European Journal of Orthodontics 33 (2011) 84–92
doi:10.1093/ejo/cjq033
Advance Access Publication 16 July 2010

Meta-analysis of skeletal mandibular changes during Fränkel appliance treatment

Letizia Perillo*, Rosangela Cannavale*, Fabrizia Ferro*, Lorenzo Franchi**, Caterina Masucci**, Paolo Chiodini*** and Tiziano Baccetti**
Departments of Orthodontics, *Second University of Naples, **University of Florence and ***Department of Medicine and Public Health, Second University of Naples, Italy

Correspondence to: Dr Letizia Perillo, Department of Orthodontics, Second University of Naples, Via De Crecchio, 80100 Naples, Italy. E-mail: letizia.perillo@unina2.it

SUMMARY The purpose of this study was to perform a meta-analysis of articles to verify the mandibular changes produced by the Fränkel-2 (FR-2) appliance during the treatment of growing patients with Class II malocclusions when compared with untreated growing Class II subjects.

The literature published from January 1966 to January 2009 was reviewed with search engines. A quality analysis was performed. The effects on primary end points were calculated with random-effect models. Heterogeneity was assessed using *Q* statistic and investigated using study-level meta-regression.

A total of nine articles were identified. The quality of the studies ranged from low to medium. Meta-analysis showed that the FR-2 was associated with enhancement of mandibular body length [0.4 mm/year 95 per cent confidence interval (CI) 0.182–0.618], total mandibular length (1.069 mm/year, 95 per cent CI 0.683–1.455), and mandibular ramus height (0.654 mm/year, 95 per cent CI 0.244–1.064). A consistent heterogeneity among studies was found for all the considered linear measurements.

The FR-2 appliance had a statistically significant effect on mandibular growth. Nevertheless, the heterogeneity of the FR-2 effects, the quality of studies, the differences in age, skeletal age, treatment duration, and the inconsistent initial diagnosis seem to overstate the benefits of the FR-2 appliance.

An evidence-based approach to the orthodontic outcomes of FR-2 appliance is needed, by selecting and comparing groups of children with the same cephalometric characteristics with and without treatment.

Introduction

Class II malocclusions occur in a variety of skeletal and dental configurations (Cozza *et al.*, 2006) among which the most common appears to be mandibular skeletal retrusion (McNamara, 1981; Pancherz *et al.*, 1997). A therapy aimed at enhancing mandibular growth is indicated in these patients.

Since the 1930s, a wide range of functional appliances designed to increase mandibular growth gained popularity in Europe and then throughout the rest of the world (McNamara *et al.*, 1996; McNamara and Brudon, 2001; Chen *et al.*, 2002; Cozza *et al.*, 2006). One of the most popular and well-characterized functional appliances is the functional regulator (FR-2; Fränkel, 1966, 1969a,b, 1973, 1983; Falck and Fränkel, 1989; Perillo *et al.*, 1996; Tulloch *et al.*, 1997, 1998; Johnston, 1998; Chen *et al.*, 2002). Unlike other functional appliances, the FR-2 has a mode of action based on orthopaedic principles that consider exercise and muscle training to be important factors in the normal development of osseous tissues (Fränkel, 1966, 1969a,b, 1973, 1983; Perillo *et al.*, 1996). A specific indication for FR-2 is represented by a Class II division 1 malocclusion associated with mandibular deficiency (Fränkel, 1983; Perillo *et al.*, 1996).

The FR-2 treatment approach has led to disparate outcomes in studies on humans (McNamara *et al.*, 1996; McNamara and Brudon, 2001; Chen *et al.*, 2002; Cozza *et al.*, 2006). Some authors (Reey and Eastwood, 1978; Luder, 1982; Pancherz, 1982, 2005; Birkebæk *et al.*, 1984; McNamara *et al.*, 1985, 1990; Haynes, 1986; Jakobsson and Paulin, 1990; Mamandras and Allen, 1990; Windmiller, 1993; Perillo *et al.*, 1996; Pancherz *et al.*, 1997; Tulloch *et al.*, 1997; Franchi *et al.*, 1999; Toth and McNamara, 1999; Tümer and Gültan, 1999; Baccetti *et al.*, 2000; Mills and McCulloch, 2000; De Almeida *et al.*, 2002; Basciftci *et al.*, 2003; Faltin *et al.*, 2003; Pangrazio-Kulbersh *et al.*, 2003; Cozza *et al.*, 2004) have suggested that mandibular growth can be increased, whereas others stated that mandibular length cannot be altered (Jakobsson, 1967; Vargervik and Harvold, 1985; Nelson *et al.*, 1993; Illing *et al.*, 1998; Chadwick *et al.*, 2001; Janson *et al.*, 2003; O'Brien *et al.*, 2003) with significant treatment effects restricted to dentoalveolar changes (Tulley, 1972; Robertson, 1983; McNamara *et al.*, 1985, 1990; Fränkel and Fränkel, 1989; Perillo *et al.*, 1996; Toth and McNamara, 1999; Chadwick *et al.*, 2001; McNamara and Brudon, 2001; De Almeida *et al.*, 2002; Cozza *et al.*, 2006).

Two systematic reviews (Chen *et al.*, 2002; Cozza *et al.*, 2006) have been performed on the efficacy of functional appliances on mandibular growth. Chen *et al.* (2002) found no significant differences between an untreated control group and subjects treated with functional appliances (FR-2 included) with the exception of linear measurements related to articulare (Ar) point. Moreover, the control and treated group did not appear to differ in the angulation of the lower incisors. The more recent systematic review, on the other hand, reported significant supplementary elongation in total mandibular length, induced by functional appliances. The FR-2 appliance, however, showed one of the lowest coefficients of efficiency when compared with other functional appliances (Herbst, twin-block).

Both systematic reviews analysed a wide variety of appliances with different modes of action (mechanical, orthopaedic, etc.) and did not focus specifically on the effects of a true functional appliance (the FR-2). Neither of the two systematic reviews performed a meta-analysis of treatment outcomes; meta-analysis investigates heterogeneity and provides a summary measure of study results.

The aim of the present investigation was, therefore, to perform a systematic review and a meta-analysis of FR-2 studies in order to assess the dental or skeletal changes induced by this appliance in growing patients with Class II malocclusions compared with changes in untreated Class II growing subjects. Moreover, because in the previous systematic reviews, only very few randomized clinical trials (RCTs) were found, the present search also included controlled clinical trials and retrospective investigations to determine weak methodologies used in those studies.

Materials and methods

Search strategy

A systematic review of the literature was developed to identify articles that address the effects of FR-2 appliance on mandibular growth. The literature search was carried out using PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Scirus, Lilacs, Embase, and Scopus. The following search terms were used: 'Class II malocclusion' and 'Fränkel appliance' or 'FR-2 appliance', alternatively, and 'Fränkel II' and 'Frankel-2' alone.

To improve the search, the 'related articles' tool was used in the PubMed search and references of retrieved studies were checked by a research librarian.

Inclusion criteria

Studies were selected if they satisfied all the following inclusion criteria: publication date from January 1966 to January 2009; original studies based on humans; prospective and retrospective longitudinal studies, RCTs, systematic reviews, meta-analyses; studies conducted on growing patients with Class II malocclusions; concurrent untreated growing subjects, historical controls with Class II malocclusions; studies with cephalometric measurements; no restrictions were set for language.

Data collection and quality analysis

A full text version was obtained for the studies considered adequate on the basis of the abstract and for those where the abstract was inconclusive. Data were collected on the following items for the retrieved studies: year of publication, origin, study design, materials (study sample, control sample), age at the start of treatment, methods of measurement, appliance wear, treatment/observation duration, age and gender matching, and reported outcomes.

A quality evaluation of the methodological soundness of each article was performed according to a modified version of the method described by Jadad *et al.* (1996). The following parameters were evaluated: prospective design, randomization, prior estimate of sample size, method error analysis, blinding in measurements, and adequate statistics. Quality score was calculated by compounding previous items. Scores ranged from 0 to 6 with higher scores indicating a better methodologic quality.

The methods and results sections of each article were read and scored by two independent blind readers (LP, RC). The evaluators discussed their findings, and when disagreement occurred, it was resolved through further discussion and re-reading.

Analysis of reported outcomes

To provide a quantitative appraisal of skeletal and dental modifications in Class II patients treated with the FR-2 appliance when compared with untreated Class II controls, the following data were evaluated for each retrieved study: total mandibular length (measured as Co–Gn or Co–Pg or Ar–Gn or Ar–Pg), mandibular body length (measured as Go–Gn or Go–Me or Go–Pg), and ramus height (Ar–Go or Co–Go). Mandibular changes were annualized to accommodate variations in treatment duration thereby allowing comparison with data of other investigations.

Statistically significant differences between the cephalometric evaluations of treated and untreated subjects were obtained.

Statistical analysis

From each study, the mean difference and standard deviation (SD) of the difference of each variable of interest were extracted. Only in one study (Chadwick *et al.*, 2001) were SDs not reported and were estimated on the basis of reported confidence intervals (CIs). In the study of McNamara *et al.* (1985), data reported for very young and young subjects were considered separately.

Meta-analysis was performed according to a modified version of the method proposed by Curtin *et al.* (2002). For each outcome, the weighted mean difference, assessed by means of inverse variance method (fixed-effects model), was calculated separately for each measurement performed. Heterogeneity was assessed using *Q* statistic (Deeks and Bradburn, 2001) in studies that used the same cephalometric measurements, among different cephalometric measurements, and for all studies (Curtin *et al.*, 2002); a *P* value of *Q* statistic lower than 0.10 was considered significant (Deeks and Bradburn, 2001). In the absence of substantial heterogeneity, the computation of the overall combined effect was based on the fixed-effect model, while if there was evidence of heterogeneity, outcomes were pooled using the random-effect model of DerSimonian and Laird (Deeks and Bradburn, 2001).

Explanatory analysis of associations between quality score and the effect of the FR-2 on cephalometric measurements was investigated using study-level meta-regression (Van Houwelingen *et al.*, 2002). Meta-regression is a model that relates the treatment effect to study-level covariates while assuming additivity of within- and between-study components of variance. Restricted maximum likelihood estimators were used (Thompson and Sharp, 1999). Permutation testing (using 1000 Monte Carlo simulations, Stata Corp., College Station, Texas, USA) was used to calculate *P* values and to reduce the chance of spurious false-positive findings (Higgins and Thompson, 2004).

Analysis was performed using Stata, version 9.0 (Stata Corp.), and R 2.4.1 (R Foundation for Statistical Computing, Vienna, Austria). The quality of outcomes of meta-analysis (Meta-analysis of Observational Studies in Epidemiology; Stroup *et al.*, 2000) was used for evaluation of the results.

Results

The PubMed search strategy identified 97 articles: 36 were selected on the basis of the abstract information. Three other articles were selected on the basis of the references of these 36 papers, so that 39 full-text articles were finally selected for further evaluation. Thirty-two of the 39 papers were excluded as they did not meet the criteria of inclusion, while seven articles were considered eligible for inclusion in the review.

From the Scirus search, five full-text articles were selected on the basis of the abstract information. Three were excluded as they did not meet the inclusion criteria, while two were included in the review. The search in the CENTRAL gave no results. Lilacs identified 38 studies: 20 full-text articles selected on the basis of the abstract information were excluded as they did not meet the inclusion criteria. Embase located 54 studies: none of these could be used because they were double publications. Scopus found 118 studies: the chosen 15 full-text articles did not meet the inclusion criteria.

The main reasons for exclusion of the studies were Class III malocclusions, no cephalometric analysis, expert opinion, case reports and double publications, other functional appliances, no data on linear mandibular measurements, adult patients, no control groups, and no quantitative data.

The review process identified a total of nine studies as reported in Figure 1.

Characteristics of the included studies (McNamara *et al.*, 1985; Haynes, 1986; Falck and Fränkel, 1989; Nelson *et al.*, 1993; Perillo *et al.*, 1996; Toth and McNamara, 1999;

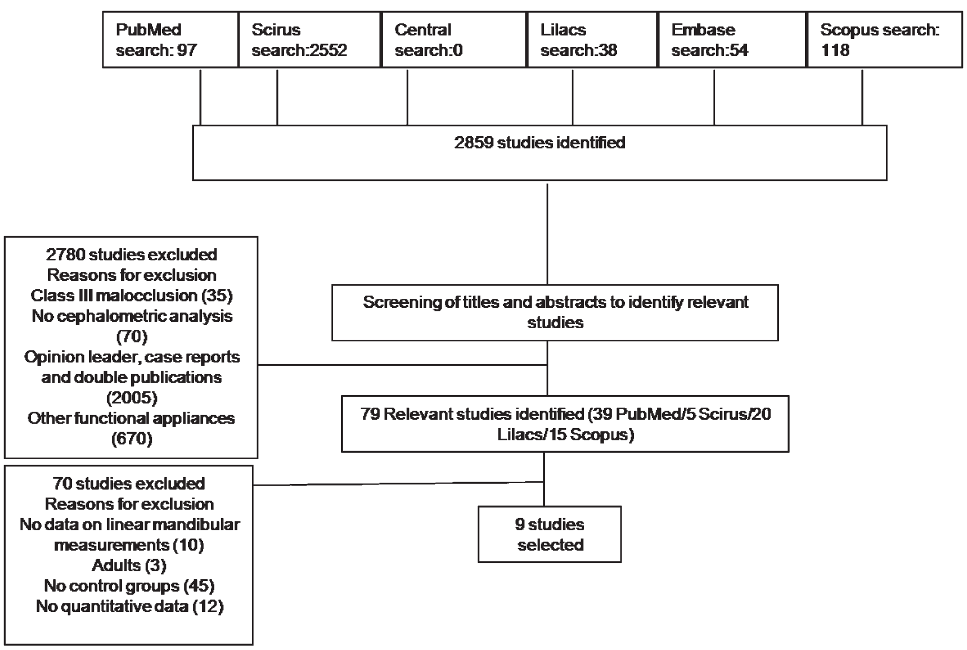

Figure 1 Flow chart of the selection process of studies on mandibular linear changes during functional regulator appliance treatment.

Chadwick *et al.*, 2001; De Almeida *et al.*, 2002; Janson *et al.*, 2003) are reported in Table 1.

The total number of patients treated with the FR-2 appliance in the nine studies was 366 and 320 for the controls.

Quality analysis of the studies

The quality of the studies ranged from low to medium (Table 1).

Seven studies (McNamara *et al.*, 1985; Falck and Fränkel, 1989; Perillo *et al.*, 1996; Toth and McNamara, 1999; Chadwick *et al.*, 2001; De Almeida *et al.*, 2002; Janson *et al.*, 2003) were retrospective clinical trials, while only two were prospective clinical trials and reported previous estimates of sample size (Haynes, 1986; Nelson *et al.*, 1993). Randomization was used in only one study (Nelson *et al.*, 1993). Two studies (McNamara *et al.*, 1985; Haynes, 1986) did not include a method error analysis, and only one (Chadwick *et al.*, 2001) used blinding in measurements. Two studies (Chadwick *et al.*, 2001; Janson *et al.*, 2003) used appropriate statistical methods, while seven (McNamara *et al.*, 1985; Haynes, 1986; Falck and Fränkel, 1989; Nelson *et al.*, 1993; Perillo *et al.*, 1996; Toth and McNamara, 1999; De Almeida *et al.*, 2002) applied parametric tests in samples that were not tested for normality.

Quantitative analysis of mandibular changes

Changes in mandibular body length. Eight studies (McNamara *et al.*, 1985; Haynes, 1986; Falck and Fränkel, 1989; Nelson *et al.*, 1993; Perillo *et al.*, 1996; Toth and McNamara, 1999; De Almeida *et al.*, 2002; Janson *et al.*, 2003) evaluated changes in mandibular dimension (Table 2 and Figure 2) using the following cephalometric measurements: Go–Pg, Go–Me, and Go–Gn. Significant heterogeneity of changes in mandibular body length was found among different cephalometric measurements (P = 0.03) and for all studies but not within studies that used the same cephalometric measurements (Table 3). Therefore, a random-effect model was used to estimate the overall effect. The FR-2 was associated with significant enhancement of mandibular body length [0.400 mm/year, 95 per cent confidence interval (CI) 0.182–0.618; Figure 2] compared with untreated subjects.

Changes in mandibular total length. Nine studies (McNamara *et al.*, 1985; Haynes, 1986; Falck and Fränkel, 1989; Nelson *et al.*, 1993; Perillo *et al.*, 1996; Toth and McNamara, 1999; Chadwick *et al.*, 2001; De Almeida *et al.*, 2002; Janson *et al.*, 2003) considered this outcome (Table 2 and Figure 2) as indicated by the following cephalometric measurements: Co–Gn, Ar–Pg, Ar–B, Ar–M, Co–Pg, and Ar–Gn.

Significant heterogeneity of changes in mandibular total length was found within and among different cephalometric measurements (P = 0.021) and for all studies (Table 3). Thus, to estimate the overall effect, a random-effect model was used. FR-2 was associated with significant enhancement of mandibular total length (1.069 mm/year, 95 per cent CI 0.683–1.455; Figure 2) compared with untreated subjects.

Changes in mandibular ramus height. Nine studies (McNamara *et al.*, 1985; Haynes, 1986; Falck and Fränkel, 1989; Nelson *et al.*, 1993; Perillo *et al.*, 1996; Toth and McNamara, 1999; Chadwick *et al.*, 2001; De Almeida *et al.*, 2002; Janson *et al.*, 2003) analysed this outcome (Table 2 and Figure 2) as indicated by the following cephalometric measurements: Co–Go and Ar–Go.

Significant heterogeneity of mandibular ramus height was found within studies that used Co–Go measurement but not within those that used Ar–Go. Significant heterogeneity of changes in mandibular ramus height was found between different cephalometric measurements (P = 0.012) and for all studies (Table 3). Therefore, a random-effect model was used to estimate the overall effect. FR-2 was associated with a significant enhancement of mandibular ramus height (0.654 mm/year, 95 per cent CI 0.244–1.064; Figure 2) compared with untreated subjects.

Association of quality score with the FR-2 effect. Despite the relevant heterogeneity of the FR-2 effect among studies, an exploratory analysis of associations between quality score and FR-2 effect was made. A significant negative association (Figure 3) was found between the effect of the FR-2 and quality score for changes in mandibular total length (P = 0.047) and mandibular ramus height (P = 0.005) but not for mandibular body length (P = 0.087).

Discussion

The aim of the present investigation was to perform a systematic review and meta-analysis of studies on the mandibular skeletal effects of the FR-2 appliance in growing patients with a Class II malocclusion versus changes occurring in untreated Class II growing subjects. More specifically, the present study aimed to determine whether the FR-2 appliance had an impact on the dimensions of the mandible in treated patients versus untreated controls. While this impact was statistically significant, it can be considered to have a modest clinical effect. The average Class II malocclusion requires molar correction of approximately 4 to 6 mm (Johnston, 1986). Thus, treatment with an appliance such as the FR-2 that produces approximately 1 mm of supplementary mandibular growth per year constitutes a partial contribution to the expected Class II correction. The mandibular change is also less than the average growth deficiency in mandibular length during the circumpubertal period in Class II subjects when compared with those with a normal occlusion, which is about 3 mm (Stahl *et al.*, 2008).

Table 1 Summarized data of the nine retrieved studies (M, male; F, female).

Author	Origin	Number of patients treated with Fränkel-2	Type of selection of Fränkel patients	Initial mean age (years/months)	Appliance wear	Mean period of treatment (months)	Number of untreated controls	Type of selection of untreated controls	Initial mean age (years/months)	Mean observation period (months)	Quality score
McNamara *et al.* (1985)	USA	51 (20M, 31F) 49 (23M, 26F)	Private practices	8.8 11.6	Not specified	23 25	36 (17M, 19F) 21 (8M, 13F)	University of Michigan, Elementary and Secondary Growth Study (UMESSGS)*	8.4 11	26 22	0
Haynes (1986)	UK	29	National Health Service	9.6 ± 0.8	12 h/day	36.5	29	National Health Service who would not accept FR treatment**	9.6 ± 0.8	36.8	2
Falck and Fränkel (1989)	Germany	60 (28M, 32F)	Department of Orthodontics	8/0 ± 12	Not specified	14.7	50 (33M, 17F)	Department of Orthodontics	7/11 ± 15	14.3	1
Nelson *et al.* (1993)	New Zealand	13 (7M, 6F)	School children referred to the Department of Orthodontics	11.7 ± 0.68	Minimum 14 h/day	18	17 (11M, 6F)	School children referred to the Department of Orthodontics	11.5 ± 0.93	18	4
Perillo *et al.* (1996)	Italy	14 (6M, 8F)	University of Naples and private practitioner	8.7	At least 18 h/day	29	14 (7M, 7F)	University of Naples**	8.7	29	1
Toth and McNamara (1999)	USA	40 (21M, 19F)	Private practices and Graduate Orthodontic Clinic	10/2	24 h/day	24	40	UMESSGS*	9/11	23	1
de Almeida *et al.* (2002)	Brazil	22 (11M, 11F)	Orthodontic graduate programme	9	24 h/day	17	22 (11M, 11F)	Files of the longitudinal growth study of the University of São Paulo	8/7	13	3
Chadwick *et al.* (2001)	UK	70 (33M, 37F)	Patients seen at a single centre by a single operator	11/6	Not specified	19.92	68 (31M, 37F)	Patients declining FR-2 treatment**	10/10	22.32	1
Janson *et al.* (2003)	Brazil	18 (10M, 8F)	Orthodontic Department graduate clinic	9/3	Not specified	28	23 (13M, 10F)	Files of the longitudinal growth study at the University of São Paulo**	9/3	28	2

*Matched for age. **Matched for age and gender.

Table 2 Comparison of annualized mandibular measurements (millimeter).

Author	Mandibular body length			Total mandibular length			Mandibular ramus length		
	Cephalometric variable	Annualized mandibular growth (treated)	Annualized mandibular growth (controls)	Cephalometric variable	Annualized mandibular growth (treated)	Annualized mandibular growth (controls)	Cephalometric variable	Annualized mandibular growth (treated)	Annualized mandibular growth (controls)
McNamara *et al.* (1985) younger	Go–Pg	1.75	1.69	Co–Gn	3.2	1.1	Co–Go	1.95	0.95
McNamara *et al.* (1985) older	Go–Pg	1.75	1.59	Co–Gn	4	1.9	Co–Go	2.9	1.35
Haynes (1986)	Go–M	1.96	1.48	Ar–Pg	2.9	2.18	Ar –Go	1.44	1.29
				Ar–B	2.64	1.62			
				Ar–M	2.89	2.33			
Falck and Fränkel (1989)	Go–Pg	2.00	1.71	Co–Pg	3.4	1.76	Co–Go	2.3	1.14
				Ar–Pg	3.33	1.82	Ar–Go	2.27	1.02
Nelson *et al.* (1993)	Go–Pg	1.65	1.02	Ar–Pg	3.13	2.21	Ar–Go	2.14	1.96
				Co–Pg	3.4	2.9	Co–Go	2.7	2.8
Perillo *et al.* (1996)	Go–Pg	2.5	1.1	Ar–Gn	3.3	1.8	Ar–Go	1.7	1.3
Toth and McNamara (1999)	Go–Pg	1.72	1.6	Ar–Gn	2.1	0.9	Co–Go	2.175	1.125
				Co–Gn	3.45	2.025			
Chadwick *et al.* (2001)	—	—	—	Co–Gn	2.5	1.9	—	—	—
de Almeida *et al.*(2002)	Go–Gn	1.56	0.7	Ar–Gn	2.8	1.9	Ar–Go	1.48	1.38
				Co–Gn	3.6	2.77			
Janson *et al.* (2003)	Go–Gn	1.9	1.25	Co–Gn	2.4	2.16	Co–Go	1.24	1.35

This investigation also showed the limitations of the published papers: they were heterogeneous, mostly non-randomized and retrospective, of low to medium quality, and almost all with a poorly defined skeletal diagnosis.

Heterogeneity of the effects

A consistent heterogeneity among studies was found for all the considered outcomes (Table 3). The heterogeneity was assessed also within studies that used analogous cephalometric measurements. Several considerations can be postulated to explain this heterogeneity.

Differential diagnosis. Almost all the studies identified in this systematic review lacked initial differential diagnosis in order to identify Class II malocclusions associated with mandibular deficiency. The selection criteria were generic Class II malocclusion in five papers (McNamara *et al.*, 1985; Falck and Fränkel, 1989; Nelson *et al.*, 1993; Toth and McNamara, 1999; De Almeida *et al.*, 2002), Class II division 1 malocclusions in two papers (Haynes, 1986; Janson *et al.*, 2003), an overjet greater than 6 mm in one study (Chadwick *et al.*, 2001), and mandibular deficiency associated with an aberrant muscular pattern in one paper (Perillo *et al.*, 1996).

Cephalometric measurements. Part of the heterogeneity in the results can be explained by the localization of different cephalometric landmarks in different studies, which is one of the major confounding problems in cephalometrics. In this systematic review, both condylion (Co) and Ar were accepted as the posterior end point in measuring mandibular total length and ramus height.

It is reported that measurements with Ar as an end point, such as Ar–Pg or Ar–Gn, might give significant values for supplementary mandibular growth, without a corresponding increase in Co–Pg and Co–Gn, as Co is the most accurate end point landmark (Nelson *et al.*, 1993). This meta-analysis showed significant changes for mandibular ramus height and total length using both Co and Ar points.

Age, skeletal maturation, and treatment variation. In two studies (McNamara *et al.*, 1985; Toth and McNamara, 1999), treated and control subjects were matched for age, in four papers for both age and gender (Haynes, 1986; Perillo *et al.*, 1996; Chadwick *et al.*, 2001; Janson *et al.*, 2003), while in three investigations the two groups were not matched.

The mean age at the start of treatment ranged from 8.0 to 11.7 years (Table 1). Although there was some overlap in the ages, these differences resulted in some problems when comparing studies.

Furthermore, growth does not occur at a constant rate, especially in young children. Even children of the same chronological age might not have equivalent skeletal

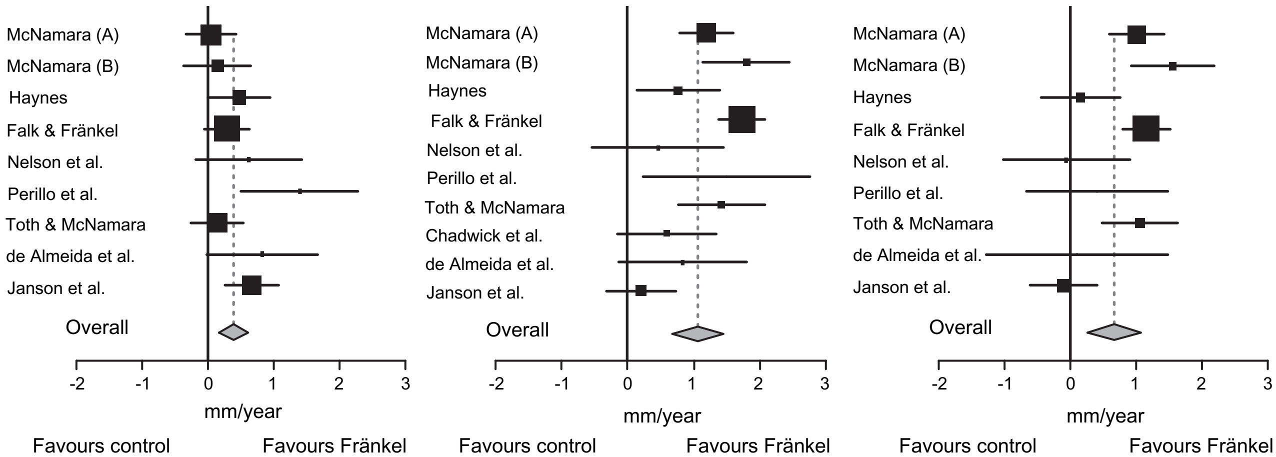

Figure 2 Meta-analysis results. Mean change in mandibular body length, mandibular total length, and mandibular ramus height with the functional regulator-2 appliance treatment in Class II malocclusion growing patients versus untreated Class II growing subjects. The overall effect represents the pooled estimate of mean change. The size of each square is inversely proportional to the variance of the study estimate. (A) Very young and (B) young subjects from McNamara *et al.* (1985).

Table 3 Meta-analyses of selected studies.

		Number of studies	*P* value for heterogeneity*	Pooled estimate (mm/year)	95% confidence interval (mm/year)
Mandibular body length					
Go–Gn	Fixed effect (FE)	2	0.731	0.699	0.336, 1.062
Go–M	FE	1	—	0.479	−0.010, 0.968
Go–Pg	FE	6	0.119	0.251	0.063, 0.440
All studies	Random effect (RE)	9	0.088	0.400	0.182, 0.618
Mandibular total length					
Ar–Gn	FE	1	—	1.500	0.176, 2.824
Ar–Pg	FE	1	—	0.761	0.117, 1.405
Co–Gn	FE	6	0.003	1.016	0.775, 1.257
Co–Pg	FE	2	0.018	1.593	1.265, 1.922
All studies	RE	10	<0.001	1.069	0.683, 1.455
Ramus height					
Ar–Go	FE	3	0.914	0.197	−0.297, 0.690
Co–Go	FE	6	<0.001	0.881	0.677, 1.086
All studies	RE	9	<0.001	0.654	0.244, 1.064

*From *Q* test; a value <0.10 was considered significant.

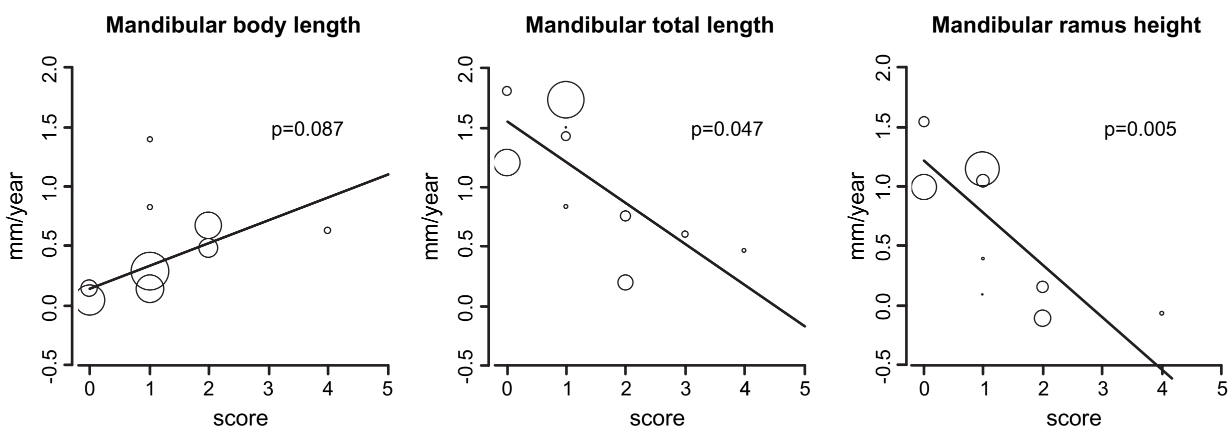

Figure 3 Meta-regression results. Association of quality score with mean change in mandibular body length, mandibular total length, and mandibular ramus height. The size of each square is inversely proportional to the variance of the study estimate.

maturity or growth potential (Baccetti *et al.*, 2005). Therefore, when studies such as those included in this review do not have skeletal maturity as a common factor, it is difficult to produce a conclusive statement regarding the amount of growth modification that might occur (Chen *et al.*, 2002). The subjects who underwent treatment at a maturational stage that was presumably pubertal (age at start of treatment 11.6 years; McNamara *et al.*, 1985) showed clinically relevant outcomes. Treatment duration differed widely among the studies, ranging from 14.7 to 36.5 months. Individual changes were annualized (i.e. expressed as change per year) to accommodate variation in intervals between radiographs (Table 1) and thus allow comparison with the data of other investigations. However, if change does not occur uniformly during the entire treatment time, this process can skew the analysis of treatment outcomes (Chen *et al.*, 2002).

Meta-analysis limitations

This meta-analysis may have some limitations. First, the inclusion of published data alone may overestimate the treatment effects. This problem can be overcome using a funnel plot, which is a graphical method to detect publication bias (Lau *et al.*, 2006). However, this method was not employed because simulation studies of funnel plots have found that bias may be incorrectly inferred if studies are heterogeneous (Schwartzer *et al.*, 2002; Terrin *et al.*, 2003).

Second, the internal validity of a meta-analysis can only be as good as the quality of the studies reviewed. Nine studies were identified by the review process with 366 patients treated with the FR-2 and 320 controls. These studies were judged to be of low/medium quality. The reason for a low/medium-quality score is that some studies had some methodological limitations (method error not reported, lack of blinding in measurement, etc.). Only one study was an RCT. In the meta-regression, it was found that low-quality studies reported higher FR-2 effects than medium-quality studies. Nevertheless, quality is only one component of heterogeneity and has an uncertain role in explaining any treatment-effect differences. Thus, quality-related differences in the treatment effect should be treated as hypothesis-generating observations.

Conclusions

The findings of the present study were as follows:

1. The FR-2 appliance had a statistically significant effect on mandibular growth. Specifically, it appeared to have an effect on total mandibular length with a low-to-moderate clinical impact.
2. The heterogeneity of the FR-2 effects, the quality of studies, the differences in age, skeletal age, treatment duration, and the inconsistent initial diagnosis seem to overstate the benefits of the FR-2 appliance.
3. This investigation also serves to highlight the limitations of the reviewed papers on FR-2 therapy. This information can be used proactively as a platform to achieve more methodologically sound investigations.

References

Baccetti T, Franchi L, Toth L R, McNamara J A Jr 2000 Treatment timing for Twin-block therapy. American Journal Orthodontics and Dentofacial Orthopedics 118: 159–170

Baccetti T, Franchi L, McNamara J A Jr 2005 The cervical vertebral maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedics. Seminars in Orthodontics 11: 119–129

Basciftci F A, Uysal T U, Büyükerkmen A, Sari Z 2003 The effects of activator treatment on the craniofacial structures of Class II division 1 patients. European Journal of Orthodontics 25: 87–93

Birkebæk L, Melsen B, Terp S 1984 A laminographic study of alterations in the temporo-mandibular joint following activator treatment. European Journal of Orthodontics 6: 257–266

Chadwick S M, Aird J C, Taylor P J S, Bearn D R 2001 Functional regulator treatment of Class II division 1 malocclusions. European Journal of Orthodontics 23: 495–505

Chen J Y, Will L A, Niederman R 2002 Analysis of efficacy of functional appliances on mandibular growth. American Journal Orthodontics and Dentofacial Orthopedics 122: 470–476

Cozza P, De Toffol L, Colagrossi S 2004 Dentoskeletal effects and facial profile changes during activator therapy. European Journal of Orthodontics 26: 293–302

Cozza P, Baccetti T, Franchi L, De Toffol L, McNamara J A Jr 2006 Mandibular changes produced by functional appliances in Class II malocclusion: a systematic review. American Journal Orthodontics and Dentofacial Orthopedics 129: 599.e1–599.e12

Curtin F, Altman D G, Elbourne D 2002 Meta-analysis combining parallel and cross-over clinical trials. I: continuous outcomes. Statistics in Medicine 21: 2131–2144

De Almeida R M, Castanha Henriques J F, Ursi W 2002 Comparative study of the Fränkel (FR-2) and bionator appliances in the treatment of Class II malocclusion. American Journal Orthodontics and Dentofacial Orthopedics 121: 458–466

Deeks J J A D, Bradburn M J 2001 Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger MD-S G, Altman D G (eds). Systematic reviews in health care. BMJ Publishing, London, pp. 285–312

Falck F, Fränkel R 1989 Clinical relevance of step-by-step mandibular advancement in the treatment of mandibular retrusion using the Fränkel appliance. American Journal Orthodontics and Dentofacial Orthopedics 96: 333–341

Faltin K Jr, Faltin R M, Baccetti T, Franchi L, Ghiozzi B, McNamara J A Jr 2003 Long-term effectiveness and treatment timing for bionator therapy. Angle Orthodontist 73: 221–230

Franchi L, Baccetti T, McNamara J A Jr 1999 Treatment and posttreatment effects of acrylic splint Herbst appliance therapy. American Journal Orthodontics and Dentofacial Orthopedics 115: 429–438

Fränkel R 1966 The theoretical concept underlying the treatment with function correctors. Transactions of the European Orthodontic Society pp. 233–254

Fränkel R 1969a The functional matrix and its practical importance in orthodontics. Transactions of the European Orthodontic Society pp. 207–218

Fränkel R 1969b The treatment of Class II, division 1 malocclusion with functional correctors. American Journal of Orthodontics 55: 265–275

Fränkel R 1973 The artificial translation of the mandible by function regulators. In: Cook J T (ed.). Transactions of the Third International Orthodontic Congress. C V Mosby, St Louis, pp. 310–323.

Fränkel R 1983 Biomechanical aspects of the form/function relationship in craniofacial morphogenesis: a clinician's approach. In: McNamara J A, Ribbens K A, Howe R E (eds). Clinical alteration of the growing face. Monograph No.14. Craniofacial growth series, center for human growth and development, University of Michigan, Ann Arbor, pp. 107–130

Fränkel R, Fränkel C 1989 Orofacial orthopedics with the function regulator. S Karger, Basel

Haynes S 1986 A cephalometric study of mandibular changes in modified function regulator (Fränkel) treatment. American Journal Orthodontics 88: 308–320

Higgins J P T, Thompson S G 2004 Controlling the risk of spurious findings from meta-regression. Statistics in Medicine 23: 1663–1682

Illing H M, Morris D O, Lee R T 1998 A prospective evaluation of Bass, Bionator and Twin Block appliances. Part I—the hard tissues. European Journal of Orthodontics 20: 501–516

Jadad A R, *et al.* 1996 Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 272: 125–128

Jakobsson S 1967 Cephalometric evaluation of treatment effect on Class II, division 1 malocclusion. American Journal of Orthodontics 53: 446–456

Jakobsson S O, Paulin G 1990 The influence of activator on skeletal growth in Angle Class II: 1 case. A roentgenocephalometric study. European Journal of Orthodontics 12: 174–184

Janson G R P, Toruno J L A, Martins D R, Henriques J F C, de Freitas M R 2003 Class II treatment effects of the Fränkel appliance. European Journal of Orthodontics 25: 301–309

Johnston L E Jr 1986 A comparative analysis of Class II treatment. In: McNamara J A Jr, Carlson D S, Vig P S, Ribbens K A (eds). Science and clinical judgment in orthodontics. Monograph No.18. Craniofacial growth series, center for human growth and development, University of Michigan, Ann Arbor, pp. 103–148

Johnston L E 1998 Growth and the Class II patient: rendering unto Caesar. Seminars in Orthodontics 4: 58–62

Lau J, Ioannidis J P A, Terrin N, Schmid C H, Olkin I 2006 The case of the misleading funnel plot. British Medical Journal 333: 597–600

Luder H U 1982 Skeletal profile changes related to two patterns of activator effects. American Journal of Orthodontics 81: 390–396

Mamandras A H, Allen L P 1990 Mandibular response to orthodontic treatment with the bionator appliance. American Journal Orthodontics and Dentofacial Orthopedics 97: 113–120

McNamara J A Jr 1981 Components of Class II malocclusion in children 8-10 years of age. Angle Orthodontist 51: 177–202

McNamara J A Jr, Brudon W L 2001 Orthodontics and dentofacial orthopedics. Needham Press, Ann Arbor, pp. 67–80

McNamara J A Jr, Bookstein F L, Shaughnessy T G 1985 Skeletal and dental changes following functional regulator therapy on Class II patients. American Journal of Orthodontics 88: 91–110

McNamara J A Jr, Howe R P, Dischinger T G 1990 A comparison of the Herbst and Fränkel appliances in the treatment of Class II malocclusion. American Journal Orthodontics and Dentofacial Orthopedics 98: 134–144

McNamara J A Jr, Peterson J E Jr, Alexander R G 1996 Three-dimensional diagnosis and management of Class II malocclusion in the mixed dentition. Seminars in Orthodontics 2: 114–137

Mills C M, McCulloch K J 2000 Posttreatment changes after successful correction of Class II malocclusions with the Twin-block appliance. American Journal Orthodontics and Dentofacial Orthopedics 118: 24–33

Nelson C, Harkness M, Herbison P 1993 Mandibular changes during functional appliance treatment. American Journal Orthodontics and Dentofacial Orthopedics 104: 153–161

O'Brien K *et al.* 2003 Effectiveness of early orthodontic treatment with the Twin-block appliance: a multicenter, randomized, controlled trial. Part I: dental and skeletal effects. American Journal Orthodontics and Dentofacial Orthopedics 124: 234–243

Pancherz H 1982 The mechanism of Class II correction in Herbst appliance treatment. A cephalometric investigation. American Journal of Orthodontics 82: 104–113

Pancherz H 2005 The Herbst appliance: a paradigm change in Class II treatment. World Journal of Orthodontics 6: 8–10

Pancherz H, Zieber K, Hoyer B 1997 Cephalometric characteristics of Class II division 1 and Class II division 2 malocclusions: a comparative study in children. Angle Orthodontist 67: 111–120

Pangrazio-Kulbersh V, Berger J L, Chermak D S, Kaczynski R, Simon E S, Haerian A 2003 Treatment effects of the mandibular anterior repositioning appliance on patients with Class II malocclusion. American Journal Orthodontics and Dentofacial Orthopedics 123: 286–295

Perillo L, Johnston L E Jr, Ferro A 1996 Permanence of skeletal changes after function regulator (FR-2) treatment of patients with retrusive Class II malocclusions. American Journal Orthodontics and Dentofacial Orthopedics 109: 132–139

Reey R W, Eastwood A 1978 The passive activator: case selection, treatment response, and corrective mechanics. American Journal of Orthodontics 73: 378–409

Robertson N R E 1983 An examination of treatment changes in children treated with the function regulator of Fränkel. American Journal of Orthodontics 83: 299–310

Schwartzer G, Artes G, Schumacher M 2002 Inflation of type I error rate in two statistical tests for the detection of publication bias in meta-analysis with binary outcomes. Statistics in Medicine 21: 2465–2477

Stahl F, Baccetti T, Franchi L, McNamara J A Jr 2008 Longitudinal growth changes in untreated subjects with Class II division 1 malocclusion. American Journal Orthodontics and Dentofacial Orthopedics 134: 125–137

Stroup D F *et al.* 2000 MSc for the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group. Journal of the American Medical Association 283: 2008–2012

Terrin N, Schmid C H, Lau J, Olkin I 2003 Adjusting for publication bias in the presence of heterogeneity. Statistics in Medicine 22: 2113–2126

Thompson S G, Sharp S J 1999 Explaining heterogeneity in meta-analysis: a comparison of methods. Statistics in Medicine 18: 2693–2708

Toth L R, McNamara J A Jr 1999 Treatment effects produced by the Twin-block appliance and the FR-2 appliance of Fränkel compared with an untreated Class II sample. American Journal Orthodontics and Dentofacial Orthopedics 116: 597–609

Tulley W J 1972 The scope and limitations of treatment with the activator. American Journal of Orthodontics 61: 562–577

Tulloch J F C, Proffit W R, Phillips C 1997 Influences on the outcome of early treatment for Class II malocclusion. American Journal Orthodontics and Dentofacial Orthopedics 111: 533–542

Tulloch J F C, Phillips C, Proffit W R 1998 Benefit of early Class II treatment: progress report of a two-phase randomized clinical trial. American Journal Orthodontics and Dentofacial Orthopedics 113: 63–72

Tümer N, Gültan S 1999 Comparison of the effects of monoblock and twin-block appliances on the skeletal and dentoalveolar structures. American Journal Orthodontics and Dentofacial Orthopedics 116: 460–468

Van Houwelingen H C, Arends L R, Stijnen T 2002 Advanced methods in meta-analysis: multivariate approach and meta-regression. Statistics in Medicine 21: 589–624

Vargervik K, Harvold E P 1985 Response to activator treatment in Class II malocclusions. American Journal of Orthodontics 88: 242–251

Windmiller E C 1993 The acrylic-splint Herbst appliance: a cephalometric evaluation. American Journal Orthodontics and Dentofacial Orthopedics 104: 73–84