

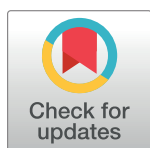
RESEARCH ARTICLE

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

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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

CRD42018092139

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 temporomandibular 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 (χ^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 ≥ 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

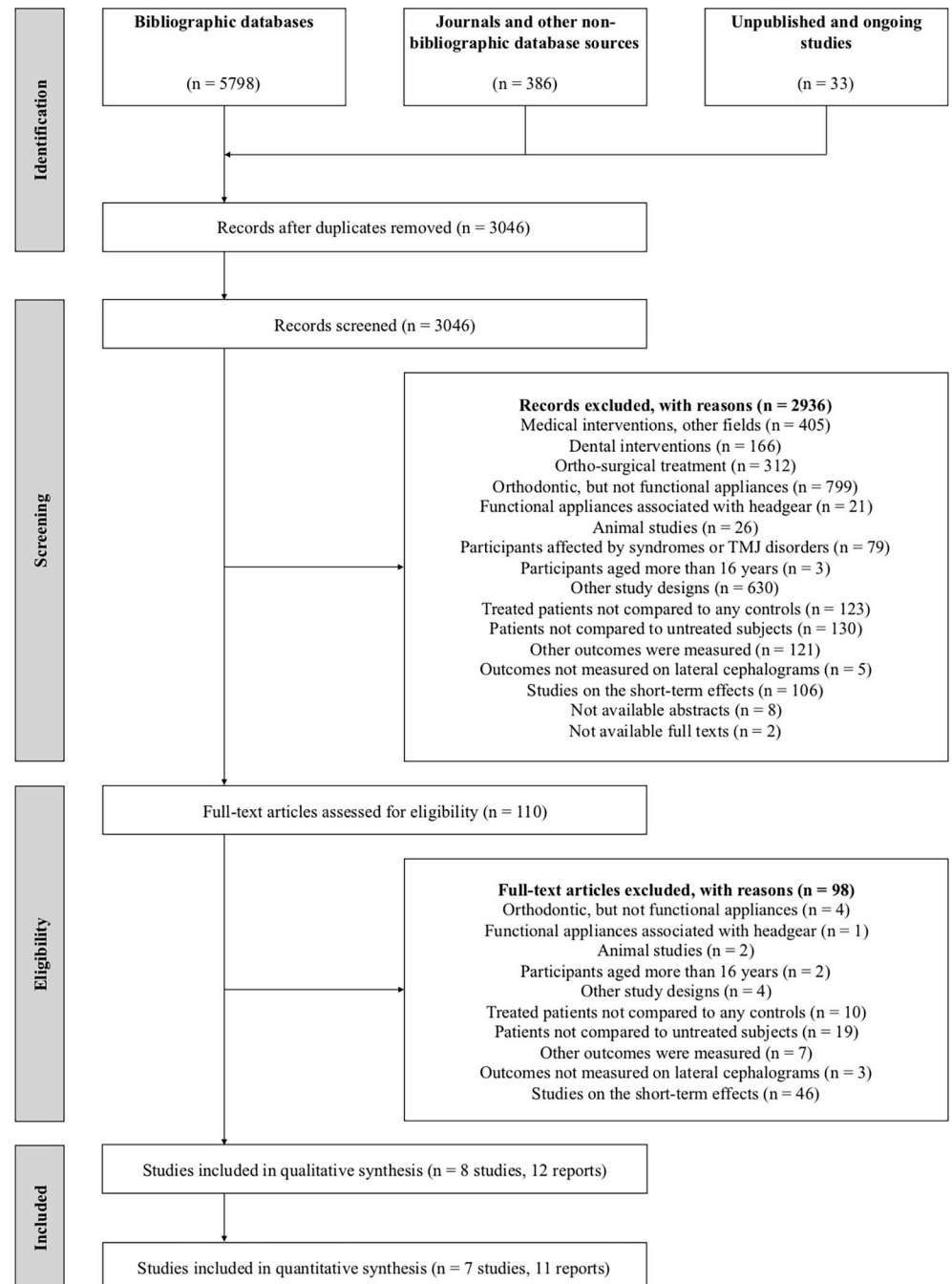


Fig 1. PRISMA flow diagram.

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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, $P < 0.00001$, $I^2 = \text{Not applicable}$, 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, $P < 0.00001$, $I^2 = \text{Not applicable}$, 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, $P = 0.001$, $I^2 = \text{Not applicable}$, 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.

<https://doi.org/10.1371/journal.pone.0221624.t006>

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 | |
| | | | | | | | | | | |
| 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

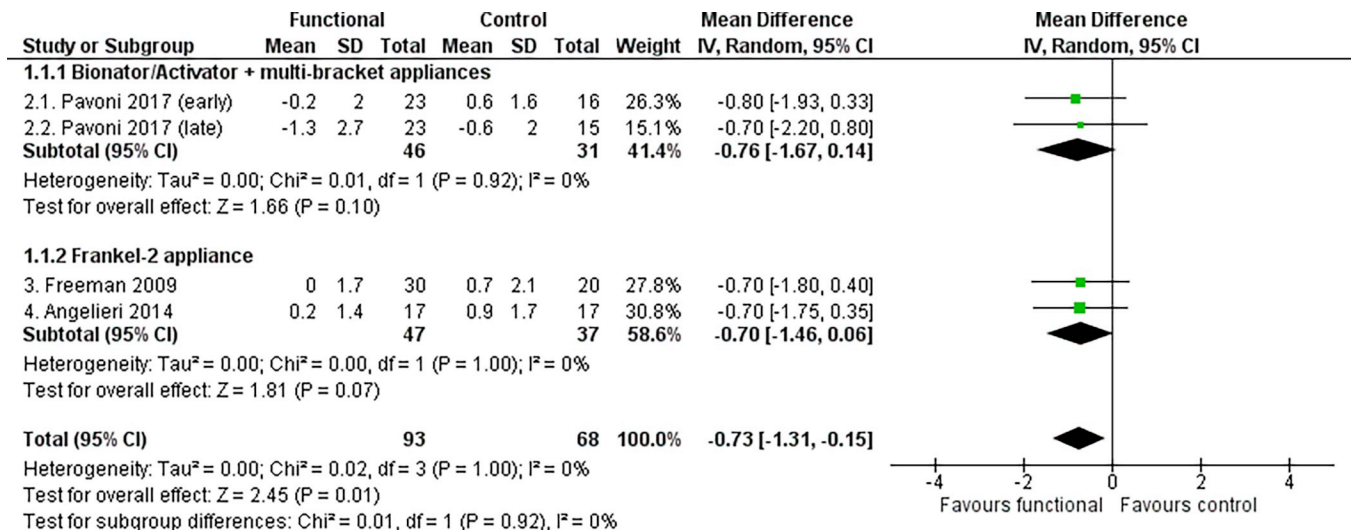


Fig 2. Meta-analysis; Outcome: SNA angle; Time point: End of growth according to the CVM method.

<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].

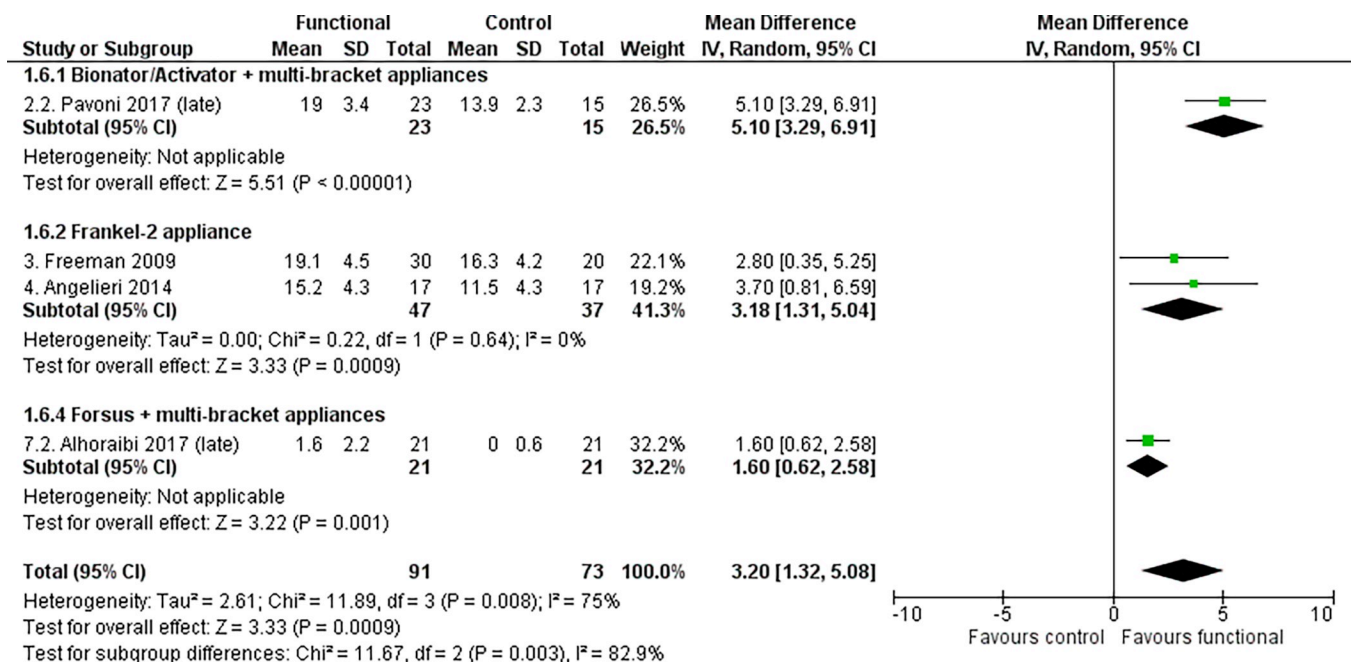


Fig 3. Meta-analysis; Outcome: Co-Gn distance; Time point: Above 18 years of age.

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

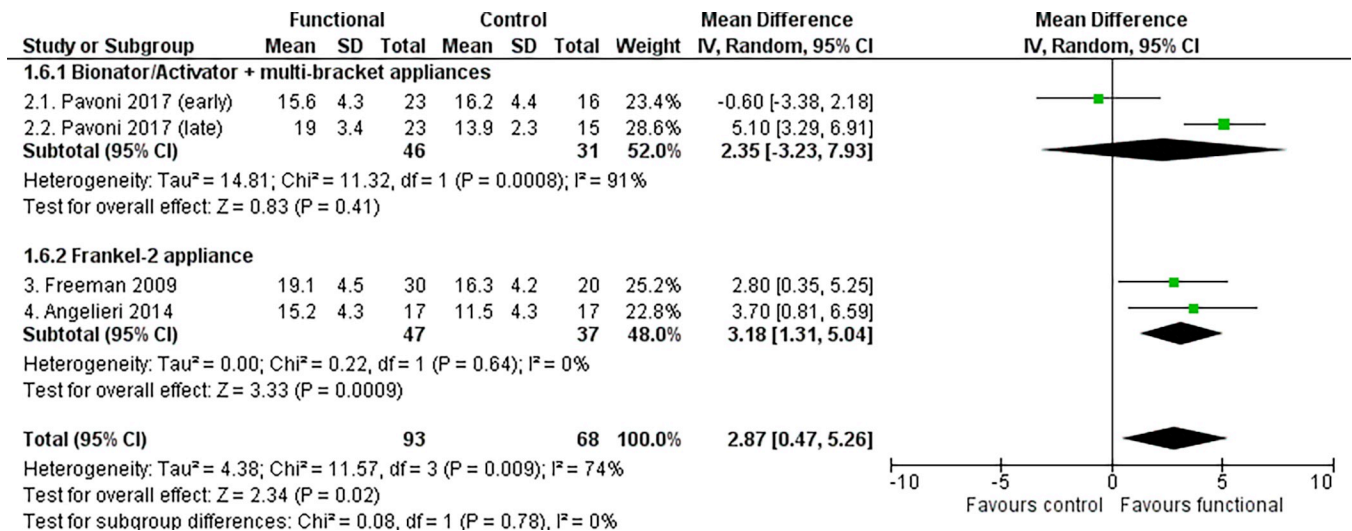


Fig 4. Meta-analysis; Outcome: Co-Gn distance; Time point: End of growth according to the CVM method.

<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

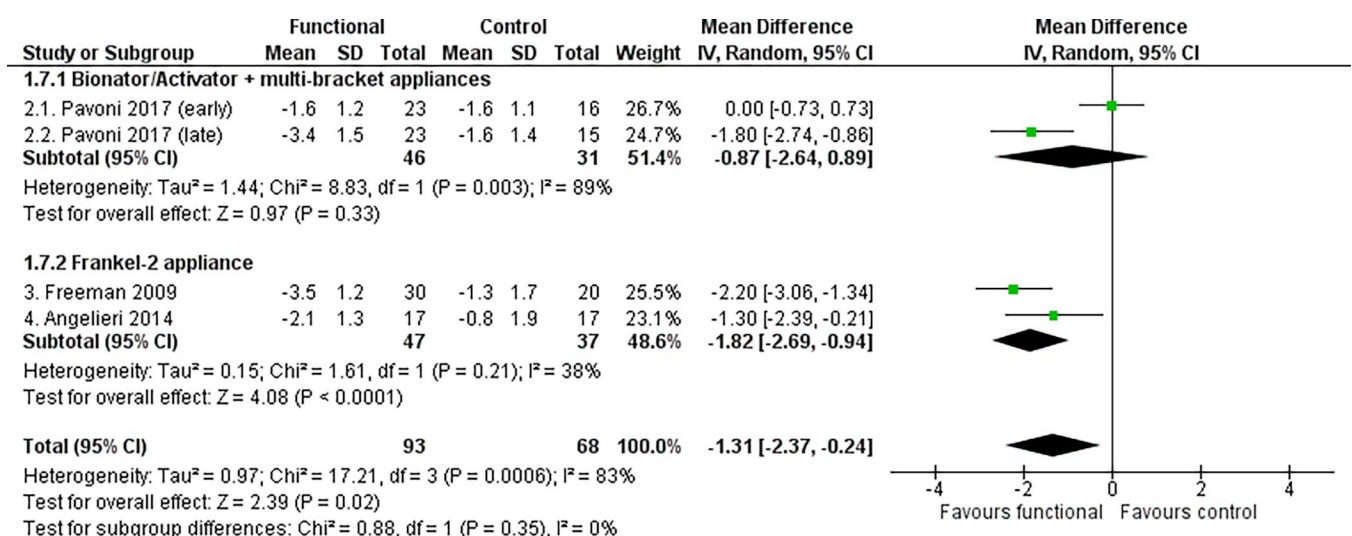


Fig 5. Meta-analysis; Outcome: ANB angle; Time point: End of growth according to the CVM method.

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

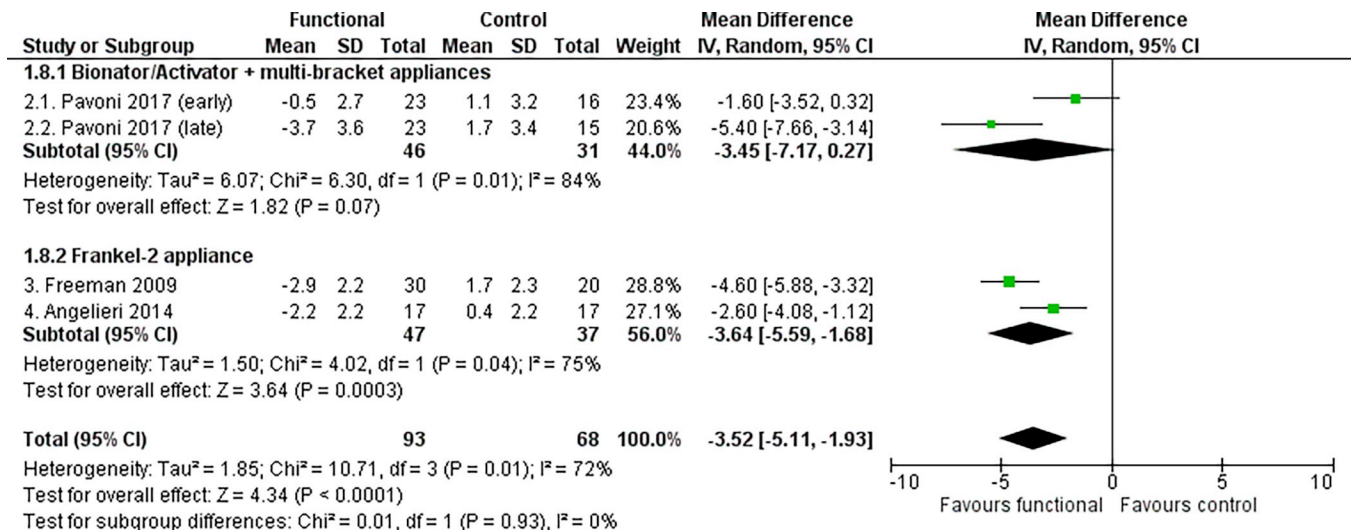


Fig 6. Meta-analysis; Outcome: Wits appraisal; Time point: End of growth according to the CVM method.

<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 clinically 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).

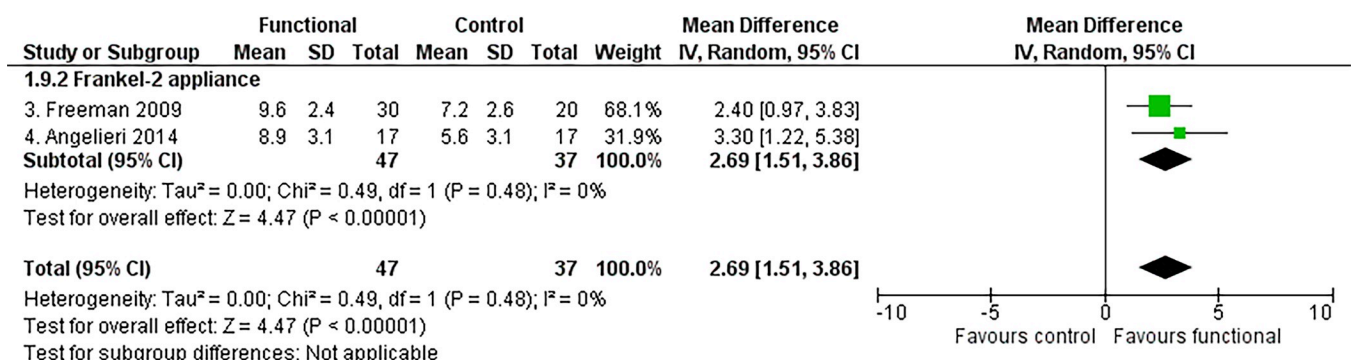


Fig 7. Meta-analysis; Outcome: Co-Gn/Co-A difference; Time point: End of growth according to the CVM method.

<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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References

1. Kelly JE, Sanchez M, Van Kirk LE. An Assessment of the Occlusion of the Teeth of Children 6–11 Years, United States. *Vital Health Stat* 11. 1973;(130):1–60. PMID: [25209689](#)
2. Kelly JE, Harvey CR. An assessment of the occlusion of the teeth of youths 12–17 years. *Vital Health Stat* 11. 1977;(162):1–65. PMID: [302520](#)
3. McNamara JA Jr. Components of class II malocclusion in children 8–10 years of age. *Angle Orthod*. 1981; 51(3):177–202. [https://doi.org/10.1043/0003-3219\(1981\)051<0177:COCIMI>2.0.CO;2](https://doi.org/10.1043/0003-3219(1981)051<0177:COCIMI>2.0.CO;2) PMID: [7023290](#)
4. Pancherz H, Zieber K, Hoyer B. Cephalometric characteristics of Class II division 1 and Class II division 2 malocclusions: a comparative study in children. *Angle Orthod*. 1997; 67(2):111–20. [https://doi.org/10.1043/0003-3219\(1997\)067<0111:CCOCID>2.3.CO;2](https://doi.org/10.1043/0003-3219(1997)067<0111:CCOCID>2.3.CO;2) PMID: [9107375](#)
5. Stahl F, Baccetti T, Franchi L, McNamara JA Jr. Longitudinal growth changes in untreated subjects with Class II Division 1 malocclusion. *Am J Orthod Dentofacial Orthop*. 2008; 134(1):125–37. <https://doi.org/10.1016/j.ajodo.2006.06.028> PMID: [18617112](#)
6. Perinetti G, Primožič J, Furlani G, Franchi L, Contardo L. Treatment effects of fixed functional appliances alone or in combination with multibracket appliances: A systematic review and meta-analysis. *Angle Orthod*. 2015; 85(3):480–92. <https://doi.org/10.2319/102813-790.1> PMID: [25188504](#)
7. Nucera R, Lo Giudice A, Rustico L, Matarese G, Papadopoulos MA, Cordasco G. Effectiveness of orthodontic treatment with functional appliances on maxillary growth in the short term: A systematic review and meta-analysis. *Am J Orthod Dentofacial Orthop*. 2016; 149(5):600–611.e3. <https://doi.org/10.1016/j.ajodo.2015.09.030> PMID: [27131242](#)
8. Wedrychowska-Szulc B1, Syryńska M. Patient and parent motivation for orthodontic treatment—a questionnaire study. *Eur J Orthod*. 2010; 32(4):447–52. <https://doi.org/10.1093/ejo/cjp131> PMID: [20008018](#)
9. Van Wezel NA, Bos A, Pahl C. Expectations of treatment and satisfaction with dentofacial appearance in patients applying for orthodontic treatment. *Am J Orthod Dentofacial Orthop*. 2015; 147(6):698–703. <https://doi.org/10.1016/j.ajodo.2015.01.024> PMID: [26038073](#)
10. Naini FB, Donaldson AN, Cobourne MT, McDonald F. Assessing the influence of mandibular prominence on perceived attractiveness in the orthognathic patient, clinician, and layperson. *Eur J Orthod*. 2012; 34(6):738–46. <https://doi.org/10.1093/ejo/cjr098> PMID: [21846874](#)
11. Seehra J, Fleming PS, Newton T, DiBiase AT. Bullying in orthodontic patients and its relationship to malocclusion, self-esteem and oral health-related quality of life. *J Orthod*. 2011; 38(4):247–56. <https://doi.org/10.1179/14653121141641> PMID: [22156180](#)
12. Proffit WR, Fields HW. Contemporary orthodontics. St. Louis: Mosby; 2000.
13. Singer J. Posttreatment change: a reality. *Am J Orthod*. 1975; 67(3):277–89. PMID: [1054910](#)

14. Bjork A. Variations in the growth pattern of the human mandible: longitudinal radiographic study by the implant method. *J Dent Res*. 1963; 42(1)Pt 2:400–11.
15. Love RJ, Murray JM, Mamandras AH. Facial growth in males 16 to 20 years of age. *Am J Orthod Dentofacial Orthop*. 1990; 97(3):200–6. [https://doi.org/10.1016/S0889-5406\(05\)80052-6](https://doi.org/10.1016/S0889-5406(05)80052-6) PMID: 2309666
16. Bishara SE, Treder JE, Jakobsen JR. Facial and dental changes in adulthood. *Am J Orthod Dentofacial Orthop*. 1994; 106(2):175–86. [https://doi.org/10.1016/S0889-5406\(94\)70036-2](https://doi.org/10.1016/S0889-5406(94)70036-2) PMID: 8059754
17. West KS, McNamara JA Jr. Changes in the craniofacial complex from adolescence to midadulthood: a cephalometric study. *Am J Orthod Dentofacial Orthop*. 1999; 115(5):521–32. PMID: 10229884
18. Pecora NG, Baccetti T, McNamara JA Jr. The aging craniofacial complex: a longitudinal cephalometric study from late adolescence to late adulthood. *Am J Orthod Dentofacial Orthop*. 2008; 134(4):496–505. <https://doi.org/10.1016/j.ajodo.2006.11.022> PMID: 18929267
19. Fishman LS. Radiographic evaluation of skeletal maturation. A clinically oriented method based on hand-wrist films. *Angle Orthod*. 1982; 52(2):88–112. [https://doi.org/10.1043/0003-3219\(1982\)052<0088:REOSM>2.0.CO;2](https://doi.org/10.1043/0003-3219(1982)052<0088:REOSM>2.0.CO;2) PMID: 6980608
20. Franchi L, Baccetti T, McNamara JA Jr. Mandibular growth as related to cervical vertebral maturation and body height. *Am J Orthod Dentofacial Orthop*. 2000; 118(3):335–40. <https://doi.org/10.1067/mod.2000.107009> PMID: 10982936
21. Koretsi V, Zymperdikas VF, Papageorgiou SN, Papadopoulos MA. Treatment effects of removable functional appliances in patients with Class II malocclusion: a systematic review and meta-analysis. *Eur J Orthod*. 2015; 37(4):418–34. <https://doi.org/10.1093/ejo/cju071> PMID: 25398303
22. Perinetti G, Primožič J, Franchi L, Contardo L. Treatment Effects of Removable Functional Appliances in Pre-Pubertal and Pubertal Class II Patients: A Systematic Review and Meta-Analysis of Controlled Studies. *PLoS One*. 2015; 10(10):e0141198. <https://doi.org/10.1371/journal.pone.0141198> PMID: 26510187
23. Pacha MM, Fleming PS, Johal A. A comparison of the efficacy of fixed versus removable functional appliances in children with Class II malocclusion: A systematic review. *Eur J Orthod*. 2016; 38(6):621–630. <https://doi.org/10.1093/ejo/cjv086> PMID: 26628629
24. Zymperdikas VF, Koretsi V, Papageorgiou SN, Papadopoulos MA. Treatment effects of fixed functional appliances in patients with Class II malocclusion: a systematic review and meta-analysis. *Eur J Orthod*. 2016; 38(2):113–26. <https://doi.org/10.1093/ejo/cjv034> PMID: 25995359
25. Ishaq RA, AlHammadi MS, Fayed MM, El-Ezz AA, Mostafa Y. Fixed functional appliances with multi-bracket appliances have no skeletal effect on the mandible: A systematic review and meta-analysis. *Am J Orthod Dentofacial Orthop*. 2016; 149(5):612 <https://doi.org/10.1016/j.ajodo.2015.11.023> PMID: 27131243
26. Batista KB, Thiruvengkatachari B, Harrison JE, O'Brien KD. Orthodontic treatment for prominent upper front teeth (Class II malocclusion) in children and adolescents. *Cochrane Database Syst Rev*. 2018; 3: CD003452. <https://doi.org/10.1002/14651858.CD003452.pub4> PMID: 29534303
27. Bondemark L, Holm AK, Hansen K, Axelsson S, Mohlin B, Brattstrom V, Paulin G, Pietila T. Long-term stability of orthodontic treatment and patient satisfaction. A systematic review. *Angle Orthod*. 2007; 77(1):181–91. <https://doi.org/10.2319/011006-16R.1> PMID: 17029533
28. Bock NC, von Bremen J, Ruf S. Stability of Class II fixed functional appliance therapy—a systematic review and meta-analysis. *Eur J Orthod*. 2016; 38(2):129–39. <https://doi.org/10.1093/ejo/cjv009> PMID: 25820407
29. Brindeiro D, Cavalcanti Y, Castanha Henriques JF. Long-term stability of post-treatment Class II correction with fixed and removable functional appliances. PROSPERO. 2017. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017075897.
30. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1.0). The Cochrane Collaboration. 2011. Available from: <http://www.cochrane-handbook.org>.
31. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009; 6(7):e1000097. <https://doi.org/10.1371/journal.pmed.1000097> PMID: 19621072
32. Mallett S, Clarke M. The typical Cochrane review. How many trials? How many participants? *Int J Technol Assess Health Care*. 2002; 18(4):820–3. PMID: 12602082
33. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. *BMJ*. 2005; 331(7524):1064–5. <https://doi.org/10.1136/bmj.38636.593461.68> PMID: 16230312
34. Hopewell S, Clarke M, Lefebvre C, Scherer R. Handsearching versus electronic searching to identify reports of randomized trials. *Cochrane Database Syst Rev*. 2007; (2):MR000001.

35. Scherer RW, Langenberg P, von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database Syst Rev.* 2007;(2):MR000005.
36. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ.* 1994; 309(6964):1286–91. <https://doi.org/10.1136/bmj.309.6964.1286> PMID: 7718048
37. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016; 355:i4919. <https://doi.org/10.1136/bmj.i4919> PMID: 27733354
38. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials.* 2015; 45(Pt A):139–45. <https://doi.org/10.1016/j.cct.2015.09.002> PMID: 26343745
39. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003; 327(7414):557–60. <https://doi.org/10.1136/bmj.327.7414.557> PMID: 12958120
40. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to meta-analysis. Chichester: Wiley; 2009.
41. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, Atkins D, Kunz R, Montori V, Jaeschke R, Rind D, Dahm P, Akl EA, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol.* 2013; 66(2):151–7. <https://doi.org/10.1016/j.jclinepi.2012.01.006> PMID: 22542023
42. Wieslander L, Lagerström L. The effect of activator treatment on class II malocclusions. *Am J Orthod.* 1979; 75(1):20–6. PMID: 283692
43. Pavoni C, Cretella Lombardo E, Franchi L, Lione R, Cozza P. Treatment and post-treatment effects of functional therapy on the sagittal pharyngeal dimensions in Class II subjects. *Int J Pediatr Otorhinolaryngol.* 2017; 101:47–50. <https://doi.org/10.1016/j.ijporl.2017.07.032> PMID: 28964309
44. Falck F. Long-term results of treatment of distal occlusion with the function regulator. *Fortschr Kieferorthop.* 1991; 52(5):263–7. PMID: 1757015
45. Freeman DC, McNamara JA Jr, Baccetti T, Franchi L, Fränkel C. Long-term treatment effects of the FR-2 appliance of Fränkel. *Am J Orthod Dentofacial Orthop.* 2009; 135(5):570.e1-6. <https://doi.org/10.1016/j.ajodo.2007.11.029> PMID: 19409337
46. Angelieri F, Franchi L, Cevdanes LH, Scanavini MA, McNamara JA Jr. Long-term treatment effects of the FR-2 appliance: a prospective evaluation 7 years post-treatment. *Eur J Orthod.* 2014; 36(2):192–9. <https://doi.org/10.1093/ejo/cjt026> PMID: 23736378
47. Wigal TG. Long-term follow-up of patients treated with the edgewise crowned Herbst appliance in the mixed dentition. M.Sc. Thesis, Ann Arbor: West Virginia University. 2008.
48. Drosen C, Bock NC, von Bremen J, Pancherz H, Ruf S. Long-term effects of Class II Herbst treatment on the pharyngeal airway width. *Eur J Orthod.* 2018; 40(1):82–89. <https://doi.org/10.1093/ejo/cjx032> PMID: 28453618
49. Alhoraibi L. Long-Term Effects Induced by the Forsus Fatigue Resistant Device in Class II Malocclusion Patients Treated at Pre-Peak, Peak, And Post-Peak Growth Periods. M.Sc. Thesis, Ann Arbor: State University of New York at Buffalo. 2017.
50. Faltin KJ, Faltin RM, Baccetti T, Franchi L, Ghiozzi B, McNamara JA Jr. Long-term effectiveness and treatment timing for Bionator therapy. *Angle Orthod.* 2003; 73(3):221–30. [https://doi.org/10.1043/0003-3219\(2003\)073<0221:LEATTF>2.0.CO;2](https://doi.org/10.1043/0003-3219(2003)073<0221:LEATTF>2.0.CO;2) PMID: 12828429
51. Malta LA, Baccetti T, Franchi L, Faltin K Jr, McNamara JA Jr. Long-term dentoskeletal effects and facial profile changes induced by bionator therapy. *Angle Orthod.* 2010; 80(1):10–7. <https://doi.org/10.2319/031609-156.1> PMID: 19852634
52. Franchi L, Pavoni C, Faltin K Jr, McNamara JA Jr, Cozza P. Long-term skeletal and dental effects and treatment timing for functional appliances in Class II malocclusion. *Angle Orthod.* 2013; 83(2):334–40. <https://doi.org/10.2319/052912-450.1> PMID: 22931200
53. Wigal TG, Dischinger T, Martin C, Razmus T, Gunel E, Ngan P. Stability of Class II treatment with an edgewise crowned Herbst appliance in the early mixed dentition: Skeletal and dental changes. *Am J Orthod Dentofacial Orthop.* 2011; 140(2):210–23. <https://doi.org/10.1016/j.ajodo.2010.02.036> PMID: 21803259
54. Sloan J, Symonds T, Vargas-Chanes D, Fridley B. Practical guidelines for assessing the clinical significance of health-related quality of life changes within clinical trials. *Drug Inf J.* 2003; 37(1):23–31.

55. Papageorgiou SN, Koretsi V, Jäger A. Bias from historical control groups used in orthodontic research: a meta-epidemiological study. *Eur J Orthod*. 2017; 39(1):98–105. <https://doi.org/10.1093/ejo/cjw035> PMID: [27129869](https://pubmed.ncbi.nlm.nih.gov/27129869/)
56. Heneghan C, Goldacre B, Mahtani KR. Why clinical trial outcomes fail to translate into benefits for patients. *Trials*. 2017; 18(1):122. <https://doi.org/10.1186/s13063-017-1870-2> PMID: [28288676](https://pubmed.ncbi.nlm.nih.gov/28288676/)
57. Santiago RC, de Miranda Costa LF, Vitral RW, Fraga MR, Bolognese AM, Maia LC. Cervical vertebral maturation as a biologic indicator of skeletal maturity. *Angle Orthod*. 2012; 82(6):1123–31. <https://doi.org/10.2319/103111-673.1> PMID: [22417653](https://pubmed.ncbi.nlm.nih.gov/22417653/)

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., I ²) 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 - 13 th March 2018 | https://www.ncbi.nlm.nih.gov/pubmed/advanced |
| EMBASE | OVID; 1974 - 15 th March 2018 | https://www.embase.com/search/advanced |
| Cochrane Central Register of Controlled Trials (CENTRAL) | Cochrane Library; 1993 - 13 th 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 - 13 th March 2018 | http://pesquisa.bvsalud.org/portal/advanced/?lang=en |
| General search engines | | |
| Google Scholar | 2004 - 14 th March 2018 | https://scholar.google.it/ |
| Turning Research into Practice (TRIP) database | 1997 - 14 th March 2018 | https://www.tripdatabase.com/ |
| Citation indexes | | |
| Web of Science Core Collection - Science Citation Index / Science Citation Index Expanded | Web of Science; 1945 - 15 th March 2018 | https://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch |
| Scopus | Elsevier; 2004 - 13 th March 2018 | https://www.scopus.com/ |
| Dissertation and theses databases | | |
| ProQuest Dissertations & Theses Global | 1938 - 15 th March 2018 | https://search.proquest.com/pqdtglobal/advanced |
| ProQuest Dissertations and Theses – UK & Ireland | 1950 - 15 th March 2018 | https://search.proquest.com/pqdtuk/advanced |
| Grey literature databases | | |
| OpenGrey, formerly System for Information on Grey Literature (SIGLE) | 1993 - 13 th March 2018 | http://www.opengrey.eu/ |
| Journals and other non-bibliographic database sources | | |
| Hand-searching | | |
| American Journal of Orthodontics and Dentofacial Orthopaedics | 1915 - 16 th March 2018 | https://www.ajodo.org/ |
| Angle Orthodontist | 1931 - 16 th March 2018 | https://www.angle.org/ |
| Australian Journal of Orthodontics | 2010 - 16 th March 2018 | https://www.aso.org.au/australasian-orthodontic-journal |
| European Journal of Orthodontics | 1979 - 16 th March 2018 | https://academic.oup.com/ejo |
| Journal of Clinical Orthodontics | 1967 - 16 th March 2018 | https://www.jco-online.com/ |
| Journal of Orthodontics | 1973 - 16 th March 2018 | https://www.tandfonline.com/loi/yjor20 |
| Orthodontics & Craniofacial Research | 1998 - 16 th March 2018 | https://onlinelibrary.wiley.com/journal/16016343 |
| Progress in Orthodontics | 2013 - 16 th March 2018 | https://progressinorthodontics.springeropen.com/ |
| Seminars in Orthodontics | 1995 - 16 th March 2018 | https://www.semortho.com/ |
| Tables of contents | | |
| British Library Direct | 1930 - 16 th March 2018 | https://ondemand.bl.uk/onDemand/home |
| Current Contents Connect – Clinical Medicine | Web of Science; 1998 - 15 th 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 - 15 th 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 - 15 th 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 - 15 th March 2018 | https://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch |
| ISI Proceedings | 2004 - 16 th 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 - 13 th March 2018 | http://onlinelibrary.wiley.com/cochranelibrary/search/ |
| Database of Abstracts of Reviews of Effects (DARE) | Cochrane Library; 1993 - 13 th March 2018 | http://onlinelibrary.wiley.com/cochranelibrary/search/ |
| Health Technology Assessment Database (HTA Database) | Cochrane Library; 1993 - 13 th March 2018 | http://onlinelibrary.wiley.com/cochranelibrary/search/ |
| NHS Economic Evaluation Database (NHS EED) | Cochrane Library; 1993 - 13 th March 2018 | http://onlinelibrary.wiley.com/cochranelibrary/search/ |
| Unpublished and ongoing studies | | |
| ClinicalTrials.gov register | From inception - 16 th March 2018 | https://clinicaltrials.gov/ |
| Current controlled trials metaRegister of Controlled Trials (mRCT) – active and archived registers | From inception - 16 th March 2018 | https://www.controlled-trials.com/mrct/ |
| International prospective register of systematic reviews (PROSPERO) | From inception - 16 th March 2018 | https://www.crd.york.ac.uk/prospero/#searchadvanced |

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

| Search | Query | Hits |
|----------------|---|---------|
| <i>MEDLINE</i> | | |
| #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 |
|---------------|---|---------|
| <i>EMBASE</i> | | |
| #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 |
|-------------------------|---|------|
| <i>Cochrane Library</i> | | |
| #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 |
|---|--|--------|
| <i>Cochrane Library</i> | | |
| #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 |
| <i>Cochrane Central Register of Controlled Trials (CENTRAL)</i> | | 76 |
| <i>Cochrane Database of Systematic Reviews (CDSR)</i> | | 63 |
| <i>Database of Abstracts of Reviews of Effects (DARE)</i> | | 3 |
| <i>Health Technology Assessment Database (HTA Database)</i> | | 1 |
| <i>NHS Economic Evaluation Database (NHS EED)</i> | | 1 |
| Search | Query | Hits |
| <i>Latin America and the Caribbean (LILACS)</i> | | |
| | (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 |
| <i>Google Scholar</i> | | |
| | "Class II malocclusion" AND "functional appliances" AND "long term" | 1510 |
| Search | Query | Hits |
| <i>Turning Research into Practice (TRIP) database</i> | | |
| | "Class II malocclusion" AND "functional appliances" AND "long term" | 14 |
| Search | Query | Hits |
| <i>Science Citation Index / Science Citation Index Expanded</i> | | |
| #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 |
|---|--|---------|
| <i>Science Citation Index / Science Citation Index Expanded</i> | | |
| #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 |
|---------------|---|------|
| <i>Scopus</i> | | |
| | ALL ("Class II malocclusion" AND "functional appliances" AND "long term") | 512 |

| Search | Query | Hits |
|--|---|------|
| <i>ProQuest Dissertation & Theses Global</i> | | |
| | "Class II malocclusion" AND "functional appliances" AND "long term" | 112 |

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

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

| Search | Query | Hits |
|-------------------------------|---|------|
| <i>British Library Direct</i> | | |
| | "Class II malocclusion" AND "functional appliances" AND "long term" | 9 |

| Search | Query | Hits |
|---|--|--------|
| <i>Current Contents Connect - Clinical Medicine</i> | | |
| #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 |
|---|---|--------|
| <i>Current Contents Connect - Clinical Medicine</i> | | |
| #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 |
|---|--|-------|
| <i>Scientific Electronic Library Online (SciELO) Citation Index</i> | | |
| #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 |
|------------------------------|--|---------|
| <i>BIOSIS Citation Index</i> | | |
| #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 |
|--|--|------|
| <i>Conference Proceedings Citation Index - Science</i> | | |
| #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 |
|---|--|--------|
| <i>Conference Proceedings Citation Index - Science</i> | | |
| #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 |
| <i>ISI Proceedings</i> | | |
| | "Class II malocclusion" AND "functional appliances" AND "long term" | 10 |
| Search | Query | Hits |
| <i>ClinicalTrials.gov register</i> | | |
| | Condition: Class II malocclusion; Intervention: functional appliances | 14 |
| Search | Query | Hits |
| <i>Current controlled trials metaRegister of Controlled Trials (mRCT) – active and archived registers</i> | | |
| | "Class II malocclusion" AND "functional appliances" | 2 |
| Search | Query | Hits |
| <i>International prospective register of systematic reviews (PROSPERO)</i> | | |
| | Class II malocclusion AND functional appliances | 17 |

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

| Study | Reference | Reason for exclusion |
|-----------------------|------------------|--|
| 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 exclusion |
|----------------------|-------|---|
| 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 than 16 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 than 16 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 | | | | | | | Diff | 95% CI | P |
|------------------------|-----------------|---------|-----|----|---------|-----|----|------|------------|--------|---|
| | | Treated | | | Control | | | | | | |
| | | 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.

References

1. Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. *Lancet*. 2002;359:57-61.
2. Perinetti G, Primožič J, Furlani G, Franchi L, Contardo L. Treatment effects of fixed functional appliances alone or in combination with multibracket appliances: A systematic review and meta-analysis. *Angle Orthod*. 2015;85:480-92.
3. Koretsi V, Zymperdikas VF, Papageorgiou SN, Papadopoulos MA. Treatment effects of removable functional appliances in patients with Class II malocclusion: a systematic review and meta-analysis. *Eur J Orthod*. 2015;37:418-34.
4. Zymperdikas VF, Koretsi V, Papageorgiou SN, Papadopoulos MA. Treatment effects of fixed functional appliances in patients with Class II malocclusion: a systematic review and meta-analysis. *Eur J Orthod*. 2016;38:113-26.
5. Nucera R, Lo Giudice A, Rustico L, Matarese G, Papadopoulos MA, Cordasco G. Effectiveness of orthodontic treatment with functional appliances on maxillary growth in the short term: A systematic review and meta-analysis. *Am J Orthod Dentofacial Orthop*. 2016;149:600-611.e3.
6. Batista KB, Thiruvengkatachari B, Harrison JE, O'Brien KD. Orthodontic treatment for prominent upper front teeth (Class II malocclusion) in children and adolescents. *Cochrane Database Syst Rev*. 2018;3:CD003452.
7. Sunnak R, Johal A, Fleming PS. Is orthodontics prior to 11 years of age evidence-based? A systematic review and meta-analysis. *J Dent*. 2015 May;43(5):477-86.
8. Nimri KA1, Richardson A. Applicability of interceptive orthodontics in the community. *Br J Orthod*. 1997;24(3):223-8.
9. Fishman LS. Radiographic evaluation of skeletal maturation. A clinically oriented method based on hand-wrist films. *Angle Orthod*. 1982;52:88-112.

10. Franchi L, Baccetti T, McNamara JA Jr. Mandibular growth as related to cervical vertebral maturation and body height. *Am J Orthod Dentofacial Orthop.* 2000;118:335-40.
11. Santiago RC, de Miranda Costa LF, Vitral RW, Fraga MR, Bolognese AM, Maia LC. Cervical vertebral maturation as a biologic indicator of skeletal maturity. *Angle Orthod.* 2012;82(6):1123-31.
12. McNamara JA Jr, McNamara L, Graber LW. Optimizing Orthodontic and Dentofacial Orthopedic Treatment Timing. In: Graber TM, Vanarsdall RL, Vig KWL, editors. *Orthodontics: current principles and techniques.* 5th ed. St. Louis: Elsevier Mosby; 2012. pp. 477-514.
13. Ishaq RA, AlHammadi MS, Fayed MM, El-Ezz AA, Mostafa Y. Fixed functional appliances with multibracket appliances have no skeletal effect on the mandible: A systematic review and meta-analysis. *Am J Orthod Dentofacial Orthop.* 2016;149:612-24.
14. Sackett DL. Bias in analytic research. *J Chronic Dis.* 1979;32:51-63.
15. Perinetti G, Primožič J, Franchi L, Contardo L. Treatment Effects of Removable Functional Appliances in Pre-Pubertal and Pubertal Class II Patients: A Systematic Review and Meta-Analysis of Controlled Studies. *PLoS One.* 2015;10:e0141198.
16. Pacha MM, Fleming PS, Johal A. A comparison of the efficacy of fixed versus removable functional appliances in children with Class II malocclusion: A systematic review. *Eur J Orthod.* 2016;38:621-630.
17. Stahl F, Baccetti T, Franchi L, McNamara JA Jr. Longitudinal growth changes in untreated subjects with Class II Division 1 malocclusion. *Am J Orthod Dentofacial Orthop.* 2008;134:125-37.
18. Ackerman JL, Nguyen T, Proffit WR. The decision-making process in orthodontics. In: Graber TM, Vanarsdall RL, Vig KWL, editors. *Orthodontics: current principles and techniques.* 5th ed. St. Louis: Elsevier Mosby; 2012. pp. 3-58.
19. SEDENTEXCT project. Guidelines on CBCT for Dental and Maxillofacial Radiology. European Commission. 2011. Available from:

<http://www.sedentext.eu/content/guidelines-cbct-dental-and-maxillofacial-radiology>.

20. Bjork A. Variations in the growth pattern of the human mandible: longitudinal radiographic study by the implant method. *J Dent Res*. 1963;42:400-11.
21. Love RJ, Murray JM, Mamandras AH. Facial growth in males 16 to 20 years of age. *Am J Orthod Dentofacial Orthop*. 1990;97:200-6.
22. Bishara SE, Treder JE, Jakobsen JR. Facial and dental changes in adulthood. *Am J Orthod Dentofacial Orthop*. 1994;106:175-86.
23. West KS, McNamara JA Jr. Changes in the craniofacial complex from adolescence to midadulthood: a cephalometric study. *Am J Orthod Dentofacial Orthop*. 1999;115:521-32.
24. Pecora NG, Baccetti T, McNamara JA Jr. The aging craniofacial complex: a longitudinal cephalometric study from late adolescence to late adulthood. *Am J Orthod Dentofacial Orthop*. 2008;134:496-505.
25. Littlewood SJ, Millett DT, Doubleday B, Bearn DR, Worthington HV. Retention procedures for stabilising tooth position after treatment with orthodontic braces. *Cochrane Database Syst Rev*. 2016;1:CD002283.
26. Bondemark L, Holm AK, Hansen K, Axelsson S, Mohlin B, Brattstrom V, Paulin G, Pietila T. Long-term stability of orthodontic treatment and patient satisfaction. A systematic review. *Angle Orthod*. 2007;77:181-91.
27. Bock NC, von Bremen J, Ruf S. Stability of Class II fixed functional appliance therapy--a systematic review and meta-analysis. *Eur J Orthod*. 2016;38:129-39.

S2 Appendix. References to studies excluded from this review.

1. AAO Council on Scientific Affairs (COSA). Functional appliances and long-term effects on mandibular growth. *Am J Orthod Dentofacial Orthop.* 2005;128(3):271-2.
2. Al-Jewair TS, Preston CB, Moll EM, Dischinger T. A comparison of the MARA and the AdvanSync functional appliances in the treatment of Class II malocclusion. *Angle Orthod.* 2012;82(5):907-14.
3. Al-Jewair T. Treatment Effects of the Edgewise Mandibular Anterior Repositioning Appliance (MARA) in Patients with Class II Malocclusions: A Cephalometric Study. M.Sc. Thesis, Ann Arbor: State University of New York at Buffalo. 2013.
4. Alió-Sanz JJ, Iglesias-Conde C, Lorenzo-Pernía J, Iglesias-Linares A, Mendoza-Mendoza AC, Solano-Reina E. Cranial base and maxillary changes in patients treated with Frankel's functional regulator (1b). *Med Oral Patol Oral Cir Bucal.* 2012;17(4):e689-e96.
5. Angelieri F, Bommarito S, Kanashiro LK, Sannomyia EK, Andreoli FAM. Estabilidade das alterações tegumentares promovidas pelo aparelho regulador de função Fränkel 2 (RF-2). *Ortodontia.* 2009;42(5):363-8.
6. Baccetti T, McNamara JA. The impact of functional jaw orthopedics in subjects with unfavorable class II skeletal patterns. *Prog Orthod.* 2010;11(2):118-26.
7. Ball JV, Hunt NP. Vertical skeletal change associated with Andresen, Harvold, and Begg treatment. *Eur J Orthod.* 1991;13(1):47-52.
8. Barnett GA. Skeletal and dentoalveolar effects of Class II treatment using a CrossBow appliance compared to an untreated control group. M.Sc. Thesis, Ann Arbor: State University of Alberta (Canada). 2007.
9. Bavbek NC, Tuncer BB, Turkoz C, Ulusoy C, Tuncer C. Changes in airway dimensions and hyoid bone position following class II correction with forsus fatigue resistant device. *Clin Oral Investig.* 2016;20(7):1747-55.
10. Berg R. Post-retention analysis of treatment problems and failures in 264 consecutively

- treated cases. *Eur J Orthod.* 1979;1(1):55-68.
11. Berg R. Stability of deep overbite correction. *Eur J Orthod.* 1983;5(1):75-83.
 12. Bigliazzi R, Franchi L, Bertoz AP, McNamara JA, Jr., Faltin K, Jr., Bertoz FA.
Morphometric analysis of long-term dentoskeletal effects induced by treatment with
Balters bionator. *Angle Orthod.* 2015;85(5):790-8.
 13. Bolmgren GA, Moshiri F. Bionator treatment in Class II, division 1. *Angle Orthod.*
1986;56(3):255-62.
 14. Bredy E, Jungto H. The elastic-open Klammt activator--results of follow-up. *Fortschr
Kieferorthop.* 1987;48(2):87-93.
 15. Byloff-Clar H, Droschl H. Results of follow-up studies in closed-bite. *Osterr Z Stomatol.*
1970;67(6):217-21.
 16. Cacciatore G, Ghislanzoni LT, Alvetto L, Giuntini V, Franchi L. Treatment and
posttreatment effects induced by the Forsus appliance: A controlled clinical study. *Angle
Orthod.* 2014;84(6):1010-7.
 17. Casellas JC. Skeletal and dental changes with the acrylic splint Herbst appliance. M.Sc.
Thesis, Ann Arbor: West Virginia University. 2001.
 18. Chen DR, McGorray SP, Dolce C, Wheeler TT. Effect of early Class II treatment on the
incidence of incisor trauma. *Am J Orthod Dentofacial Orthop.* 2011;140(4):e155-60.
 19. Chhibber A, Upadhyay M, Uribe F, Nanda R. Long-term stability of Class II correction
with the Twin Force Bite Corrector. *J Clin Orthod.* 2010;44(6):363-76.
 20. Cozza P, De Toffol L. Functional appliance treatment of severe Class II malocclusion in
the early mixed dentition. *J Clin Orthod.* 2003;37(2):69-74.
 21. Craig WH. Cephalometric Evaluation of the Chateau Functional Appliance. M.Sc. in
Dentistry Thesis, Ann Arbor: Baylor College of Dentistry. 1977.
 22. Criswell GR. Skeletal and dental effects of a novel application of the MARA appliance in
adolescent patients with Class II malocclusions. M.Sc. Thesis, Ann Arbor: University of
California, San Francisco. 2011.

23. Dalci O, Altug AT, Memikoglu UT. Treatment effects of a twin-force bite corrector versus an activator in comparison with an untreated Class II sample: a preliminary report. *Aust Orthod J*. 2014;30(1):45-53.
24. DeVincenzo JP. Changes in mandibular length before, during, and after successful orthopedic correction of Class II malocclusions, using a functional appliance. *Am J Orthod Dentofacial Orthop*. 1991;99(3):241-57.
25. Dolce C, McGorray SP, Brazeau L, King GJ, Wheeler TT. Timing of Class II treatment: skeletal changes comparing 1-phase and 2-phase treatment. *Am J Orthod Dentofacial Orthop*. 2007;132(4):481-9.
26. Dolce C, Schader RE, McGorray SP, Wheeler TT. Centrographic analysis of 1-phase versus 2-phase treatment for Class II malocclusion. *Am J Orthod Dentofacial Orthop*. 2005;128(2):195-200.
27. Dos Santos-Pinto PR, Martins LP, dos Santos-Pinto A, Gandini Júnior LG, Raveli DB, dos Santos-Pinto CCM. Mandibular growth and dentoalveolar development in the treatment of Class II, division 1, malocclusion using balters bionator according to the skeletal maturation. *Dental Press J Orthod*. 2013;18(4):43-52.
28. Drage KJ, Hunt NP. Overjet relapse following functional appliance therapy. *Br J Orthod*. 1990;17(3):205-13.
29. Ehmer U, Tabanci J. Growth and therapy in Angle class II/2--a longitudinal cephalometric study. *Fortschr Kieferorthop*. 1990;51(4):208-12.
30. Falck F. Sagittal and vertical changes in mandibular retrognathism. A telerradiological longitudinal study of patients with functional regulators compared to a control group. *Stomatol DDR*. 1983;33(3):182-95.
31. Faxen Sepanian V, Paulsson-Bjornsson L, Kjellberg H. A long-term controlled follow-up study of objective treatment need on young adults treated with functional appliances. *Swed Dent J*. 2014;38(1):39-46.
32. Filip P. Late result in jaw orthopedic treatment by the Andresen-Haupls system. *Den Nor*

- Tannlaegeforen Tid. 1970;80(5):326-34.
33. Flores-Mir C, Barnett G, Higgins DW, Heo G, Major PW. Short-term skeletal and dental effects of the Xbow appliance as measured on lateral cephalograms. *Am J Orthod Dentofacial Orthop.* 2009;136(6):822-32.
 34. Foncatti CF, Castanha Henriques JF, Janson G, Caldas W, Garib DG. Long-term stability of Class II treatment with the Jasper jumper appliance. *Am J Orthod Dentofacial Orthop.* 2017;152(5):663-71.
 35. Franchi L, Baccetti T, McNamara JA. Treatment and posttreatment effects of acrylic splint Herbst appliance therapy. *Am J Orthod Dentofacial Orthop.* 1999;115(4):429-38.
 36. Franchi L, Baccetti T. Prediction of individual mandibular changes induced by functional jaw orthopedics followed by fixed appliances in Class II patients. *Angle Orthod.* 2006;76(6):950-4.
 37. Franchi L, Baccetti T, Giuntini V, Masucci C, Vangelisti A, Defraia E. Outcomes of two-phase orthodontic treatment of deepbite malocclusions. *Angle Orthod.* 2011;81(6):945-52.
 38. Franchi L, Pavoni C, Faltin K, Bigliazzi R, Gazzani F, Cozza P. Thin-plate spline analysis of mandibular shape changes induced by functional appliances in Class II malocclusion: a long-term evaluation. *J Orofac Orthop.* 2016;77(5):325-33.
 39. Frankel R, Frankel C. A functional approach to treatment of skeletal open bite. *Am J Orthod.* 1983;84(1):54-68.
 40. Fry JR. A comparison of the soft tissue outcomes of one and two phase Class II orthodontic treatment. M.Sc. Thesis, Ann Arbor: University of Southern California. 2006.
 41. Ghislanzoni LT, Toll DE, Defraia E, Baccetti T, Franchi L. Treatment and posttreatment outcomes induced by the Mandibular Advancement Repositioning Appliance; a controlled clinical study. *Angle Orthod.* 2011;81(4):684-91.
 42. Han S, Choi YJ, Chung CJ, Kim JY, Kim KH. Long-term pharyngeal airway changes after bionator treatment in adolescents with skeletal Class II malocclusions. *Korean J Orthod.* 2014;44(1):13-9.

43. Hansen K, Pancherz H. Long-term effects of Herbst treatment in relation to normal growth development: a cephalometric study. *Eur J Orthod.* 1992;14(4):285-95.
44. Humphrey MP. Post-treatment stability of the dentoalveolar effects caused by the Forsus fatigue resistant device. M.Sc. in Dentistry Thesis, Ann Arbor: Saint Louis University. 2016.
45. Jacob HB, dos Santos-Pinto A, Buschang PH. Dental and skeletal components of Class II open bite treatment with a modified Thurow appliance. *Dental Press J Orthod.* 2014;19(1):19-25.
46. Jakobsone G, Latkauskiene D, McNamara JA, Jr. Mechanisms of Class II correction induced by the crown Herbst appliance as a single-phase Class II therapy: 1 year follow-up. *Prog Orthod.* 2013;14:27.
47. Janson G, Nakamura A, Chiqueto K, Castro R, de Freitas MR, Henriques JF. Treatment stability with the eruption guidance appliance. *Am J Orthod Dentofacial Orthop.* 2007;131(6):717-28.
48. Johannesen B. A cephalometric follow-up study of overjet and incisor stability in treated class II, division 1. *Trans Eur Orthod Soc.* 1972:231-49.
49. Karlowska I. Late results of treatment with elastic appliances of the author's own design. *Czas Stomatol.* 1971;24(2):207-13.
50. Keeling SD, Wheeler TT, King GJ, Garvan CW, Cohen DA, Cabassa S, et al. Anteroposterior skeletal and dental changes after early Class II treatment with bionators and headgear. *Am J Orthod Dentofacial Orthop.* 1998;113(1):40-50.
51. Keski-Nisula K, Keski-Nisula L, Salo H, Voipio K, Varrela J. Dentofacial changes after orthodontic intervention with eruption guidance appliance in the early mixed dentition. *Angle Orthodontist.* 2008;78(2):324-31.
52. Knight H. The effects of three methods of orthodontic appliance therapy on some commonly used cephalometric angular variables. *Am J Orthod Dentofacial Orthop.* 1988;93(3):237-44.

53. Koroluk LD, Tulloch JF, Phillips C. Incisor trauma and early treatment for Class II Division 1 malocclusion. *Am J Orthod Dentofacial Orthop.* 2003;123(2):117-25; discussion 25-6.
54. Lall R, Kumar GA, Maheshwari A, Kumar M. A retrospective cephalometric evaluation of dental changes with activator and activator headgear combination in the treatment of skeletal class II malocclusion. *J Contemp Dent Pract.* 2011;12(1):14-8.
55. Lima KJ, Henriques JF, Janson G, Pereira SC, Neves LS, Cancado RH. Dentoskeletal changes induced by the Jasper jumper and the activator-headgear combination appliances followed by fixed orthodontic treatment. *Am J Orthod Dentofacial Orthop.* 2013;143(5):684-94.
56. Livieratos FA, Johnston Jr LE. A comparison of one-stage and two-stage nonextraction alternatives in matched Class II samples. *Am J Orthod Dentofacial Orthop.* 1995;108(2):118-31.
57. Luder HU. Skeletal profile changes related to two patterns of activator effects. *Am J Orthod.* 1982;81(5):390-6.
58. Lux CJ, Rubel J, Starke J, Conradt C, Stellzig PA, Komposch PG. Effects of early activator treatment in patients with class II malocclusion evaluated by thin-plate spline analysis. *Angle Orthod.* 2001;71(2):120-6.
59. Madone G, Ingervall B. Stability of results and function of the masticatory system in patients treated with the Herren type of activator. *Eur J Orthod.* 1984;6(2):92-106.
60. Madone G, Ingervall B. Stability of the results and function of the jaws after correction of distal bite using the Herren activator. *Schweiz Monatsschr Zahnmed.* 1984;94(5):453-61.
61. Mills CM, McCulloch KJ. Posttreatment changes after successful correction of Class II malocclusions with the twin block appliance. *Am J Orthod Dentofacial Orthop.* 2000;118(1):24-33.
62. Mongini F, Schmid W. Treatment of mandibular asymmetries during growth. A longitudinal study. *Eur J Orthod.* 1987;9(1):51-67.

63. Morris DO, Illing HM, Lee RT. A prospective evaluation of Bass, Bionator and Twin Block appliances. Part II--The soft tissues. *Eur J Orthod.* 1998;20(6):663-84.
64. Mortenson DR. Soft tissue changes from Herbst appliance treatment: A cephalometric longitudinal study. M.Sc. Thesis, Ann Arbor: University of Louisville. 2004.
65. Nelson B, Hagg U, Hansen K, Bendeus M. A long-term follow-up study of Class II malocclusion correction after treatment with Class II elastics or fixed functional appliances. *Am J Orthod Dentofacial Orthop.* 2007;132(4):499-503.
66. O'Brien K, Wright J, Conboy F, Appelbe P, Davies L, Connolly I, et al. Early treatment for Class II Division 1 malocclusion with the Twin-block appliance: a multi-center, randomized, controlled trial. *Am J Orthod Dentofacial Orthop.* 2009;135(5):573-9.
67. Omblus J, Malmgren O, Pancherz H, Hagg U, Hansen K. Long-term effects of Class II correction in Herbst and Bass therapy. *Eur J Orthod.* 1997;19(2):185-93.
68. Pancherz H. Relapse after activator treatment. A biometric, cephalometric, and electromyographic study of subjects with and without relapse of overjet. *Am J Orthod.* 1977;72(5):499-512.
69. Pancherz H, Hansen K. Occlusal changes during and after Herbst treatment: a cephalometric investigation. *Eur J Orthod.* 1986;8(4):215-28.
70. Pancherz H, Littmann C. Morphology and position of mandible in Herbst treatment. Cephalometric analysis of changes to end of growth period. *Inf Orthod Kieferorthop.* 1989;21(4):493-513.
71. Pancherz H, Anehus-Pancherz M. The headgear effect of the Herbst appliance: a cephalometric long-term study. *Am J Orthod Dentofacial Orthop.* 1993;103(6):510-20.
72. Pancherz H, Anehus-Pancherz M. Facial profile changes during and after Herbst appliance treatment. *Eur J Orthod.* 1994;16(4):275-86.
73. Pancherz H, Ruf S, Kohlhas P. "Effective condylar growth" and chin position changes in Herbst treatment: a cephalometric roentgenographic long-term study. *Am J Orthod Dentofacial Orthop.* 1998;114(4):437-46.

74. Pancherz H, Fischer S. Amount and direction of temporomandibular joint growth changes in Herbst treatment: a cephalometric long-term investigation. *Angle Orthod.* 2003;73(5):493-501.
75. Pancherz H, Bjerklin K, Hashemi K. Late adult skeletofacial growth after adolescent Herbst therapy: a 32-year longitudinal follow-up study. *Am J Orthod Dentofacial Orthop.* 2015;147(1):19-28.
76. Pancherz H, Bjerklin K. The Herbst appliance 32 years after treatment. *J Clin Orthod.* 2015;49(7):442-51.
77. Pangrazio MN, Pangrazio-Kulbersh V, Berger JL, Bayirli B, Movahhedian A. Treatment effects of the mandibular anterior repositioning appliance in patients with Class II skeletal malocclusions. *Angle Orthod.* 2012;82(6):971-7.
78. Pavoni C, Lombardo EC, Lione R, Faltin K, Jr., McNamara JA, Jr., Cozza P, et al. Treatment timing for functional jaw orthopaedics followed by fixed appliances: a controlled long-term study. *Eur J Orthod.* 2017.
79. Perillo L, Johnston LE, Jr., Ferro A. Permanence of skeletal changes after function regulator (FR-2) treatment of patients with retrusive Class II malocclusions. *Am J Orthod Dentofacial Orthop.* 1996;109(2):132-9.
80. Perillo L, Castaldo MI, Cannavale R, Longobardi A, Grassia V, Rullo R, et al. Evaluation of long-term effects in patients treated with Frankel-2 appliance. *Eur J Paediatr Dent.* 2011;12(4):261-6.
81. Phelan A, Tarraf NE, Taylor P, Honscheid R, Drescher D, Baccetti T, et al. Skeletal and dental outcomes of a new magnetic functional appliance, the Sydney Magnoglide, in Class II correction. *Am J Orthod Dentofacial Orthop.* 2012;141(6):759-72.
82. Righellis EG. Treatment effects of Frankel, activator and extraoral traction appliances. *Angle Orthod.* 1983;53(2):107-21.
83. Sander FG, Wichelhaus A. Skeletal and dental changes during the use of the bite-jumping plate. A cephalometric comparison with an untreated Class-II group. *Fortschr*

- Kieferorthop. 1995;56(3):127-39.
84. Sawrie DC. Cephalometric evaluation of Bionator therapy in the early treatment of Class II malocclusions. Master of Dental Science Thesis, Ann Arbor: The University of Tennessee Health Science Center. 2007.
 85. Scalzone A, D'Apuzzo F, Scalzone PP, Vitale V, Cannavale R, Perillo L. Twin Block treatment in growing Class II patients: Dento-skeletal effects. Dental Cadmos. 2015;83(10):654-9.
 86. Schadlbauer E. Long-term results after activator treatment. Inf Orthod Kieferorthop. 1984;16(4):419-29.
 87. Schutz-Fransson U, Bjerklin K, Lindsten R. Long-term follow-up of orthodontically treated deep bite patients. Eur J Orthod. 2006;28(5):503-12.
 88. Siara-Olds NJ, Pangrazio-Kulbersh V, Berger J, Bayirli B. Long-term dentoskeletal changes with the Bionator, Herbst, Twin Block, and MARA functional appliances. Angle Orthod. 2010;80(1):18-29.
 89. Sivakumar A, Valiathan A. Stability and functional appliances. Am J Orthod Dentofacial Orthop. 2005;128(6):687.
 90. Stuber P. The stimulation of the rotation of the mandible with Angle Class II/1 and II/2 malocclusion with functional regulators and activators as compared to the control group. Stomatol DDR. 1990;40(3):112-4.
 91. Stuber P. The possibility of stimulating mandibular growth in mandibular retrognathism with functional regulators and activators compared to a control group--a 6-year cephalometric longitudinal study. Fortschr Kieferorthop. 1990;51(6):361-5.
 92. Thompson WD. Dental and skeletal changes from Herbst appliance treatment: A cephalometric longitudinal study. M.Sc. Thesis, Ann Arbor: University of Louisville. 2001.
 93. Tomblyn T. A Radiographic Study of Patients Treated with the Reinforced Banded Herbst Appliance. M.Sc. Thesis, Ann Arbor: West Virginia University. 2015.

94. Tomblyn T, Rogers M, Andrews L, 2nd, Martin C, Tremont T, Gunel E, et al.
Cephalometric study of Class II Division 1 patients treated with an extended-duration, reinforced, banded Herbst appliance followed by fixed appliances. *Am J Orthod Dentofacial Orthop.* 2016;150(5):818-30.
95. Tulloch JF, Phillips C, Proffit WR. Benefit of early Class II treatment: progress report of a two-phase randomized clinical trial. *Am J Orthod Dentofacial Orthop.* 1998;113(1):62-72, quiz 3-4.
96. Ulusoy C, Canigur Bavbek N, Tuncer BB, Tuncer C, Turkoz C, Gencturk Z. Evaluation of airway dimensions and changes in hyoid bone position following class II functional therapy with activator. *Acta Odontol Scand.* 2014;72(8):917-25.
97. Valant JR. Cephalometric and Dental Evaluation of the Herbst Appliance in Class II Patients. M.Sc. in Dentistry, Ann Arbor: Baylor College of Dentistry. 1983.
98. VanLaecken R, Martin CA, Dischinger T, Razmus T, Ngan P. Treatment effects of the edgewise Herbst appliance: A cephalometric and tomographic investigation. *Am J Orthod Dentofacial Orthop.* 2006;130(5):582-93.
99. Vardimon AD, Koklu S, Iseri H, Shpack N, Fricke J, Mete L. An assessment of skeletal and dental responses to the functional magnetic system (FMS). *Am J Orthod Dentofacial Orthop.* 2001;120(4):416-26.
100. Voudouris JC, Woodside DG, Altuna G, Kuftinec MM, Angelopoulos G, Bourque PJ. Condyle-fossa modifications and muscle interactions during Herbst treatment, part 1. New technological methods. *Am J Orthod Dentofacial Orthop.* 2003;123(6):604-13.
101. Voudouris JC, Woodside DG, Altuna G, Angelopoulos G, Bourque PJ, Lacouture CY. Condyle-fossa modifications and muscle interactions during Herbst treatment, Part 2. Results and conclusions. *Am J Orthod Dentofacial Orthop.* 2003;124(1):13-29.
102. Weschler D, Pancherz H. Efficiency of three mandibular anchorage forms in Herbst treatment: a cephalometric investigation. *Angle Orthod.* 2005;75(1):23-7.
103. Wheeler TT, McGorray SP, Dolce C, Taylor MG, King GJ. Effectiveness of early

- treatment of Class II malocclusion. *Am J Orthod Dentofacial Orthop.* 2002;121(1):9-17.
104. Wortham JR, Dolce C, McGorray SP, Le H, King GJ, Wheeler TT. Comparison of arch dimension changes in 1-phase vs 2-phase treatment of Class II malocclusion. *Am J Orthod Dentofacial Orthop.* 2009;136(1):65-74.
 105. Yassaei S, Tabatabaei Z, Ghafurifard R. Stability of pharyngeal airway dimensions: tongue and hyoid changes after treatment with a functional appliance. *Int J Orthod Milwaukee.* 2012;23(1):9-15.
 106. Yassaei S, Jamilian A, Joshan N. Effects of Twin-Block and Faramand-LL appliances on soft tissue profile in the treatment of Class II division 1 malocclusion. *Int J Orthod Milwaukee.* 2014;25(4):57-62.
 107. Yuksel S, Kaygisiz E, Ulusoy C, Keykubat A. Post-treatment evaluation of a magnetic activator device in Class II high-angle malocclusions. *Eur J Orthod.* 2010;32(4):425-9.
 108. Zelderloo A, Cadenas De Llano-Pérula M, Verdonck A, Fieuws S, Willems G. Cephalometric appraisal of Class II treatment effects after functional and fixed appliances: A retrospective study. *Eur J Orthod.* 2017;39(3):334-41.

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

Maxillary/upper jaw changes

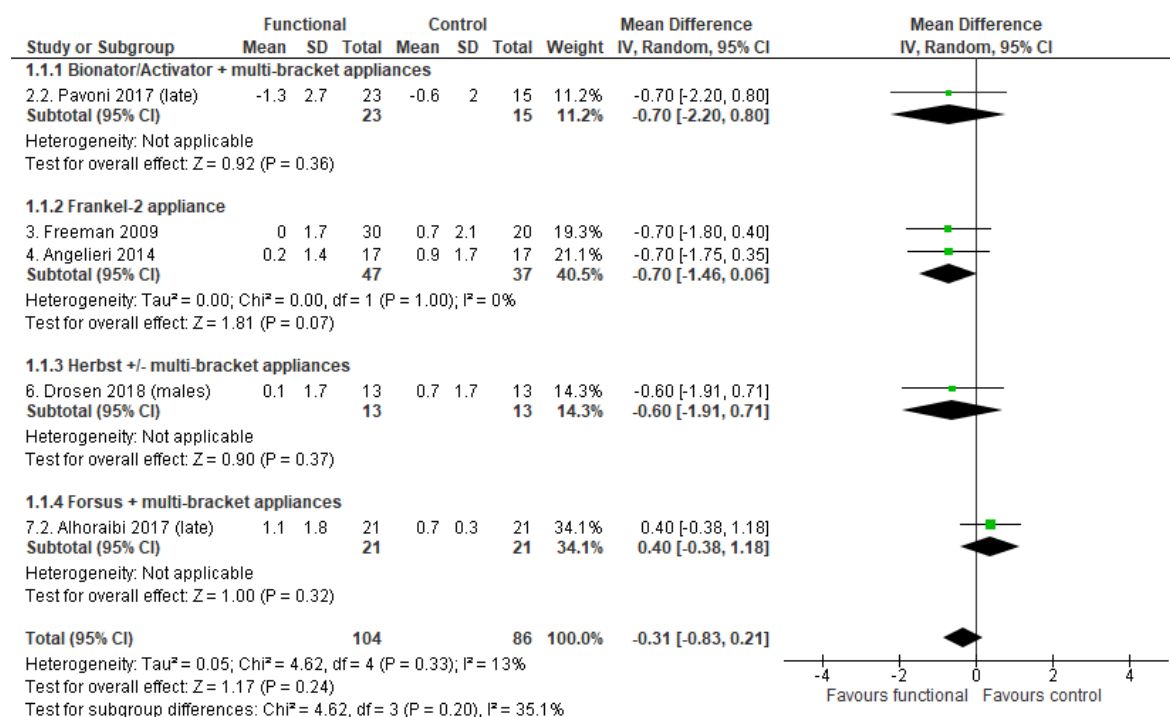


Figure 1. Meta-analysis; Outcome: SNA angle; Time point: above 18 years of age.

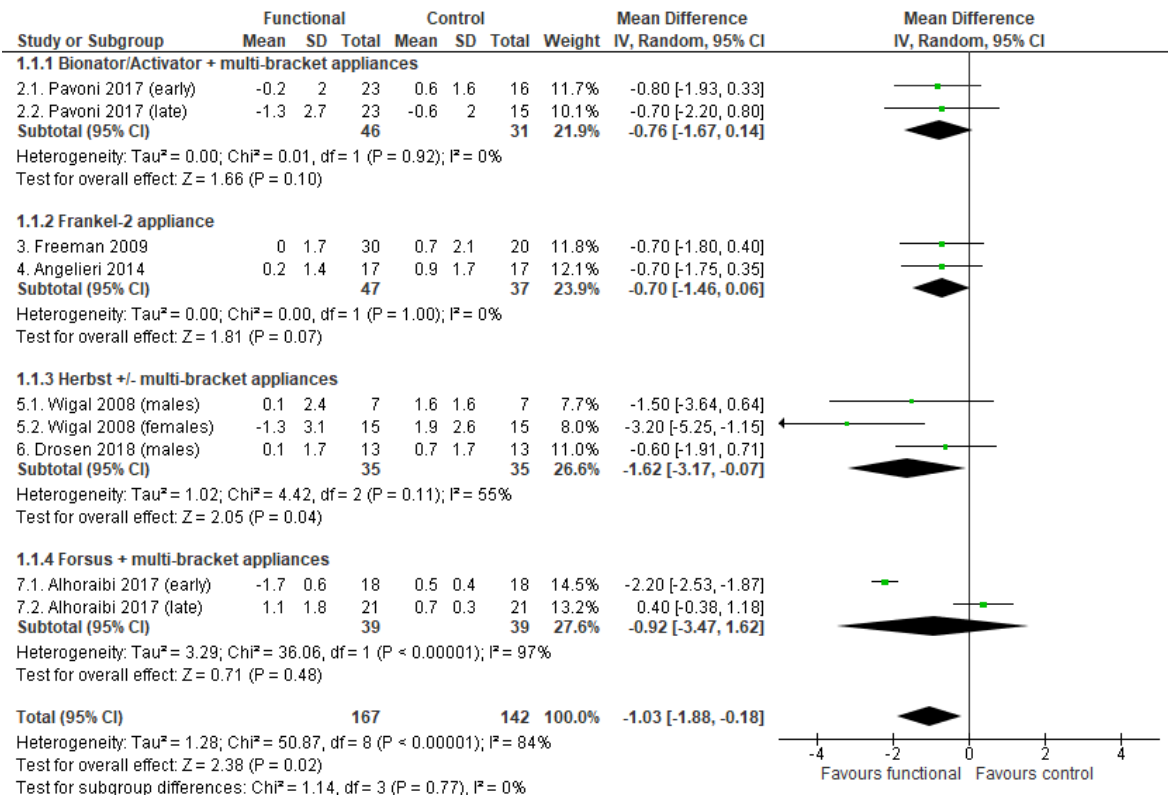


Figure 2. Meta-analysis; Outcome: SNA angle; Time point: After a post-retention period of at least 3 years.

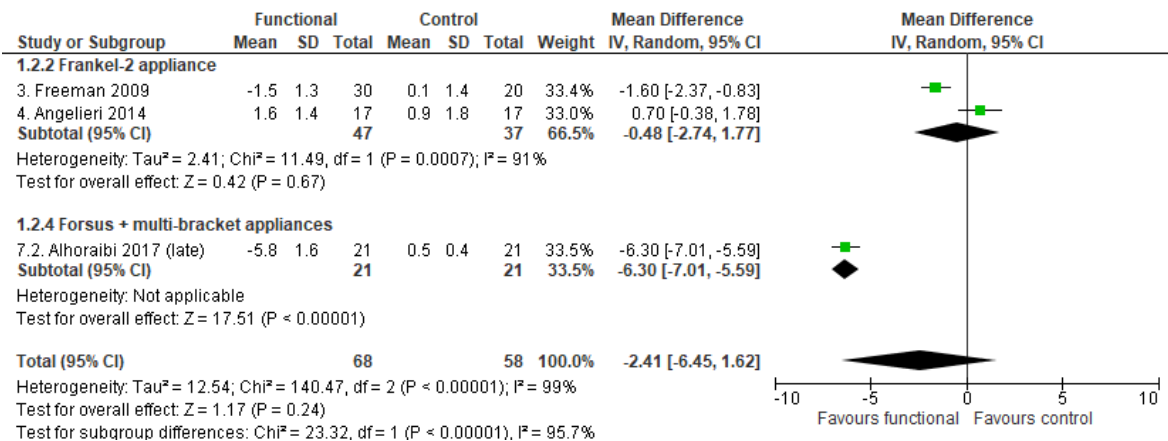


Figure 3. Meta-analysis; Outcome: A to N perpendicular distance; Time point: above 18 years of age.

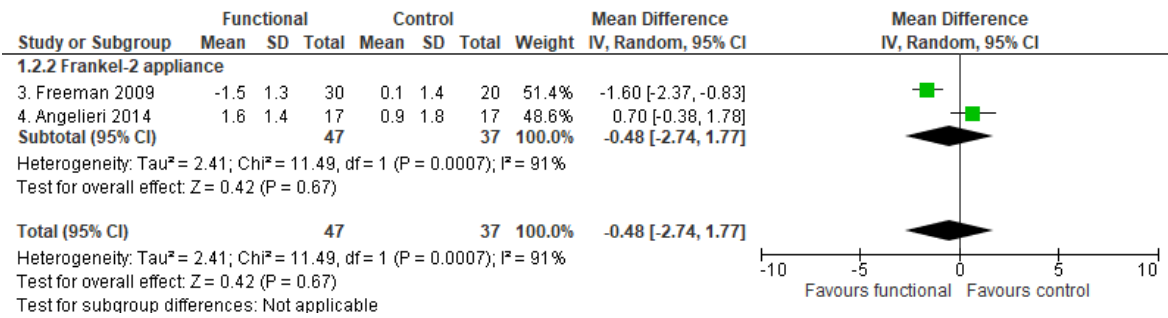


Figure 4. Meta-analysis; Outcome: A to N perpendicular distance; Time point: end of growth according to the CVM method.

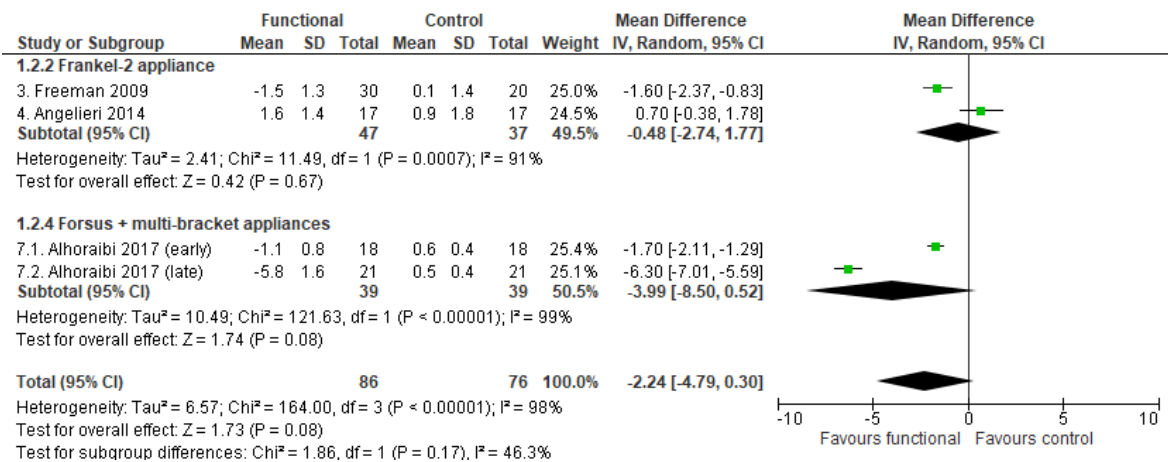


Figure 5. Meta-analysis; Outcome: A to N perpendicular distance; Time point: After a post-retention period of at least 3 years.

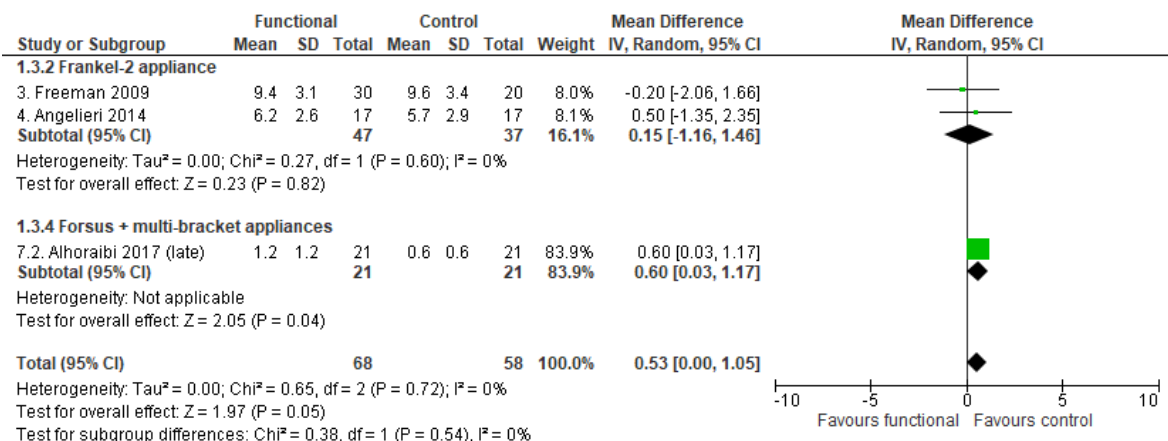


Figure 6. Meta-analysis; Outcome: Co-A distance; Time point: above 18 years of age.

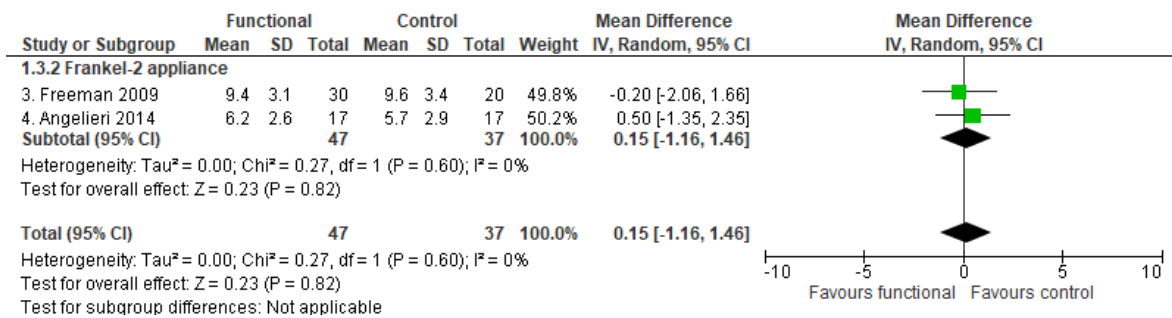


Figure 7. Meta-analysis; Outcome: Co-A distance; Time point: end of growth according to the CVM method.

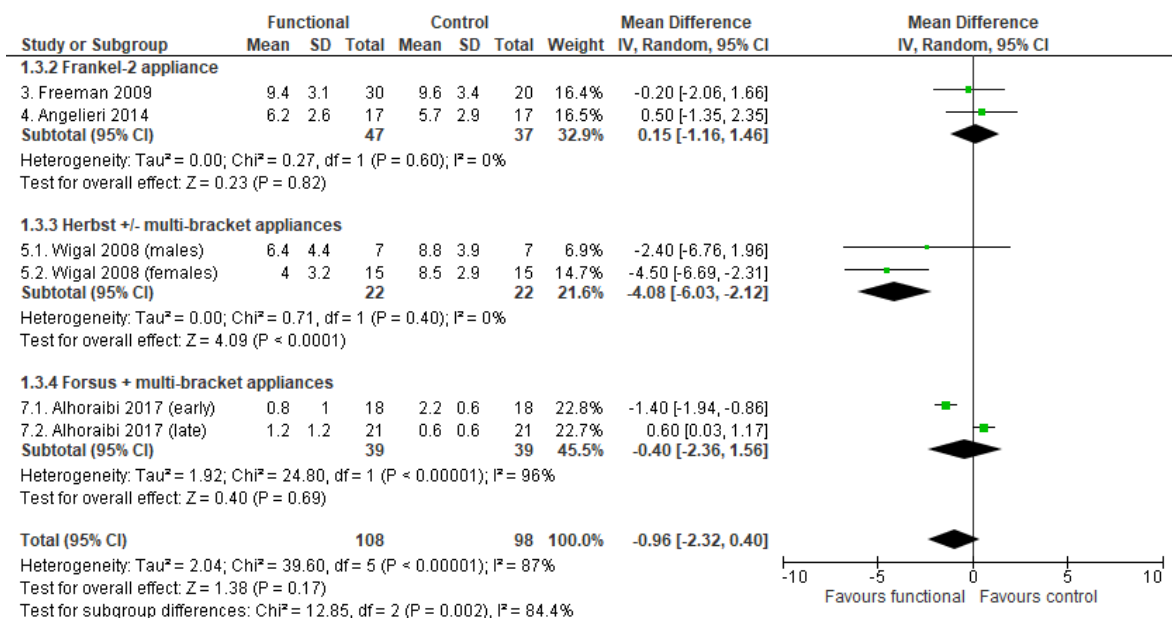


Figure 8. Meta-analysis; Outcome: Co-A distance; Time point: After a post-retention period of at least 3 years.

Mandibular/lower jaw changes

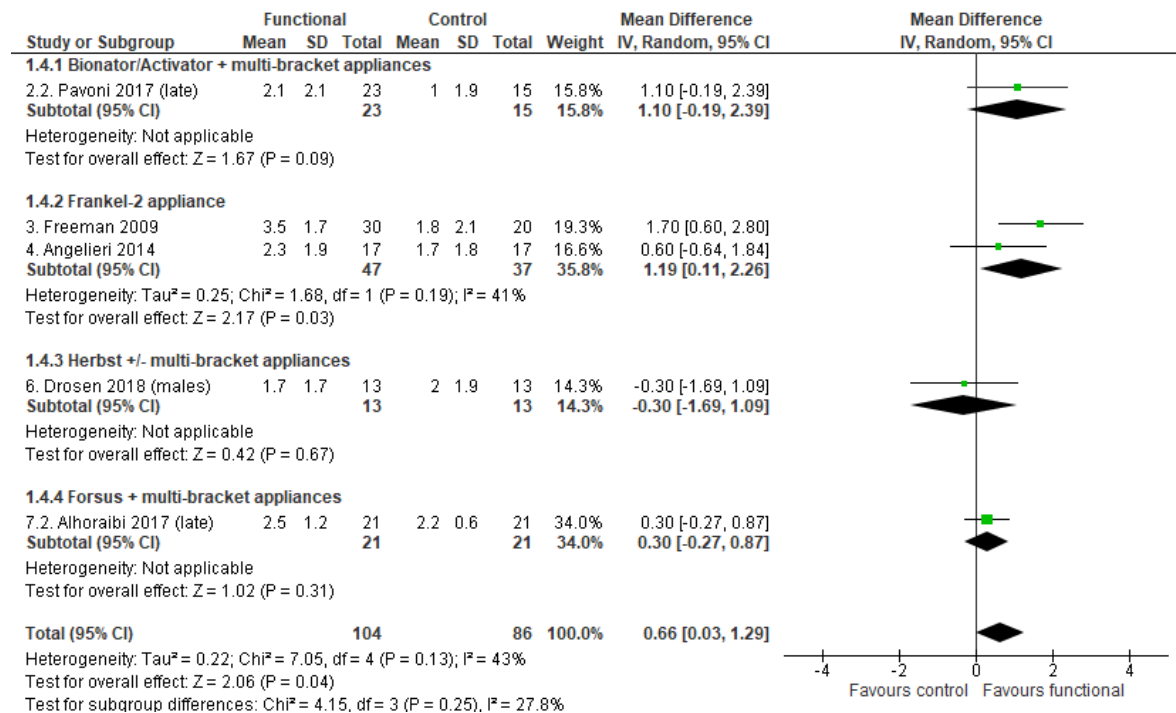


Figure 9. Meta-analysis; Outcome: SNB angle; Time point: above 18 years of age.

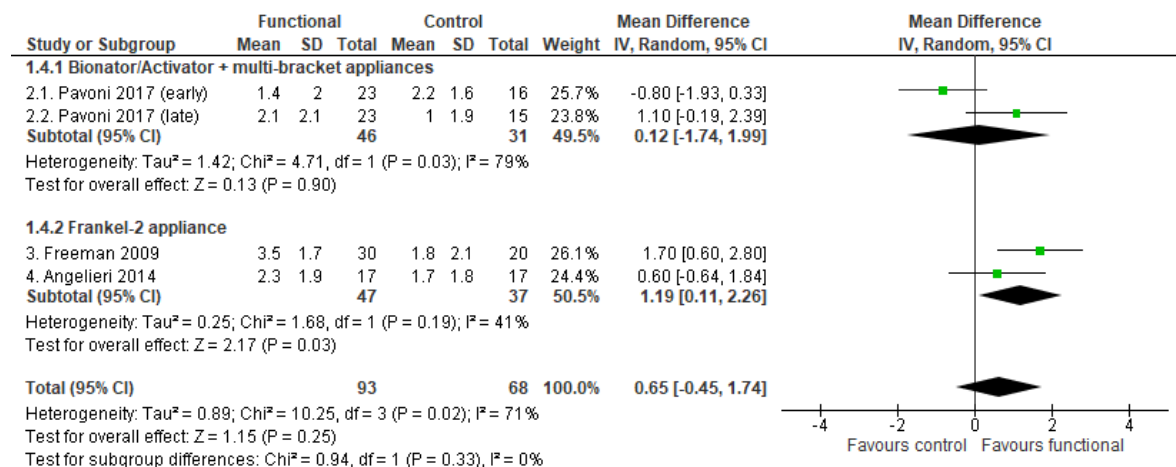


Figure 10. Meta-analysis; Outcome: SNB angle; Time point: end of growth according to the CVM method.

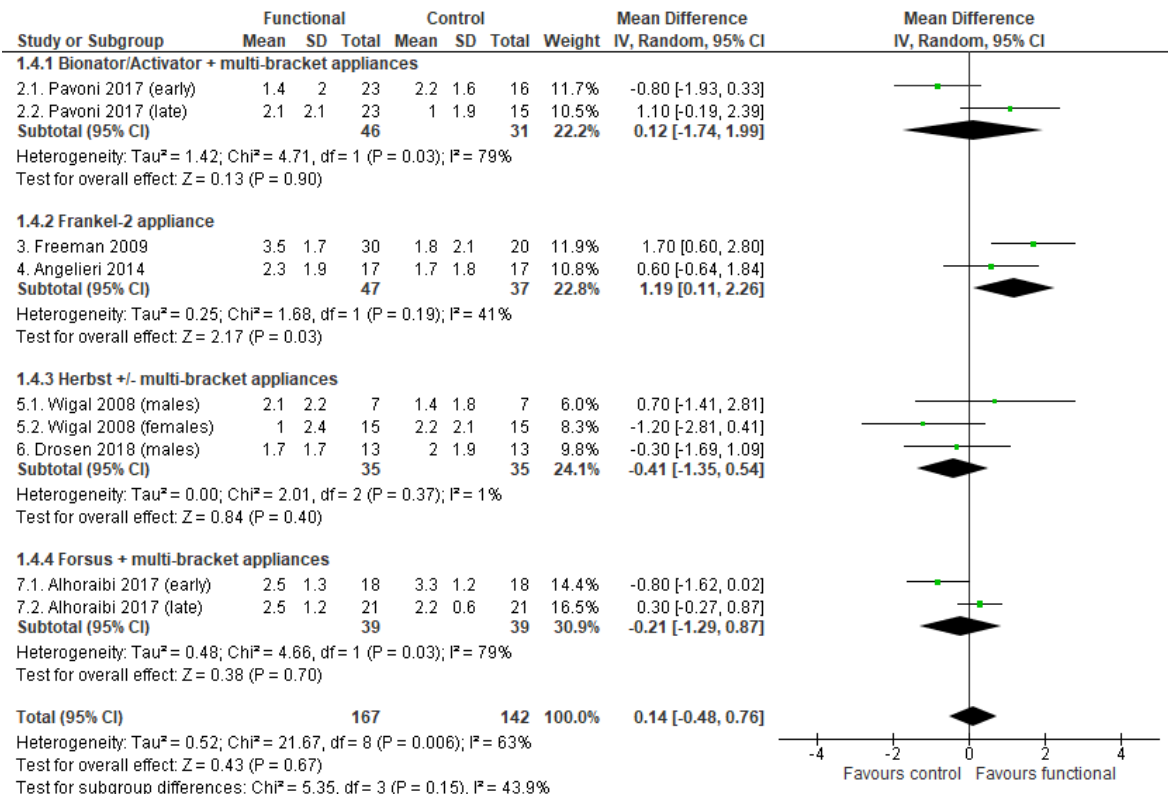


Figure 11. Meta-analysis; Outcome: SNB angle; Time point: After a post-retention period of at least 3 years.

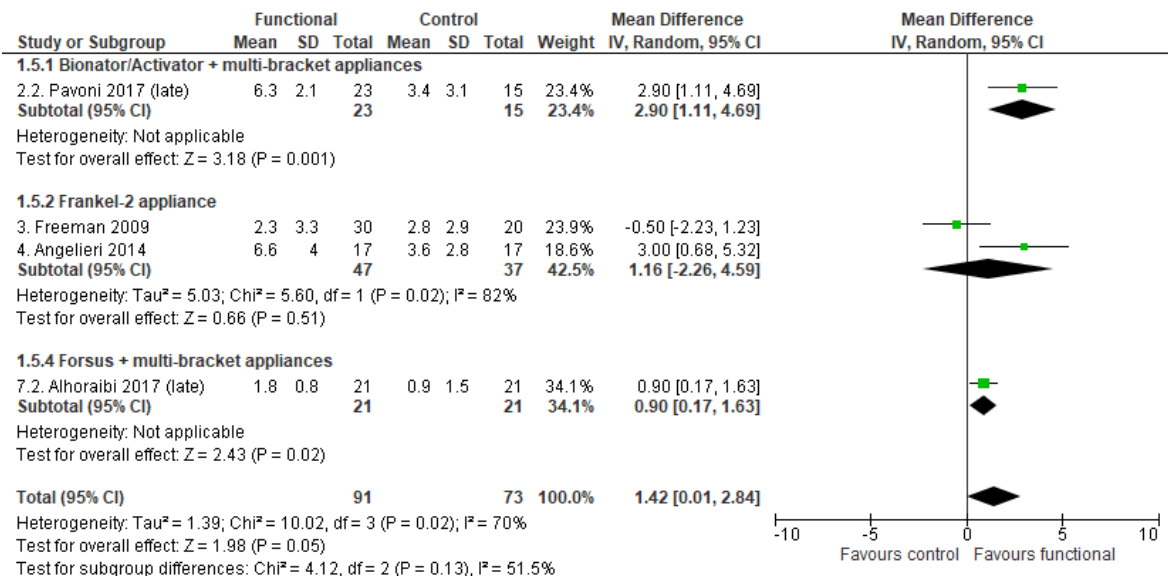


Figure 12. Meta-analysis; Outcome: Pg to N perp distance; Time point: above 18 years of age.

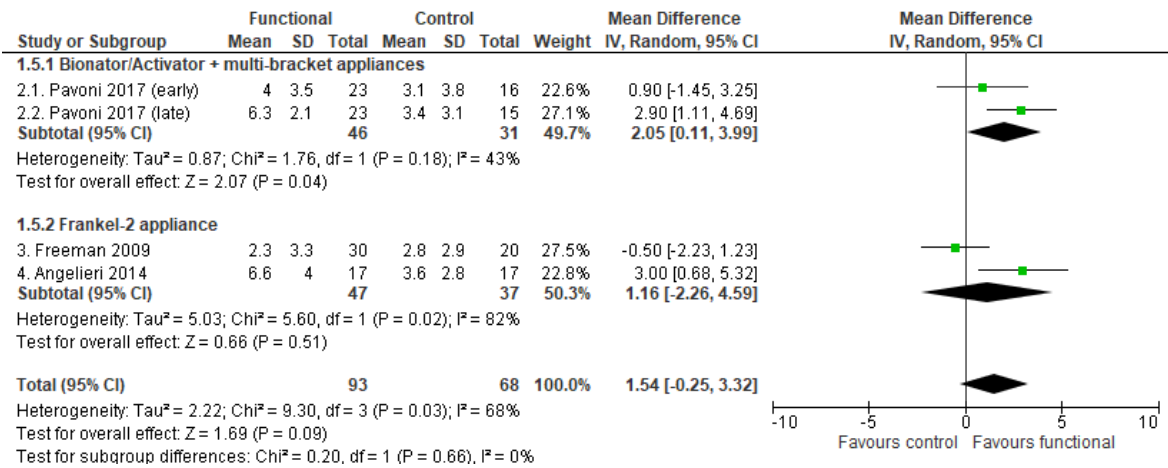


Figure 13. Meta-analysis; Outcome: Pg to N perp distance; Time point: end of growth according to the CVM method.

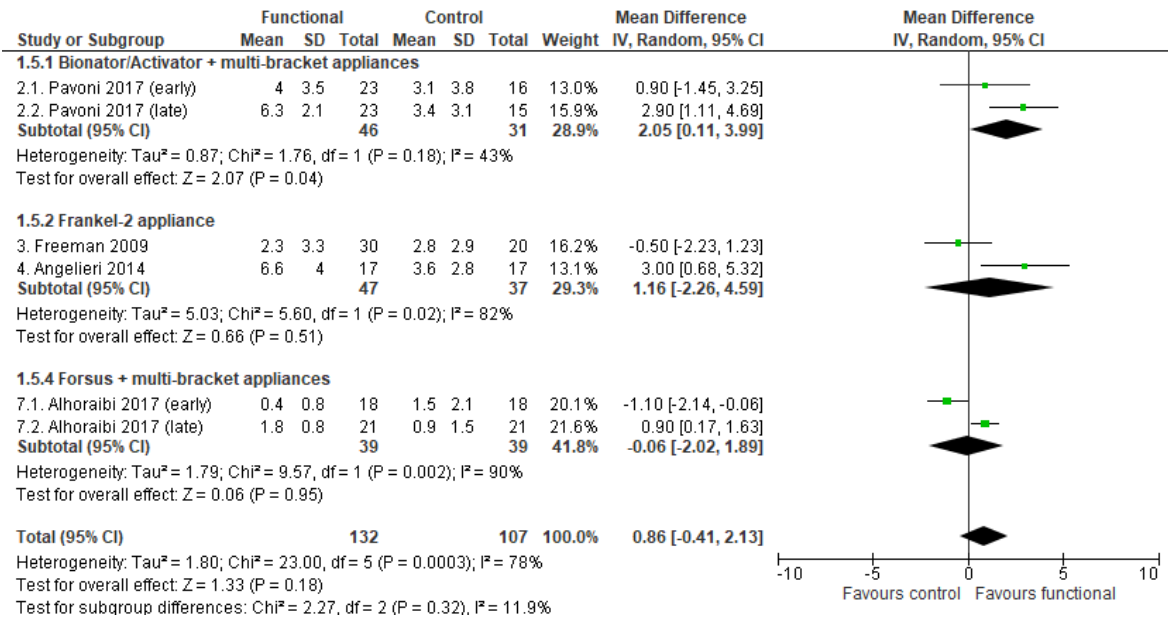


Figure 14. Meta-analysis; Outcome: Pg to N perpendicular distance; Time point: After a post-retention period of at least 3 years.

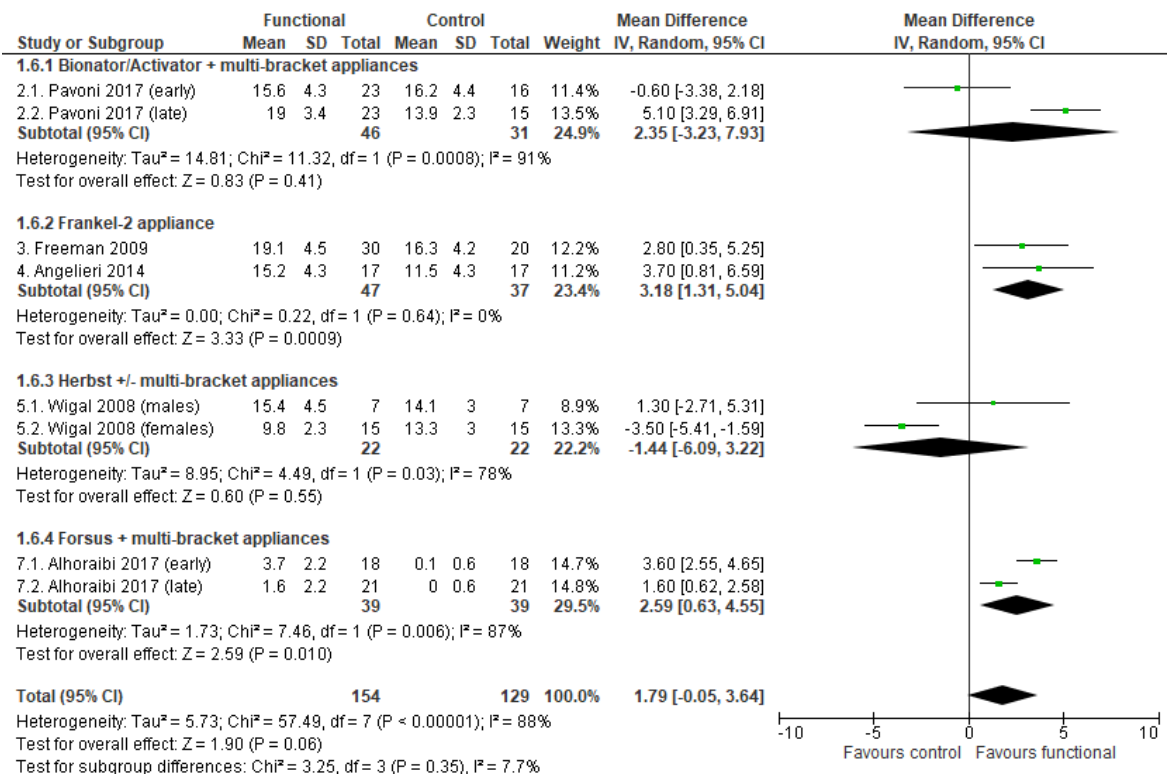


Figure 15. Meta-analysis; Outcome: Co-Gn distance; Time point: After a post-retention period of at least 3 years.

Maxillo-mandibular changes

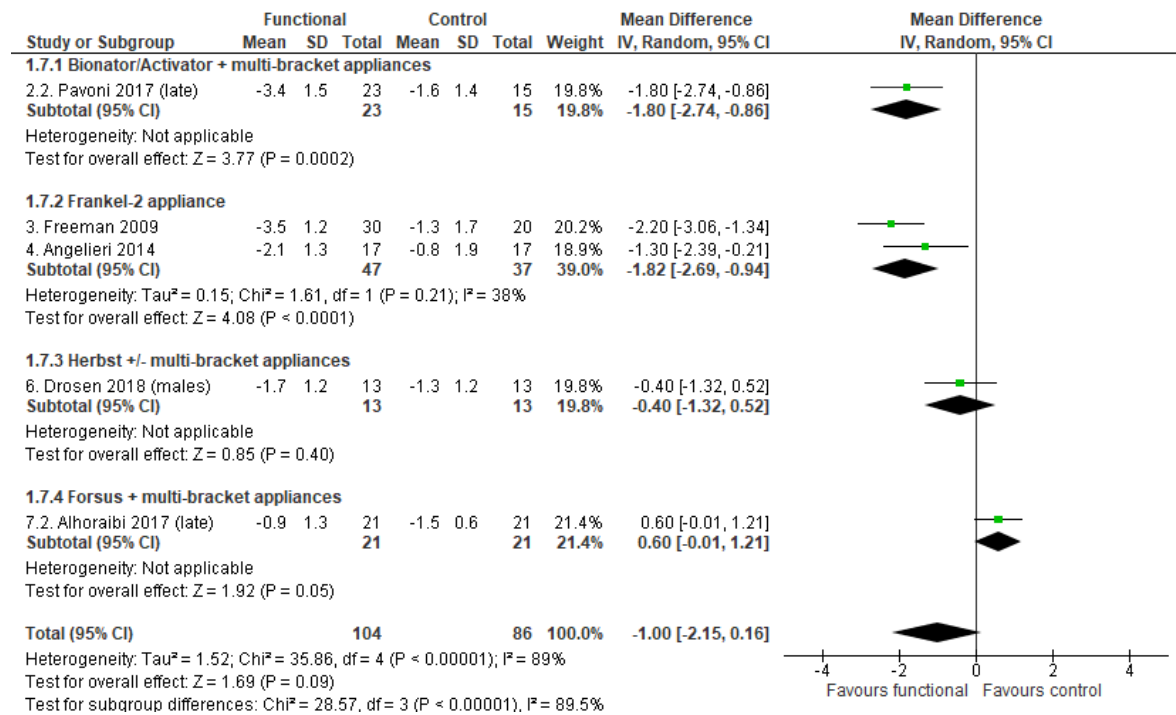


Figure 16. Meta-analysis; Outcome: ANB angle; Time point: above 18 years of age.

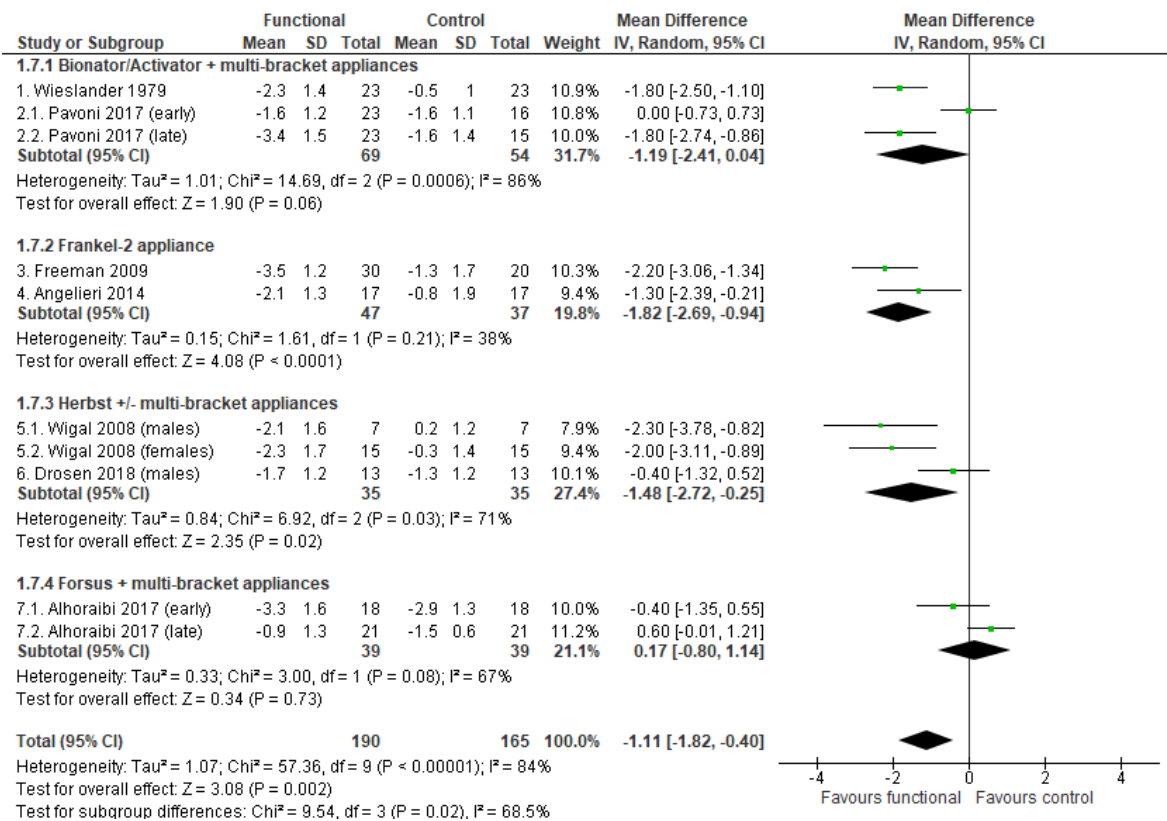


Figure 17. Meta-analysis; Outcome: ANB angle; Time point: After a post-retention period of at least 3 years.

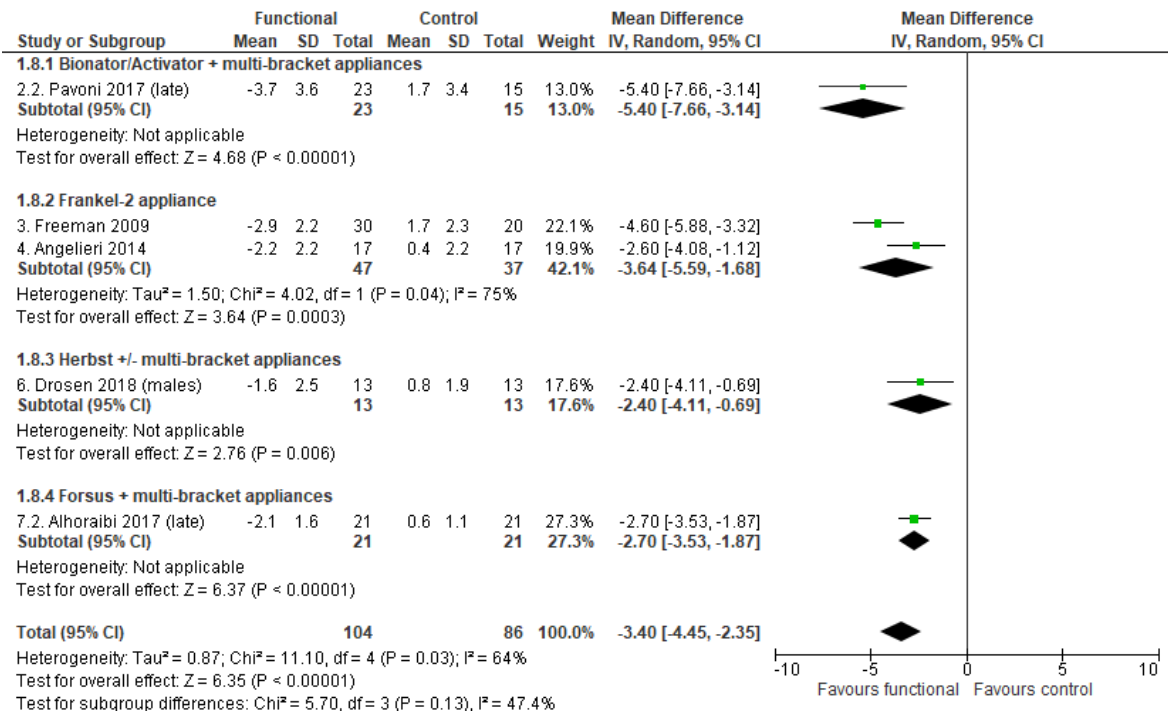


Figure 18. Meta-analysis; Outcome: Wits appraisal; Time point: above 18 years of age.

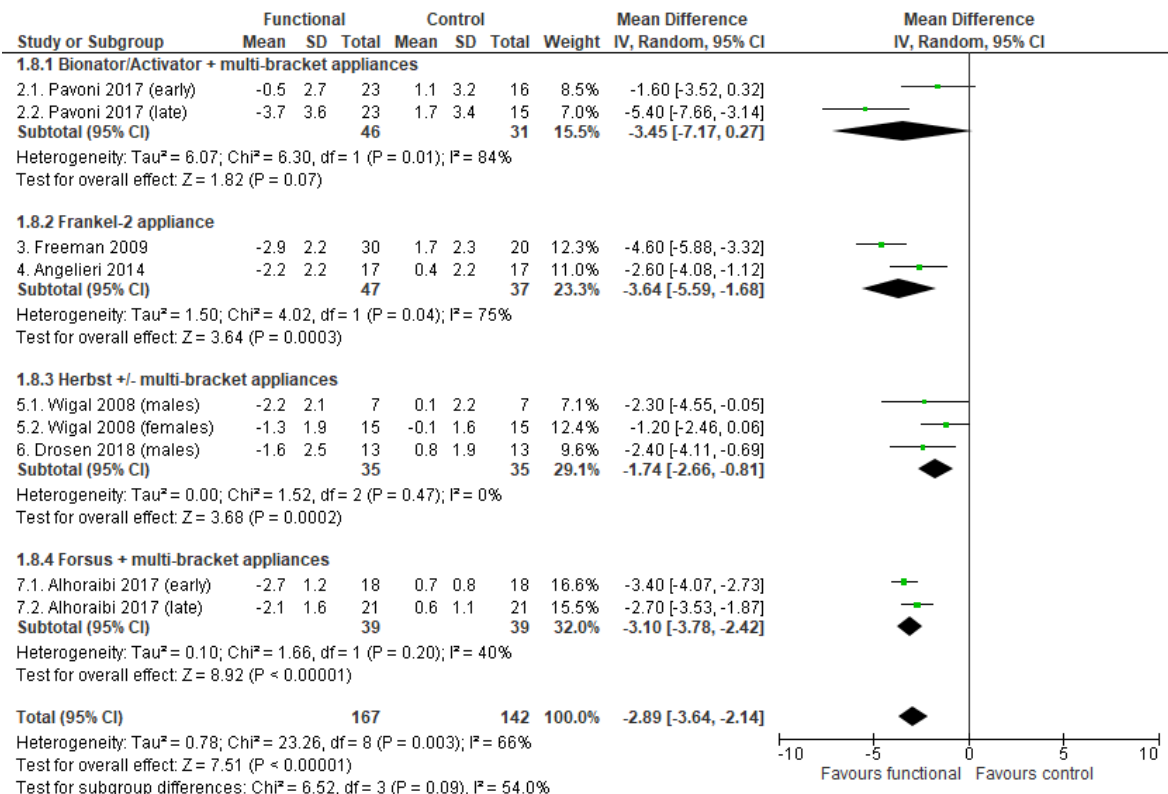


Figure 19. Meta-analysis; Outcome: Wits appraisal; Time point: After a post-retention period of at least 3 years.

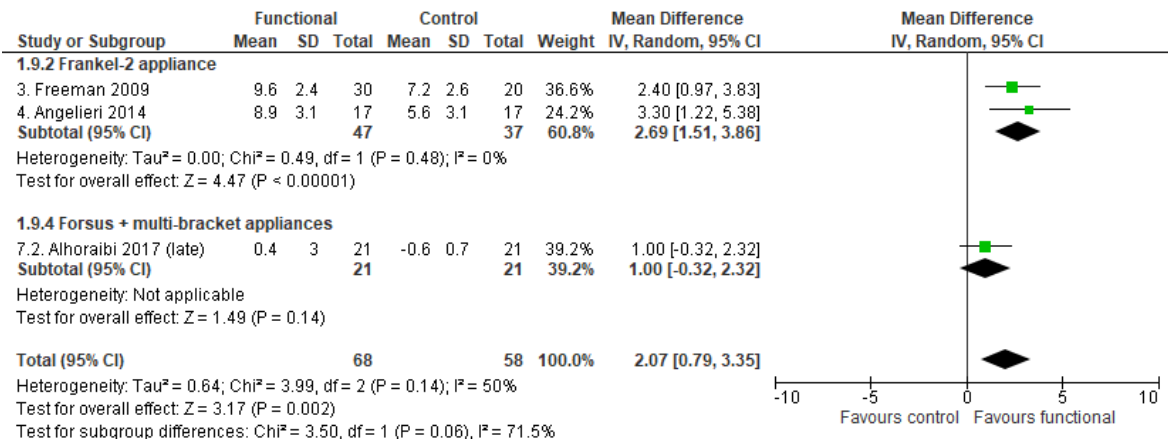


Figure 20. Meta-analysis; Outcome: Co-Gn/Co-A difference; Time point: above 18 years of age.

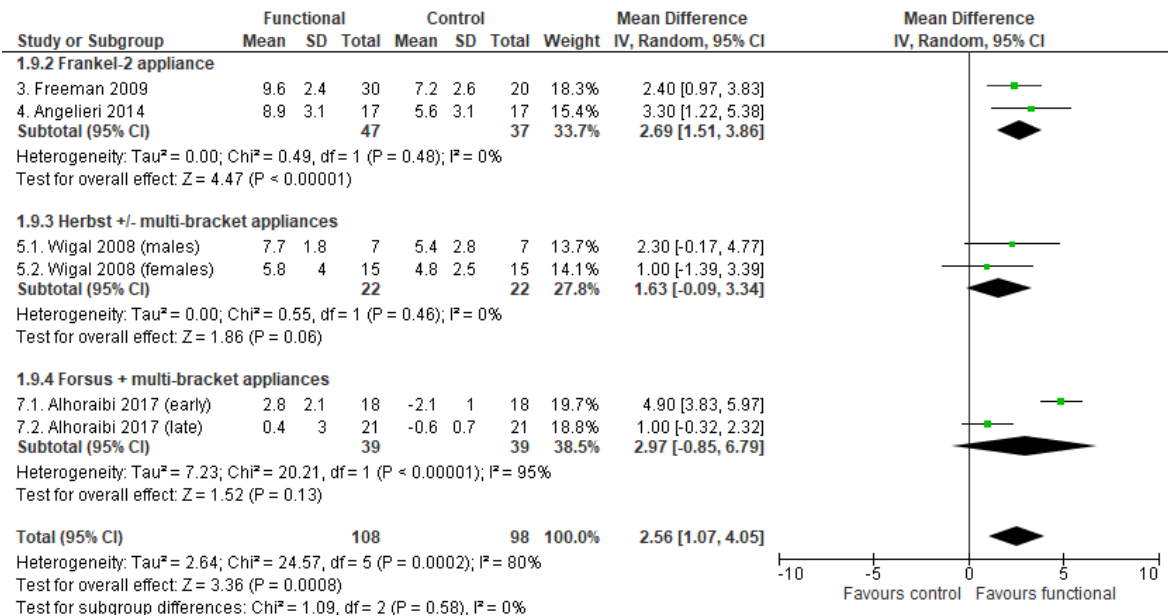


Figure 21. Meta-analysis; Outcome: Co-Gn/Co-A difference; Time point: After a post-retention period of at least 3 years.

Additional analysis

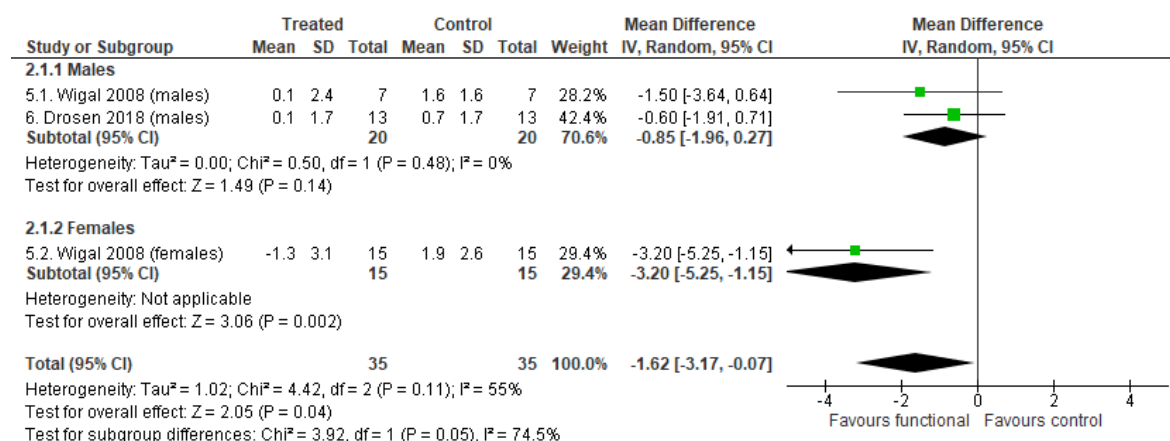


Figure 22. Subgroup analysis based on gender (males, females); Outcome: SNA angle.

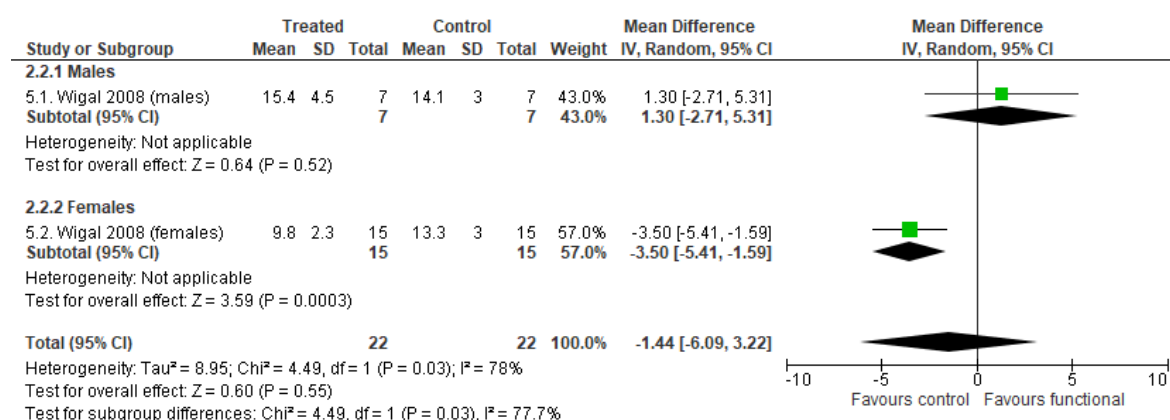


Figure 23. Subgroup analysis based on gender (males, females); Outcome: Co-Gn distance.

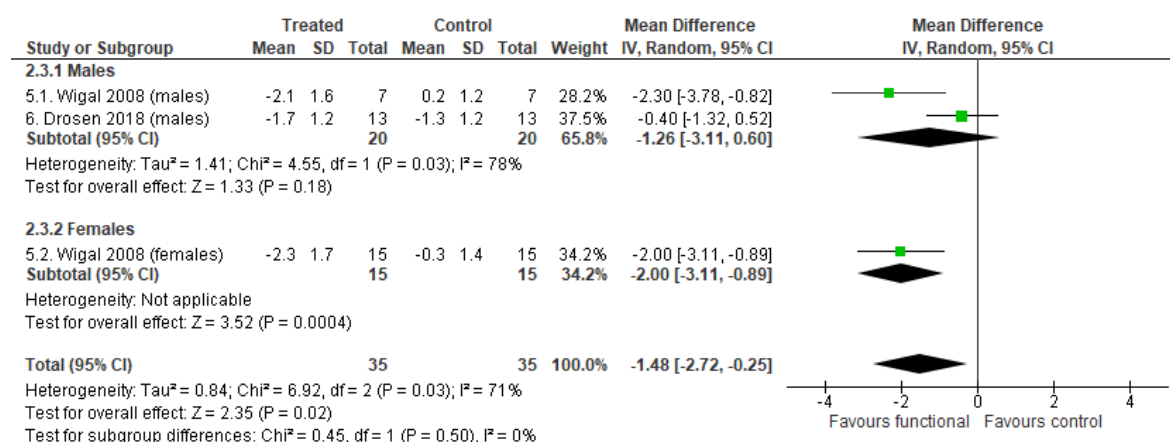


Figure 24. Subgroup analysis based on gender (males, females); Outcome: ANB angle.

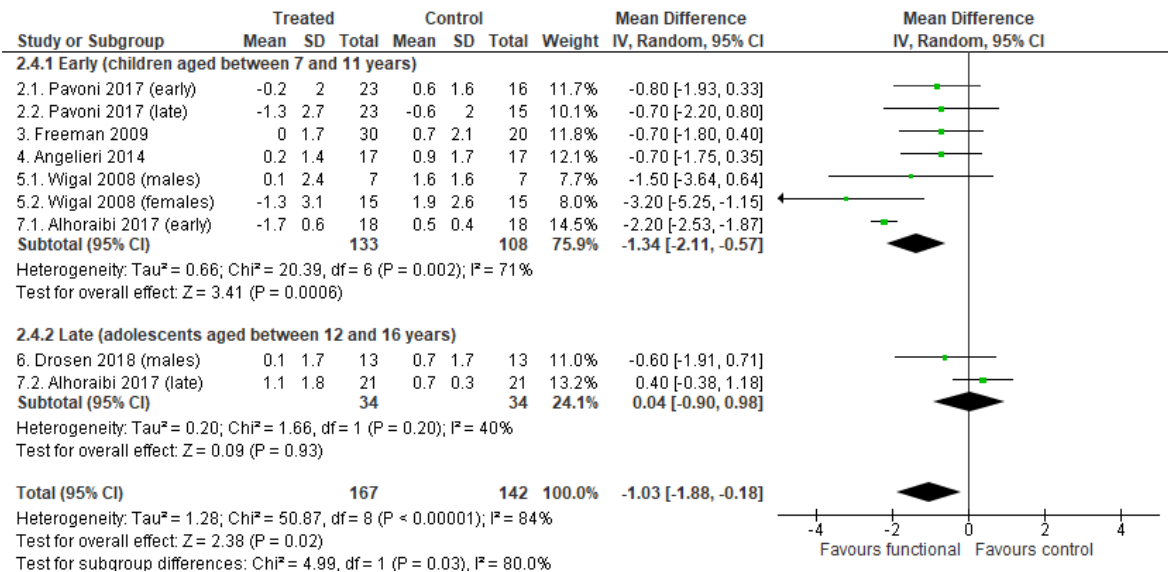


Figure 25. Subgroup analysis based on the beginning of the functional appliance therapy;

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.

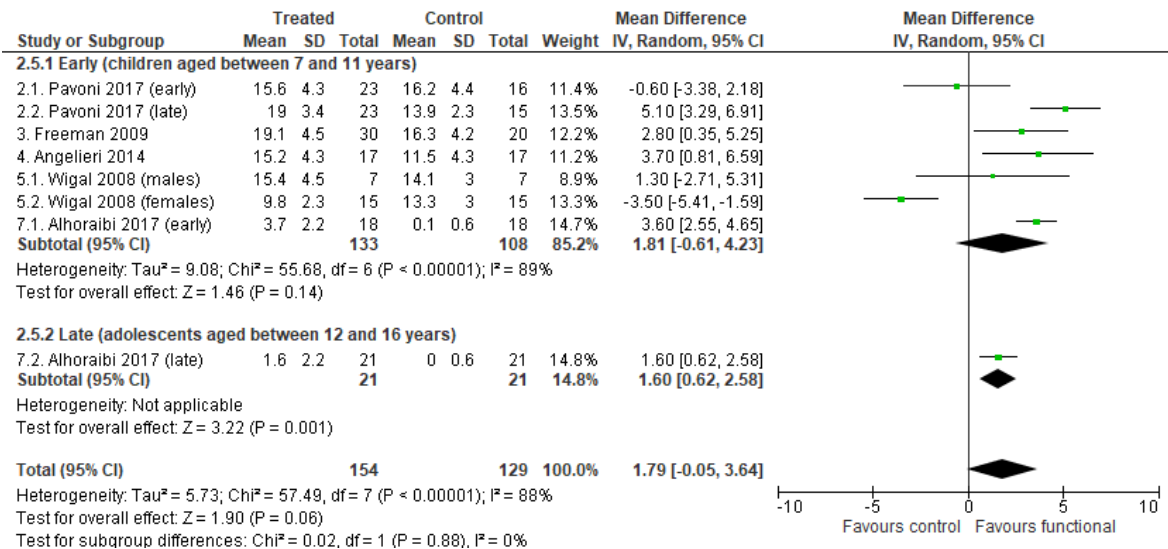


Figure 26. Subgroup analysis based on the beginning of the functional appliance therapy;

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.

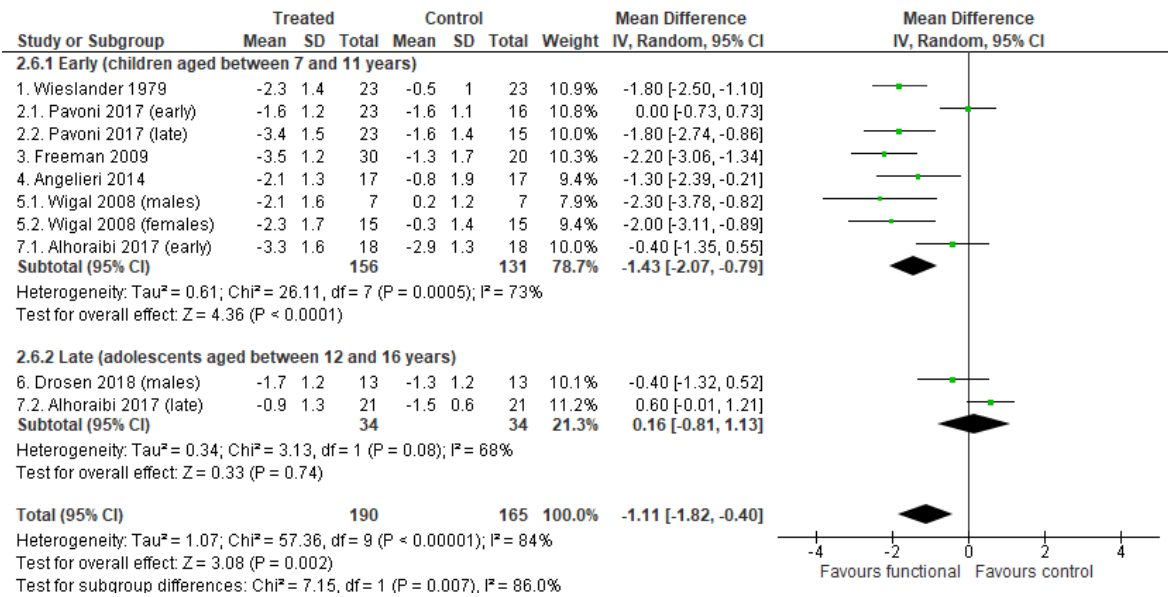


Figure 27. Subgroup analysis based on the beginning of the functional appliance therapy;

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.

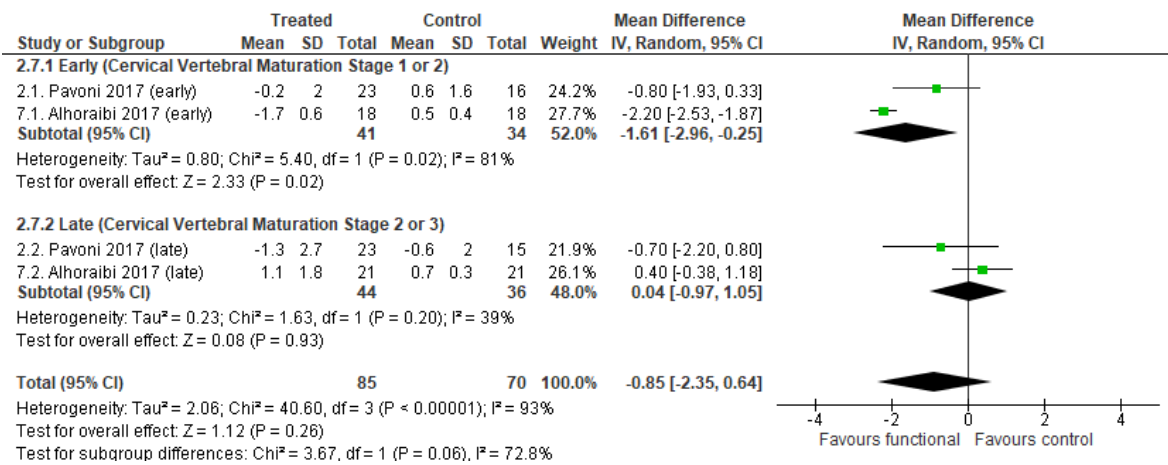


Figure 28. Subgroup analysis based on the start of the treatment; Outcome: SNA angle. Early

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.

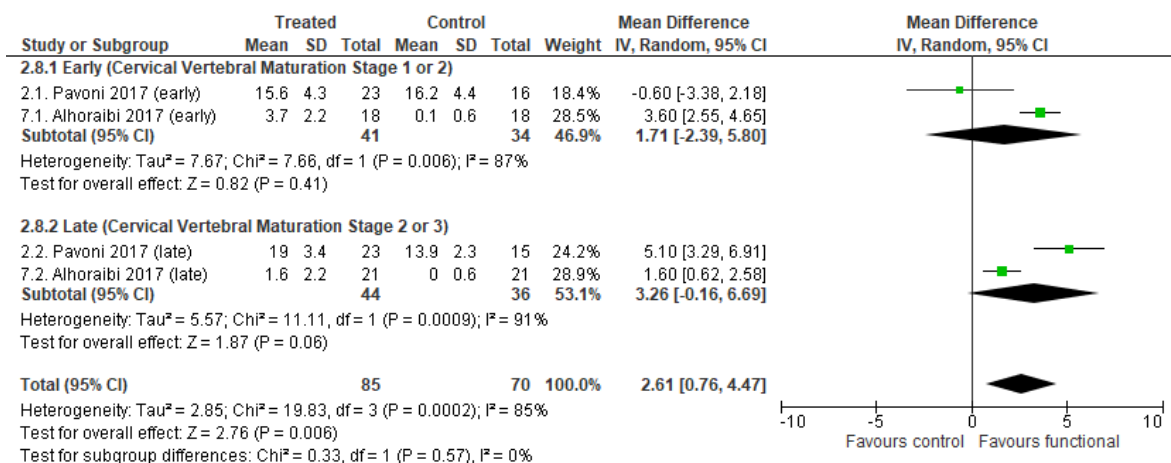


Figure 29. Subgroup analysis based on the start of the treatment; Outcome: Co-Gn distance.

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.

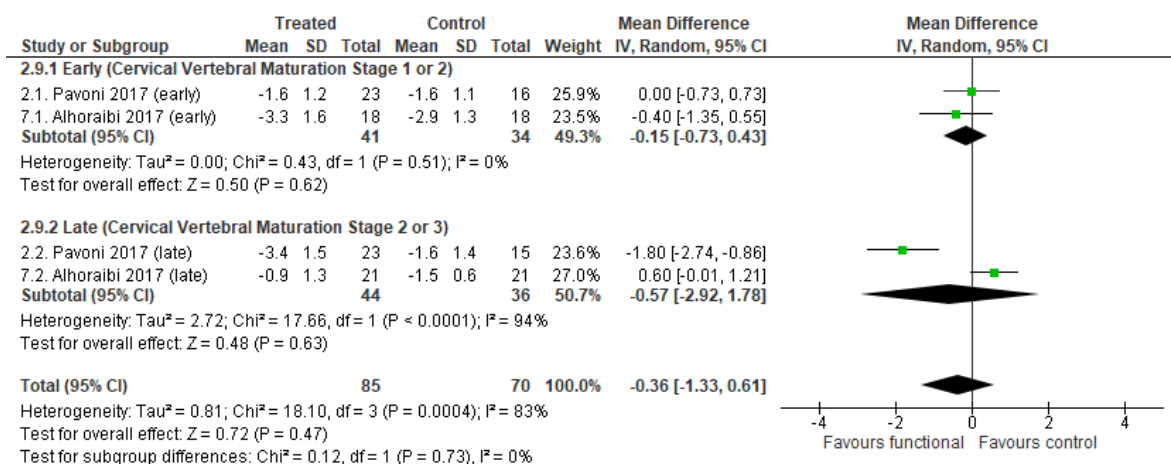


Figure 30. Subgroup analysis based on the start of the treatment; Outcome: ANB angle. Early treatments, with patients presenting with Cervical Vertebral Maturation Stage [CVMS] 1 or 2 at the first observation; late treatments, with subjects presenting with CVMS 2 or 3.

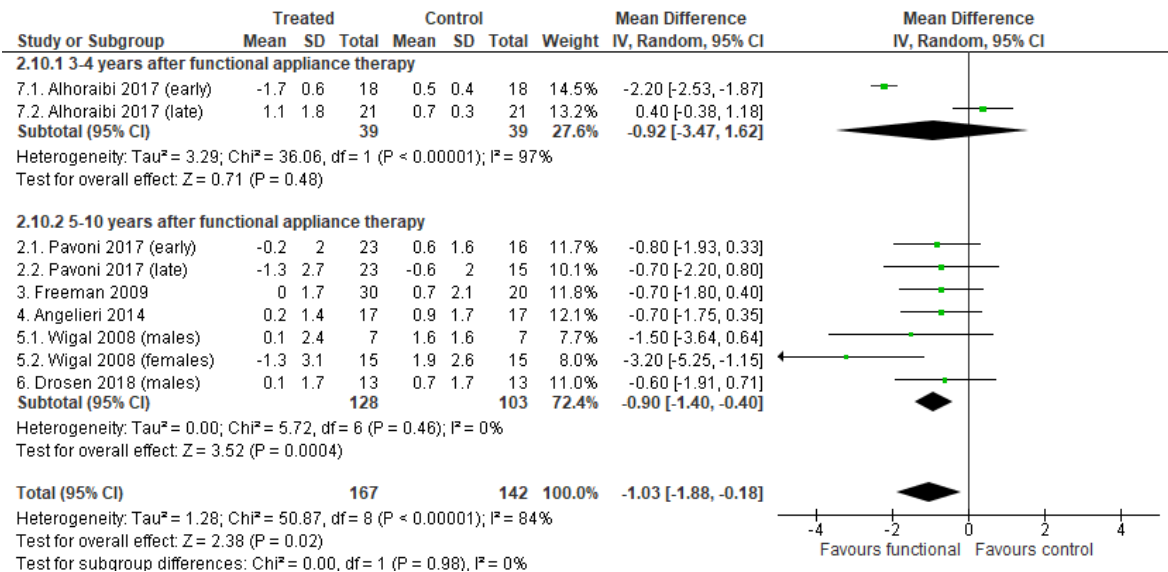


Figure 31. Subgroup analysis based on the post-retention period duration (3-4, 5-10 years after active treatment with functional appliances); Outcome: SNA angle.

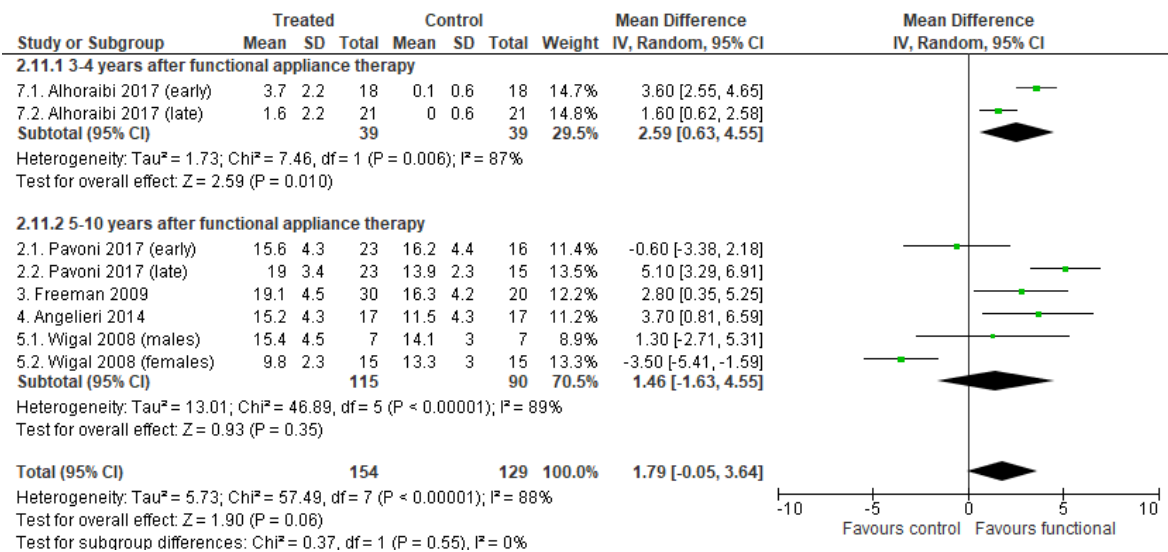


Figure 32. Subgroup analysis based on the post-retention period duration (3-4, 5-10 years after active treatment with functional appliances); Outcome: Co-Gn distance.

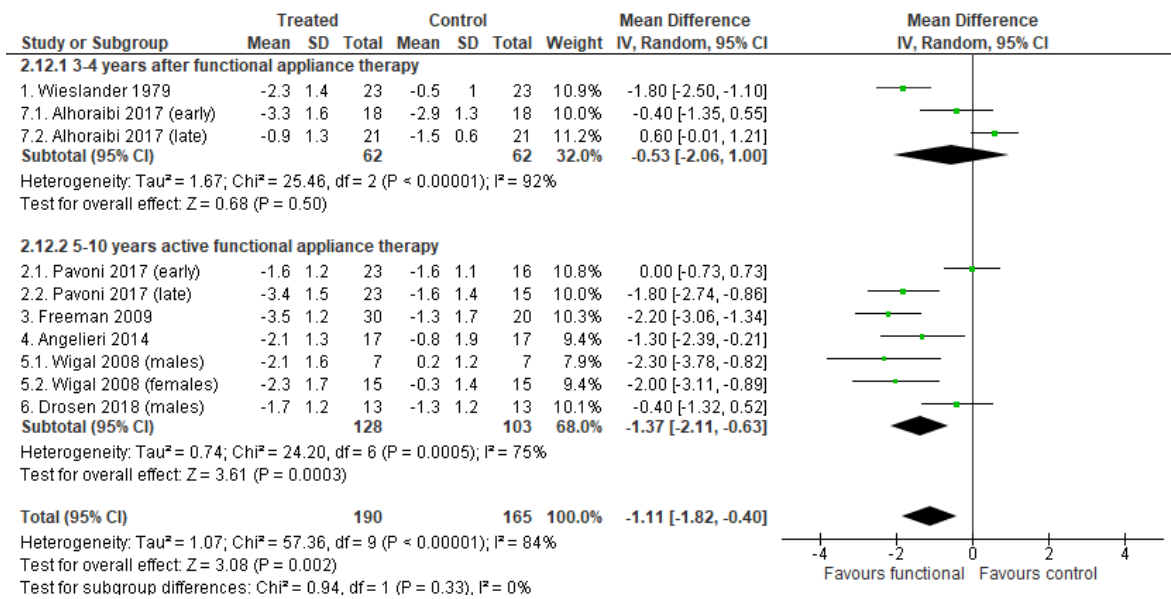


Figure 33. Subgroup analysis based on the post-retention period duration (3-4, 5-10 years after active treatment with functional appliances); Outcome: ANB angle.

Sensitivity analysis

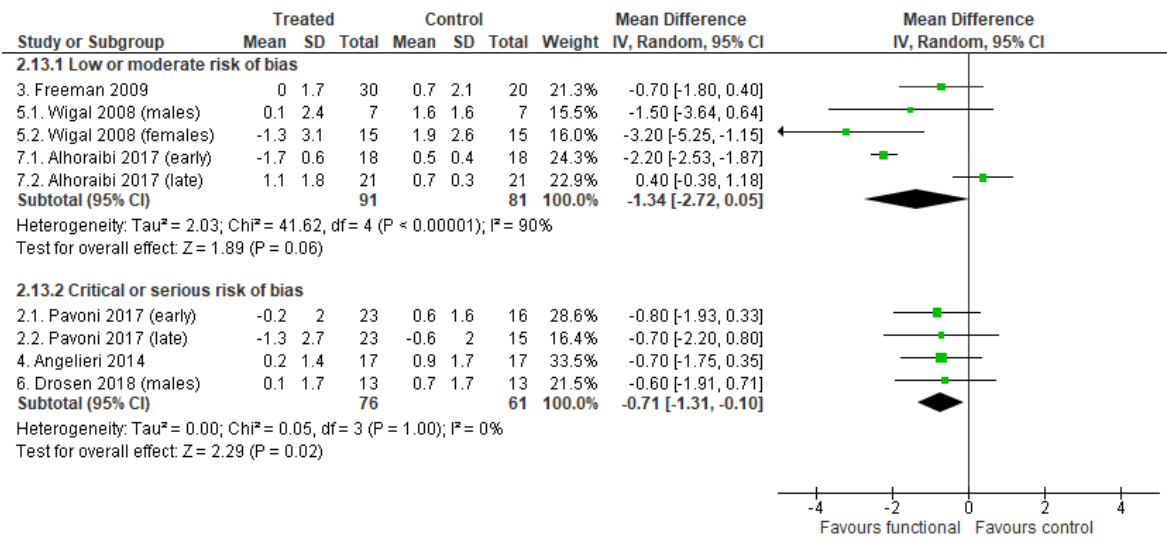


Figure 34. Sensitivity analysis based on the study quality assessment; Outcome: SNA angle.

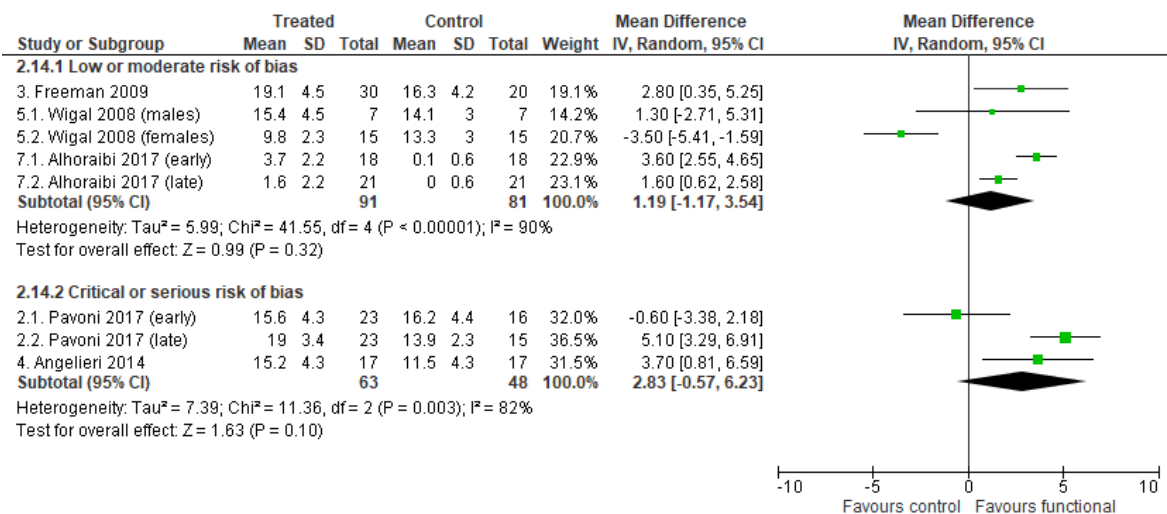


Figure 35. Sensitivity analysis based on the study quality assessment; Outcome: Co-Gn distance.

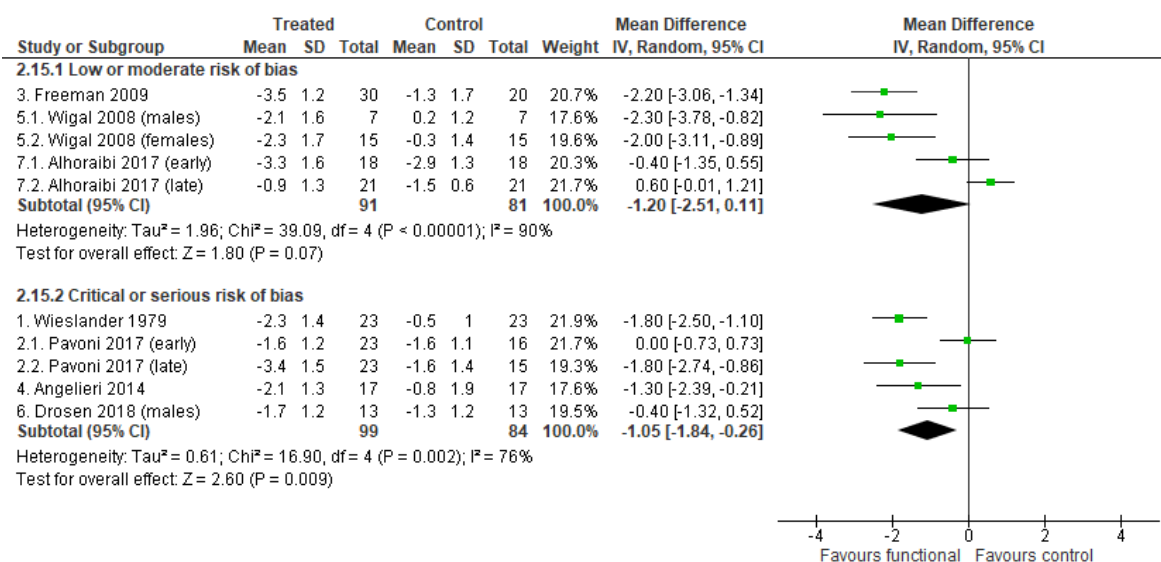


Figure 36. Sensitivity analysis based on the study quality assessment; Outcome: ANB angle.