



Supplemental material
is available online.

Periodontal health during orthodontic treatment with clear aligners and fixed appliances

A meta-analysis

Qian Jiang, MDS; Jialing Li, MDS; Li Mei, PhD; Jing Du, MDS; Luca Levrini, MD;
Gian Marco Abbate, DDS; Huang Li, PhD

ABSTRACT

Background. Clear aligners have become increasingly popular because of their esthetics and comfort. The authors' aim in this systematic review was to compare periodontal health in patients undergoing orthodontic treatment with clear aligners with that of those undergoing orthodontic treatment with fixed appliances.

Types of Studies Reviewed. The authors systematically searched the PubMed, Web of Science, Cochrane Library, and Embase databases to collect related studies. After extracting data and assessing quality, the authors performed a meta-analysis and trial sequential analysis. The authors used the Grading of Recommendations Assessment, Development and Evaluation system to assess the quality of the evidence.

Results. The authors included 9 studies in the quantitative synthesis analysis. Clear aligners were better for periodontal health, including plaque index (mean difference [MD], -0.53 ; 95% confidence interval [CI], -0.85 to -0.20 ; $P = .001$), gingival index (MD, -0.27 ; 95% CI, -0.37 to -0.17 ; $P < .001$), and probing depth (MD, -0.35 ; 95% CI, -0.67 to -0.03 ; $P = .03$), than were fixed appliances. However, the trial sequential analysis outcome indicated a false-positive meta-analysis result for probing depth. The authors downgraded the level of the evidence because of the risk of bias and inconsistency.

Conclusions and Practical Implications. Clear aligners were better for periodontal health than fixed appliances and might be recommended for patients at high risk of developing gingivitis. However, high-quality studies still are required.

Key Words. Gingivitis; orthodontic appliances; literature review.

JADA 2018;149(8):712-720

<https://doi.org/10.1016/j.adaj.2018.04.010>

The demand for orthodontic treatment has increased in both adult and young patients.^{1,2} Fixed appliances are the most common and traditional treatment method used in contemporary orthodontics.³ However, the placement of orthodontic brackets and bands usually makes proper plaque removal more challenging. The increases in food deposits and dental plaque often lead to enamel demineralization and gingival inflammation if patients cannot maintain good oral hygiene.⁴⁻⁶ In contrast, clear aligners have had advantages such as esthetics, comfort,^{7,8} and convenience for oral hygiene because they are removable.⁹

Clear aligners, which have been available since 1999,⁹ have become increasingly popular.¹⁰ Clinicians have considered them to be safe, esthetic, and comfortable orthodontic appliances for patients.¹¹ The advantage of clear aligners over traditional fixed appliances on periodontal conditions, however, is still under debate. Investigators have reported that clear aligners allowed adequate oral hygiene and reduced the risk of developing negative periodontal complications compared with fixed appliances.^{12,13} Investigators in other studies have found that

This article has an accompanying online continuing education activity available at:
<http://jada.ada.org/ce/home>.

Copyright © 2018
American Dental
Association. All rights
reserved.

clear aligners cover the whole dentition and the marginal gingiva nearly the entire day and lead to inferior periodontal health.^{14,15} Although authors of a 2015 systematic review compared the effect of fixed appliances and clear aligners on periodontal health, their inclusion and exclusion criteria were ambiguous, and they included only 5 heterogeneous studies, which precluded quantitative synthesis.¹⁵ Our aim in this systematic review was to compare periodontal health in patients undergoing orthodontic treatment with clear aligners and those undergoing orthodontic treatment with fixed appliances with an updated and expanded literature database search through August 14, 2017.

METHODS

Types of studies and participant characteristics

We included human randomized controlled trials (RCTs) and human cohort studies. Participants included healthy humans. We excluded studies in which participants had systemic diseases (for example, advanced periodontal disease or Sjögren syndrome) or a history of long-standing antibiotic therapy.

Intervention, comparison, and outcome

We included studies in which the investigators used clear aligners and fixed appliances as intervention and control. The primary outcome was the effect on periodontal health. We implemented no restrictions regarding the follow-up time, the type of fixed appliances, or the number of participants.

Search strategy

We developed detailed search strategies for MEDLINE and adapted them for the other databases (eTables 1-4, available online at the end of this article). The search strategies included a combination of controlled vocabulary and free terms. We searched PubMed, Web of Science, Cochrane Library, and Embase. We manually searched the references of included articles to capture any other relevant studies. We restricted searches to trials in human participants with the full text published in English. We first performed the literature search in December 2016 and updated it on August 14, 2017.

We also searched unpublished literature in ClinicalTrials.gov, OpenGrey, the World Health Organization's International Clinical Trial Registry Platform, the Database of Abstracts of Reviews of Effects, Health Technology Assessment, the Turning Research Into Practice database, the International Federation of Pharmaceutical Manufacturers & Associations clinical trials portal, the International Standard Randomised Controlled Trial Number registry, the UK National Research Register, Eli Lilly and Company Clinical Study Registration and Results, OpenSIGLE, and the Pharmaceutical Industry Clinical Trials Database. We identified 1 article on ClinicalTrials.gov. We contacted the corresponding authors of this article to obtain the missing data, but there was no response at the time we wrote this review.

Data collection and analysis

Two independent investigators (Q.J., J.L.) assessed the articles and extracted data according to the inclusion and exclusion criteria. These 2 independent investigators (Q.J., J.L.) assessed the methodological quality of the trials included in this review. They resolved any discrepancies through discussion and consultation with a third investigator (H.L.). We assessed RCTs by using the evaluation method described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.¹⁶ We assessed the methodological quality of the cohort studies by using the Newcastle-Ottawa Scale for cohort studies.¹⁷ We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of evidence in relation to review questions via software (GRADEprofler 3.6, McMaster University).

Statistical analysis

We also used software (RevMan 5.0, The Nordic Cochrane Centre) to perform the meta-analyses. We used the random-effects model to synthesize results to accommodate heterogeneity across studies.

ABBREVIATION KEY

API:	Approximal plaque index.
BOP:	Bleeding on probing.
GI:	Gingival index.
GRADE:	Grading of Recommendations Assessment, Development and Evaluation.
MeSH:	Medical Subject Headings.
NA:	Not applicable.
NBP:	Nonbleeding papillae after probing.
OHI-S:	Simplified Oral Hygiene Index.
PBI:	Papillary bleeding index.
PD:	Probing depth.
PI:	Plaque index.
RCT:	Randomized controlled trial.
SBI:	Sulcus bleeding index.
TSA:	Trial sequential analysis.

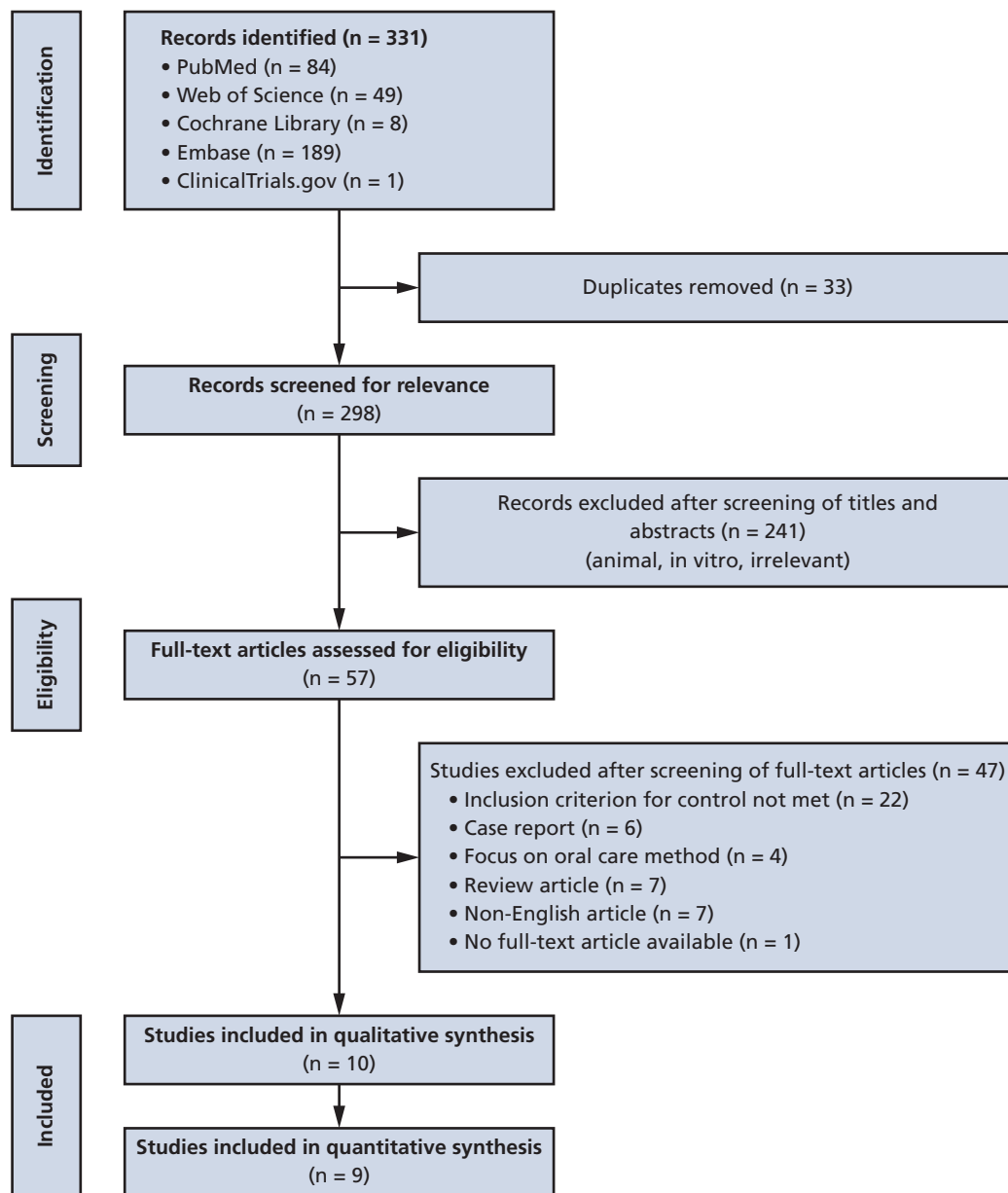


Figure 1. Study flowchart.

Trial sequential analysis

We used the trial sequential analysis (TSA) program (Version 0.9 beta, Copenhagen Trial Unit, Centre for Clinical Intervention Research) for the TSAs. Meta-analyses can increase the power and precision of the estimated intervention effects but may lead to overestimation of treatment effects and produce false-positive results because of systematic bias and random errors.^{18,19} The bias may originate from outcome measure bias, publication bias, premature stopping of trials with positive results, and small trial bias.¹⁸ The TSA, which can be used to analyze the pooled results of a meta-analysis, has been recommended for revealing insufficient information size and potentially false-positive results in meta-analyses.^{18,19} The required information size is an important and major factor in the TSA, so we performed this analysis at the level of 5% of type I error and 20% risk of type II error (a statistical test power of 80%) according to methods described in a previous study.²⁰

RESULTS

We scrutinized 57 full-text articles for relevance (Figure 1). After applying the inclusion and exclusion criteria, we excluded 47 studies that did not meet the inclusion criteria with the reasons

Table. Characteristics of the 10 included studies.

STUDY	COUNTRY	STUDY DESIGN	NO. OF PARTICIPANTS	NO. OF FIXED APPLIANCES	NO. OF CLEAR ALIGNERS	OUTCOME INDEXES	FOLLOW-UP, MO	QUALITY
Dubey and Colleagues, ²² 1993	India	Cohort study	50	25	25	GI,* PI†	1	Medium
Petti and Colleagues, ²⁴ 1997	Italy	Cohort study	30	15	15	PD,‡ PI, NBP§	Nearly 2 and 3	Medium
Miethke and Vogt, ¹⁴ 2005	Italy	Cohort study	60	30	30	PI, GI, PBI,¶ PD	Nearly 1, 2, and 3	Medium
Miethke and Brauner, ²⁶ 2007	Italy	Cohort study	60	30	30	PI, GI, PBI, PD	Nearly 1, 2, and 3	Medium
Rego and Colleagues, ²⁵ 2010	United States	Cohort study	48	30	18	PI, GI, PD	11 to 31.6	Medium
Karkhanechi and Colleagues, ²¹ 2013	United States	Cohort study	42	22	20	PD, PI, GI, BOP#	1.5, 6, and 12	Medium
Abbate and Colleagues, ¹² 2015	United States	RCT**	47	25	22	PD, PI	3, 6, and 12	Medium
Azaripour and Colleagues, ⁹ 2015	Germany	Cohort study	100	50	50	GI, API,†† SBI‡‡	More than 6	High
Levrini and Colleagues, ¹³ 2015	Italy	RCT	20	10	10	PD, PI, BOP	1, and 3	Medium
Machorowska-Pieniążek and Colleagues, ²³ 2016	Poland	RCT	37	20	17	GI, PI	At least 6	Medium

* GI: Gingival index. † PI: Plaque index. ‡ PD: Probing depth. § NBP: Nonbleeding papillae after probing. ¶ PBI: Papillary bleeding index. # BOP: Bleeding on probing. ** RCT: Randomized controlled trial. †† API: Approximal plaque index. ‡‡ SBI: Sulcus bleeding index.

given in eTable 5 (available online at the end of this article). Finally, we included 10 trials^{9,12-14,21-26} in the systematic review, with 464 participants in total; 207 used clear aligners, and 257 used fixed appliances (Figure 1 and Table).

Study characteristics and risk of bias

Of the 10 articles included in this review, 3 were RCTs,^{12,13,23} and 7 were cohort studies.^{9,14,21,22,24-26} We classified 2 studies^{9,25} as cohort studies according to the study design and observation period, although the investigators in these studies claimed that they were cross-sectional studies. The study authors classified the 464 participants as healthy. Investigators in 1 study²³ found that the type of orthodontic appliance did not affect the amount of dental plaque and gingival condition during their 35-day study. However, they reported only the medians of the periodontal indexes, which were not suitable for meta-analysis. Therefore, we e-mailed the corresponding authors and asked for their original experimental data, but we had received no response at the time we wrote this review.

The remaining 9 studies included 427 patients (190 patients used clear aligners, and 237 patients used fixed appliances). Among these 9 studies, investigators in 8 studies reported plaque index (PI), investigators in 6 studies reported gingival index (GI), and investigators in 7 studies reported probing depth (PD) as the primary study outcomes. The investigators used several different indexes for periodontal bleeding evaluation, including papillary bleeding index (PBI), sulcus bleeding index (SBI), bleeding on probing (BOP), and nonbleeding papillae after probing. However, none of them was used in more than 2 studies, so we did not perform a quantitative synthesis for periodontal bleeding evaluation.

The most common risk of bias was lack of blinding of participants, personnel, and outcome assessments. The table^{9,12-14,21-26} summarizes the basic characteristics and methodological quality assessments of all eligible studies. eTable 6^{9,12-14,21-26} (available online at the end of this article) details the risk of bias assessments for all included studies.

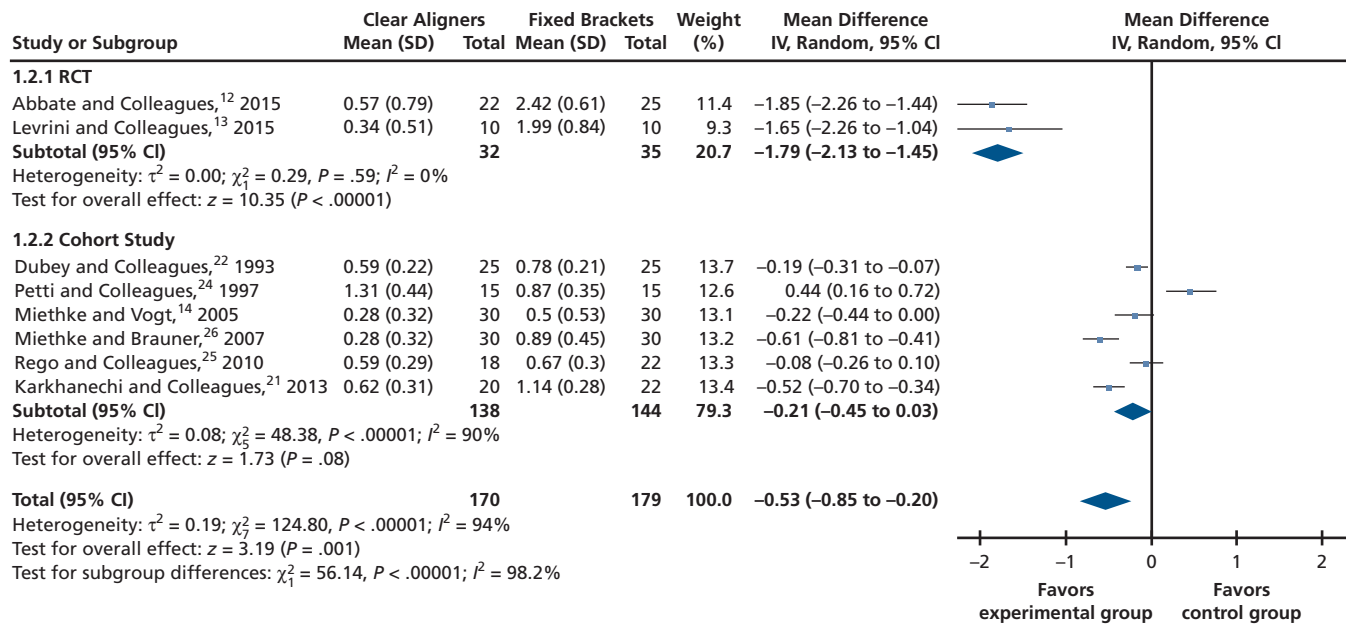


Figure 2. Forest plot comparing plaque index in patients with clear aligners with that in patients with fixed appliances. CI: Confidence interval. IV: Inverse variance. RCT: Randomized controlled trial. SD: Standard deviation.

Synthesis Results for PI

Investigators in 8 studies involving 349 participants reported the values of PI. We performed subgroup analysis according to study type (Figure 2).^{12-14,21,22,24-26} We identified heterogeneity across the included studies ($P < .001$; $I^2 = 94\%$), and we used a random-effects model to summarize mean effect size. Both the RCTs (mean difference [MD], -1.79; 95% confidence interval [CI], -2.13 to -1.45; $P = .059$) and the cohort studies (MD, -0.21; 95% CI, -0.45 to 0.03; $P < .001$) (Figure 2)^{12-14,21,22,24-26} had significantly lower PI scores in patients wearing clear aligners than in those wearing fixed appliances. Consistently, the subtotal analysis result had a similar outcome (MD, -0.53; 95% CI, -0.85 to -0.20; $P = .001$) (Figure 2).^{12-14,21,22,24-26}

Synthesis Results for GI

Investigators in 6 studies involving 360 participants reported the results of GI. All of these studies were cohort studies, so we did not perform subgroup analysis. We identified heterogeneity across the included studies ($P = .09$; $I^2 = 48\%$). The meta-analysis had significantly lower GI scores in patients using clear aligners than in those using fixed appliances (MD, -0.27; 95% CI, -0.37 to -0.17; $P < .001$) (Figure 3).^{9,14,21,22,24-26}

Synthesis Results for PD

Investigators in 7 studies involving 307 participants reported PD results. We performed subgroup analysis according to study type (Figure 4).^{12-14,21,24-26} The pooled result for PD was not significant in the RCT subgroup (MD, -0.21; 95% CI, -1.19 to 0.77; $P = .003$) (Figure 4),^{12-14,21,24-26} whereas the pooled result for PD in the cohort studies had a significant difference between clear aligners and fixed appliances (MD, -0.39; 95% CI, -0.75 to -0.03; $P < .001$) (Figure 4).^{12-14,21,24-26} The subtotal result of the meta-analysis indicated significantly better periodontal health (PD values) in patients wearing clear aligners than in those wearing fixed appliances (MD, -0.35; 95% CI, -0.67 to -0.03; $P = .03$) (Figure 4).^{12-14,21,24-26}

Subgroup Analysis Based on Follow-up

The follow-up in the included studies varied from 1.0 to 31.6 months (Table).^{9,12-14,21-26} Because the duration of follow-up could influence the effect of orthodontic appliances on periodontal health, we performed a subgroup analysis on follow-up time. The pooled results indicated that clear aligners, in comparison with fixed appliances, allowed significantly better periodontal health, including PI (MD, -0.75; 95% CI, -1.06 to -0.45; $P < .001$), GI (MD, -0.30; 95% CI, -0.43

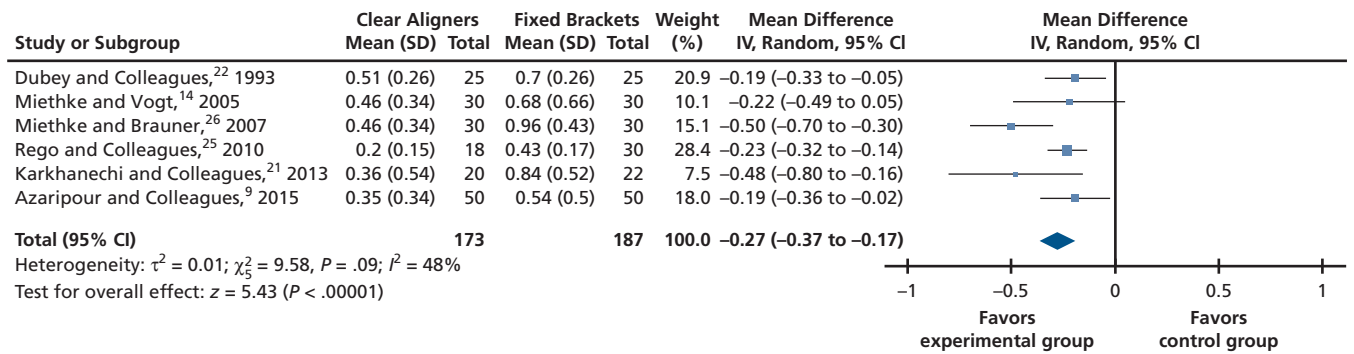


Figure 3. Forest plot comparing gingival index in patients with clear aligners with that in patients with fixed appliances. CI: Confidence interval. IV: Inverse variance. SD: Standard deviation.

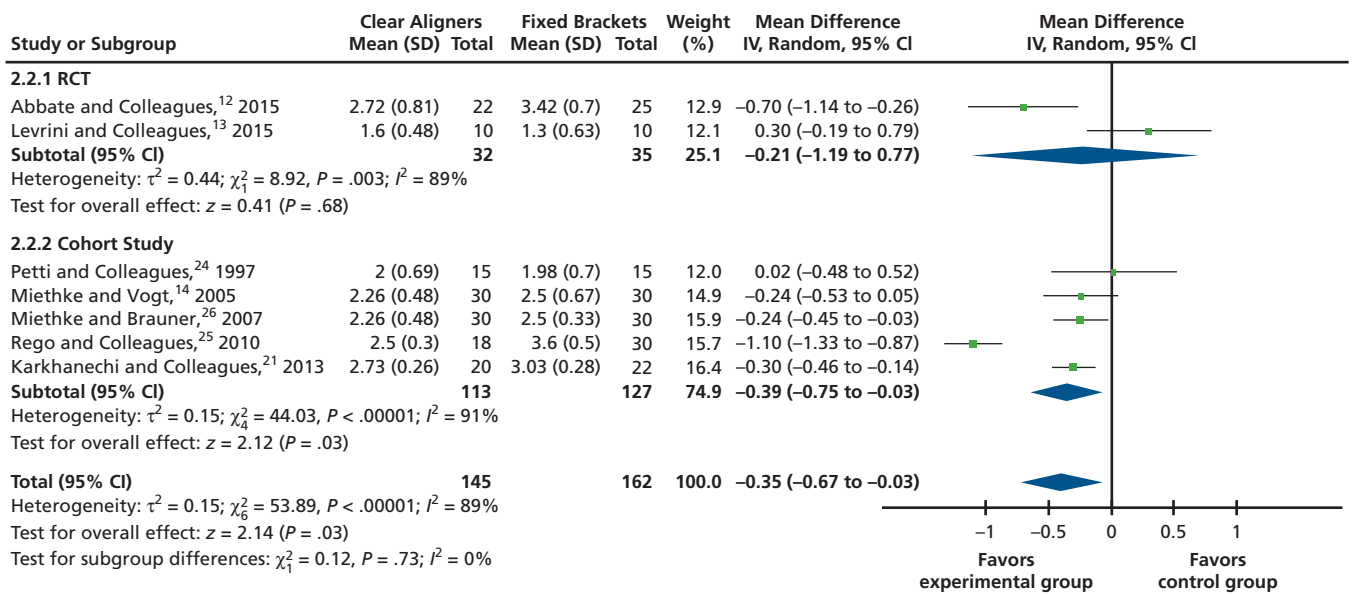


Figure 4. Forest plot comparing probing depth in patients with clear aligners with that in patients with fixed appliances. CI: Confidence interval. IV: Inverse variance. RCT: Randomized controlled trial. SD: Standard deviation.

to -0.18 ; $P < .001$), and PD (MD, -0.25 ; 95% CI, -0.41 to -0.10 ; $P < .001$) (eFigure 1, available online at the end of this article).^{12-14,21,24-26}

Grading of evidence and TSAs

We downgraded the level of the evidence because of the risk of bias and inconsistency of the articles included in the review (eTable 7, available online at the end of this article).¹³ The TSA results helped confirm significantly lower PI and GI scores in patients using clear aligners than in those using fixed appliances. However, it revealed a false-positive result of the meta-analysis for PD (eFigure 2, available online at the end of this article), indicating an insufficient sample size for a confirmed result for PD. Approximately 731 additional patients would have been required for a definite answer.

DISCUSSION

Fixed orthodontic appliances can promote plaque accumulation and impair gingival health²⁷ because orthodontic brackets, bands, and ligating devices can impede toothbrushing severely and decrease natural self-cleansing by the saliva and tongue.^{2,28} If patients cannot maintain good oral hygiene, the accumulated plaque could cause enamel demineralization and gingivitis.^{29,30} In contrast, removable appliances, which can be taken out of the mouth for toothbrushing and prophylaxis, are associated with a reduced risk of developing caries and gingivitis in patients undergoing

orthodontic treatment.^{14,26} Clear aligners, a type of removable appliance, may have an advantage over fixed appliances for oral hygiene and periodontal health, as we found in the meta-analysis and TSA results in this study.

In this study, we performed both qualitative and quantitative analyses of the included studies. The results indicated that the clear aligners allowed relatively better periodontal health conditions (PI, GI, and PD) than did fixed appliances. These findings are consistent with those of a previous review in which the investigators found that periodontal health (GI, PBI, BOP, and PD) was better in patients with clear aligners than in those with fixed appliances.¹⁵ However, that review had ambiguous inclusion and exclusion criteria and included 5 studies of high heterogeneity.^{13,14,21,26,31} In contrast, in this review, we specified the inclusion and exclusion criteria, included 10 studies with good homogeneity and used an expanded literature retrieval (through August 2017). The 10 studies in our review included 4 studies from the previous review (we excluded the article by Low and colleagues³¹ because it did not meet the specified inclusion criteria), and 6 additional studies.^{9,12,22-25}

In this study, in addition to using quantitative meta-analysis, we used the GRADE system to assess the quality of the evidence and performed TSA to reveal insufficient information size and potentially false-positive results. The TSA outcomes helped confirm the meta-analysis results for PI and GI, indicating that the samples size was sufficient. However, the TSA outcomes revealed a false-positive result of the meta-analysis for PD (eFigure 2, available online at the end of this article), indicating that the evidence was insufficient to draw a definitive conclusion about PD.

Of the 10 studies included in this meta-analysis, 9 involved use of buccal fixed appliances as controls; investigators in only 1 study used lingual fixed appliances as the control.²⁶ The authors of that study also published another article with the same data on clear aligners.^{14,26} Lingual appliances are more difficult to clean than are buccal appliances.³² The use of different types of fixed appliances (that is, buccal appliances and lingual appliances) may increase the heterogeneity of the studies included in the meta-analysis.

All authors of the 10 included articles worked at universities rather than companies, but the authors of only 3 articles^{9,13,25} clearly stated their financial support (eTable 8, available online at the end of this article).^{9,12-14,21-26} In addition, only 3 studies were RCTs,^{12,13,23} and the other 7 were cohort studies.^{9,14,21,22,24-26} Although high-quality RCTs often are considered the reference standard for clinical trials,³³ high-quality cohort studies also can be sufficient for this topic because the selection of orthodontic appliances usually is influenced highly by the patient's socioeconomic status and esthetic requirements. The random assignment of patients into different treatment groups is difficult to perform unless the study has other financial support. The RCT is still a preferred design for future research, but the cohort study is also acceptable if there is a clear conflict of interest statement.

A limitation of this systematic review is that the general quality of the available RCTs was not high. Because it was easy to distinguish fixed appliances from clear aligners, blinding of personnel and participants was impossible in practice. Investigators in most of the included studies did not describe clearly whether the outcome assessments were blinded. To minimize the possible effect of inadequate blinding, investigators in 1 of the included studies claimed that the outcome assessment was performed by operators who were unaware of the experimental protocol¹³ and in another claimed that the operators strictly respected the international criteria for determining periodontal index scores.¹² Blinding of the outcome assessment could be practically possible and implemented but only if there were no appliances or attachments on the teeth—for example, before bonding and after debonding of the appliances.

Investigators in the included studies used 7 clinical indexes to assess periodontal health: PI, GI, PD, PBI, SBI, BOP, and nonbleeding papillae after probing. Generally, periodontal health indexes can be classified into 3 main categories: oral hygiene indexes, gingivitis indexes, and periodontal disease indexes. In orthodontic clinical practice, clinicians use oral hygiene and gingivitis indexes more often than periodontal disease indexes because the gingival problems caused by oral biofilms in patients undergoing orthodontic treatment are mainly gingivitis and rarely progress to periodontal disease during orthodontic treatment.³⁴

Clinicians can assess oral hygiene status by using the Simplified Oral Hygiene Index (OHI-S), including the Simplified Debris Index, and the Simplified Calculus Index.³⁵ The OHI-S is a rapid,

simple, and reliable method for evaluating oral hygiene status, and investigators have used it widely in epidemiologic investigations.³⁶ PI is also a commonly used clinical index. According to the PI system Silness and Løe introduced, clinicians can use PI to evaluate the plaques that accumulate around the teeth, gingival margin, and pocket, which can be seen with the naked eye.³⁷ Another PI system is the internationally accepted Turesky modification of the Quigley and Hein Index, which involves the use of a plaque-disclosing agent for soft deposit evaluation, with a relatively more objective and reliable scoring result than that of PI.³⁸ Therefore, the OHI-S and the Turesky modification of the Quigley and Hein Index, which clinicians often use for a basic periodontal health evaluation, could be recommended for oral hygiene evaluation in patients undergoing orthodontic treatment.

The gingivitis indexes mainly are based on the clinical features of inflammation, such as color, texture, shape, and bleeding.³⁹ The visual signs of gingivitis include edema, redness of the gingival margin, and smooth texture of the free gingiva.⁴⁰ Investigators frequently have used GI to evaluate gingival condition and record qualitative gingival changes in clinical trials.^{41,42} However, bleeding is a more sensitive indicator of gingivitis than are edema and color change⁴³ because bleeding is objective and easy to identify.^{44,45} In the literature, investigators have used many bleeding indexes, such as the bleeding index, SBI, PBI, and BOP; among these, some investigators simply assessed bleeding as present or absent, and some used a grading system in an attempt to assess bleeding severity.⁴⁵ In clinical practice, the use of a graded bleeding index is more likely to help identify sites at risk of developing further destructive activity⁴⁵ and, hence, deserve a relatively higher recommendation.

In this systematic review, the follow-up duration of the included studies varied from 1.0 to 31.6 months.^{22,25} Considering that the alteration of periodontal PD takes time and that the average duration of orthodontic treatment is 19.9 months (95% CI, 19.58 to 20.22 months),⁴⁶ we recommend a long-term follow-up, such as more than 20 months, for future studies. In addition, to blind the investigators on the outcome assessments, investigators in future studies also can consider assessing the periodontal indexes before bonding and after debonding of orthodontic brackets.

CONCLUSIONS

Within the limitations of this systematic review, clear aligners were better for periodontal health than were fixed appliances, but the quality of the evidence was medium. High-quality RCTs are needed to make a conclusive recommendation. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: <https://doi.org/10.1016/j.ada.2018.04.010>.

Ms. Jiang is a resident, Nanjing Stomatological Hospital, Medical School of Nanjing University, Nanjing, Jiangsu, People's Republic of China.

Dr. Jialing Li is an attending orthodontist, Orthodontic Department, Nanjing Stomatological Hospital, Medical School of Nanjing University, Nanjing, Jiangsu, People's Republic of China.

Dr. Mei is a senior lecturer, Discipline of Orthodontics, Department of Oral Sciences, Sir John Walsh Research Institute, Faculty of Dentistry, University of Otago, Dunedin, New Zealand.

Ms. Du is a resident, Stomatological Hospital of Chongqing Medical University, Chongqing, Sichuan, People's Republic of China.

Dr. Levrini is a professor, Department of Morphological and Surgical Sciences, University of Insubria, Varese, Italy.

Dr. Abbate is a professor, Department of Morphological and Surgical Sciences, University of Insubria, Varese, Italy.

Dr. Huang Li is a professor, Orthodontic Department, Nanjing Stomatological Hospital, Medical School of Nanjing University, Nanjing, Jiangsu, People's Republic of China. Address correspondence to Dr. Huang Li, Nanjing Stomatological Hospital, Medical School of Nanjing University, Nanjing, 210008, Jiangsu, China, e-mail lihuang76@nju.edu.cn.

Disclosure. None of the authors reported any disclosures.

Drs. Jiang and Li contributed equally to this article and should be considered co-first authors.

The work was supported by grants 81470712 and 81670960 from the National Natural Science Foundation of China, by grant BK20171123 from the Natural Science Foundation of Jiangsu Province, and by grant YKK17140 from the Medical Science and Technology Development Foundation, Nanjing Department of Health.

1. Bollen AM, Cunha-Cruz J, Bakko DW, Huang GJ, Hujoel PP. The effects of orthodontic therapy on periodontal health: a systematic review of controlled evidence. *JADA*. 2008;139(4):413-422.

2. Ren Y, Jongsma MA, Mei L, van der Mei HC, Busscher HJ. Orthodontic treatment with fixed appliances and biofilm formation: a potential public health threat? *Clin Oral Invest*. 2014;18(7):1711-1718.

3. Sandic MZ, Popovic B, Carkic J, Nikolic N, Glisic B. Changes in subgingival microflora after placement and removal of fixed orthodontic appliances. *Srp Arh Celok Lek*. 2014;142(5-6):301-305.

4. Tufekci E, Dixon JS, Gunsolley JC, Lindauer SJ. Prevalence of white spot lesions during orthodontic treatment with fixed appliances. *Angle Orthod.* 2011; 81(2):206-210.
5. Attin R, Thon C, Schlagenhauf U, et al. Recolonization of mutans streptococci on teeth with orthodontic appliances after antimicrobial therapy. *Eur J Orthod.* 2005; 27(5):489-493.
6. Alexander SA. Effects of orthodontic attachments on the gingival health of permanent second molars. *Am J Orthod Dentofacial Orthop.* 1991;100(4):337-340.
7. Walton DK, Fields HW, Johnston WM, et al. Orthodontic appliance preferences of children and adolescents. *Am J Orthod Dentofacial Orthop.* 2010;138(6):698.e1-698.e12.
8. Fujiyama K, Honjo T, Suzuki M, Matsuoka S, Deguchi T. Analysis of pain level in cases treated with Invisalign aligner: comparison with fixed edgewise appliance therapy. *Prog Orthod.* 2014;15:64.
9. Azaripour A, Weusmann J, Mahmoodi B, et al. Braces versus Invisalign®: gingival parameters and patients' satisfaction during treatment: a cross-sectional study. *BMC Oral Health.* 2015;15:69.
10. Rossini G, Parrini S, Castroflorio T, Deregibus A, Debernardi CL. Efficacy of clear aligners in controlling orthodontic tooth movement: a systematic review. *Angle Orthod.* 2015;85(5):881-889.
11. Krieger E, Seiferth J, Marinello I, et al. Invisalign® treatment in the anterior region: were the predicted tooth movements achieved? *J Orofac Orthop.* 2012;73(5):365-376.
12. Abbate GM, Caria MP, Montanari P, et al. Periodontal health in teenagers treated with removable aligners and fixed orthodontic appliances. *J Orofac Orthop.* 2015;76(3):240-250.
13. Levrini L, Mangano A, Montanari P, Margherini S, Caprioglio A, Abbate GM. Periodontal health status in patients treated with the Invisalign® system and fixed orthodontic appliances: a 3 months clinical and microbiological evaluation. *Eur J Dent.* 2015;9(3):404-410.
14. Miethke RR, Vogt S. A comparison of the periodontal health of patients during treatment with the Invisalign system and with fixed orthodontic appliances. *J Orofac Orthop.* 2005;66(3):219-229.
15. Rossini G, Parrini S, Castroflorio T, Deregibus A, Debernardi CL. Periodontal health during clear aligners treatment: a systematic review. *Eur J Orthod.* 2015;37(5):539-543.
16. Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. Available at: <http://handbook-5-1.cochrane.org/>. Accessed January 24, 2017.
17. Newcastle-Ottawa Scale. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed January 24, 2017.
18. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol.* 2008;61(8):763-769.
19. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive: trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol.* 2009;38(1):287-298.
20. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol.* 2009;9:86.
21. Karkhanechi M, Chow D, Sipkin J, et al. Periodontal status of adult patients treated with fixed buccal appliances and removable aligners over one year of active orthodontic therapy. *Angle Orthod.* 2013;83(1):146-151.
22. Dubey R, Jalili VP, Garg S. Oral hygiene and gingival status in orthodontic patients. *J Pierre Fauchard Acad.* 1993;7(2):43-54.
23. Machorowska-Pieniżek A, Skucha-Nowak M, Mertas A, et al. Effects of Brazilian propolis on dental plaque and gingiva in patients with oral cleft malformation treated with multibracket and removable appliances: a comparative study. *Evid Based Complement Alternat Med.* 2016;2016:2038407.
24. Petti S, Barbato E, Simonetti D'Arca A. Effect of orthodontic therapy with fixed and removable appliances on oral microbiota: a six-month longitudinal study. *New Microbiol.* 1997;20(1):55-62.
25. Rego RO, Oliveira CA, dos Santos-Pinto A, et al. Clinical and microbiological studies of children and adolescents receiving orthodontic treatment. *Am J Dent.* 2010;23(6):317-323.
26. Miethke RR, Brauner K. A comparison of the periodontal health of patients during treatment with the Invisalign system and with fixed lingual appliances. *J Orofac Orthop.* 2007;68(3):223-231.
27. Anhoury P, Nathanson D, Hughes CV, et al. Microbial profile on metallic and ceramic bracket materials. *Angle Orthod.* 2002;72(4):338-343.
28. Turkkahraman H, Sayin MO, Bozkurt FY, et al. Archwire ligation techniques, microbial colonization, and periodontal status in orthodontically treated patients. *Angle Orthod.* 2005;75(2):231-236.
29. Lo BA, Di Marco R, Milazzo I, et al. Microbiological and clinical periodontal effects of fixed orthodontic appliances in pediatric patients. *New Microbiol.* 2008; 31(2):299-302.
30. Peng Y, Wu R, Qu W, et al. Effect of visual method vs plaque disclosure in enhancing oral hygiene in adolescents and young adults: a single-blind randomized controlled trial. *Am J Orthod Dentofacial Orthop.* 2014; 145(3):280-286.
31. Low B, Lee W, Seneviratne CJ, Samaranyake LP, Hägg U. Ultrastructure and morphology of biofilms on thermoplastic orthodontic appliances in 'fast' and 'slow' plaque formers. *Eur J Orthod.* 2011;33(5):577-583.
32. Hohoff A, Stamm T, Kuhne N, et al. Effects of a mechanical interdental cleaning device on oral hygiene in patients with lingual brackets. *Angle Orthod.* 2003;73(5): 579-587.
33. Bondemark L, Ruf S. Randomized controlled trial: the gold standard or an unobtainable fallacy? *Eur J Orthod.* 2015;37(5):457-461.
34. Willmot D. Orthodontic treatment and the compromised periodontal patient. *Eur J Dent.* 2008;2(1): 1-2.
35. Greene JC, Vermillion JR. The Simplified Oral Hygiene Index. *JADA.* 1964;68(1):7-13.
36. Wei SH, Lang NP. Periodontal epidemiological indices for children and adolescents, part II: evaluation of oral hygiene, III—clinical applications. *Pediatr Dent.* 1982; 4(1):64-73.
37. Malmö University Oral Health Database. Silness-Löe Index. Available at: <http://www.mah.se/CAPP/Methods-and-Indices/Oral-Hygiene-Indices/Silness-Loe-Index/>. Accessed April 23, 2018.
38. Deinzer R, Jahns S, Harnacke D. Establishment of a new marginal plaque index with high sensitivity for changes in oral hygiene. *J Periodontol.* 2014;85(12): 1730-1738.
39. Grellman AP, Zanatta FB. Diagnosis of gingivitis: state of the art. *J Dent Oral Disord.* 2016;2(3):1017.
40. Egelberg J. The topography and permeability of vessels at the dento-gingival junction in dogs. *J Periodontol Res Suppl.* 1967;1:1-39.
41. Silness J, Löe H. Periodontal disease in pregnancy, 3: response to local treatment. *Acta Odontol Scand.* 1966; 24(6):747-759.
42. Löe H. The gingival index, the plaque index and the retention index systems. *J Periodontol.* 1967;38(6:suppl): 610-616.
43. Benamghar L, Penaud J, Kaminsky P, Abt F, Martin J. Comparison of gingival index and sulcus bleeding index as indicators of periodontal status. *Bull World Health Organ.* 1982;60(1):147-151.
44. Lang NP, Schätzle MA, Löe H. Gingivitis as a risk factor in periodontal disease. *J Clin Periodontol.* 2009;36- (suppl 10):3-8.
45. Newbrun E. Indices to measure gingival bleeding. *J Periodontol.* 1996;67(6):555-561.
46. Tsihlaki A, Chin SY, Pandis N, Fleming PS. How long does treatment with fixed orthodontic appliances last? A systematic review. *Am J Orthod Dentofacial Orthop.* 2016;149(3):308-318.

eTable 1. Search strategy for MEDLINE via PubMed.

SEARCH NO.	SEARCH TERMS
1	"Orthodontic Appliances, Removable" [MeSH]*
2	"remov* aligner" OR "remov* appliances" OR "clear aligner" OR "invisalign" OR "thermoplastic orthodontic appliances" OR "remov* orthodontic device" [Title/Abstract]
3	1 or 2
4	"periodont*" OR "gingiv*" OR "oral health" OR "oral hygiene" OR "PI" [†] OR "plaque index" OR "PD" [‡] OR "probing depth" OR "GI" [§] OR "gingiva index" [Title/Abstract]
5	3 AND 4

* MeSH: Medical Subject Headings. † PI: Plaque index. ‡ PD: Probing depth. § GI: Gingival index.

eTable 2. Search strategy for Web of Science.

SEARCH NO.	SEARCH TERMS
1	Topic (remov* aligner) OR Topic (remov* appliances) OR Topic (clear aligner) OR Topic (invisalign) OR Topic (thermoplastic orthodontic appliances)
2	Topic (periodont*) OR Topic (gingiv*) OR Topic (oral health) OR Topic (oral hygiene) OR Topic (PI)* OR Topic (plaque) OR Topic (plaque index) OR Topic (PD) [†] OR (probing depth) OR (GI) [‡] OR (gingiva index)
3	1 AND 2

* PI: Plaque index. † PD: Probing depth. ‡ GI: Gingival index.

eTable 3. Search strategy for Cochrane Library.

SEARCH NO.	SEARCH TERMS
1	removable aligner OR removable appliances OR clear aligner OR invisalign OR thermoplastic orthodontic appliances
2	periodont* OR gingiv* OR oral health OR oral hygiene OR PI* OR plaque index OR PD [†] OR probing depth OR GI [‡] OR gingiva index
3	1 AND 2

* PI: Plaque index. † PD: Probing depth. ‡ GI: Gingival index.

eTable 4. Search strategy for Embase.

SEARCH NO.	SEARCH TERMS
1	"remov* aligner" OR "remov* appliances" OR "clear aligner" OR "invisalign" OR "thermoplastic orthodontic appliances"
2	"periodont*" OR "gingiv*" OR "oral health" OR "oral hygiene" OR "PI"* OR "plaque index" OR "PD" [†] OR "probing depth" OR "GI" [‡] OR "gingiva index"
3	1 AND 2

* PI: Plaque index. † PD: Probing depth. ‡ GI: Gingival index.

eTable 5. Articles excluded from the review.

ARTICLE	REASON FOR EXCLUSION
Newman GV. Treatment of migrating teeth with removable appliances. <i>JADA</i> . 1966;73(4):870-873.	Case report
Herren P. Indications and contraindications for removable and fixed orthodontic appliances. <i>SSO Schweiz Monatsschr Zahnheilkd</i> . 1975;85(3):291-308.	Review article
Khimitliiska Khr, Mutafchiev V. Oral hygiene in children with orthodontic appliances. <i>Stomatologija (Sofia)</i> . 1979;61(6):341-345.	Non-English article
Yamauchi K, Yamada K. Oral hygiene of orthodontic patients. <i>Shikai Tenbo</i> . 1979;53(5):707-718.	Non-English article
Melsen B. Removable orthodontic appliances. <i>Dent Clin North Am</i> . 1981;25(1):157-176.	Review article
Addy M, Shaw WC, Hansford P, Hopkins M. The effect of orthodontic appliances on the distribution of <i>Candida</i> and plaque in adolescents. <i>Br J Orthod</i> . 1982;9(3):158-163.	Focus on oral care method
Goultschin J, Zilberman Y. Gingival response to removable orthodontic appliances. <i>Am J Orthod</i> . 1982;81(2):147-149.	Inclusion criterion for control not met
Botero B. Treatment of malocclusion with removable appliances, III: clinical cases. <i>Acta Clin Odontol</i> . 1983;6(11):22-25.	Inclusion criterion for control not met
Bredy E, Lutterberg B, Laffers U. Effect of orthodontic removable appliances on the marginal periodontium: longitudinal study. <i>Stomatol DDR</i> . 1986;36(5):256-262.	Non-English article
Pender N. Aspects of oral health in orthodontic patients. <i>Br J Orthod</i> . 1986;13(2):95-103.	Focus on oral care method
Akkaya S. Interrelationships between orthodontics and periodontics. <i>Turk Ortodonti Derg</i> . 1989;2(2):322-327.	Review article
Steinhardt J. The periodontal findings during orthodontic treatment: a cross-sectional study. <i>Fortschr Kieferorthop</i> . 1989;50(6):540-550.	Non-English article
Akkaya S. An evaluation of appliance hygiene index on patients wearing removable orthodontic appliance. <i>Turk Ortodonti Derg</i> . 1990;3(1):1-5.	Inclusion criterion for control not met
Bernau R, Bredy E. The treatment of adults with removable appliances? A contribution to orthodontic-prosthetic collaboration. <i>Fortschr Kieferorthop</i> . 1990;51(1):23-28.	Inclusion criterion for control not met
Owin K, Diedrich P. Changes in periodontal parameters during orthodontic treatment. <i>Dtsch Zahnarztl Z</i> . 1990;45(2):109-112.	Non-English article
Tuncer AV, Baylas H. Examination of the effects of various orthodontic appliances on periodontal tissues. <i>Turk Ortodonti Derg</i> . 1990;3(1):13-18.	Non-English article
Tawse-Smith A, Rivillas CC, Orozco PS, Diaz JE, Pack AR. Clinical effects of removable acrylic appliance design on gingival tissues: a short-term study. <i>J Int Acad Periodontol</i> . 2001;3(1):22-27.	Inclusion criterion for control not met
Vlaskalic V, Boyd RL. Clinical evolution of the Invisalign appliance. <i>J Calif Dent Assoc</i> . 2002;30(10):769-776.	Review article
Chenin DA, Trosien AH, Fong PF, Miller RA, Lee RS. Orthodontic treatment with a series of removable appliances. <i>JADA</i> . 2003;134(9):1232-1239.	Case report
Meier B, Wiemer KB, Miethke RR. Invisalign®: patient profiling—analysis of a prospective survey. <i>J Orofac Orthop</i> . 2003;64(5):352-358.	Inclusion criterion for control not met
Wites M, Panuszka J, Dyras M. Evaluation of oral and orthodontic appliance hygiene in orthodontically treated patients. <i>Przegl Lek</i> . 2003;60(suppl 6):126-128.	Non-English article
Travess H, Roberts-Harry D, Sandy J. Orthodontics, part 6: risks in orthodontic treatment. <i>Br Dent J</i> . 2004;196(2):71-77.	Review article
Turpin DL. Clinical trials needed to answer questions about Invisalign. <i>Am J Orthod Dentofacial Orthop</i> . 2005;127(2):157-158.	Inclusion criterion for control not met
Duong T, Kuo E. Finishing with Invisalign. <i>Prog Orthod</i> . 2006;7(1):44-55.	Inclusion criterion for control not met
Corsair AJ. Restoration of a smile using Invisalign and soft-tissue grafting. <i>Dent Today</i> . 2007;26(9):100, 102.	Inclusion criterion for control not met
Kim TW, Echarri P. Clear aligner: an efficient, esthetic, and comfortable option for an adult patient. <i>World J Orthod</i> . 2007;8(1):13-18.	Inclusion criterion for control not met
Boyd RL. Esthetic orthodontic treatment using the Invisalign appliance for moderate to complex malocclusions. <i>J Dent Educ</i> . 2008;72(8):948-967.	Inclusion criterion for control not met
Sterental R. A new helping-hand concept for Invisalign users. <i>Dent Today</i> . 2008;27(9):118, 120-121.	Inclusion criterion for control not met
Boyd RL. Periodontal and restorative considerations with clear aligner treatment to establish a more favorable restorative environment. <i>Compend Contin Educ Dent</i> . 2009;30(5):280-282, 284, 286-288.	Case report
Giancotti A, Di Girolamo R. Treatment of severe maxillary crowding using Invisalign and fixed appliances. <i>J Clin Orthod</i> . 2009;43(9):583-589.	Case report

(continued)

eTable 5. Continued

ARTICLE	REASON FOR EXCLUSION
Kravitz ND, Kusnoto B, BeGole E, Obrez A, Agran B. How well does Invisalign work? A prospective clinical study evaluating the efficacy of tooth movement with Invisalign. <i>Am J Orthod Dentofacial Orthop.</i> 2009;135(1):27-35.	Inclusion criterion for control not met
Guarnen, MP, Gracco A, Sicilians G. Invisalign: state-of-the-art. <i>Mondo Ortodontico.</i> 2010;32(2):95-105.	Case report
Lee JW, Lee SJ, Lee CK, Kim BO. Orthodontic treatment for maxillary anterior pathologic tooth migration by periodontitis using clear aligner. <i>J Periodontal Implant Sci.</i> 2011;41(1):44-50.	Inclusion criterion for control not met
Uribe F, Cutrera A, Nanda R. A segmented appliance for space closure followed by Invisalign and fixed appliances. <i>Orthodontics (Chic.).</i> 2011;12(4):386-395.	Case report
Krieger E, Seiferth J, Marinello I, et al. Invisalign® treatment in the anterior region: were the predicted tooth movements achieved? <i>J Orofac Orthop.</i> 2012;73(5):365-376.	Inclusion criterion for control not met
Lalic M, Aleksic E, Gajic M, Milic J, Malesevic D. Does oral health counseling effectively improve oral hygiene of orthodontic patients? <i>Eur J Paediatr Dent.</i> 2012;13(3):181-186.	Focus on oral care method
Castroflorio T, Garino F, Lazzaro A, Debernardi C. Upper-incisor root control with Invisalign appliances. <i>J Clin Orthod.</i> 2013;47(6):346-351.	Inclusion criterion for control not met
Jambi S, Thiruvengkatchari B, O'Brien KD, Walsh T. Orthodontic treatment for distalising upper first molars in children and adolescents. <i>Cochrane Database Syst Rev.</i> 2013;10:CD008375.	Review article
Malik OH, McMullin A, Waring DT. Invisible orthodontics, part 1: Invisalign. <i>Dent Update.</i> 2013;40(3):203-204, 207-210, 213-215.	Inclusion criterion for control not met
Mampieri G, Giancotti A. Invisalign technique in the treatment of adults with pre-restorative concerns. <i>Prog Orthod.</i> 2013;14:40.	Inclusion criterion for control not met
Pathak AK, Sharma DS. Biofilm associated microorganisms on removable oral orthodontic appliances in children in the mixed dentition. <i>J Clin Pediatr Dent.</i> 2013;37(3):335-339.	Inclusion criterion for control not met
Kuncio DA. Invisalign: current guidelines for effective treatment. <i>N Y State Dent J.</i> 2014;80(2):11-14.	Review article
Sheridan JJ. The readers' corner: Invisalign. <i>J Clin Orthod.</i> 2014;48(6):371-374.	Inclusion criterion for control not met
Needham R, Waring DT, Malik OH. Invisalign treatment of Class III malocclusion with lower-incisor extraction. <i>J Clin Orthod.</i> 2015;49(7):429-441.	Inclusion criterion for control not met
Align Technology. Comparison of oral hygiene & root resorption during orthodontic treatment (RCT). 2016. ClinicalTrials.gov Identifier: NCT02745626.	No full text available
University of Dundee. Orthodontic reduction of an increased overbite in adolescents: the mechanism and rate of occlusal adaptation. 2016. ClinicalTrials.gov Identifier: NCT02925468.	Inclusion criterion for control not met
Lin F, Yao L, Bhikoo C, Guo J. Impact of fixed orthodontic appliance or clear-aligner on daily performance, in adult patients with moderate need for treatment. <i>Patient Prefer Adherence.</i> 2016;10:1639-1645.	Focus on oral care method

eTable 6. Risk of bias assessments in the included studies.*

ITEM	AUTHORS' JUDGMENT	DESCRIPTION
Dubey and Colleagues,²² 1993		
Representativeness of the Exposed Cohort	1	Comment: Truly representative of the exposed cohort
Selection of the Nonexposed Cohort	1	Comment: Nonexposed cohort drawn from the same community as the exposed cohort Quote: "This study was carried out on 75 patients (35 males and 40 females) age ranging from 11 to 21 years, randomly selected out of about 600 patients undergoing orthodontic treatment in the Department of orthodontics, College of Dentistry Indore."
Ascertainment of Exposure	1	Comment: Patients underwent different treatment methods—exposure is assured
Demonstration That Outcome of Interest Was Not Present at Start of Study	0	Comment: No description
Comparability of Cohorts on the Basis of the Design or Analysis	1	Comment: Study controls for the most important factors Quote: "All the subjects brushing twice a day, in the morning and before retiring by using Bass method with the help of super soft brush and standard paste."
Assessment of Outcome	0	Comment: No description
Follow-Up Long Enough for Outcomes to Occur	0	Comment: Follow-up shorter than 6 months Quote: "The oral hygiene status of all above subjects were scored and recorded weekly for the period of one month by using plaque Index and Gingival Index."
Adequacy of Follow-Up of Cohorts	1	Comment: Complete follow-up
Total	5	Medium
Petti and Colleagues,²⁴ 1997		
Representativeness of the Exposed Cohort	1	Comment: Truly representative of the exposed cohort
Selection of the Nonexposed Cohort	1	Comment: Nonexposed cohort drawn from the same community as the exposed cohort
Ascertainment of Exposure	1	Comment: Orthodontic treatment has the secure record.
Demonstration That Outcome of Interest Was Not Present at Start of Study	0	Comment: No description
Comparability of Cohorts on the Basis of the Design or Analysis	1	Comment: Study controls for the most important factors Quote: "Before starting treatment, subjects received oral hygiene instructions (tooth brushing, according to the technique of Bass, and dental flossing)."
Assessment of Outcome	0	Comment: Self-report Quote: "When appliances were inserted, children were examined by one dentist."
Follow-Up Long Enough for Outcomes to Occur	1	Comment: Follow-up time is enough. Quote: "The subjects were longitudinally followed for six months."
Adequacy of Follow-Up of Cohorts	1	Comment: Complete follow-up
Total	6	Medium
Miethke and Vogt,¹⁴ 2005		
Representativeness of the Exposed Cohort	1	Comment: Truly representative of the exposed cohort
Selection of the Nonexposed Cohort	1	Comment: Nonexposed cohort drawn from the same community as the exposed cohort
Ascertainment of Exposure	1	Comment: Orthodontic treatment has the secure record
Demonstration That Outcome of Interest Was Not Present at Start of Study	1	Comment: Yes Quote: "Initially, all patients were asked to maintain the personal oral hygiene they had followed thus far. At that time and at the next two evaluations, any gingival inflammation was evaluated as were plaque deposit and sulcus depth."
Comparability of Cohorts on the Basis of the Design or Analysis	0.5	Comment: Study controls for some factors Quote: "The participants in this study were healthy, taking no antibiotics, nor did they use any plaque-inhibiting agents."
Assessment of Outcome	0	Comment: Self-report Quote: "Evaluation was performed by one of the authors (S.V.), who had 5 years of clinical experience in periodontics and as an assistant professor in a university clinic."
Follow-Up Long Enough for Outcomes to Occur	1	Comment: Follow-up is more than 6 months Quote: "All patients wore their appliances for a minimum of 6 months."

* For randomized controlled trials, high quality was indicated by 7 or more yesses; medium quality, by 4 or more yesses; and low quality, by fewer than 4 yesses. For cohort studies, high quality was indicated by scores of 7 or higher; medium quality, by scores of 4 or higher; and low quality, by scores lower than 4. † NA: Not applicable.

eTable 6. Continued

ITEM	AUTHORS' JUDGMENT	DESCRIPTION
Adequacy of Follow-Up of Cohorts	1	Comment: Complete follow-up Quote: "All results are graphically represented in the form of Box-Whisker-Plots."
Total	6.5	Medium
Miethke and Brauner,²⁶ 2007		
Representativeness of the Exposed Cohort	1	Comment: Truly representative of the exposed cohort
Selection of the Nonexposed Cohort	1	Comment: Nonexposed cohort drawn from the same community as the exposed cohort
Ascertainment of Exposure	1	Comment: Orthodontic treatment has the secure record
Demonstration That Outcome of Interest Was Not Present at Start of Study	0	Comment: No description
Comparability of Cohorts on the Basis of the Design or Analysis	0.5	Comment: Study controls for some factors Quote: "This study's participants were physically healthy, taking no antibiotics, nor did they use any plaque-inhibiting agents."
Assessment of Outcome	0	Comment: Self-report Quote: "The exams were carried out in the same manner during the subsequent two control visits by the same orthodontist (K.B.)."
Follow-Up Long Enough for Outcomes to Occur	1	Comment: Follow-up is more than 6 months Quote: "All the lingual patients wore their appliances for at least 6 months."
Adequacy of Follow-Up of Cohorts	1	Comment: Complete follow-up Quote: "All our results are graphically represented in the form of Box-Whisker-Plots."
Total	5.5	Medium
Rego and Colleagues,²⁵ 2010		
Representativeness of the Exposed Cohort	1	Comment: Truly representative of the exposed cohort
Selection of the Nonexposed Cohort	1	Comment: Nonexposed cohort drawn from the same community as the exposed cohort
Ascertainment of Exposure	1	Comment: Orthodontic treatment has the secure record
Demonstration That Outcome of Interest Was Not Present at Start of Study	1	Comment: Yes Author Reply: "Do patients have any gingival inflammation? - Yes, as stated on Table 2 (Gingival Index row), all patients presented gingival inflammation. However some studies consider that up to 20%-25% of gingival bleeding is not of clinical relevance."
Comparability of Cohorts on the Basis of the Design or Analysis	0.5	Comment: Study controls for some factors Quote: "Subjects were excluded if they had: (1) taken antibiotics or anti-inflammatory drugs within the previous 3 months, (2) received periodontal therapy within 6 months, or (3) had a chronic medical disease or condition that could affect their periodontium."
Assessment of Outcome	0	Comment: Self-report Quote: "Examinations were performed by a single calibrated clinician."
Follow-Up Long Enough for Outcomes to Occur	1	Comment: Follow-up time is enough Quote: "Fixed orthodontic appliances had been in place for an average of 21.8±9.8 months prior to the study. Removable orthodontic appliances had been in place for an average of 9.8±2.9 months."
Adequacy of Follow-Up of Cohorts	1	Comment: Complete follow-up
Total	6.5	Medium
Karkhanechi and Colleagues,²¹ 2013		
Representativeness of the Exposed Cohort	1	Comment: Truly representative of the exposed cohort
Selection of the Nonexposed Cohort	1	Comment: Nonexposed cohort drawn from the same community as the exposed cohort
Ascertainment of Exposure	1	Comment: Orthodontic treatment has the secure record
Demonstration That Outcome of Interest Was Not Present at Start of Study	1	Comment: Yes. Exclusion criteria included history of periodontitis as evidenced by the presence of attachment loss
Comparability of Cohorts on the Basis of the Design or Analysis	1	Comment: Study controls for the most important factor Quote: "Both groups received a full mouth scaling and prophylaxis 1 week prior to, and full oral hygiene instructions on the day the appliances or aligners were delivered."
Assessment of Outcome	0	Comment: No description

(continued)

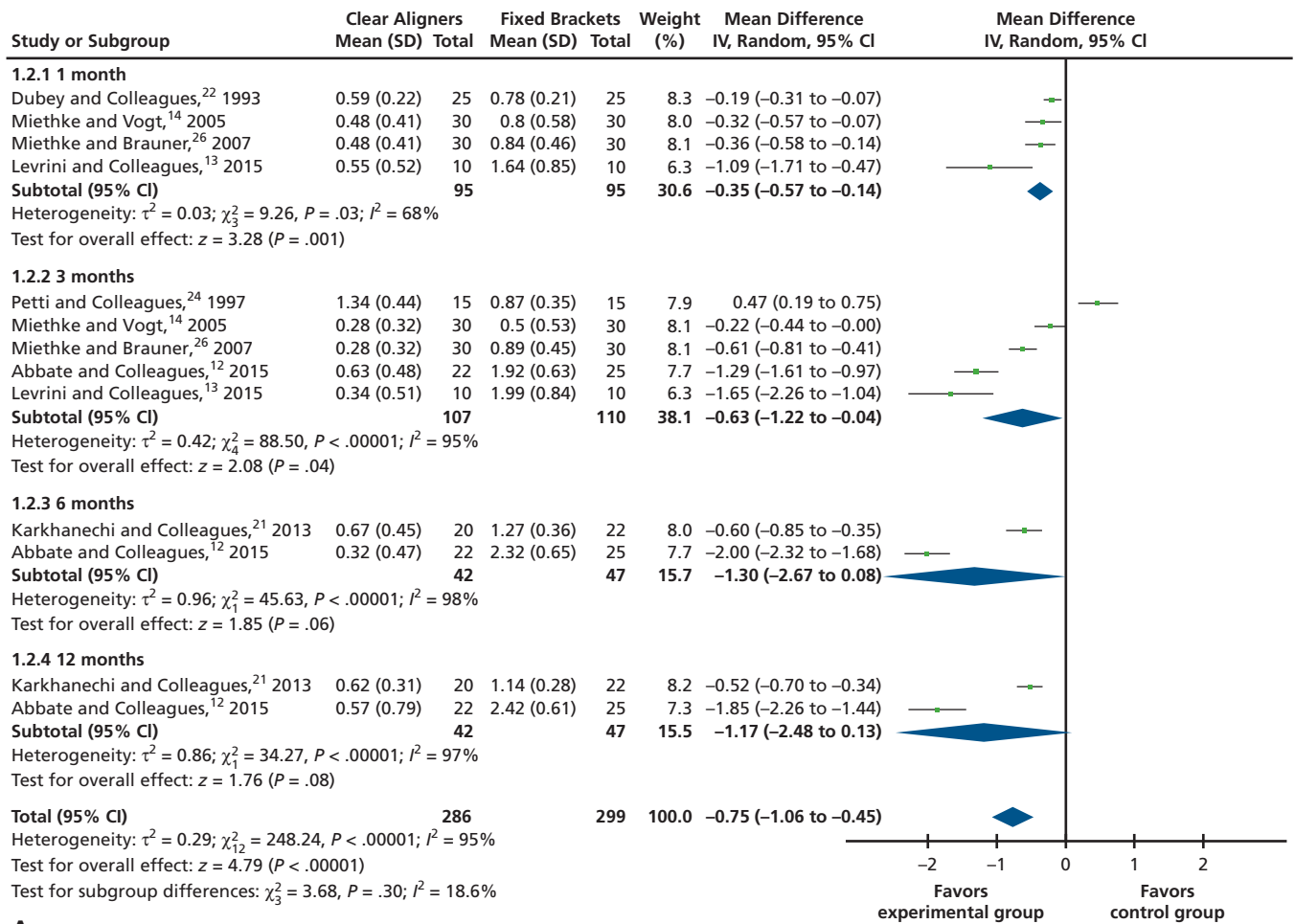
eTable 6. Continued

ITEM	AUTHORS' JUDGMENT	DESCRIPTION
Follow-Up Long Enough for Outcomes to Occur	1	Comment: Follow-up is more than 6 months Quote: "These clinical measurements were repeated at 6 weeks, 6 months, and 12 months (± 14 days) after initiation of orthodontic therapy."
Adequacy of Follow-Up of Cohorts	0	Comment: Follow-up rate less than 90% and no description of those lost
Total	6	Medium
Abbate and Colleagues,¹² 2015		
Random Sequence Generation	No	Author Reply: "We created a list with the participants as they were recruited and then two sealed envelopes with the two treatment options. We drew one of the envelopes and that assigned the treatment to the first patient of the list, then we alternated the two treatment options through the list of the patients."
Allocation Concealment	Yes	Quote: "Using sealed envelopes (to 'blind' the decision on the treatment to be performed), each teenager was randomly assigned to one of the two experimental groups: 25 patients were treated with Invisalign [®] aligners and 25 with fixed orthodontic appliances."
Blinding of Participants and Personnel	No	Comment: Blinding of participants and personnel is impossible
Blinding of Outcome Assessment	No	Comment: Blinding of outcome assessment is impossible unless operators take the periodontal assessment after finishing orthodontic treatment and taking off the appliances
Incomplete Outcome Data Addressed	Yes	Quote: "The group treated with Invisalign [®] lost 3 patients (dropouts) due to their having used antibiotics for systemic diseases, which obviously would have compromised the reliability of all the clinical and microbiological procedures' results."
Free of Selective Reporting	Yes	Comment: The authors reported periodontal assessments for all treatment groups at all time points
Loss to Follow-Up Less Than 10%	Yes	Comment: Loss to follow-up was less than 10%. At the 12-month examination, 47 participants in whom evaluation was possible completed the study. A total of 3 participants were lost after the baseline visit Quote: "The group treated with Invisalign [®] lost 3 patients (dropouts) due to their having used antibiotics for systemic diseases, which obviously would have compromised the reliability of all the clinical and microbiological procedures' results."
Baseline Characteristics Balanced	Yes	Comment: The authors observed no significant differences between 2 groups at baseline Quote: "Most of the two experimental groups' indices under study were similar at the beginning of treatment."
Eligibility Criteria Specified	Yes	Comment: The authors reported inclusion and exclusion criteria
Total	NA [†]	Medium
Azaripour and Colleagues,⁹ 2015		
Representativeness of the Exposed Cohort	1	Comment: Truly representative of the exposed cohort
Selection of the Nonexposed Cohort	1	Comment: Nonexposed cohort drawn from the same community as the exposed cohort
Ascertainment of Exposure	1	Comment: Orthodontic treatment has the secure record
Demonstration That Outcome of Interest Was Not Present at Start of Study	1	Comment: Yes. Exclusion criteria included history of periodontitis and diseases that affect periodontal health
Comparability of Cohorts on the Basis of the Design or Analysis	1	Comment: Study controls for the most important factor Quote: "All patients received the same oral hygiene instructions before and during orthodontic treatment. This included the proper use of toothbrush, dental floss and interdental brushes. Patients were recommended to use all three measures of oral care three times daily."
Assessment of Outcome	0	Comment: Self-report Quote: "One calibrated examiner performed all oral examinations."
Follow-Up Long Enough for Outcomes to Occur	1	Comment: Follow-up time is enough Quote: "FOA or Invisalign [®] for at least six months."
Adequacy of Follow-Up of Cohorts	1	Comment: Complete follow-up Quote: "All patients in our study were very cooperative."
Total	7	High
Levrini and Colleagues,¹³ 2015		
Random Sequence Generation	Unclear	Comment: Insufficient information regarding the blinding of personnel Quote: "Sixty-seven patients referred to our clinic for orthodontic treatment and were randomly selected to the test Invisalign treatment group and the fixed appliance treatment group."

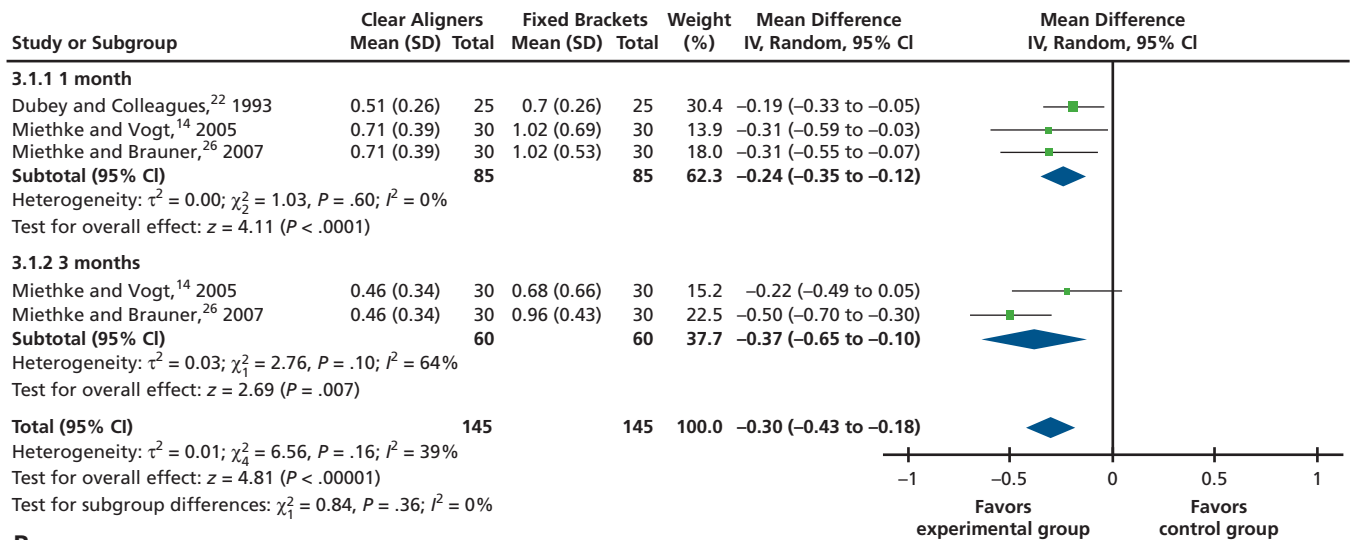
(continued)

eTable 6. Continued

ITEM	AUTHORS' JUDGMENT	DESCRIPTION
Allocation Concealment	Unclear	Comment: Insufficient information to judge Quote: "Sixty-seven patients referred to our clinic for orthodontic treatment and were randomly selected to the test Invisalign treatment group and the fixed appliance treatment group."
Blinding of Participants and Personnel	No	Comment: Blinding of participants and personnel is impossible
Blinding of Outcome Assessment	No	Comment: Blinding of outcome assessment is impossible unless operators take the periodontal assessment after finishing orthodontic treatment and taking off the appliances
Incomplete Outcome Data Addressed	Yes	Quote: "All these data were analyzed at the T0 (beginning of the treatment) T1 (1-month) and T2 (3 months)."
Free of Selective Reporting	Yes	Comment: The authors reported periodontal assessments (bleeding on probing, probing depth, and plaque index) for all treatment groups at all time points
Loss to Follow-Up Less Than 10%	Yes	Comment: There were no missing data according to the results
Baseline Characteristics Balanced	Yes	Comment: The authors observed no significant differences between 2 groups at baseline Quote: "This periodontal assessment was performed at the beginning of the orthodontic treatment (T0). No significant difference was found between the two groups at baseline."
Eligibility Criteria Specified	Yes	Comment: The authors reported inclusion and exclusion criteria
Total	NA	Medium
Machorowska-Pieniązek and Colleagues,²³ 2016		
Random Sequence Generation	Unclear	Comment: Insufficient information regarding the blinding of personnel
Allocation Concealment	Unclear	Comment: Insufficient information to judge
Blinding of Participants and Personnel	No	Comment: Blinding of participants and personnel is impossible
Blinding of Outcome Assessment	No	Comment: Blinding of outcome assessment is impossible unless operators take the periodontal assessment after finishing orthodontic treatment and taking off the appliances
Incomplete Outcome Data Addressed	Yes	Comment: Figure 1 showed the phases of clinical trial and addressed the incomplete data
Free of Selective Reporting	Yes	Comment: The authors reported periodontal assessments (gingival index and plaque index) for all treatment groups at all time points
Loss to Follow-Up Less Than 10%	No	Quote: "The study involved 96 patients and was completed by 85 patients, including 33 girls and 52 boys."
Baseline Characteristics Balanced	Yes	Comment: Baseline examination showed no significant difference
Eligibility Criteria Specified	Yes	Comment: The authors reported inclusion and exclusion criteria
Total	NA	Medium

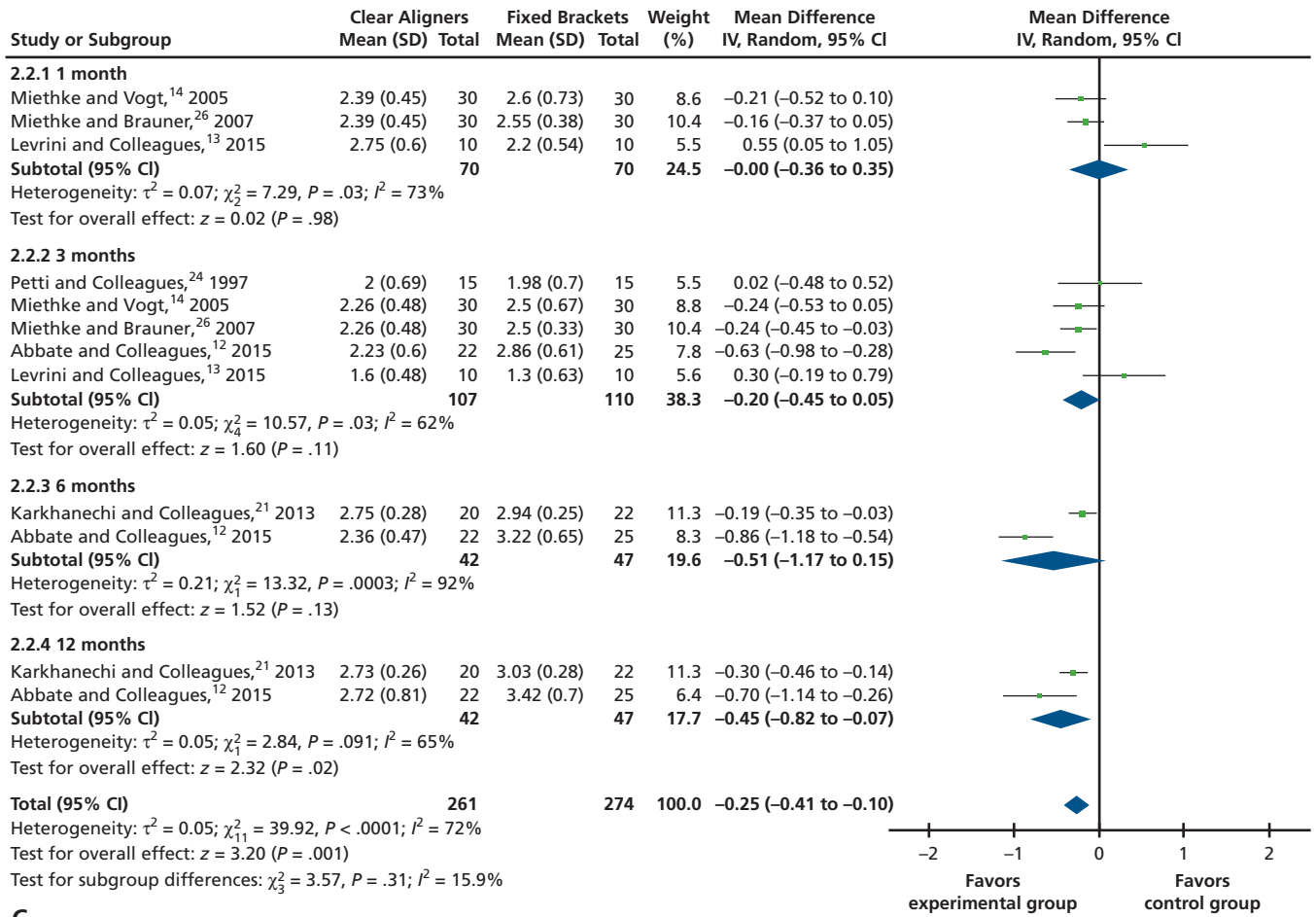


A



B

Figure 1. Subgroup analysis on the duration of follow-up comparing the periodontal health in patients with clear aligners with that in patients with fixed appliances. **A.** Forest plot of PI using random-effects model. **B.** Forest plot of GI using random-effects model. **C.** Forest plot of PD using random-effects model. CI: Confidence interval. IV: Inverse variance. SD: Standard deviation.



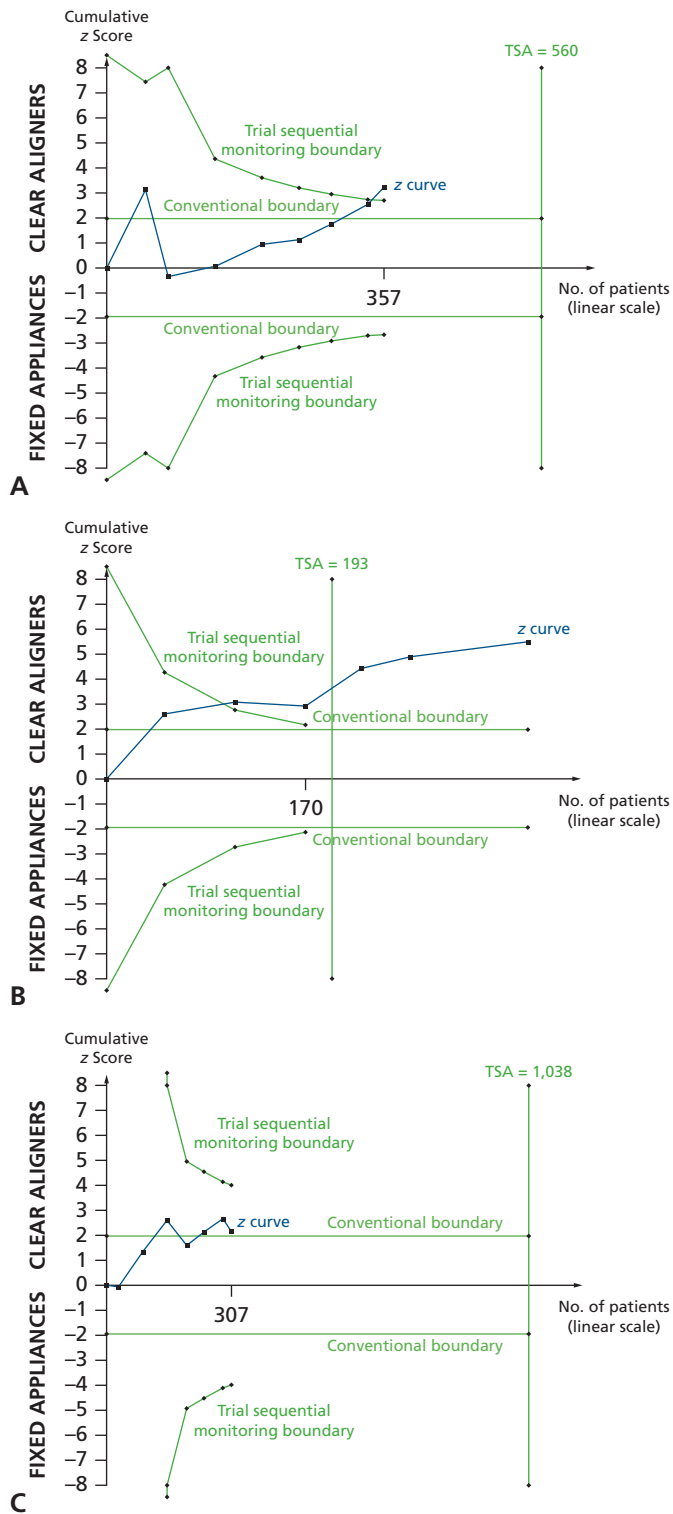
C

eFigure 1. Continued

eTable 7. Grade profile table.

CERTAINTY ASSESSMENT							SUMMARY OF FINDINGS				
No. of Studies	Study Design	Risk of Bias*	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients		Effect		
							Clear Aligners	Fixed Brackets	Relative 95% CI [†]	MD [§]	Absolute Certainty
Clear Aligners Versus Fixed Appliances for Plaque Index in RCTs [‡]											
2	RCTs	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	32	35	1.45 to 2.13 lower	MD [§] 1.79 lower	Moderate
Clear Aligners Versus Fixed Appliances for Plaque Index in Observational Studies											
6	Observational studies	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	138	144	0.03 to 0.45 lower	MD 0.21 lower	Moderate
Clear Aligners Versus Fixed Appliances for Gingival Index in RCTs											
6	RCTs	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	173	187	0.17 to 0.37 lower	MD 0.27 lower	Moderate
Clear Aligners Versus Fixed Appliances for Probing Depth in RCTs											
2	RCTs	Serious	Serious [¶]	No serious indirectness	No serious imprecision	None	32	35	0.77 to 1.19 lower	MD 0.21 lower	Low
Clear Aligners Versus Fixed Appliances for Probing Depth in Observational Studies											
6	Observational studies	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	113	127	0.03 to 0.75 lower	MD 0.39 lower	Moderate

* We rated both types of study as having an unclear risk of bias. † CI: Confidence interval. ‡ RCT: Randomized controlled trial. § MD: Mean difference. ¶ The results of the study by Levrimi and colleagues¹³ were inconsistent with the results of the other studies.



eFigure 2. Trial sequential analysis (TSA) on the pooled results of plaque index (A), gingival index (B), and probing depth (C) according to a random-effects model.

eTable 8. Financial support, conflict of interest, and institutions in the included studies.

AUTHOR	FINANCIAL SUPPORT	CONFLICT OF INTEREST	INSTITUTION
Dubey and Colleagues,²² 1993	Quote: "Unclear"	Quote: "Unclear"	College of Dentistry, Indore, India
Petti and Colleagues,²⁴ 1997	Quote: "Unclear"	Quote: "Unclear"	La Sapienza University of Rome, Italy
Miethke and Vogt,¹⁴ 2005	Quote: "Unclear"	Quote: "Unclear"	University Medicine Berlin, Germany
Miethke and Brauner,²⁶ 2007	Quote: "Unclear"	Quote: "Unclear"	University Medicine Berlin, Germany
Rego and Colleagues,²⁵ 2010	Quote: "This study was supported by the Coordenacao de Aperfeicoamento de Pessoal de Nivel Superior - CAPES (PDEE 0225/03-7), Brazil."	Quote: "None of the authors have a conflict of interest."	University at Buffalo
Karkhanechi and Colleagues,²¹ 2013	Quote: "Unclear"	Quote: "Unclear"	New York University
Abbate and Colleagues,¹² 2015	Quote: "Unclear"	Quote: "There are no conflicts of interest."	University of Insubria, Karolinska Institutet, University of Cagliari, Italy
Azaripour and Colleagues,⁹ 2015	Quote: "No external funding for this study."	Quote: "The authors report no conflicts of interest."	Johannes Gutenberg University Mainz, University of Amsterdam, the Netherlands
Levrini and Colleagues,¹³ 2015	Quote: "Financial support and sponsorship: Nil."	Quote: "Conflicts of interest: There are no conflicts of interest."	University of Insubria, Italy
Machorowska-Pieniążek and Colleagues,²³ 2016	Quote: "Unclear"	Quote: "The authors declare no conflict of interests."	Medical University of Silesia, Poland