to N perp distance; Time point: above 18 years of age.

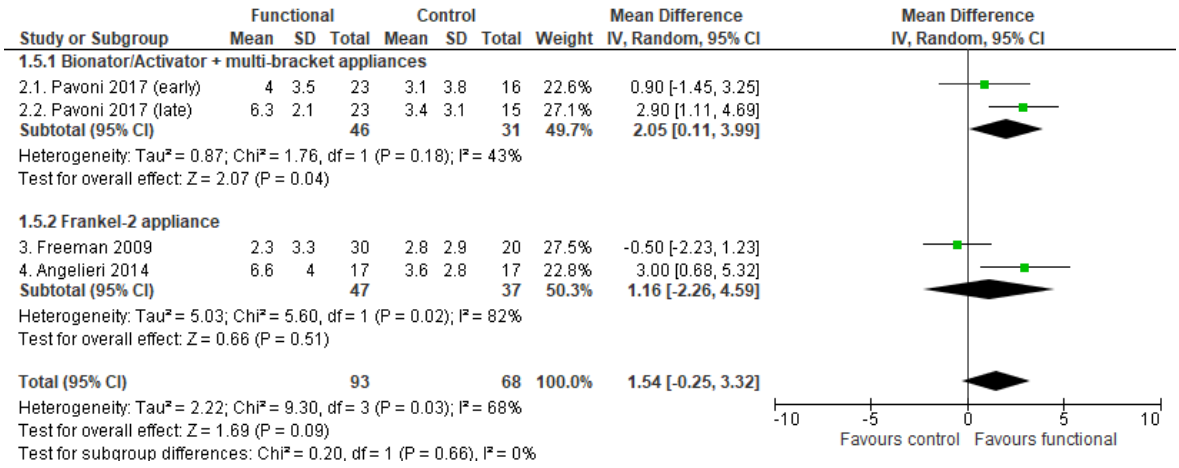

Figure 13. Meta-analysis; Outcome: Pg to N perp distance; Time point: end of growth according to the CVM method.

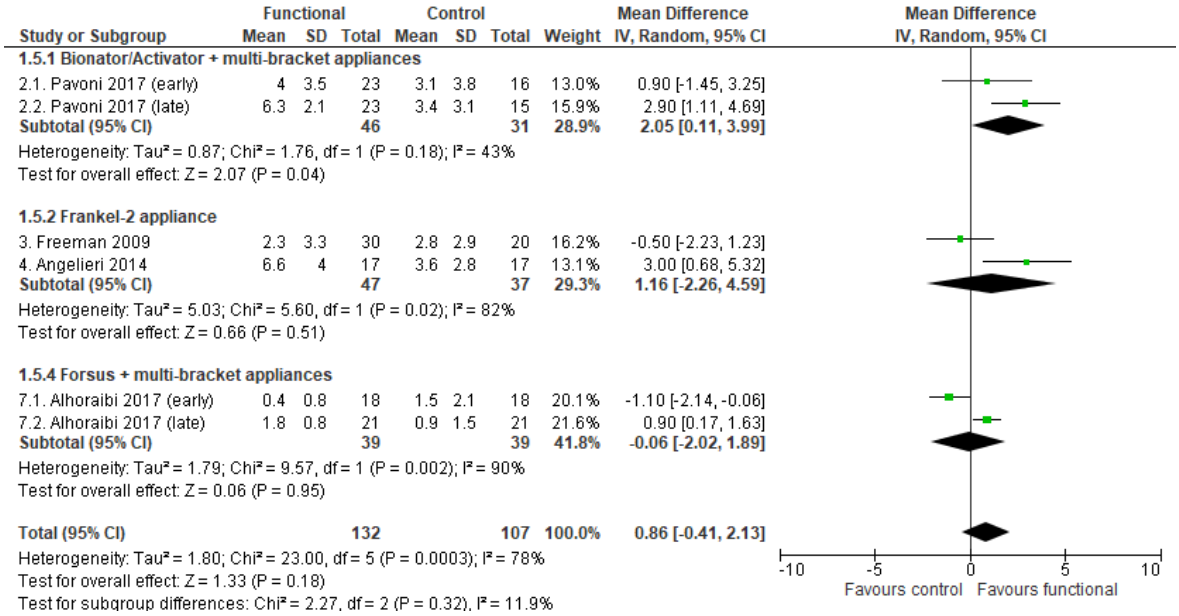

Figure 14. Meta-analysis; Outcome: Pg to N perpendicular distance; Time point: After a post-retention period of at least 3 years.

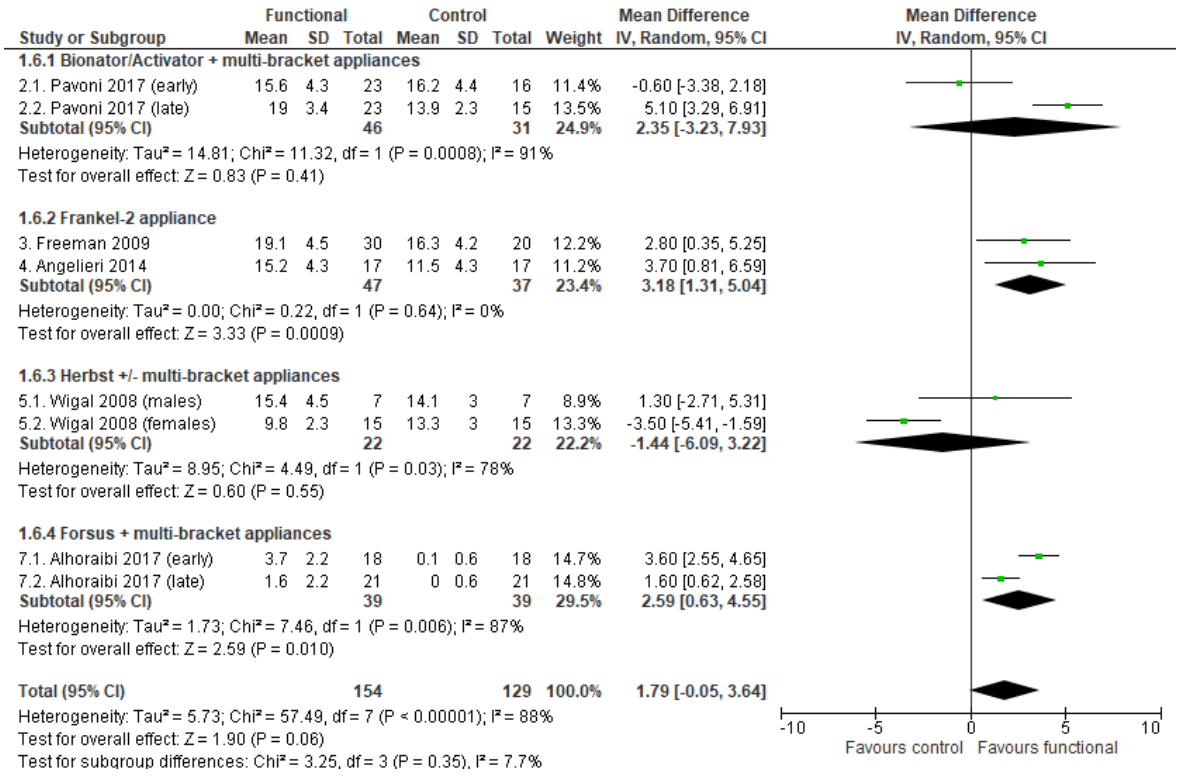

Figure 15. Meta-analysis; Outcome: Co-Gn distance; Time point: After a post-retention period of at least 3 years.

Maxillo-mandibular changes

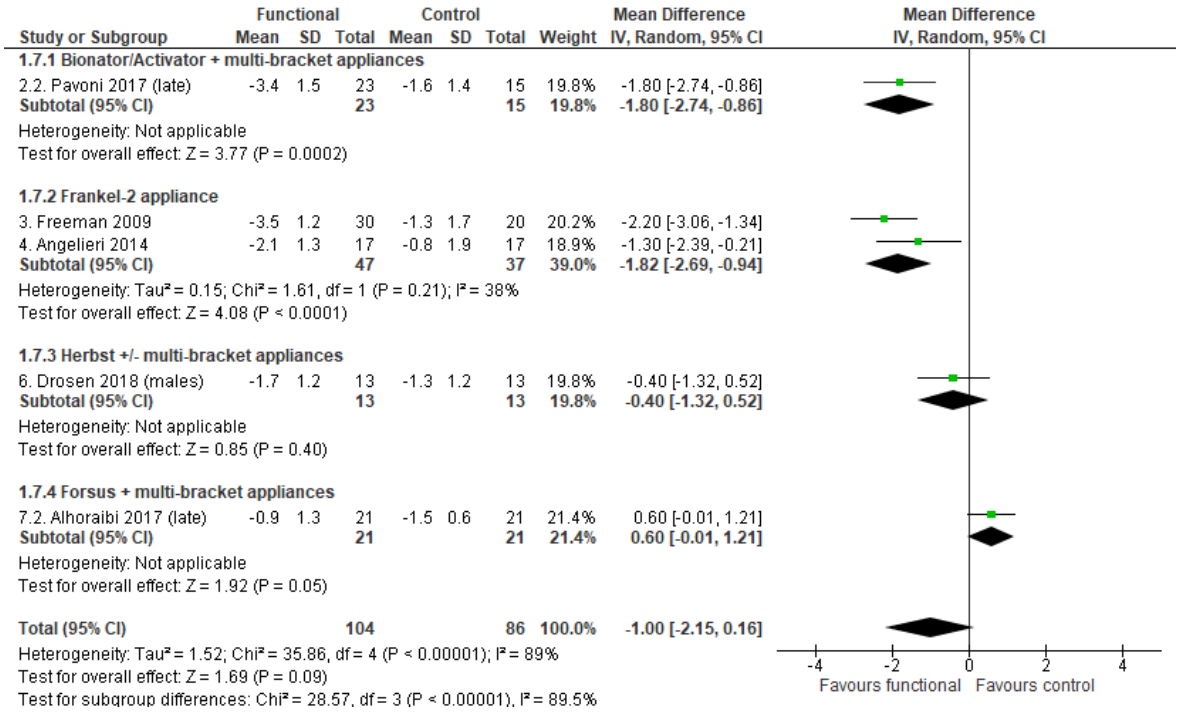

Figure 16. Meta-analysis; Outcome: ANB angle; Time point: above 18 years of age.

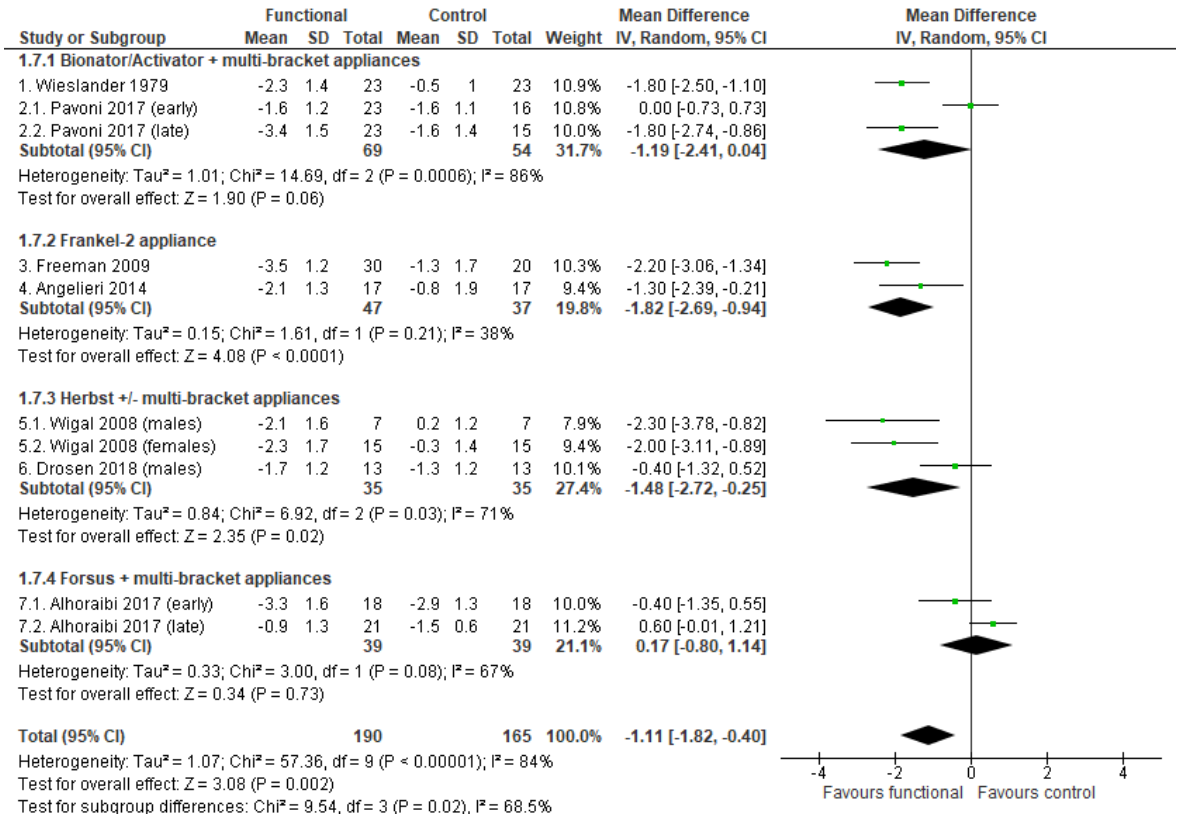

Figure 17. Meta-analysis; Outcome: ANB angle; Time point: After a post-retention period of at least 3 years.

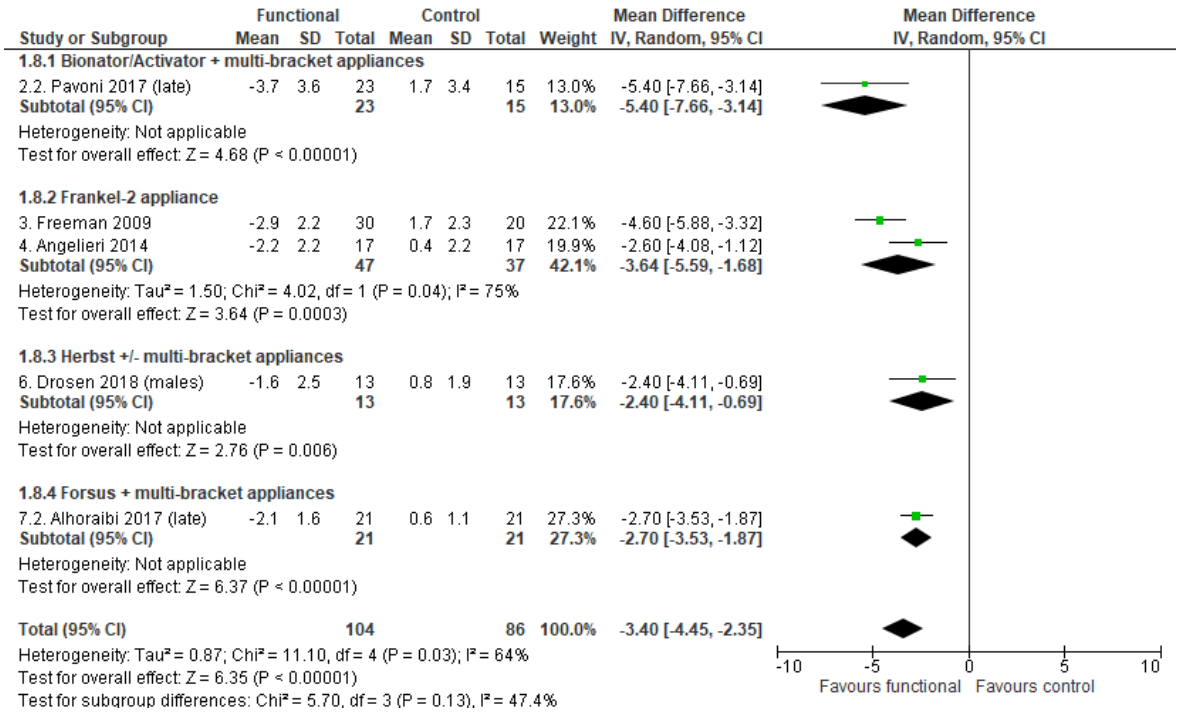

Figure 18. Meta-analysis; Outcome: Wits appraisal; Time point: above 18 years of age.

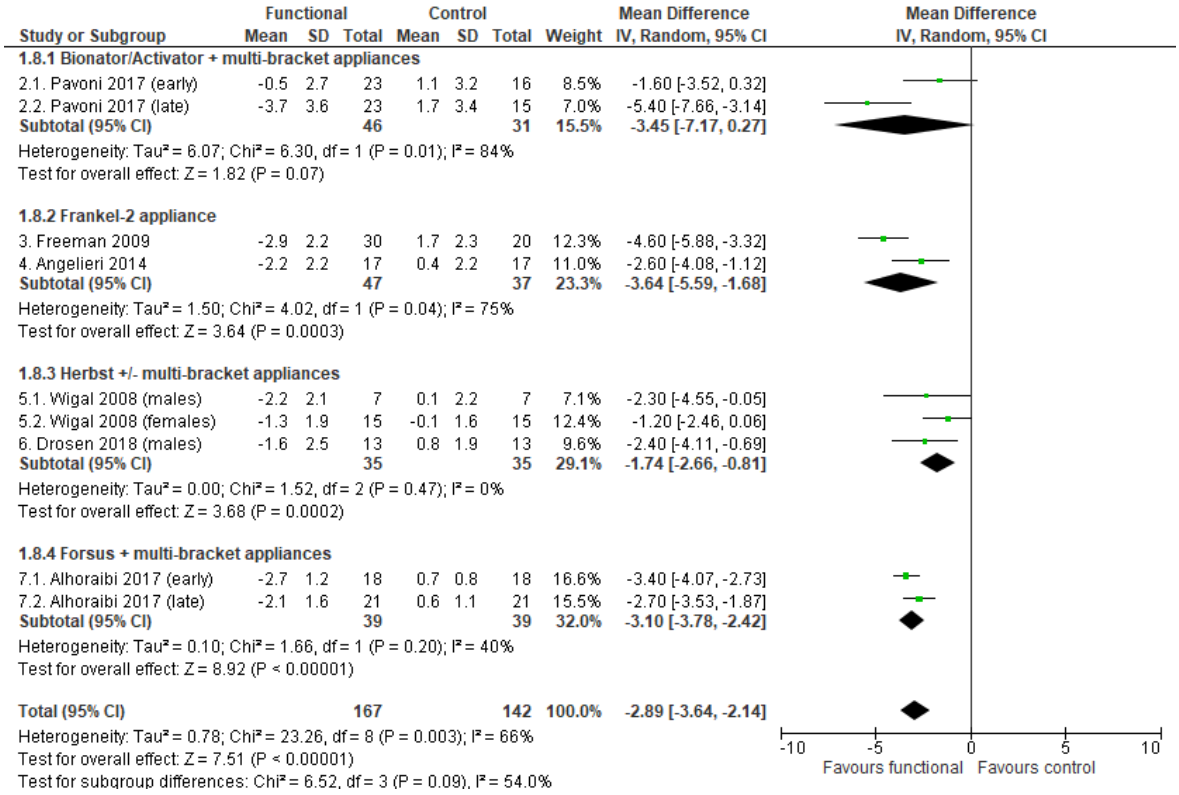

Figure 19. Meta-analysis; Outcome: Wits appraisal; Time point: After a post-retention period of at least 3 years.

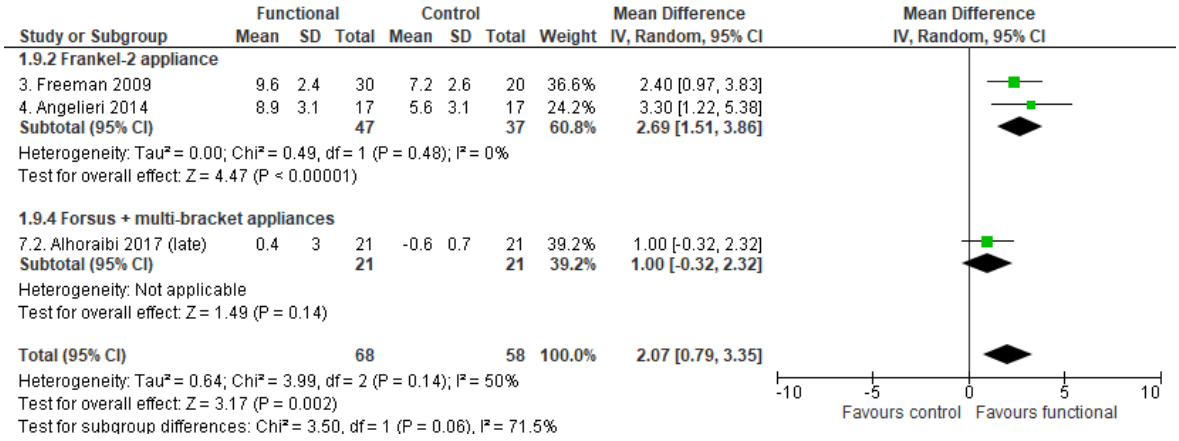

Figure 20. Meta-analysis; Outcome: Co-Gn/Co-A difference; Time point: above 18 years of age.

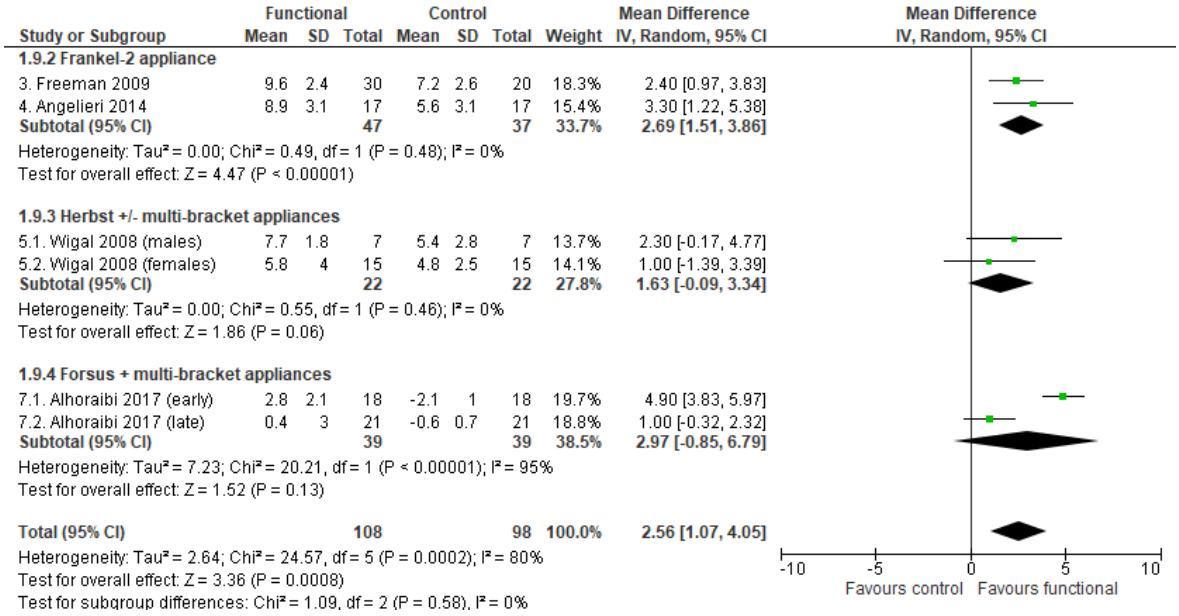

Figure 21. Meta-analysis; Outcome: Co-Gn/Co-A difference; Time point: After a post-retention period of at least 3 years.

Additional analysis

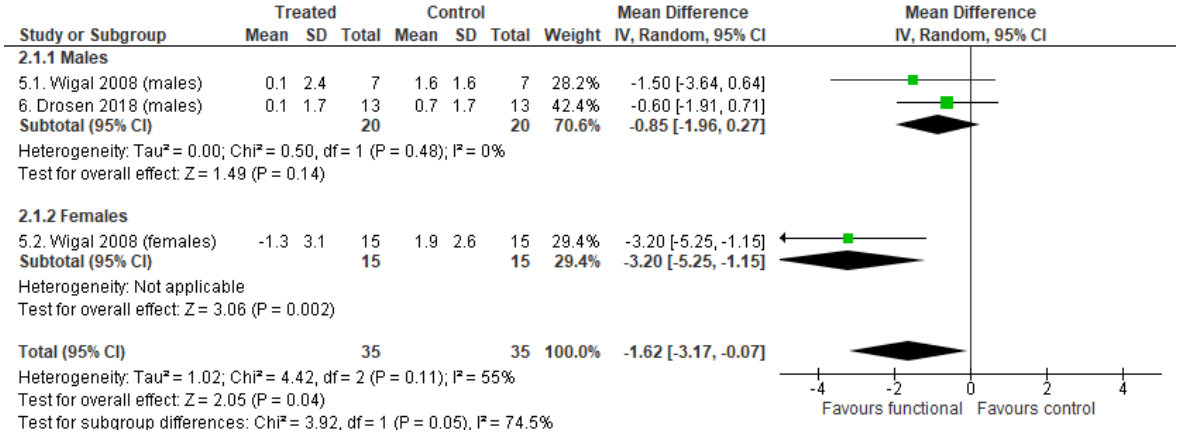

Figure 22. Subgroup analysis based on gender (males, females); Outcome: SNA angle.

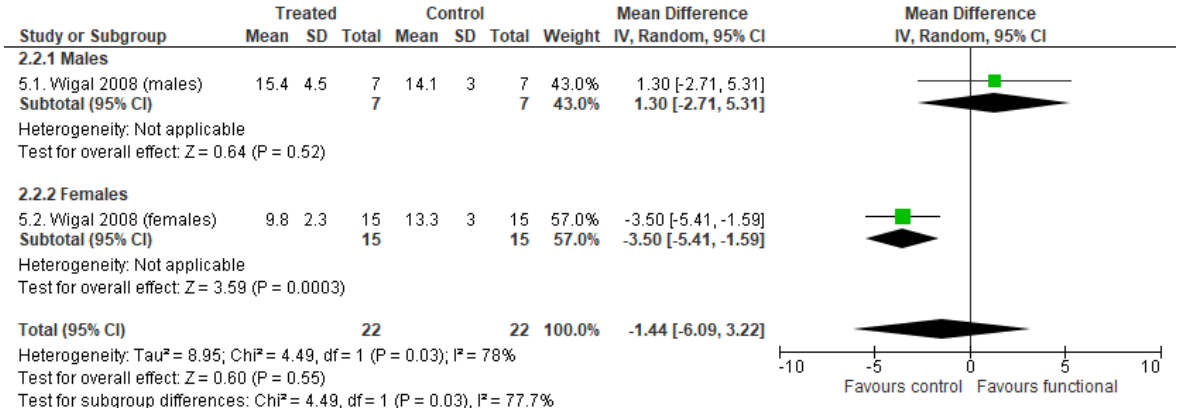

Figure 23. Subgroup analysis based on gender (males, females); Outcome: Co-Gn distance.

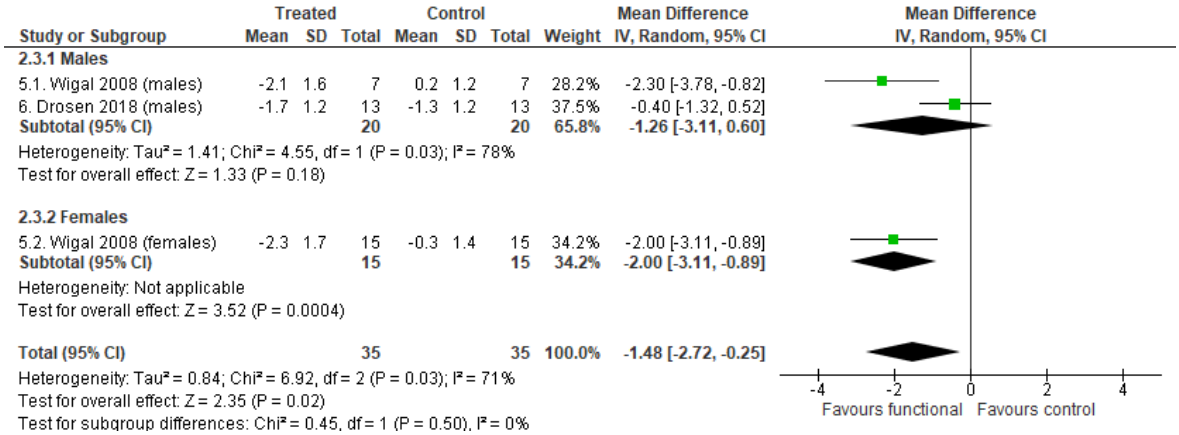

Figure 24. Subgroup analysis based on gender (males, females); Outcome: ANB angle.

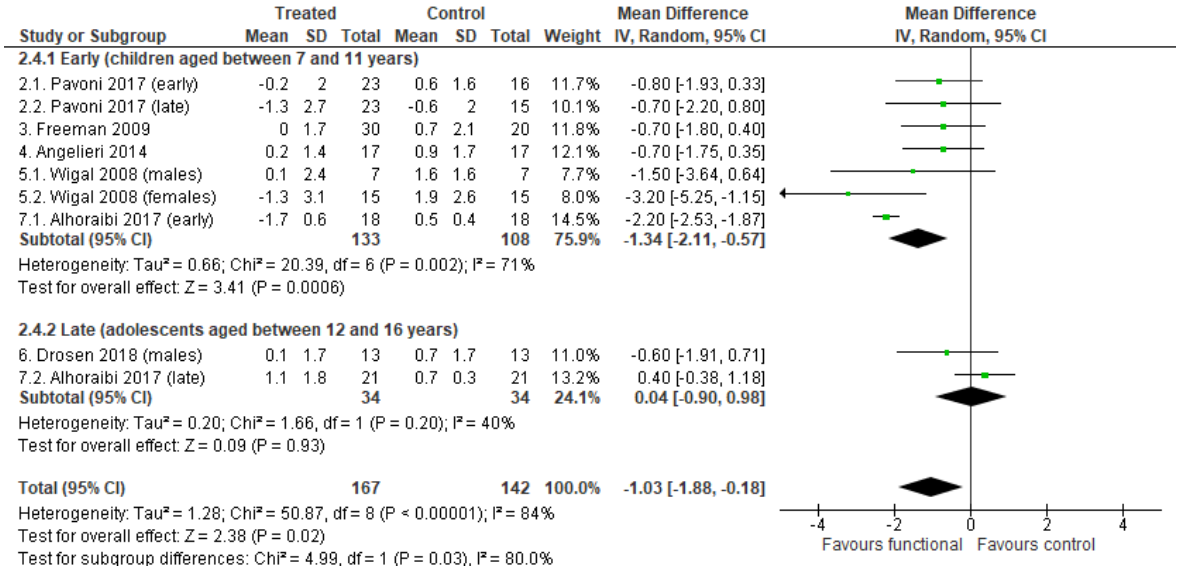

Figure 25. Subgroup analysis based on the beginning of the functional appliance therapy; Outcome: SNA angle. Early treatments, commencing in children aged between 7 and 11 years; late treatments, beginning in adolescents aged between 12 and 16 years.

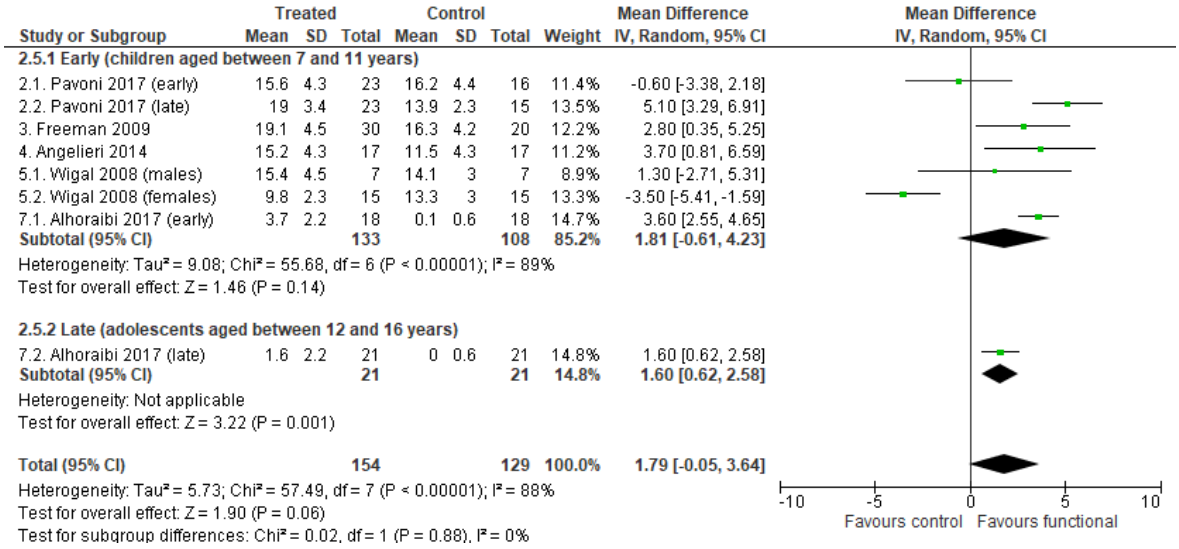

Figure 26. Subgroup analysis based on the beginning of the functional appliance therapy; Outcome: Co-Gn distance. Early treatments, commencing in children aged between 7 and 11 years; late treatments, beginning in adolescents aged between 12 and 16 years.

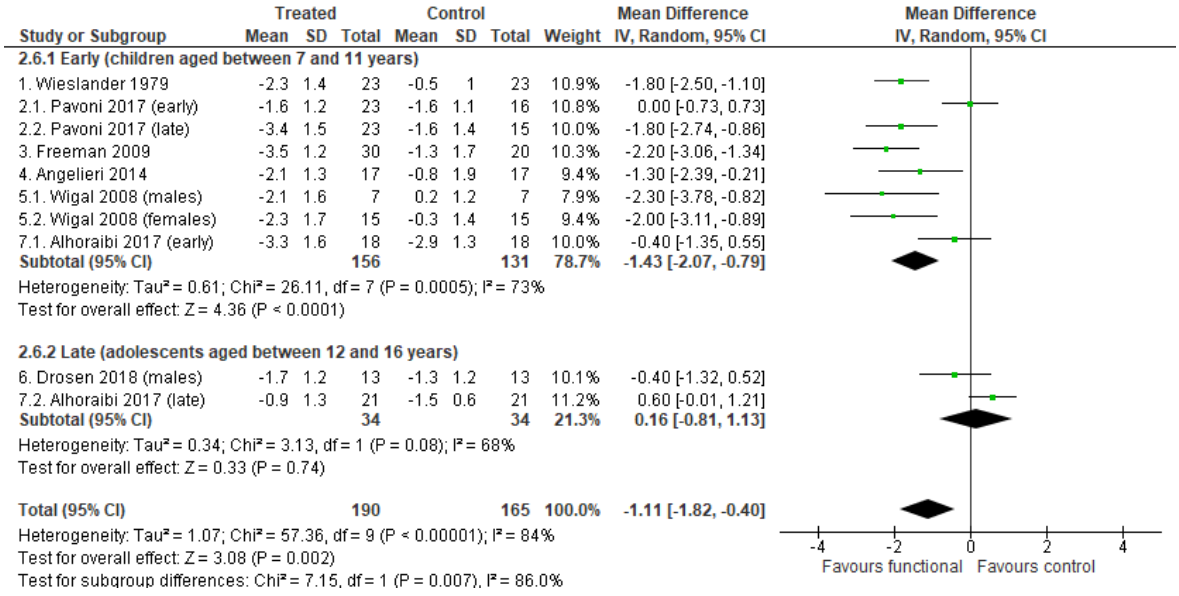

Figure 27. Subgroup analysis based on the beginning of the functional appliance therapy; Outcome: ANB angle. Early treatments, commencing in children aged between 7 and 11 years; late treatments, beginning in adolescents aged between 12 and 16 years.

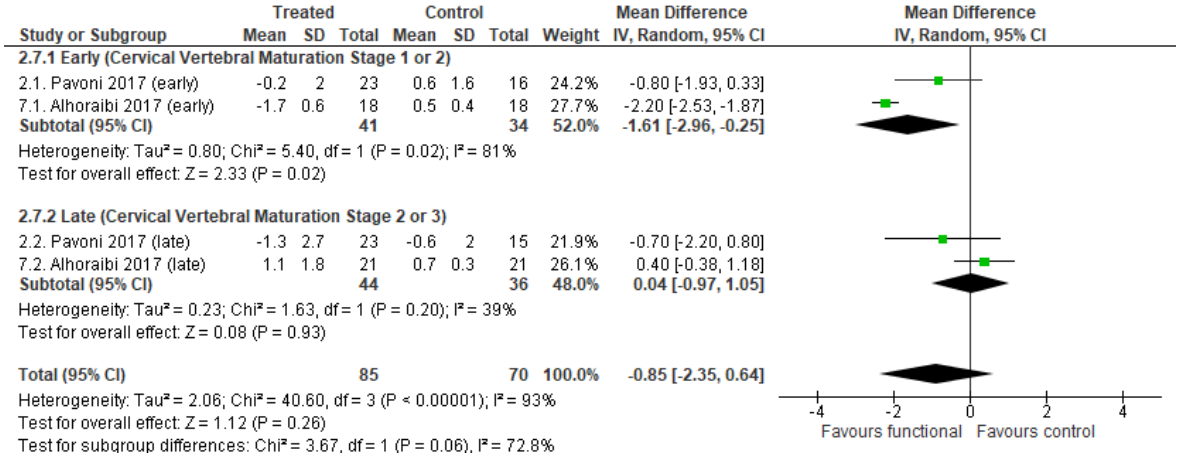

Figure 28. Subgroup analysis based on the start of the treatment; Outcome: SNA angle. Early treatments, with patients presenting with Cervical Vertebral Maturation Stage [CVMS] 1 or 2 at the first observation; late treatments, with subjects presenting with CVMS 2 or 3.

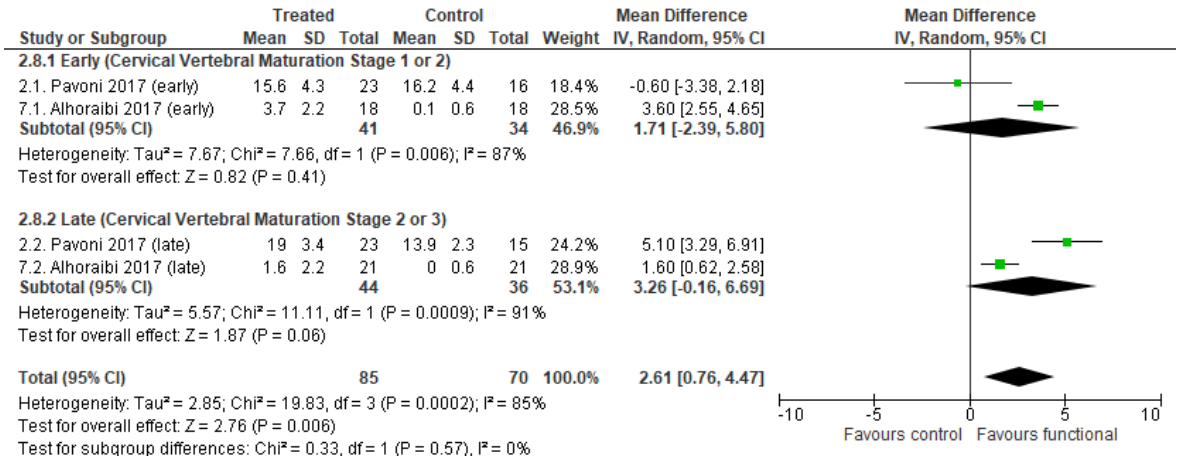

Figure 29. Subgroup analysis based on the start of the treatment; Outcome: Co-Gn distance.

Early treatments, with patients presenting with Cervical Vertebral Maturation Stage [CVMS] 1 or 2 at the first observation; late treatments, with subjects presenting with CVMS 2 or 3.

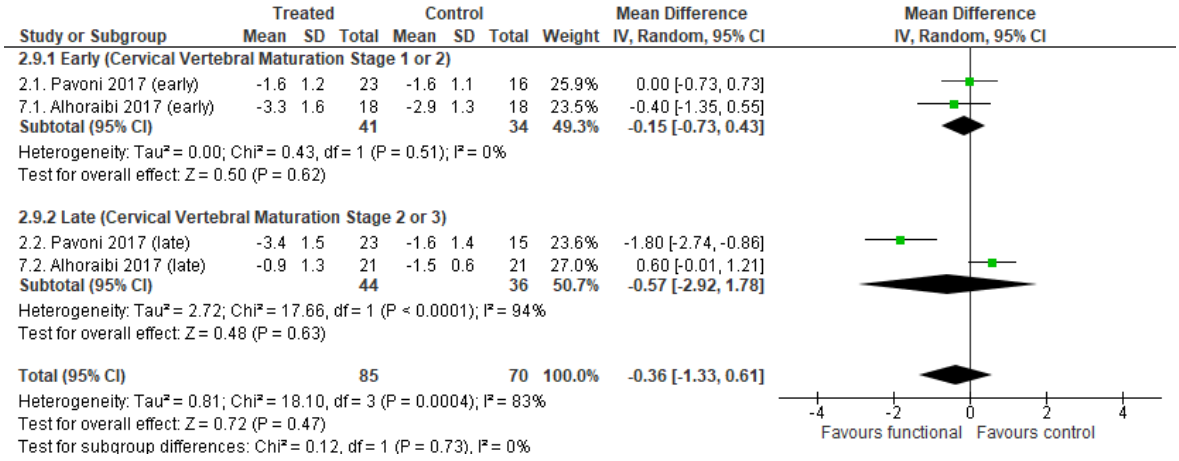

Figure 30. Subgroup analysis based on the start of the treatment; Outcome: ANB angle. Early treatments, with patients presenting with Cervical Vertebral Maturation Stage [CVMS] 1 or 2 at the first observation; late treatments, with subjects presenting with CVMS 2 or 3.

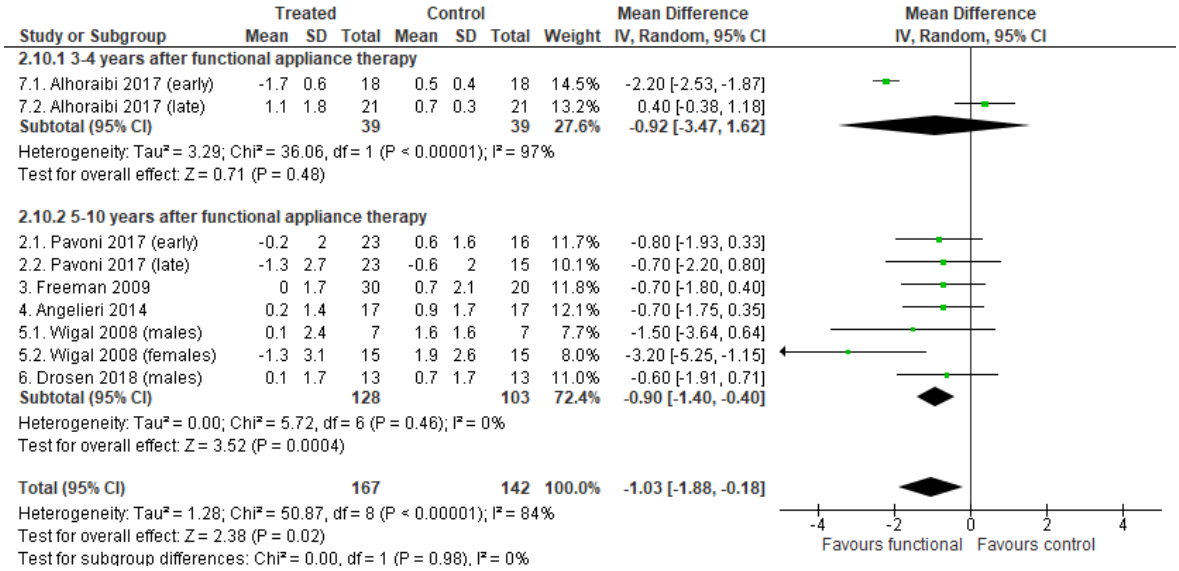

Figure 31. Subgroup analysis based on the post-retention period duration (3-4, 5-10 years after active treatment with functional appliances); Outcome: SNA angle.

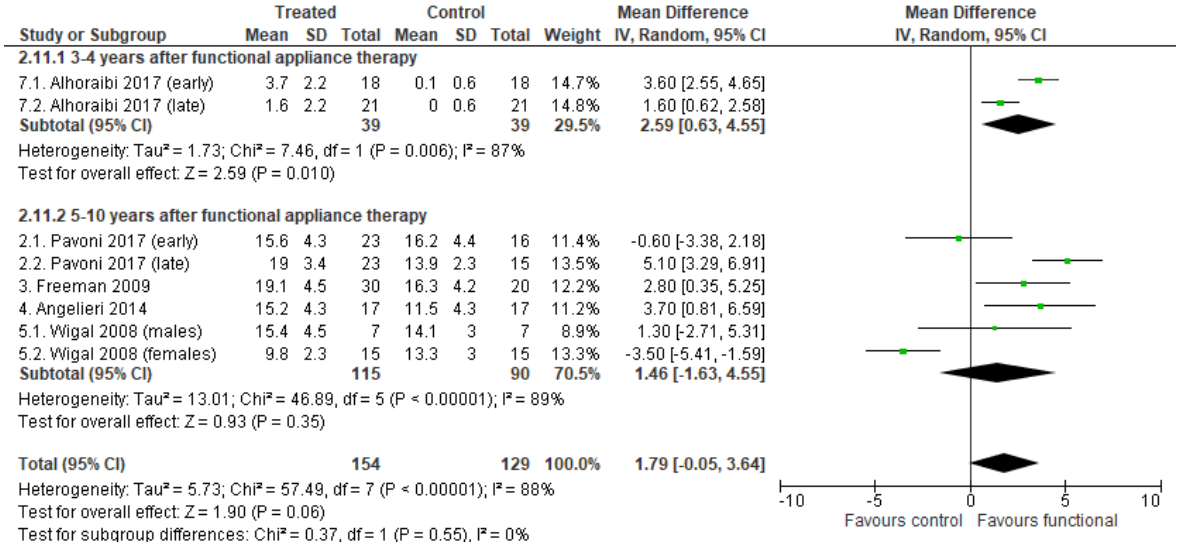

Figure 32. Subgroup analysis based on the post-retention period duration (3-4, 5-10 years after active treatment with functional appliances); Outcome: Co-Gn distance.

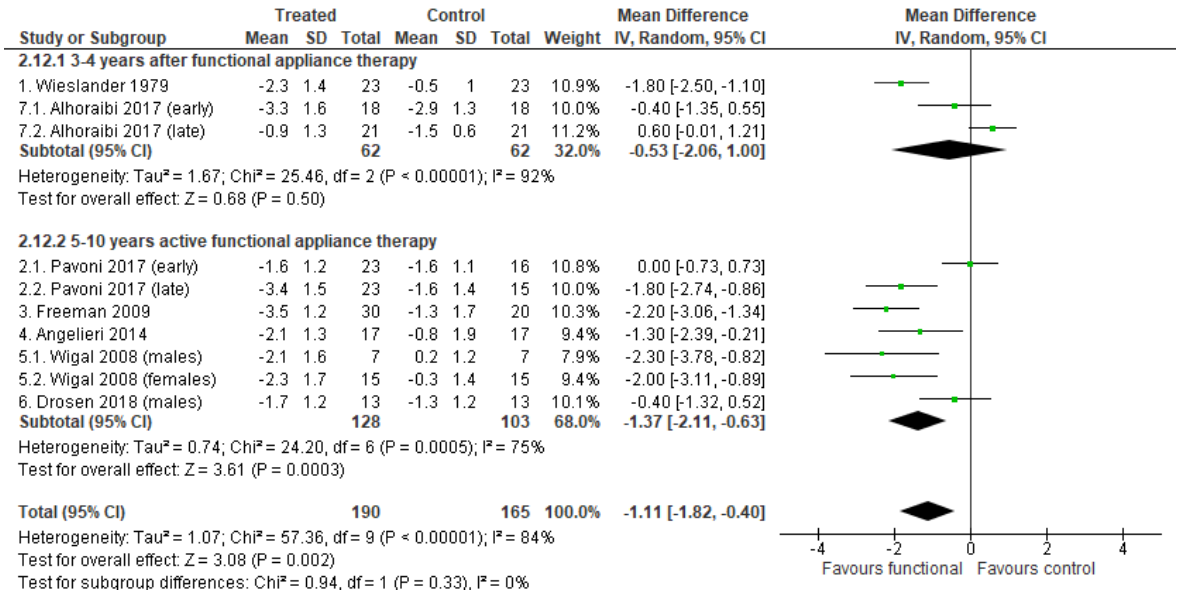

Figure 33. Subgroup analysis based on the post-retention period duration (3-4, 5-10 years after active treatment with functional appliances); Outcome: ANB angle.

Sensitivity analysis

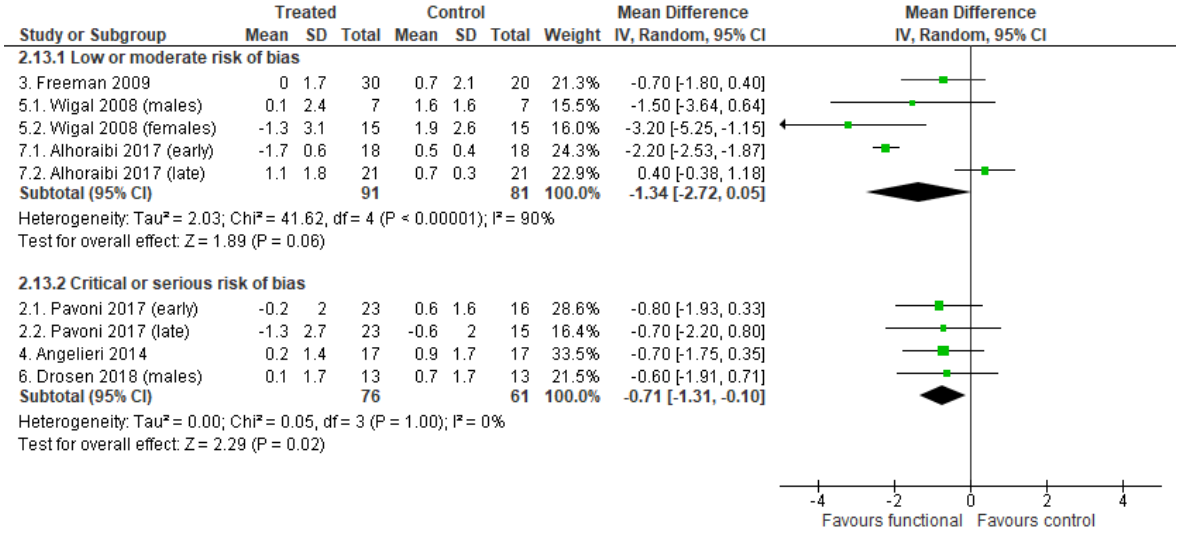

Figure 34. Sensitivity analysis based on the study quality assessment; Outcome: SNA angle.

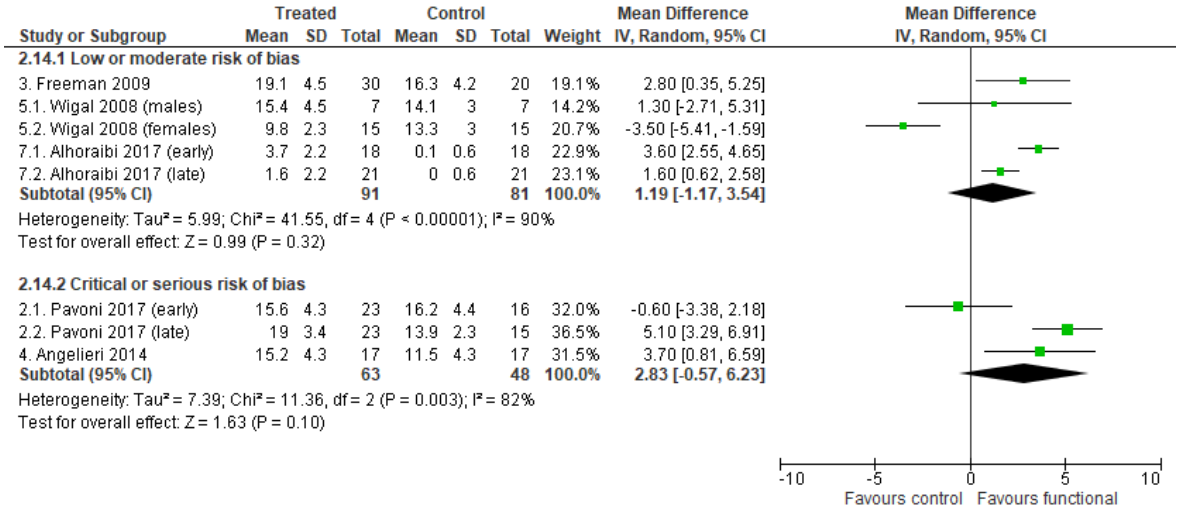

Figure 35. Sensitivity analysis based on the study quality assessment; Outcome: Co-Gn distance.

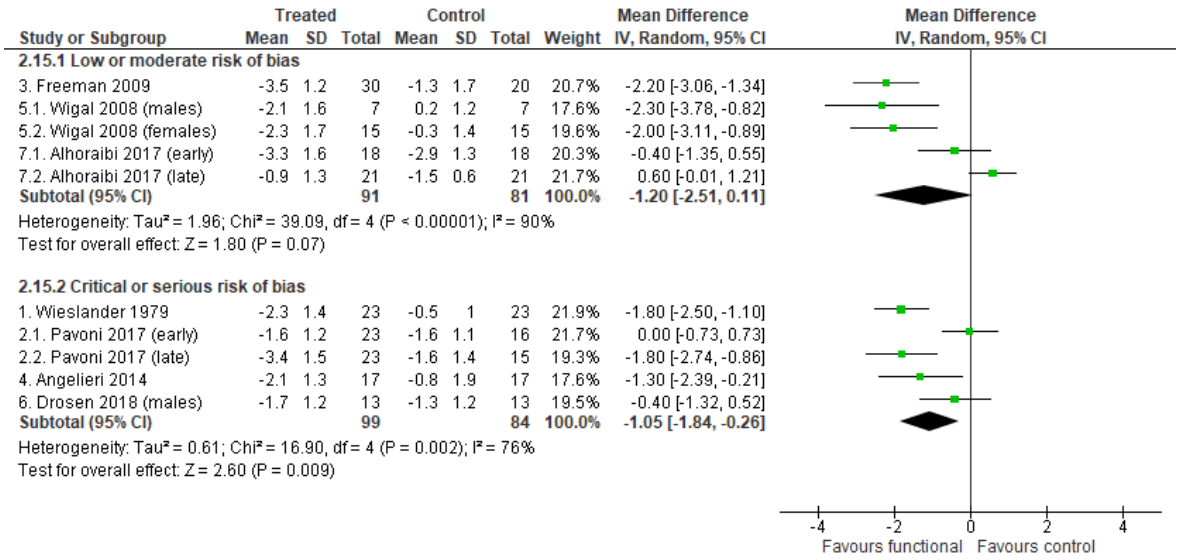

Figure 36. Sensitivity analysis based on the study quality assessment; Outcome: ANB angle.