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Original article

The evidence from systematic reviews and meta-analyses published in orthodontic literature. Where do we stand?

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Summary

Aim: To analyse meta-analyses included in systematic reviews (SRs) published in leading orthodontic journals and the Cochrane Database of Systematic Reviews (CDSR) focusing on orthodontic literature and to assess the quality of the existing evidence.

Materials and methods: Electronic searching was undertaken to identify SRs published in five major orthodontic journals and the CDSR between January 2000 and June 2014. Quality assessment of the overall body of evidence from meta-analyses was conducted using the Grading of Recommendations Assessment, Development and Evaluation working group (GRADE) tool.

Results: One hundred and fifty-seven SRs were identified; meta-analysis was present in 43 of these (27.4 per cent). The highest proportion of SRs that included a meta-analysis was found in Orthodontics and Craniofacial Research (6/13; 46.1 per cent), followed by the CDSR (12/33; 36.4 per cent) and the American Journal of Orthodontics and Dentofacial Orthopaedics (15/44; 34.1 per cent). Class II treatment was the most commonly addressed topic within SRs in orthodontics (n = 18/157; 11.5 per cent). The number of trials combined to produce a summary estimate was small for most meta-analyses with a median of 4 (range: 2–52). Only 21 per cent (n = 9) of included meta-analyses were considered to have a high/moderate quality of evidence according to GRADE, while the majority were of low or very low quality (n = 34; 79.0 per cent).

Conclusions: Overall, approximately one quarter of orthodontic SRs included quantitative synthesis, with a median of four trials per meta-analysis. The overall quality of evidence from the selected orthodontic SRs was predominantly low to very low indicating the relative lack of high quality of evidence from SRs to inform clinical practice guidelines.

Introduction

Systematic reviews (SRs) aim to combine the existing evidence on a question of interest using a transparent and systematic approach and have been considered the cornerstone of evidence-based clinical decision making. Unlike narrative reviews, a well-conducted SR is believed to minimize biases offering healthcare professionals the current state of evidence regarding a particular research question (1, 2). Publication of SRs in orthodontics has increased dramatically in recent years underlining the willingness of authors, reviewers, and editors to provide end users with up-to-date evidence relating to a particular question (3–5).

There is, however, inertia relating to translation of clinical study results into clinical practice. An approach, therefore, capable of assessing the quality of the evidence, both in respect of benefit and harm, while being cognizant of patient preferences leading to clear treatment recommendations is highly desirable. A number of complex methods have been proposed for evaluating and translating evidence into clinical practice; many of these have been somewhat confusing and impractical (6). The GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) initiative, however, has amalgamated the positives from other approaches emerging as an accepted tool for assessing the quality of the evidence and is consequently utilized for clinical recommendations (7).

While several studies assessing the methodological and reporting quality of SRs in oral health have been published (8, 9), there are currently no meta-epidemiological reports on the quality of the existing evidence informing orthodontic decisions. Therefore, the aim of the present study was to identify SRs published in leading orthodontic journals and the Cochrane Database of Systematic Reviews (CDSR) on the subject of orthodontics during the last 15 years and to assess the quality of evidence using the GRADE working group.

Materials and methods

The archives of five major orthodontic journals, *American Journal of Orthodontics and Dentofacial Orthopaedics (AJODO), Angle Orthodontist (Angle), European Journal of Orthodontics (EJO), Journal*

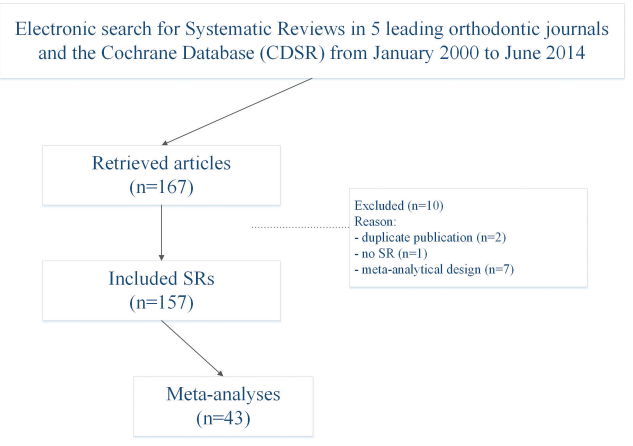

Figure 1. Flow diagram of study selection.

Table 1. Study characteristics and inclusion of a meta-analysis or otherwise (n = 157).

SR characteristics	Qualitative synthesis N (%**)	Meta-analysis N (%**)	Total N (%**)	P value
Journal				0.08***
Cochrane	21 (63.6)	12 (36.4)	33 (100.0)	
AJODO	29 (65.9)	15 (34.1)	44 (100.0)	
Angle	36 (83.7)	7 (16.3)	43 (100.0)	
EJO	16 (84.2)	3 (15.8)	19 (100.0)	
JO	5 (100.0)	0 (0.0)	5 (100.0)	
OCR	7 (53.9)	6 (46.1)	13 (100.0)	
Continent of authorship				0.09*
America	36 (83.7)	7 (16.3)	43 (100.0)	
Europe	65 (70.7)	27 (29.3)	92 (100.0)	
Asia/other	13 (59.1)	9 (40.9)	22 (100.0)	
Number of authors				0.62*
1–2	12 (70.6)	5 (29.4)	17 (100.0)	
3–4	55 (76.4)	17 (23.6)	72 (100.0)	
>4	47 (69.1)	21 (30.9)	68 (100.0)	
Methodologist involvement				0.21*
No	88 (75.2)	29 (24.8)	117 (100.0)	
Yes	26 (65.0)	14 (35.0)	40 (100.0)	
Type SR				0.12***
Interventional	72 (68.6)	33 (31.4)	105 (100.0)	
Epidemiological	34 (77.3)	10 (22.7)	44 (100.0)	
Diagnostic	8 (100.0)	0 (0.0)	8 (100.0)	
Subject				0.79***
Human	103 (71.5)	41 (28.5)	144 (100.0)	
Animal	6 (85.7)	1 (14.3)	7 (100.0)	
In vitro	5 (83.3)	1 (16.7)	6 (100.0)	
Conclusive				<0.001*
No	89 (84.0)	17 (16.0)	106 (100.0)	
Yes	25 (49.0)	26 (51.0)	51 (100.0)	
Total	114 (72.6)	43 (27.4)	157 (100.0)	

AJODO, American Journal of Orthodontics and Dentofacial Orthopaedics; EJO, European Journal of Orthodontics; JO, Journal of Orthodontics; OCR, Orthodontics and Craniofacial Research; SR, systematic review.

*Chi-square.

**Row percentage.

***Fisher's exact.

of Orthodontics (JO), and Orthodontics and Craniofacial Research (OCR), as well as the CDSR covering orthodontic literature were electronically searched from January 2000 to June 2014. These journals were chosen on the basis of impact factor and on the relative frequency of SRs published within them. Reviews were considered eligible for inclusion if the terms 'systematic review' or 'meta-analysis' were stated in the title or abstract or if it was apparent in the text that a systematic review had been undertaken. Narrative reviews, surveys, historical reviews, and case reports with extensive literature reviews were excluded. Similarly, reviews mislabelled as systematic reviews but lacking a methodology section were omitted from further analysis. One of the authors (DK) screened all titles, abstracts and if necessary full texts to identify eligible studies, after initial piloting. A second author (NP) was consulted where uncertainty existed. Disagreements were resolved through discussion with the second author. Full text articles for all potentially relevant for inclusion SRs were obtained.

The following information was extracted at the SR and meta-analysis level:

- Whether a meta-analysis was undertaken within each SR.
- Review characteristics, such as journal of publication, continent of authorship, number of authors, methodologist involvement, type of SR, orthodontic-related topic.
- Information recorded at the meta-analysis level included number of studies, number of meta-analyses per SR, type of summary estimate used, and the inclusion of a forest plot.
- Quality assessment of the overall body of evidence from meta-analyses was conducted using the GRADE tool.

According to GRADE the overall body of evidence is rated as high, moderate, low, and very low.

A finding of high quality of evidence indicates that further research is very unlikely to change our confidence in the estimated effect. Moderate quality of evidence suggests that further research is likely to have an important impact on our confidence in the estimated effect and may change the estimate. Low quality of evidence means that further research is very likely to have an important impact on our confidence in the estimated effect and is likely to change the estimate. Finally, very low quality of evidence means that any estimated effect is very uncertain. Assessment is based on the following domains: risk of bias or limitations in study design, inconsistency, indirectness, imprecision, and publication bias (7, 10). For the first four domains the quality of evidence has three levels and may be downgraded on the basis of either 'serious' or 'very serious' risks, whereas the presence of publication bias is a dichotomous outcome and may therefore either be undetected or suspected.

Limitations in study design were recorded based on the available SR author's evaluation of the quality of the included studies. Therefore, downgrading from low to unclear (serious) or high (very

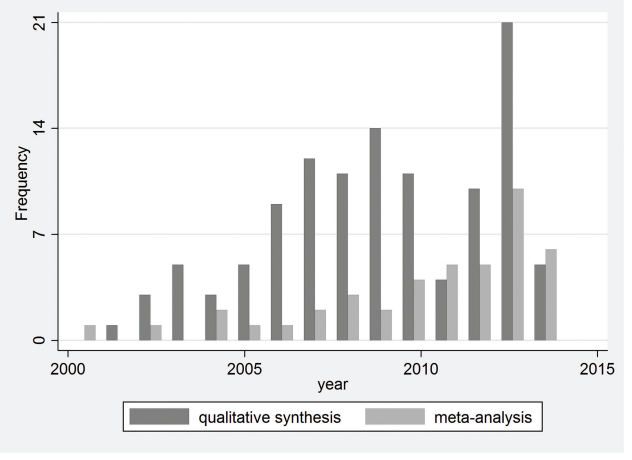

Figure 2. Distribution of SRs published within the years 2000–14. SR, systematic review.

Table 2. Distribution of SRs per orthodontic subject (n = 157).

Orthodontic subject	Qualitative synthesis *N* (%*)	Meta-analysis *N* (%*)	Total *N* (%*)
Class II	13 (72.2)	5 (27.8)	18 (100.0)
Class III	3 (42.9)	4 (57.1)	7 (100.0)
Alternative methods for tooth movement with (corticotomy, etc.)	2 (66.7)	1 (33.3)	3 (100.0)
Apnea	2 (50.0)	2 (50.0)	4 (100.0)
Arch dimensions	2 (100.0)	0 (0.0)	2 (100.0)
Biomechanics	9 (64.3)	5 (35.7)	14 (100.0)
Bonding	6 (54.5)	5 (45.5)	11 (100.0)
Canines	3 (100.0)	0 (0.0)	3 (100.0)
Cleft	4 (66.7)	2 (33.3)	6 (100.0)
Crossbites	9 (81.8)	2 (18.2)	11 (100.0)
Dental anomalies	3 (60.0)	2 (40.0)	5 (100.0)
Diagnosis	12 (100.0)	0 (0.0)	12 (100.0)
Implants	10 (83.3)	2 (16.7)	12 (100.0)
Open bite	1 (50.0)	1 (50.0)	2 (100.0)
Oral hygiene/fluoride	9 (69.2)	4 (30.8)	13 (100.0)
Orthognathic surgery	6 (85.7)	1 (14.3)	7 (100.0)
Root resorption	5 (83.3)	1 (16.7)	6 (100.0)
Self-ligating	0 (0.0)	2 (100.0)	2 (100.0)
Temporomandibular joint	6 (66.7)	3 (33.3)	9 (100.0)
Treatment need/aesthetics	4 (80.0)	1 (20.0)	5 (100.0)
Treatment stability/retention	5 (100.0)	0 (0)	5 (100.0)
Total	114 (72.6)	43 (27.4)	157 (100.0)

SR, systematic review.
*Row percentage.

serious) risk of bias was necessary when most information was from studies with moderate/unclear or high risk of bias, respectively (11). Inconsistency describes the variability of the results across the included studies and may relate to either clinical or statistical differences. Inconsistency is contingent upon study settings and methodology, variability in estimates, confidence interval overlapping, or statistical heterogeneity (12). Indirectness deals with the presence of head-to-head comparisons to address the SR question (13). Imprecision may reflect the presence of a relatively small overall sample size, a limited number of events or wide confidence intervals around the summary estimate, resulting in uncertainty in the results (14). The rating in respect of publication bias was based on the description of the literature search by the SR authors (grey literature, trial registries for unpublished studies), as well as the implementation of statistical tests when applicable (15).

Descriptive statistics on the characteristics of the SRs and meta-analyses were undertaken. Cross-tabulations were conducted to investigate associations between inclusion of a meta-analysis and study characteristics. Chi-squared and Fisher's exact tests were applied where appropriate. The level of statistical significance was pre-specified at $P < 0.05$. Statistical analyses were performed with STATA version 12.0 software (Stata Corporation, College Station, Texas, USA).

Results

After the inclusion criteria were applied, 157 SRs were identified, 43 of which included a meta-analysis (27.4 per cent; Figure 1 , Supplementary material). OCR represented the highest proportion of SRs that included a quantitative synthesis (6/13; 46.1 per cent), followed by the CDSR (12/33; 36.4 per cent) and AJODO (15/44; 34.1 per cent) (Table 1). AJODO (44/157; 28.0 per cent) and Angle (43/157; 27.4 per cent) also had the highest number of SRs published within the last 15-year period. The number of published SRs increased gradually over time, with 31/157 SRs published in 2013 (19.8 per cent), 10 of which included meta-analyses (10/43; 23.3 per cent; Figure 2). Interventional SRs (33/105; 31.4 per cent) and those involving a methodologist/statistician in the authorship of the study (14/40; 35 per cent) were found to more frequently involve meta-analysis (Table 1). Moreover, SRs with a meta-analysis were more likely to be conclusive in the interpretation of their data ($P < 0.001$; Table 1).

The most commonly addressed topic within orthodontic SRs was Class II treatment (18/157; 11.5 per cent), followed by treatment mechanics(14/157; 8.9 per cent) and oral hygiene or fluoride supplementation (13/157; 8.3 per cent). The proportion of meta-analysis was higher in topics related to self-ligation (2/2; 100 per cent) and Class III treatment (4/7; 57.1 per cent; Table 2), although this finding was based on a low number of events.

The number of studies included in meta-analysis for the primary outcome most frequently ranged between 2 and 4 ($n = 28$; 65.1 per cent), with a median number of 4 (range: 2–52). The median number of meta-analyses for multiple outcomes within the same SR was 3 (range: 1–25). The majority of studies used a forest plot for graphical representation of the individual trial estimates and the summary estimate (39/43; 90.7 per cent), while 28 out of 43 (65.1 per cent) meta-analyses utilized mean difference as a measure for the estimate of the effect. There was a slight preponderance of significant results over non-significant ($n = 24$ versus $n = 19$; Table 3).

GRADE evaluation for the overall body of evidence resulted in high/moderate quality of evidence in only nine meta-analyses (21.0 per cent), with the remaining studies rated as either low or very low ($n = 34$; 79.0 per cent; Table 4).

Table 3. Characteristics of studies including a meta-analysis ($n = 43$).

	SR with meta-analysis	
Study characteristics	*N*	%
Number of meta-analysis conducted within the same SR		
1–4	29	67.4
5–10	9	20.9
>10	5	11.7
Number of studies included in meta-analysis for primary outcome		
2–4	28	65.1
5–10	11	25.6
>10	4	9.3
Forest plot inclusion		
No	4	9.3
Yes	39	90.7
Type of summary estimate		
Mean difference	28	65.1
Risk ratio	3	7.0
Odds ratio	7	16.3
Hazard ratio	1	2.3
Proportions	3	7.0
Correlations	1	2.3
Significance		
No	19	44.2
Yes	24	55.8
Total	43	100

SR, systematic review.

Table 4. Distribution of overall quality of evidence according to GRADE from included meta-analyses, per journal ($n = 43$).

	Overall quality of evidence									
Journal	High		Moderate		Low		Very low		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Cochrane	0	0	3	25	3	25	6	50	12	100
AJODO	2	13	0	0	3	20	10	67	15	100
Angle	0	0	1	14	2	29	4	57	7	100
EJO	1	33	1	33	0	0	1	33	3	100
OCR	0	0	1	17	3	50	2	33	6	100
Total	3	7	6	14	11	26	23	53	43	100

AJODO, American Journal of Orthodontics and Dentofacial Orthopaedics; EJO, European Journal of Orthodontics; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OCR, Orthodontics and Craniofacial Research.

The distribution of individual GRADE domains prompting downgrading the quality of evidence included: high risk of bias resulting in two (very serious) levels of downgrading for 24 of 43 (55.8 per cent) studies, leaving only a small fraction with low risk of bias (7/43; 16.3 per cent). Serious to very serious inconsistency was detected in 27 meta-analyses (62.8 per cent) while this was also the case for imprecision in almost half of meta-analyses assessed (n = 19; 44.2 per cent). Publication bias was also suspected for 15/43 studies (34.9 per cent), while serious indirectness was identified in only two (4.7 per cent) studies (Table 5).

Discussion

A considerable increase in the number of SRs published in the CDSR and the orthodontic literature has been observed since 2007, indicating a persistent trend, which seems set to continue. The prevalence of meta-analyses within the SRs was relatively low (27.4 per cent), but in agreement with earlier reports from medical and orthodontic literature (16, 17), while analogous evidence from general dental research has indicated a higher proportion (43.6 per cent) of meta-analyses conducted within SRs published from 1991 to 2012 across nine dental specialties (18). SRs including a mathematical synthesis of their data, were more likely to be conclusive in the interpretation of the study results. While this may reflect a more plentiful yield of high quality studies contributing to the meta-analysis, it may also indicate the propensity of authors to interpret or provide recommendations based on quantitative data more readily than is the case when quantitative data does not exist.

Since 2010 there has been a predilection for undertaking SRs on clinical topics including treatment mechanics (11.1 per cent), Class II correction (8.6 per cent), and bonding (8.6 per cent). This pattern reflects the practical nature of orthodontics and is in keeping with the high level of interventional SRs identified in the review. Moreover, these areas are constantly evolving reflecting progress and changing clinical practice in tandem with advancement in materials and armamentarium and philosophical debate. In particular, the relative merit of well-marketed new technologies, early treatment, mechanism of Class II correction with functional appliances, and the implications of growth modification on dentofacial appearance both in the short- and long-term have been debated widely. These disagreements and controversies may well have provoked an evidence-based response to delineate the effects of these approaches through an evidence-based rather than experience-based lens. A corollary to this is the richness of clinical evidence within these topical areas, which may prompt and facilitate detailed SRs with higher level of evidence.

Wide variation in the number of meta-analyses observed for different outcomes within the same SR (ranging from 1 to 25 meta-analyses) was identified. This is in keeping with the findings of a recent study (19) with large numbers of meta-analysis likely to betray enthusiastic *post hoc* data synthesis based on the availability of information from individual studies, which may not be appropriate. It is important to precisely pre-define the research question, the primary and secondary endpoints and eligibility criteria in general before conducting a SR. The pre-registration of SR protocols on accepted international databases is a potential antidote to this issue and should be encouraged within orthodontics. Prior to instituting meta-analysis, it is also important to assess the clinical and statistical heterogeneity, in particular. More sophisticated methods for combining multiple outcomes or integrating

Table 5. Assessment of quality of evidence per GRADE item from included meta-analyses, across journals (n = 43).

	Risk of bias N (%)				Inconsistency N (%)			Indirectness N (%)			Imprecision N (%)			Publication bias N (%)		Total
Journal	Low	Moderate/ unclear	High	Not assessed*	No	Serious	Very serious	No	Serious	Very serious	No	Serious	Very serious	Undetected	Suspected	N (%)
Cochrane	3 (42.9)	2 (20)	7 (29.1)	0 (0)	3 (18.8)	4 (40)	5 (29.4)	12 (29.3)	0 (0)	0 (0)	7 (29.2)	3 (20)	2 (50)	10 (35.7)	2 (13.3)	12 (27.9)
AJODO	2 (28.5)	2 (20)	9 (37.5)	2 (100)	5 (31.1)	3 (30)	7 (41.2)	13 (31.7)	2 (100)	0 (0)	9 (37.5)	5 (33.3)	1 (25)	7 (25)	8 (53.4)	15 (34.9)
Angle	1 (14.3)	2 (20)	4 (16.7)	0 (0)	3 (18.8)	1 (10)	3 (17.6)	7 (17.1)	0 (0)	0 (0)	3 (12.5)	3 (20)	1 (25)	5 (17.9)	2 (13.3)	7 (16.2)
EJO	1 (14.3)	1 (10)	1 (4.2)	0 (0)	2 (12.5)	0 (0)	1 (5.9)	3 (7.3)	0 (0)	0 (0)	2 (8.3)	1 (6.7)	0 (0)	3 (10.7)	0 (0)	3 (7)
JO	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
OCR	0 (0)	3 (30)	3 (12.5)	0 (0)	3 (18.8)	2 (20)	1 (5.9)	6 (14.6)	0 (0)	0 (0)	3 (12.5)	3 (20)	0 (0)	3 (10.7)	3 (20)	6 (14)
Total	7(100)	10 (100)	24 (100)	2 (100)	16 (100)	10 (100)	17 (100)	41 (100)	2 (100)	0 (0)	24 (100)	15 (100)	4 (100)	28 (100)	15 (100)	43 (100)

AJODO, *American Journal of Orthodontics and Dentofacial Orthopaedics*; *EJO*, *European Journal of Orthodontics*; GRADE, Grading of Recommendations Assessment, Development and Evaluation; *JO*, *Journal of Orthodontics*; *OCR*, *Orthodontics and Craniofacial Research*; SR, systematic review.

*Risk of bias of included studies was not assessed by the authors of the SR.

evidence concerning multiple treatment interventions should also be considered (20, 21) and have recently been reported in orthodontic research (22).

The present study aimed to assess the quality of evidence in the subgroup of meta-analyses examined. Evaluating the quality of evidence from meta-analyses is a critical step that will facilitate evidence-based clinical decision making and provide recommendations for practice. Of all 43 meta-analyses assessed, a very limited number of studies presented high/moderate quality of evidence overall. This suggests that nearly 80 per cent of the available evidence in orthodontic literature is of low/very low quality, reflecting the uncertainty of confidence in the estimated treatment effect, as well as the limitations of the existing studies in informing practice recommendations. Meta-epidemiological studies both from medical and oral health literature have been sparse, indicating lack of awareness regarding quality of evidence and clinical decision making. A similar report from gynaecological literature has been conducted in a very limited number of SRs (n = 13) finding quality of evidence related to non-surgical treatment of stress urinary incontinence ranging from low to high (23).

Limitations in study design (risk of bias), inconsistency of the results, and imprecision were the most frequent reasons for seriously compromising the quality of evidence from meta-analyses, highlighting the need for larger and higher quality individual trials to guide clinical decisions. Although the majority of meta-analyses reported performing search of unpublished or 'grey' literature for relevant studies, assessment of publication bias through statistical methods (e.g. funnel plot asymmetry) was usually not possible due to the limited number of studies eligible for quantitative synthesis. Indirectness was rarely a reason for downgrading the quality of evidence in orthodontic meta-analyses, as direct head-to-head comparisons between interventions were almost always performed.

The restriction of study selection only to journals covering orthodontic literature might have been a limitation of the present cross-sectional investigation; however, it was felt that a comprehensive database search might not identify all possible SRs strictly related to orthodontic research and might not be fully representative of material perused by practicing orthodontic specialists. Furthermore, the inclusion of SRs from the CDSR is likely to have augmented the quality of SRs provided and offer a best case scenario, with broader topics typically assessed within these reviews. Notwithstanding this it is possible that orthodontic SRs have been published within general dental and non-orthodontic specialty journals as many of these have higher impact factor. While reviews in higher impact journals have been shown to be of improved methodological quality (24), there is a risk that these reviews will fail to reach the target audience effectively. Ultimately, however, if the quality and utility of SRs is to improve, a broader and more robust body of clinical trials is required.

Conclusions

An increasing number of SRs is being published in the orthodontic literature over the last 15 years. A relatively limited proportion of these (27 per cent) involved meta-analysis.

The overall quality of evidence from the selected meta-analyses according to GRADE was low to very low indicating the need for further high quality individual studies to inform clinical practice within orthodontics.

Supplementary material

Supplementary material is available at *European Journal of Orthodontics* online.

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