

Effectiveness of different adjunctive interventions in the management of orthodontically induced white spot lesions: A systematic review of systematic reviews and meta-analyses

Skuteczność różnych metod leczenia poortodontycznych białych plam próchnicowych – przegląd systematyczny z przeglądów systematycznych i metaanaliz

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Abstract

The purposes of this review were to appraise the current evidence on the management of orthodontically induced white spot lesions (OIWSLs) and to choose the best evidence from among conflicting systematic reviews.

The published literature was searched from inception through November 2019 in 5 databases. Only systematic reviews and/or meta-analyses were eligible for inclusion. Methodological quality was assessed using A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2). The Jadad decision algorithm was applied to choose the best available evidence from among discordant reviews.

Thirteen publications were included. The interventions reported in the management of OIWSLs were topical fluorides, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP)-containing products, fluoride-containing bonding materials, laser therapy, resin infiltration, and micro-abrasion. The methodological quality of the reviews ranged between moderate and critically low according to the AMSTAR-2 tool. Based on the Jadad decision algorithm criteria, topical fluorides yielded a 25–30% prevention of OIWSLs; however, their effect on reversing OIWSLs was unclear. The CPP-ACP products were effective in both preventing and reversing OIWSLs. No differences were noted between fluoride-releasing adhesives and conventional adhesives. Laser irradiation was effective in preventing OIWSLs, with some concerns about the argon laser at a certain setting. Finally, there is a lack of reliable evidence supporting the efficacy of resin infiltration or micro-abrasion due to the limited number of available studies.

Based on the currently available information, topical fluorides and laser irradiation are effective in preventing OIWSLs. The CPP-ACP products are effective in preventing and reversing OIWSLs. Fluoride-releasing adhesives have no effect on OIWSL prevention.

Key words: orthodontics, dental care, tooth demineralization, tooth remineralization, white caries spot

Słowa kluczowe: ortodoncja, opieka stomatologiczna, demineralizacja zębów, remineralizacja zębów, biała plama próchnicowa

Introduction

Achieving optimal occlusion with minimal treatment complications is an essential demand for orthodontic treatment.¹ Orthodontically induced white spot lesions (OIWSLs) are considered one of the most prominent complications, with a prevalence of 68.4% in patients undergoing multi-bracketed fixed orthodontic treatment.² This high percentage of prevalence is due to the irregular and non-uniform surfaces of fixed appliances, which can encourage plaque stagnation and limit natural self-cleansing mechanisms (Fig. 1,2).³⁻⁵

Primarily, patients seek orthodontic treatment in an attempt to improve function and esthetics.⁴ However, these common white, chalky, opaque spots with limited

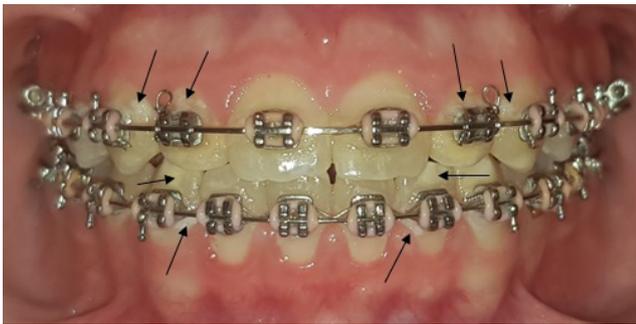


Fig. 1. Clinical case undergoing multi-bracketed fixed orthodontic treatment and developing several orthodontically induced white spot lesions (OIWSLs)

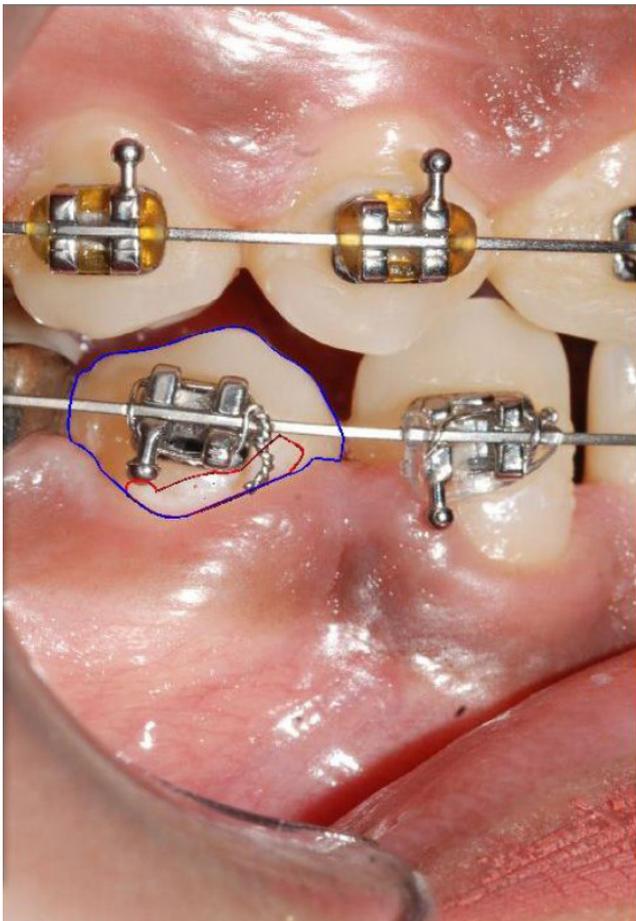


Fig. 2. Orthodontically induced white spot lesion (OIWSL)

spontaneous reversibility may seriously jeopardize esthetic appearance and the patient's satisfaction with the results of treatment.^{4,6,7} Worse still, untreated white spot lesions (WSLs) may lead to tooth cavitation, requiring a subsequent restorative procedure.⁸

It is important to differentiate OIWSLs from other, non-carious white spots, such as fluorosis, developmental enamel hypomineralization or enamel hypoplasia. Firstly, OIWSLs are typically found on the buccal tooth surfaces and around the perimeter of orthodontic brackets whereas non-carious spots usually cover the entire tooth surface and are not associated with orthodontic treatment.^{9,10} Secondly, the consistency and texture of the surface of a clean, dry tooth can be gently assessed with a periodontal probe. Orthodontically induced white spot lesions appear rough, opaque and porous, while non-carious lesions appear mostly smooth and shiny.¹⁰

Numerous research projects have been conducted on the effectiveness of various interventions in the management of OIWSLs. Mainly, the approaches involved either preventing the formation of lesions or reversing the existing ones through 2 basic strategies – remineralizing the enamel or masking the lesions.⁷

Recently, exponential growth in the systematic reviews focusing on this issue has been noticed. However, given the breadth of this topic area, decision-makers have become overwhelmed by a plethora of reviews reporting contradictory conclusions. Thus, a systematic review of the published reviews (an overview or umbrella review) was a logical and appropriate next step, in order to summarize the body of evidence and choose from among the disparate findings of various reviews.

Methods

Protocol and registration

The methodology of this review was formulated in advance by strictly adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. The systematic review protocol was written during the first phase of this review and registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42019135137, which is freely available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=135137.

Question

The research question with regard to the effectiveness of different adjunctive interventions in the management of OIWSLs was defined according to the PICO format:

- P (population) – healthy patients of any age and from any ethnic group who underwent multi-bracketed fixed orthodontic treatment;

- I (intervention) – any adjunctive intervention that would prevent or reverse (manage) OIWSLs;
- C (comparison) – a control group that was not exposed to an adjunctive intervention;
- O (outcome) – any measurement that would reflect the efficacy of the applied intervention, such as changes in the incidence or size of the lesions, or any quantitative assessment of enamel mineral loss.

Eligibility criteria

The following criteria were used to consider articles eligible for this review:

- only systematic reviews and/or meta-analyses were eligible for inclusion;
- only interventions that involve remineralizing the enamel or masking the lesions were included;
- due to the scarcity of randomized controlled trials (RCTs) on this subject, the design of the primary studies of the eligible reviews were either controlled clinical trials (CCTs) (randomized or non-randomized) or prospective observational studies with concurrent comparison.

Trials, narrative literature reviews, reviews including the methods of improving patients' oral hygiene, reviews including laboratory primary studies, and reviews discussing the management of naturally developed WSLs (i.e., without orthodontic treatment) were excluded.

Search strategy

A comprehensive electronic search was performed from inception through November 2019 in the following databases: Cochrane Library, Scopus, Web of Science,

CINAHL via EBSCO, and PubMed. Additionally, the bibliographies of the relevant reviews were screened for further possible reviews. No restrictions were applied on the search strategy with regard to the language, the publication date or the publication status. More details on the search strategy can be found in Supplementary Table 1.

Study selection and data extraction

The authors of the present study independently assessed the identified results of the search and extracted necessary data. The screening process was initiated by assessing titles and abstracts. Then, the full text of each relevant article was evaluated in depth. Articles that failed to meet one or more of the eligibility criteria were eliminated. After filtration, the required data was extracted from the studies using a standardized form that included the authors' names, setting, the number of primary studies, interventions, the number of participants, outcomes, the quality of primary studies, and main findings. Any disagreement between the 2 reviewers was discussed until a resolution was reached.

Quality assessment of the selected reviews

The methodological quality of the obtained systematic reviews was assessed independently by the 2 reviewers utilizing A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2).¹¹ The AMSTAR-2 checklist includes 16 domains that assess the multiple steps of conducting a systematic review, of which 7 domains are considered critical.

Supplementary Table 1. Search strategy

Database	Search strategy	Results
Cochrane Library from inception up to November 30, 2019 Title Abstract Key Word with no limits	#1 orthodontic* OR "orthodontic treatment" #2 "White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz* #3 manag* OR reduc* OR prevent* OR revers* #4 "systematic review" OR "meta-analysis" #5 #1 AND #2 AND #3 AND #4	#5 = 33 (reviews)
Scopus from inception up to November 30, 2019 Title Abstract Key Word with no limits	#1 orthodontic* OR "orthodontic treatment" #2 "White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz* #3 manag* OR reduc* OR prevent* OR revers* #4 "systematic review" OR "meta-analysis" #5 #1 AND #2 AND #3 AND #4	#5 = 33
Web of Science from inception up to November 30, 2019 TS – Topic with no limits	#1 TS = (orthodontic* OR "orthodontic treatment") #2 TS = ("White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz*) #3 TS = (manag* OR reduc* OR prevent* OR revers*) #4 TS = ("systematic review" OR "meta-analysis") #5 #1 AND #2 AND #3 AND #4	#5 = 24
CINAHL via EBSCO from inception up to November 30, 2019 TX – All Text with no limits	(orthodontic* OR "orthodontic treatment") AND ("White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz*) AND (manag* OR reduc* OR prevent* OR revers*) AND ("systematic review" OR "meta-analysis")	15
PubMed from inception up to November 30, 2019 All fields with no limits	(orthodontic* OR "orthodontic treatment") AND ("White lesions" OR "White spot lesions" OR "White spots" OR demineraliz* OR decalcif* OR remineraliz*) AND (manag* OR reduc* OR prevent* OR revers*) AND ("systematic review" OR "meta-analysis")	36

The overall confidence of the results of a systematic review was reported according to the following categories:

- high confidence of the results – no or only one non-critical weakness was found;
- moderate confidence – more than one non-critical weakness was found;
- low confidence – one critical flaw with/without a non-critical weakness was found;
- critically low confidence – more than one critical flaw with/without a non-critical weakness was found.

The overall confidence of the results of the selected systematic reviews was rated electronically by filling out the online AMSTAR-2 checklist (https://amstar.ca/Amstar_Checklist.php).

Choice of the best body of evidence

The Jadad decision algorithm is a simple guide that was designed to interpret discordant reviews and to help decision-makers select the most relevant and valid ones from among them.¹² In this review, when an intervention was addressed by numerous systematic reviews with conflicting results, the Jadad decision algorithm was applied independently by the 2 reviewers. The results were then compared in order to robustly determine the systematic review which provided the best available evidence.

Results

Search results

A total of 141 references were retrieved through the search. After removing duplicates, 82 references were screened for eligibility by titles and abstracts. As a result, 33 articles were considered potentially relevant, and therefore checked in depth. Ultimately, 13 reviews were included. The detailed literature search process is provided in Fig. 3. The excluded reviews are presented in Supplementary Table 2 with the reasons for exclusion.

Characteristics of the selected reviews

The 13 reviews included in this review were published between 2004 and 2019; 4 of them were integrated into meta-analyses.^{4,13–15} The addressed adjunctive interventions were topical fluoride application (assessed by 10 systematic reviews),^{4,6,8,13–19} the application of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) or other casein derivatives (assessed by 4 systematic reviews),^{6,17,18,20} fluoride-releasing bonding materials (assessed by 4 systematic reviews),^{13–15,21} laser therapy (assessed by 1 systematic review),³ resin infiltration (assessed by 1 systematic review),⁶ and micro-abrasion (assessed by 1 systematic review).⁶ The characteristics of the systematic reviews are summarized in Table 1.

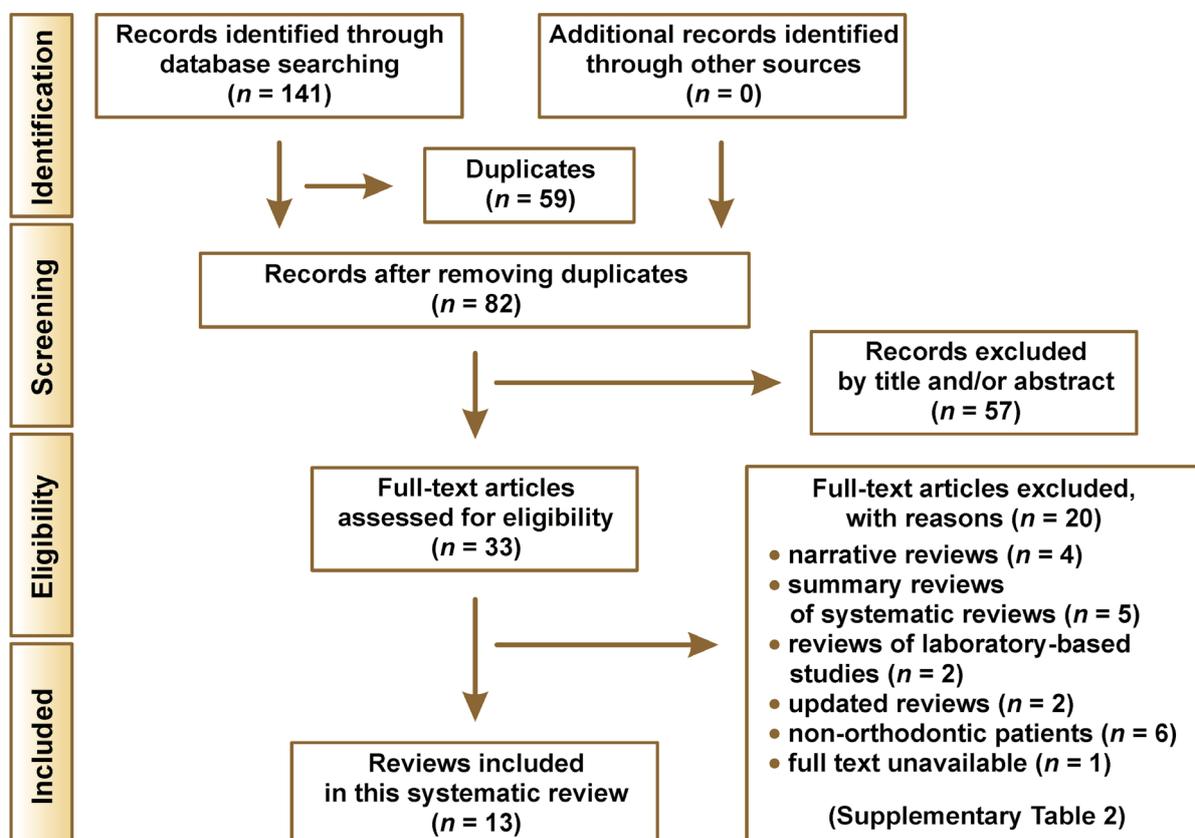


Fig. 3. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

Supplementary Table 2. Excluded studies and the reasons for exclusion

No.	Study	Reason for exclusion
1	Aravind N, Pandiyan S. Demineralisation around orthodontic brackets – A review. <i>Res J Pharm Technol.</i> 2016;9(9):1536–1540.	narrative review
2	Raj BJR, Pradeep S. Remineralising agents in dentistry. <i>Res J Pharm Technol.</i> 2016;9(10):1734–1736.	narrative review
3	Faghiehian R, Shirani M, Tarrahi MJ, Zakizade M. Efficacy of the resin infiltration technique in preventing initial caries progression: A systematic review and meta-analysis. <i>Pediatr Dent.</i> 2019;41(2):88–94.	non-orthodontic patients
4	Hani TB, O'Connell AC, Duane B. Casein phosphopeptide-amorphous calcium phosphate products in caries prevention. <i>Evid Based Dent.</i> 2016;17(2):46–47.	summary review of a systematic review (Raphael S, Blinkhorn A. Is there a place for Tooth Mousse in the prevention and treatment of early dental caries? A systematic review. <i>BMC Oral Health.</i> 2015;15(1):113.)
5	Martinez-Mier EA. Fluoride-containing orthodontic adhesives may reduce the occurrence of enamel demineralization in patients with fixed orthodontic appliances. <i>J Evid Based Dent Pract.</i> 2011;11(3):132–134.	summary review of a systematic review (Rogers S, Chadwick B, Treasure E. Fluoride-containing orthodontic adhesives and decalcification in patients with fixed appliances: A systematic review. <i>Am J Orthod Dentofacial Orthop.</i> 2010;138(4):390.e1–e390.e8.)
6	Kalha AS. Topical fluorides and decalcification around fixed orthodontic appliances. <i>Evid Based Dent.</i> 2006;7(2):38–39.	summary review of a systematic review (Chadwick BL, Roy J, Knox J, Treasure ET. The effect of topical fluorides on decalcification in patients with fixed orthodontic appliances: A systematic review. <i>Am J Orthod Dentofacial Orthop.</i> 2005;128(5):601–606.)
7	O'Neill J. Little evidence exists about optimal caries-prevention strategies during orthodontic treatment. <i>Evid Based Dent.</i> 2004;5(4):97.	summary review of a systematic review (Derks A, Katsaros C, Frencken JE, van't Hof MA, Kuijpers-Jagtman AM. Caries-inhibiting effect of preventive measures during orthodontic treatment with fixed appliances. <i>Caries Res.</i> 2004;38(5):413–420.)
8	Cheng LL. Limited evidence indicates fluoride may prevent demineralized white lesions during orthodontic treatment. <i>J Am Dent Assoc.</i> 2015;146(9):699–701.	summary review of a systematic review (Benson PE, Parkin N, Dyer F, Millett DT, Furness S, Germain P. Fluorides for the prevention of early tooth decay (demineralised white lesions) during fixed brace treatment. <i>Cochrane Database Syst Rev.</i> 2013;12:CD003809.)
9	Taha AA, Patel MP, Hill RG, Fleming PS. The effect of bioactive glasses on enamel remineralization: A systematic review. <i>J Dent.</i> 2017;67:9–17.	review of laboratory-based studies
10	Rahimi F, Sadeghi M, Mozaffari HR. Efficacy of fluoride varnish for prevention of white spot lesions during orthodontic treatment with fixed appliances: A systematic review study. <i>Biomed Res Ther.</i> 2017;4(8):1513–1526.	review of laboratory-based studies
11	Cosma LL, Şuhani RD, Mesaroş A, Badea ME. Current treatment modalities of orthodontically induced white spot lesions and their outcome – a literature review. <i>Med Pharm Rep.</i> 2019;92(1):25–30.	narrative review
12	Bergstrand F, Twetman S. Evidence for the efficacy of various methods of treating white-spot lesions after debonding of fixed orthodontic appliances. <i>J Clin Orthod.</i> 2003;37(1):19–21.	neither abstract nor full-text available (a request was sent to the corresponding author and the journal to get the article; however, no response was received)
13	Li J, Xie X, Wang Y, et al. Long-term remineralizing effect of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) on early caries lesions in vivo: A systematic review. <i>J Dent.</i> 2014;42(7):769–777.	non-orthodontic patients
14	Paula ABP, Fernandes AR, Coelho AS, et al. Therapies for white spot lesions – a systematic review. <i>J Evid Based Dent Pract.</i> 2017;17(1):23–38.	non-orthodontic patients
15	Raphael S, Blinkhorn A. Is there a place for Tooth Mousse in the prevention and treatment of early dental caries? A systematic review. <i>BMC Oral Health.</i> 2015;15(1):113.	non-orthodontic patients
16	Borges AB, Caneppele TMF, Masterson D, Maia LC. Is resin infiltration an effective esthetic treatment for enamel development defects and white spot lesions? A systematic review. <i>J Dent.</i> 2017;56:11–18.	non-orthodontic patients
17	Indrapriyadharshini K, Madan Kumar PD, Sharma K, Iyer K. Remineralizing potential of CPP-ACP in white spot lesions – a systematic review. <i>Indian J Dent Res.</i> 2018;29(4):487–496.	non-orthodontic patients
18	Benson PE, Parkin N, Millett DT, Dyer F, Vine S, Shah A. Fluorides for the prevention of white spots on teeth during fixed brace treatment. <i>Cochrane Database Syst Rev.</i> 2004;3:CD003809.	updated in 2013; the updated version is included in this review
19	Sudjalim TR, Woods MG, Manton DJ. Prevention of white spot lesions in orthodontic practice: A contemporary review. <i>Aust Dent J.</i> 2006;51(4):284–289;quiz 347.	narrative review
20	Bergstrand F, Twetman S. A review on prevention and treatment of post-orthodontic white spot lesions – evidence-based methods and emerging technologies. <i>Open Dent J.</i> 2011;5:158–162.	updated in 2016; the updated version is included in this review

Table 1. Characteristics of the included reviews assessing the effectiveness of different interventions in managing orthodontically induced white spot lesions (OIWSLs)

Study/setting	Study design	No. of primary studies	Age of participants*	Interventions/ No. of studies in each	No. of participants
Tasios et al. ¹⁵ 2019, Greece	systematic review and meta-analysis	23	mean age of 14.4 years	– fluoride varnish (4) – fluoride varnish under banding cement (2) – fluoride-releasing adhesives (8) – flat-surface sealants (5) – active reminders (4)	1,473 in total
Sardana et al. ¹⁶ 2019, China	systematic review	3	mean age of 13.3 years (for 1 study) range of 11–16 years/13–21 years (for 2 studies)	self-applied topical fluorides	505 (prevention of OIWSLs) 26 (reversal of OIWSLs)
Pithon et al. ²⁰ 2019, Brazil	systematic review	11	mean age of 14.87 years	CPP-ACP	not addressed
Sardana et al. ⁴ 2019, China	systematic review and meta-analysis	11	mean age of 15.21 years	professional topical fluoride application in order to prevent or reverse OIWSLs	518 (prevention of OIWSLs) 693 (reversal of OIWSLs)
Raghis et al. ³ 2018, Syria	systematic review	8	mean age of 13.45 years	laser irradiation: – CO ₂ laser – Nd:YAG laser – argon laser – Optodan laser	183
Nascimento et al. ¹³ 2016, Brazil	systematic review and meta-analysis	7	NA	fluoride-releasing materials (cementation materials, varnish and sealant)	1,867 teeth
Lapenaite et al. ¹⁷ 2016, Lithuania	systematic review	11	NA	fluoride products or casein derivatives	998 (studies on fluoride) 314 (studies on casein derivatives)
Sonesson et al. ⁶ 2016, Denmark	systematic review	7	≤30 years	– remineralizing agents (fluoride, CCP-ACP) – micro-abrasion – resin infiltration	not addressed
Chen et al. ¹⁸ 2013, China	systematic review	7 (3 – fluoride vs control; 2 – CPP-ACP vs control; 2 – fluoride vs CPP-ACP)	NA	remineralizing agents (fluoride, CCP-ACP)	173 (studies on fluoride) 110 (studies on CPP-ACP) 86 (studies on fluoride vs CPP-ACP)
Benson et al. ⁸ 2013, UK	systematic review	3	mean age of 15 years (for 2 studies) adults up to 45 years (for 1 study)	fluorides	458
Rogers et al. ²¹ 2010, UK	systematic review	10	NA	fluoride-containing adhesives	not addressed
Chadwick et al. ¹⁹ 2005, UK	systematic review	6	NA	topical fluorides	not addressed
Derks et al. ¹⁴ 2004, the Netherlands	systematic review and meta-analysis	15	NA	fluorides, chlorhexidine, polymeric coating or fluoride-releasing sealant, and bonding material	847 (fluorides) 111 (chlorhexidine) 59 (polymeric coating or fluoride-releasing sealant) 297 (bonding material)

CPP-ACP – casein phosphopeptide-amorphous calcium phosphate; Nd:YAG laser – neodymium-doped yttrium aluminum garnet laser;

QLF – quantitative light-induced fluorescence; *M* – mean; *SD* – standard deviation; *CI* – confidence interval;

SEM – scanning electron microscopy; NA – not applicable.

*The mean age of the participants was calculated based on the available data (mean age) provided in the included reviews.

Outcomes	Quality of primary studies	Results
<ul style="list-style-type: none"> – incidence of OIWSLs – severity of OIWSLs 	<ul style="list-style-type: none"> unclear risk (7) high risk (16) 	<ul style="list-style-type: none"> – Fluoride varnish, flat-surface sealants and active reminders were associated with a reduced development and magnitude of lesions; however, the strength of this recommendation is mostly low. – No statistically significant difference was found for fluoride varnish under banding cement. – No statistically significant improvement was found for fluoride-releasing adhesives.
<ul style="list-style-type: none"> – changes in the incidence of OIWSLs as the primary outcome (studies on prevention) – reduction in the size of OIWSLs or mean fluorescence values or the prevalence of OIWSLs as the primary outcomes (studies on reversal) 	<ul style="list-style-type: none"> low risk(1) high risk (2) 	Although the review did not confirm the effectiveness of self-applied fluorides in the reversal of OIWSLs, it did partially substantiate the positive role (although indirectly) of self-applied fluorides in the prevention of OIWSLs based on a single trial with a low risk of bias.
prevention or treatment of OIWSLs around orthodontic braces	<ul style="list-style-type: none"> low risk (9) unclear risk (2) 	The CPP-ACP products were effective in the prevention and treating of OIWSLs.
<ul style="list-style-type: none"> – difference in the incidence of OIWSLs – change in the mean QLF scores or the mean DIAGNOdent scores 	<ul style="list-style-type: none"> low risk (5) medium risk (4) high risk (2) 	<ul style="list-style-type: none"> – Professional topical fluoride application brought about a 25–30% reduction in the incidence of OIWSLs (pooling 3 studies). – The standardized mean difference was found to be 0.57 less in the professional topical fluoride application group than in the control group (95% CI: from 0.23 to –0.91) in the studies evaluating the reversal of OIWSLs (pooling 3 studies); however, the effect of professional topical fluoride application on the reversal of OIWSLs was unclear due to concerns in interpreting the DIAGNOdent values.
<ul style="list-style-type: none"> – formation or non-formation of OIWSLs assessed clinically or with digital images – degree of decalcification – changes in the enamel structure after laser application 	<ul style="list-style-type: none"> unclear risk (all studies) 	Laser irradiation was effective in inhibiting demineralization during orthodontic treatment.
<ul style="list-style-type: none"> – risk of patients developing OIWSLs – the <i>M</i> and <i>SD</i> values of the extent of OIWSLs acc. to the Gorelick scale 	<ul style="list-style-type: none"> high risk (all studies) 	<ul style="list-style-type: none"> – The pooled relative risk of developing OIWSLs when using cementation materials as compared to control was 0.35 (95% CI: 0.15–0.81); hence, patients using fluoride-releasing materials were at a lower risk of developing OIWSLs (pooling 4 studies). The risk reduction was statistically significant for fluoride varnish, but not for sealant (only 1 study was included for each intervention). – The pooled mean difference in the extent of OIWSLs between the experimental and control groups was statistically significant for cementation materials, but not for varnish and sealant.
prevention of OIWSLs	not addressed	The results showed positive effects of the fluoride products and casein derivatives on preventing OIWSLs (4 out of 6 studies revealed the effectiveness of the fluoride products in preventing OIWSLs; 3 out of 5 studies revealed the effectiveness of casein derivatives in preventing OIWSLs).
extent, hardness or appearance of OIWSLs with a follow-up period of at least 8 weeks, as assessed with visual clinical scores, photographs, caries detection devices, or patient/therapist satisfaction	<ul style="list-style-type: none"> low risk (2) high risk (5) 	There is a lack of reliable scientific evidence to support remineralizing or camouflaging strategies to manage OIWSLs (2 out of 4 trials revealed a significant effect of fluoride, 1 out of 3 trials revealed a significant effect of CCP-ACP, the 2 included trials on resin infiltration revealed a significant effect, and 1 trial revealed a significant effect of micro-abrasion).
difference in the severity of OIWSLs between the experimental and control groups as the primary outcome (severity was expressed in terms of the area over the whiteness of the lesion or as the amount of mineral loss or the lesion depth)	<ul style="list-style-type: none"> medium risk (1) high risk (6) 	There is a lack of reliable evidence to support the effectiveness of remineralizing agents in the treatment of OIWSLs (1 out of 3 studies revealed the ineffectiveness of fluorides in managing OIWSLs; 1 study indicated that CPP-ACP was effective in managing OIWSLs, while another one found no significant difference as compared to control; 1 study indicated that fluoride was more effective than CPP-ACP, while another one found no difference).
<ul style="list-style-type: none"> – presence or absence of new lesions by participant – differences in the size and severity of OIWSLs between the experimental and control groups – any quantitative assessment of enamel mineral loss, such as fluorescent light techniques or microradiography, used with in situ caries models – any participant-assessed outcomes, such as the perception of the lesions and oral health-related quality of life data – adverse effects 	<ul style="list-style-type: none"> low risk (1) medium risk (1) high risk (1) 	<ul style="list-style-type: none"> – Applying fluoride varnish every 6 weeks at the time of the orthodontic review during treatment is effective, but this finding is based on a single study. – None of the included studies reported data on the size and severity of OIWSLs, the quantitative assessment of enamel mineral loss, patient's perception, oral health-related quality of life, and adverse effects.
any outcome measures of decalcification and the presence of OIWSLs	not addressed	It is impossible to make recommendations on the use of fluoride-containing adhesives during fixed orthodontic treatment. However, there is evidence to suggest that glass ionomer cement is more effective than composite resin in the prevention of OIWSLs, but the evidence is weak.
any valid outcome measure of decalcification, both before and after treatment	not addressed	The use of topical fluorides in addition to a fluoride toothpaste reduced the incidence of decalcification in populations with both fluoridated and non-fluoridated water supplies (all the included studies found a significant difference). Different preparations and formats appear to decrease decalcification, but there is no evidence that any method is superior. There is some evidence that the potency of fluoride preparations might be important.
any demineralization scores	not addressed	The use of a toothpaste and gel with a high fluoride concentration of 1,500–5,000 ppm, or complementary chlorhexidine during orthodontic treatment showed a demineralization-inhibiting effect. The use of a polymeric tooth coating on the tooth surface around the brackets or a fluoride-releasing bonding material showed almost no demineralization-inhibiting effect. Pooling data was only applied for the studies assessing fluoride-releasing bonding materials, where the overall prevented fraction was 20% (SEM 0.09). However, this effect was not statistically significant.

Methodological quality of the included reviews

The methodological quality of the reviews ranged between a critically low to moderate confidence of the results. In other words, all the reviews were fraught with some methodological shortcomings. The AMSTAR-2 questions and the results for the reviews are presented in Table 2. The detailed supporting reasons for each assessment are provided in Supplementary Table 3. With regard to the 7 critical domains of the AMSTAR-2 tool, most reviews failed to contain an explicit statement that the review methods were established prior to the conduct of the review (69.23% of the included reviews), did not use a satisfactory technique to assess the risk of bias in each individual study (53.84% of the included reviews), and did not account for the risk of bias in individual studies when interpreting and discussing the results (46.15% of the included reviews).

Effects of interventions

Effect of topical fluorides in the management of OIWSLs

Ten systematic reviews provided the results from studies evaluating the effectiveness of topical fluorides in the management of OIWSLs: Tasios et al. 2019,¹⁵ Sardana et al. 2019,¹⁶

Sardana et al. 2019 (Epub 2018),⁴ Nascimento et al. 2016,¹³ Lapenaite et al. 2016,¹⁷ Sonesson et al. 2016,⁶ Chen et al. 2013,¹⁸ Benson et al. 2013,⁸ Chadwick et al. 2005,¹⁹ and Derks et al. 2004.¹⁴ Different forms were utilized to apply topical fluorides, including fluoride varnish, fluoride gel, fluoridated mouth rinse, fluoridated toothpaste, fluoridated water, and fluoride chewing sticks.

Some of these reviews deduced that topical fluorides were effective in managing OIWSLs,^{4,8,13–15,17,19} while others failed to find reliable significant evidence.^{6,16,18} All the reviews were addressing the same review question, but the recruited trials and the selection criteria varied among them. In this case, the Jadad algorithm suggests that the best available review be selected according to the superiority in its publication status, the methodological quality of its primary studies, language restrictions, and the analysis of data on individual patients. As a result, Sardana et al. 2019⁴ was selected (Fig. 4). The detailed steps of the Jadad decision algorithm used from the beginning until the final constructive decision are presented in Supplementary Table 4.

Sardana et al. 2019⁴ addressed the use of professional fluorides and recruited 11 RCTs published between 2007 and 2017. All primary studies used a parallel-arm design. The results indicated that fluorides led to a 25–30% reduction in the incidence of OIWSLs; however, their effect on reversing lesions was unclear due to concerns in interpreting the DIAGNOdent values.

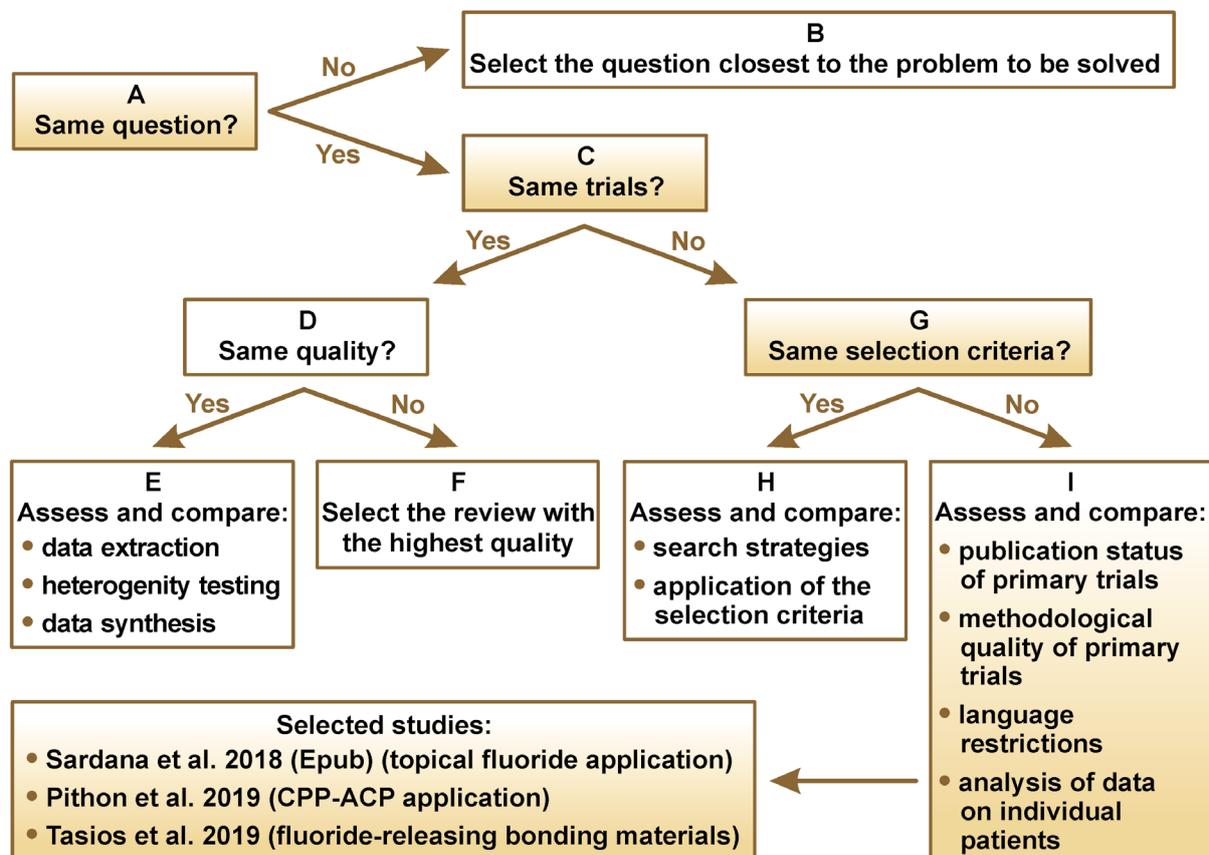


Fig. 4. Flow diagram of the Jadad decision algorithm for conflicting reviews on efficacy of topical fluorides, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and fluoride-releasing adhesives

Table 2. The AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews-2) criteria for the included reviews

Domains	Tasios 2019 ¹⁵	Sardana 2019 ¹⁶	Pithon 2019 ²⁰	Sardana 2019 ⁴	Raghis 2018 ³	Nascimento 2016 ¹³	Lapenaite 2016 ¹⁷	Sonesson 2016 ⁶	Chen 2013 ¹⁸	Benson 2013 ⁸	Rogers 2010 ²¹	Chadwick 2005 ¹⁹	Derks 2004 ¹⁴
1. Did the research questions and inclusion criteria for the review include the components of PICO?	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	no	no	no
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	yes	yes	yes	yes	no	no	no	no	no	no	no	no	no
3. Did the review authors explain their selection of the study designs for inclusion in the review?	yes	no	no	no	no	no	no	no	no	no	no	no	no
4. Did the review authors use a comprehensive literature search strategy?	yes	yes	yes	yes	yes	no	P yes	P yes	P yes	P yes	yes	no	P yes
5. Did the review authors perform study selection in duplicate?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
6. Did the review authors perform data extraction in duplicate?	yes	yes	no	yes	yes	yes	no	yes	yes	yes	yes	yes	no
7. Did the review authors provide a list of the excluded studies and justify the exclusions?	yes	yes	yes	yes	yes	no	no	yes	yes	yes	yes	no	yes
8. Did the review authors describe the included studies in adequate detail?	yes	yes	P yes	yes	P yes	P yes	no	P yes	P yes	yes	P yes	P yes	P yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	- RCTs: yes - non-RCTs: no	yes	- RCTs: yes - non-RCTs: yes	yes	- RCTs: yes - non-RCTs: no	yes	no	- RCTs: yes - non-RCTs: no	yes	yes	no	no	no
10. Did the review authors report on the sources of funding for the studies included in the review?	no	no	no	no	no	no	no	no	no	yes	no	no	no
11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of the results?	- RCTs: yes - non-RCTs: no	-	-	yes	-	yes	-	-	-	-	-	-	no
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	yes	-	-	yes	-	no	-	-	-	-	-	-	no
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	yes	yes	no	yes	no	yes	no	yes	yes	yes	no	no	no
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	yes	yes	no	no	yes	yes	no	no	no	no	yes	no	no
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the results of the review?	no	-	-	yes	-	no	-	-	-	-	-	-	no
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	yes	yes	no	yes	yes	no	no	no	yes	yes	yes	no	no
Quality results	CL	M	L	M	CL	L	CL	L	M	M	CL	CL	CL

RCT – randomized critical trial; P yes – partial yes; M – moderate; L – low; CL – critically low.

Supplementary Table 3. Detailed supporting reasons for the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews-2) assessment of each included review

Domains	Tasios 2019 ¹⁵	Sardana 2019 ¹⁶
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes: As stated on page 2 in the "Eligibility criteria" section: "According to the Participants-Intervention-Comparison-Outcome study design (PICOS)..."	Yes: As stated on page 2: "The Population-Intervention-Control-Outcome (PICO) schema was used to direct the inclusion of studies as follows:..."
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes: As stated on page 2: "The review protocol was made a priori, registered in PROSPERO (CRD42017079352) and all post hoc changes were appropriately noted".	Yes: As stated on page 2: "The methodology of the review was formulated in advance by strictly adhering to the PRISMA guidelines".
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes: As stated on page 2: "due to the scarcity of RCTs on this subject, included were randomized or quasi-randomized prospective controlled human trials".	No: Authors did not provide the explanation for including RCTs and quasi-randomized CCTs only.
4. Did the review authors use a comprehensive literature search strategy?	Yes: <ul style="list-style-type: none"> - Authors searched 9 databases. - Authors searched trial registries: metaRegister of Controlled Trials. - Authors searched DOAJ and PQDT. - The reference lists and Google Scholar citation lists of the eligible full-text articles as well as the reference lists of relevant systematic reviews were screened manually for additional studies. - Key words and the search strategy were provided in Appendix Table 1. - No restrictions were applied on the language, publication year or status. 	Yes: <ul style="list-style-type: none"> - Authors searched 4 databases. - Grey literature (www.opengrey.com) was searched to find any registered trial or unpublished material. - The reference lists of the eligible articles were screened manually for additional studies. - Key words were provided in Table 1. - No restrictions were applied on the publication year or status. However, only articles written in English were included.
5. Did the review authors perform study selection in duplicate?	Yes: As stated in the abstract: "Study selection, data extraction and risk of bias assessment were done independently in duplicate".	Yes: As stated on page 3: "After the removal of duplicates, 2 authors (DS and MS) independently screened titles and their respective abstracts in a standardized manner to determine their inclusion/exclusion in the review".
6. Did the review authors perform data extraction in duplicate?	Yes: As stated in the abstract: "Study selection, data extraction and risk of bias assessment were done independently in duplicate".	Yes: As stated on page 3: "The characteristics of the respective studies and their data were extracted individually by 2 authors (DS and MS) on a piloted pro forma".
7. Did the review authors provide a list of the excluded studies and justify the exclusions?	Yes: The list of the studies identified from the literature and their inclusion/exclusion status with reasons was provided in Appendix Table 2.	Yes: As stated on page 3: "The detailed reasons for the exclusion of the remaining 70 articles are presented in Supplementary Appendix 2".
8. Did the review authors describe the included studies in adequate detail?	Yes: Populations, interventions, comparators, outcomes, the study design, the study setting, and follow-up were all described in details in Tables 1 and 2 as well as in the text.	Yes: Populations, interventions, comparators, outcomes, the study design, the study setting, and follow-up were all described in Table 2.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. No: Non-randomized controlled trials were assessed by the RoB tool rather than the ROBINS-I tool.	Yes: Randomized controlled trials were appropriately assessed by the RoB-2 tool. Non-randomized trials were not included.
10. Did the review authors report on the sources of funding for the studies included in the review?	No: Funding for primary studies was not reported in the review or in the "Other bias" section referring to the RoB tool.	No: Funding for primary studies was not reported in the review.
11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of the results?	Yes: For RCTs, authors used an appropriate technique to combine the study results and adjusted for heterogeneity. No: Authors did not report separate summary estimates for NRSIs.	Meta-analysis was not performed.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes: Authors performed sensitivity analyses and presented them in Appendix Table 8.	Meta-analysis was not performed.
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes: The risk of bias in individual studies was accounted for, especially when applying the GRADE criteria.	Yes: The risk of bias was accounted for when interpreting results such as: "Since this deduction is made based on 2 trials – 1 with a low risk of overall bias and 1 with a high risk of bias – this conclusion should be interpreted with caution, and the present review recommends further trials to confirm this". Moreover, the risk of bias was accounted for when evaluating the overall quality of evidence.
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes: The impact of heterogeneity was accounted for when discussing the results of the review.	Yes: As stated: "All 3 trials were quite heterogeneous in regards to the intervention (high-fluoride vs low-fluoride toothpaste; the composition of the fluoride agent), control group and outcome (2 assessed prevention at debonding and 1 assessed reversal at 26 weeks). Hence, it is quite difficult to give any recommendation by pooling the results qualitatively" and "The trials included in the review were of considerable heterogeneity, and this hampers providing the recommendations/guidelines pertaining to the concentration of fluoride, the fluoride carrier or the fluoride agent in the carrier".
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the results of the review?	No: Publication bias was not considered in the review.	Meta-analysis was not performed.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes: As stated on page 10: "All authors declare that there is no conflict of interest".	Yes: As stated in the abstract: "This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors".

Continued Supplementary Table 3

	Pithon 2019 ²⁰	Sardana 2019 ⁴	Raghis 2018 ³
1.	Yes: As stated on page 2: "To be included in the review, studies needed to comply with the following selection criteria, according to the PICOS strategy..."	Yes: As stated on page 2: "The PICO schema for individual studies was used to determine the eligibility criteria and is presented in Table 1".	Yes: As stated on page 323: "These review questions were developed according to the population, intervention, comparison, and outcome (PICO) study design".
2.	Yes: As stated on page 2: "The protocol used for the systematic review of the effectiveness of CPP-ACP-containing products was recorded in the International Prospective Register of Systematic Reviews".	Yes: As stated on page 2: "The present review was devised a priori by following the PRISMA guidelines".	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.
3.	No: Authors did not provide the explanation for including both RCTs and CCTs.	No: Authors did not provide the explanation for including RCTs and quasi-randomized CCTs only.	No: Authors did not provide the explanation for including both RCTs and CCTs.
4.	Yes: – Authors searched 5 databases. – Authors searched trial registries: ClinicalTrials. – Grey literature was searched by www.opengrey.com. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided within the text. – No restrictions were applied on the language, publication year or status.	Yes: – Authors searched 4 databases. – Grey literature (www.opengrey.com) was searched to find any registered trial or unpublished material. – The reference lists of the eligible articles and relevant reviews were screened manually for additional studies. – Key words were provided in Table 2. – Restrictions were applied on the language, including only the English language. – No limits were applied to the search strategy regarding the publication year or the current stage of the trial.	Yes: – Authors searched 5 databases. – Authors searched trial registries: ClinicalTrials and ICTRP. – Grey literature was searched by www.opengrey.com. – PQDT was searched for dissertations. – The reference lists of the eligible articles were screened manually for additional studies. – Key words and the search strategy were provided in Supplementary Material 1. – No restrictions were applied on the language, publication year or status.
5.	Yes: As stated on page 2: "The selections were performed by 2 independent researchers".	Yes: As stated in the abstract: "Two reviewers independently selected studies, extracted data and assessed the risk of bias".	Yes: As stated on page 323: "The obtained articles were independently subjected to clear inclusion and exclusion criteria by 2 authors".
6.	No: It was not stated that data was extracted in duplicate.	Yes: As stated in the abstract: "Two reviewers independently selected studies, extracted data and assessed the risk of bias".	Yes: As stated on page 323: "The data was extracted from studies according to the aims of the systematic review by the same 2 authors independently".
7.	Yes: The potentially relevant studies that were read in the full-text form, but excluded from the review were stated and cited within the text in the "Results" section (page 3) with the justification for exclusion.	Yes: The details of the reasons for the exclusion of studies after full-text reading was presented in Appendix 2.	Yes: The details of the reasons for the exclusion of studies after full-text reading was presented in Supplementary Material 2.
8.	Partial Yes: Populations, interventions, comparators, outcomes, and the study design were described. However, the study setting and follow-up were not addressed.	Yes: Populations, interventions, comparators, outcomes, the study design, the study setting, and follow-up were all described in details in Table 3 and within the text.	Partial Yes: Though populations, interventions, comparators, outcomes, the study design, and follow-up were described, the study setting was not addressed.
9.	Yes: Randomized controlled trials were appropriately assessed by the RoB-2 tool. Yes: Non-randomized controlled trials were appropriately assessed by the ROBINS-I tool.	Yes: Randomized controlled trials were appropriately assessed by the RoB-2 tool. Non-randomized trials were not included.	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. No: Non-randomized controlled trials were assessed by the RoB tool rather than the ROBINS-I tool.
10.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review or in the "Other bias" section referring to the RoB tool.
11.	Meta-analysis was not performed.	Yes: Authors used an appropriate weighted technique to combine the study results and adjusted for heterogeneity if present.	Meta-analysis was not performed.
12.	Meta-analysis was not performed.	Yes: Sensitivity analysis was performed by excluding 'high-risk' trials and trials with 'some concerns' from quantitative synthesis.	Meta-analysis was not performed.
13.	No: Authors did not account for the moderate risk of bias found in the 2 included studies when interpreting the results.	Yes: The risk of bias in individual studies was accounted for when discussing the results.	No: Authors did not account for the unclear risk of bias found in all the included studies when interpreting the results.
14.	No: Heterogeneity was not addressed.	No: Though authors performed an investigation for heterogeneity among studies, they did not discuss its impact on the results of the review.	Yes: As stated on page 325: "Heterogeneity was observed due to the study designs, treatment protocols and the assessed outcomes of the included studies".
15.	Meta-analysis was not performed.	Yes: Though funnel plots and statistical analysis were not provided, publication bias was discussed in the review as follows: "the unpublished study did not find any significant effect of 1.23% APF gel on the prevention of EWSLs during orthodontic treatment, which might have resulted in publication bias".	Meta-analysis was not performed.
16.	No: Neither funding nor conflicting interests were stated in the review.	Yes: As stated on page 9: "This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Conflicts of interest: None to be declared".	Yes: As stated on page 321: "Funding: None declared. Conflict of interest: None declared".

Continued Supplementary Table 3

	Nascimento 2016 ¹³	Lapenaite 2016 ¹⁷	Sonesson 2016 ⁶
1.	Yes: As stated on page 102: "The eligibility criteria and search strategy were based on the PICO elements (population, intervention, comparison, and outcome)".	No: The PICO components were not all included when addressing the inclusion criteria (comparison and outcome were not stated).	Yes: As stated on page 2: "The PICO was set up as follows..."
2.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.
3.	No: Authors did not provide the explanation for including only RCTs.	No: Authors did not provide the explanation for including both RCTs and quasi-RCTs.	No: Authors did not provide the explanation for including both RCTs and CCTs.
4.	No: – Authors searched only 1 database. – Trial registries and grey literature were not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided on page 102. – No restrictions were applied on the language, publication year or status.	Partial Yes: – Authors searched 5 databases. – Trial registries and grey literature were not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided on page 4. – Restrictions were applied on the language (only articles written in English) and publication year (articles published between 2008 and 2013).	Partial Yes: – Authors searched 4 databases. – Authors searched trial registries: ClinicalTrials. – Grey literature was not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words and the search strategy were provided in Supplement 1. – Restrictions were applied on the language (only articles written in English) and publication year (articles published between 2011 and Oct 31, 2015).
5.	Yes: As stated on page 102: "Two independent reviewers screened the search results".	Yes: As stated on page 4: "Three researchers independently reviewed the titles and abstracts of the potentially relevant studies".	Yes: As stated in the abstract: "Abstract lists and selected full-text papers were independently examined by 2 reviewers, and any differences were solved by consensus".
6.	Yes: As stated on page 102: "To record the study characteristics, methodological quality and results, the reviewers used a data extraction form according to the CONSORT 2010 statement. Disagreement between the 2 reviewers was solved either by consensus or by a third reviewer".	No: The review did not contain an explicit statement that authors performed data extraction in duplicate.	Yes: As stated on page 2: "Key data from the accepted studies were extracted independently by 2 authors".
7.	No: The list of the excluded studies and the reasons for exclusion were not provided. Figure 1 provided the number of the excluded studies without providing the authors' names for each study.	No: The list of the excluded studies and the reasons for exclusion were not provided.	Yes: As stated on page 3: "The excluded studies with the main reason for exclusion are shown in Table 3".
8.	Partial Yes: Populations, interventions, comparators, outcomes, and the study design were described, but not in details. Moreover, the study setting and follow-up were not addressed.	No: Though populations, interventions and comparators were described (not in details), outcomes, the study design, the study setting, and follow-up were not addressed.	Partial Yes: Populations, interventions, comparators, outcomes, the study design, and follow-up were described, but not in details. Moreover, the study setting was not addressed.
9.	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. Not-randomized trials were not included.	No: The risk of bias was not assessed.	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. No: Non-randomized controlled trials were assessed by the RoB tool rather than the ROBINS-I tool.
10.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review.
11.	Yes: Authors used an appropriate technique to combine the study results and adjusted for heterogeneity.	Meta-analysis was not performed.	Meta-analysis was not performed.
12.	No: All studies were at a high risk of bias and were all included in evidence synthesis.	Meta-analysis was not performed.	Meta-analysis was not performed.
13.	Yes: As stated: "all the included studies presented a high risk of bias, indicating that the evidence is weak".	No: The risk of bias was not assessed.	Yes: The risk of bias in individual studies was accounted for when interpreting the results, especially when applying the GRADE criteria.
14.	Yes: As stated on page 106: "The subgroup analysis showed a 65% heterogeneity between the materials, indicating that the type of material partially explained the heterogeneity. Thus, different approaches for delivering fluorides near brackets could be related to the observed heterogeneity".	No: Heterogeneity was not addressed.	No: Authors just stated in the abstract that: "No pooling of the results was possible due to study heterogeneity", without providing any further explanation.
15.	No: Publication bias was not assessed.	Meta-analysis was not performed.	Meta-analysis was not performed.
16.	No: Neither funding nor conflicting interests were stated in the review.	No: Neither funding nor conflicting interests were stated in the review.	No: Though authors mentioned their funding sources: "Funding: The project was funded through the authors' academic institutions", they did not explain how they managed the potential conflict of interest.

Continued Supplementary Table 3

	Chen 2013 ¹⁸	Benson 2013 ⁸	Rogers 2010 ²¹
1.	Yes: The PICO elements were mentioned on page 377 in the “Material and methods” section.	Yes: The PICO components were mentioned in the “Criteria for considering studies for this review” section.	No: The PICO components were not all included when addressing the inclusion criteria.
2.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.
3.	No: Authors did not provide the explanation for including only RCTs.	No: Authors did not provide the explanation for including only RCTs.	No: Authors did not provide the explanation for including all of the following: RCTs, clinical trials, and prospective observational studies with concurrent or historic comparison groups.
4.	Partial Yes: – Authors searched 4 databases. – Trial registries and grey literature were not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words and the search strategy were provided in Appendix 1. – No restrictions were applied on the language, publication year or status.	Partial Yes: – Authors searched 3 databases. – Authors searched trial registries: Cochrane Oral Health Group’s Trials Register and US NIH Trials Register. – Grey literature was not searched. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided in Appendices 1–5. – No restrictions were applied on the language.	Yes: – Authors searched 5 databases. – Authors searched trial registries: Current Controlled Trials Register and National Research Register. – Grey literature was searched by SIGLE and ISI Conference Proceedings. – The reference lists of the eligible articles were screened manually for additional studies. – Key words were provided in Table 1. – No restrictions were applied on the language, publication year or status.
5.	Yes: As stated on page 377: “The full texts of the relevant studies were scrutinized by 2 reviewers (HC and TG) independently to select the eligible studies”.	Yes: As stated on page 9: “Two review authors independently examined the title, key words and abstract of the reports identified through electronic searching”.	Yes: As stated on page 390.e3: “all the selected articles were examined by 2 independent reviewers (SR and BC) to determine whether the eligibility criteria were met”.
6.	Yes: As stated on page 377: “Data from all the eligible studies was extracted by 2 reviewers (HC and TG) independently, in duplicate”.	Yes: As stated on page 9: “Data was extracted by 2 review authors independently, in duplicate, using specially designed data extraction forms”.	Yes: As stated on page 390.e3: “data was extracted and methodological quality was assessed by 2 reviewers independently, in duplicate, using specially designed data extraction forms”.
7.	Yes: As stated on page 378: “The list of the excluded articles and the reasons for exclusion are in Appendix II”.	Yes: Authors provided the list of the excluded studies with the reasons for exclusion in Table “Characteristics of excluded studies”.	Yes: Authors mentioned within the text on page 390.e3 in the “Results” section the relevant studies that were excluded from the review with the justification for exclusion.
8.	Partial Yes: Populations, interventions, comparators, outcomes, the study design, and follow-up were described, but not in details. Moreover, the study setting was not addressed.	Yes: Populations, interventions, comparators, outcomes, the study design, the study setting, and follow up were all described in details in Table “Characteristics of included studies”.	Partial Yes: Populations, interventions, comparators, outcomes, the study design, and follow-up were described, but not in details. Moreover, the study setting was not addressed.
9.	Yes: Randomized controlled trials were appropriately assessed by the RoB tool. Not-randomized trials were not included.	Yes: Randomized controlled trails were appropriately assessed by the RoB tool. Non-randomized trials were not included.	No: The risk of bias was not assessed.
10.	No: Funding for primary studies was not reported in the review.	Yes: The sources of funding for primary studies were reported in Table “Characteristics of included studies”.	No: Funding for primary studies was not reported in the review.
11.	Meta-analysis was not performed.	Meta-analysis was not performed.	Meta-analysis was not performed.
12.	Meta-analysis was not performed.	Meta-analysis was not performed.	Meta-analysis was not performed.
13.	Yes: The risk of bias of studies was discussed with the reasons beyond this bias. Noteworthy, most trials were at a high risk of bias.	Yes: The risk of bias in individual studies was accounted for several times when interpreting and discussing the results.	No: The risk of bias was not assessed.
14.	No: Heterogeneity was not addressed.	No: Though it was planned to measure heterogeneity, reviewers did not provide the explanation for heterogeneity in the results, as meta-analysis was not conducted.	Yes: As stated on page 390.e5: “With regard to the materials used, the studies involved could be considered non-homogenous. The adhesives can all be described as containing fluoride, but they essentially have different chemical properties”.
15.	Meta-analysis was not performed.	Meta-analysis was not performed.	Meta-analysis was not performed.
16.	Yes: As stated on page 376: “The authors report no commercial, proprietary or financial interest in the products or companies described in this article”.	Yes: As stated on page 34: “No interests to declare”.	Yes: As stated on page 390.e1: “The authors of this article report no commercial, proprietary or financial interest in the products or companies described in this article”.

Continued Supplementary Table 3

	Chadwick 2005 ¹⁹	Derks 2004 ¹⁴
1.	No: The PICO components were not all included when addressing the inclusion criteria (comparison was not stated).	No: The PICO components were not all included when addressing the inclusion criteria.
2.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.	No: The review did not contain an explicit statement that the review methods were established prior to the conduct of the review.
3.	No: Authors did not provide the explanation for including all of the following: RCTs, clinical trials, and prospective observational studies with concurrent or historical comparison groups.	No: Authors did not provide the explanation for including only RCTs.
4.	No: – Authors searched 6 databases. – Trial registries and grey literature were not searched. – Key words were not provided. – No restrictions were applied on the language, publication year or status.	Partial Yes: – Authors searched 2 databases. – Trial registries, grey literature and bibliographies were not searched. – Key words and the search strategy were provided in Fig. 1. – Restrictions were applied on the language (only articles written in English).
5.	Yes: As stated on page 602: "For each stage, 2 independent reviewers were used. If their opinions differed, a third reviewer independently reviewed the article and decisions, and compared the results".	Yes: As stated on page 3: "Two observers (JE and AD) independently carried out the screening of publications based on the abstracts of the retrieved publications".
6.	Yes: As stated on page 602: "Finally, all the included studies were double-extracted onto data extraction sheets, which were compared. If there was disagreement, a third team member reviewed the article to resolve the disagreement".	No: The review did not contain an explicit statement that authors performed data extraction in duplicate.
7.	No: The list of the excluded studies and the reasons for exclusion were not provided.	Yes: The excluded studies and the reasons for exclusion were provided in Table 2.
8.	Partial Yes: Populations, interventions, comparators, outcomes, and the study design were described, but not in details. Moreover, the authors' names, the study setting and follow-up were not addressed.	Partial Yes: Populations, interventions, comparators, outcomes, and the study design were described, but not in details. Moreover, the study setting and follow-up were not addressed.
9.	No: The risk of bias was not assessed.	No: The risk of bias was not assessed.
10.	No: Funding for primary studies was not reported in the review.	No: Funding for primary studies was not reported in the review.
11.	Meta-analysis was not performed.	No: Authors did not justify combining the data in meta-analysis and did not investigate the causes of any heterogeneity.
12.	Meta-analysis was not performed.	No: The risk of bias was not assessed.
13.	No: The risk of bias was not assessed.	No: The risk of bias was not assessed.
14.	No: Heterogeneity was not addressed.	No: Heterogeneity was not addressed.
15.	Meta-analysis was not performed.	No: Publication bias was not assessed.
16.	No: Though authors mentioned their funding sources: "Funded by the Wales Office of Research and Development Health and Social Care grant No. R00/2/006", they did not explain how they managed the potential conflict of interest.	No: Neither funding nor conflicting interests were stated in the review.

PROSPERO – International Prospective Register of Systematic Reviews; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; DOAJ – Directory of Open Access Journals; PQDT – ProQuest Dissertations and Theses; CCT – controlled clinical trial; ROBINS-I – Risk Of Bias In Non-randomized Studies-of Intervention; NRSI – non-randomized studies of intervention; GRADE – Grading of Recommendations Assessment, Development and Evaluation; APF – acidulated phosphate fluoride; EWLS – enamel white spot lesions; ICTRP – International Clinical Trials Registry Platform; CONSORT – Consolidated Standards of Reporting Trials; NIH – National Institutes of Health; SIGLE – System for Information on Grey Literature in Europe; ISI – Institute for Scientific Information.

Supplementary Table 4. Detailed comparison of the reviews assessing topical fluoride application according to the Jadad decision algorithm

Are the included reviews addressing the same question?		
No.	Review	Question
1	Tasios 2019 ¹⁵	Are topical fluorides effective in the management of OIWSLs?
2	Sardana 2019 ¹⁶	Are topical fluorides effective in the management of OIWSLs?
3	Sardana 2019 ⁴	Are topical fluorides effective in the management of OIWSLs?
4	Nascimento 2016 ¹³	Are topical fluorides effective in the management of OIWSLs?
5	Lapenaite 2016 ¹⁷	Are topical fluorides effective in the management of OIWSLs?
6	Sonesson 2016 ⁶	Are topical fluorides effective in the management of OIWSLs?
7	Chen 2013 ¹⁸	Are topical fluorides effective in the management of OIWSLs?
8	Benson 2013 ⁸	Are topical fluorides effective in the management of OIWSLs?
9	Chadwick 2005 ¹⁹	Are topical fluorides effective in the management of OIWSLs?
10	Derks 2004 ¹⁴	Are topical fluorides effective in the management of OIWSLs?

Continued Supplementary Table 4

Given that the included reviews were addressing the same question, did the reviews include the same trials?		
No.	Review	Studies included
1	Tasios 2019 ¹⁵	1 – Kumar Jena 2015; 2 – Øgaard 1997; 2001; 3 – Stecksén-Blicks et al. 2007; 4 – Vivaldi-Rodrigues et al. 2006
2	Sardana 2019 ¹⁶	1 – Sonesson et al. 2014; 2 – van der Kaaij et al. 2015; 3 – Willmot 2004
3	Sardana 2019 ⁴	1 – Stecksén-Blicks et al. 2007; 2 – Jiang et al. 2013; 3 – Hutto Fretty 2014; 4 – Kirschneck et al. 2016; 5 – Du et al. 2012; 6 – Huang et al. 2013; 7 – He et al. 2016; 8 – Restrepo et al. 2016; 9 – Singh et al. 2016; 10 – Bock et al. 2017; 11 – Ebrahimi et al. 2017
4	Nascimento 2016 ¹³	1 – Vivaldi-Rodrigues et al. 2006; 2 – Stecksén-Blicks et al. 2007
5	Lapenaite 2016 ¹⁷	1 – Farhadian et al. 2008; 2 – Huang et al. 2013; 3 – Richter et al. 2011; 4 – Al Mulla et al. 2010; 5 – Du et al. 2012; 6 – Enaia et al. 2011; 7 – Baeshen et al. 2011
6	Sonesson 2016 ⁶	1 – Agarwal et al. 2013; 2 – Akin et al. 2012; 3 – Du et al. 2012; 4 – Huang et al. 2013
7	Chen 2013 ¹⁸	1 – Willmot 2004; 2 – Du et al. 2012; 3 – Baeshen et al. 2011; 4 – Andersson et al. 2007
8	Benson 2013 ⁸	1 – Luther 200; 2 – Stecksén-Blicks et al. 2007; 3 – Øgaard 2006
9	Chadwick 2005 ¹⁹	1 – Hirschfield 1978; 2 – Boyd 1992; 3 – Boyd 1993; 4 – D'Agostino et al. 1988; 5 – Denes 1991; 6 – Alexander 2000
10	Derks 2004 ¹⁴	1 – D'Agostino et al. 1988; 2 – Alexander and Ripa 2000

Given that different trials were included, did the included reviews use the same selection criteria?		
No.	Review	Studies included
1	Tasios 2019 ¹⁵	Population: Human patients of any age, sex, ethnicity, or malocclusion. Intervention: Any intervention administered at the beginning of treatment with the aim to prevent the development of OIWSLs. Control: A control/placebo group or other intervention. Outcome: The incidence and severity of OIWSLs. Study design: Randomized or quasi-randomized prospective controlled trials, including both parallel and within-person randomized trials. Limitations: No limitations concerning the language, publication year or status were applied.
2	Sardana 2019 ¹⁶	Population: Patients undergoing multi-bracketed fixed orthodontic treatment or patients who had OIWSLs at the end of multi-bracketed fixed orthodontic treatment. Intervention: Self-applied topical fluorides in the form of fluoridated dentifrices, mouth rinses or home-applied gels used by patients. Control: Standard treatment, placebo control or no intervention control. Standard treatment (or routine treatment) was pre-defined as the use of any fluoride dentifrice containing 1000 / 1055 / 1100 / 1250 ppm of fluoride, as these are the most common concentrations in over-the-counter available dentifrices which have been found to effectively prevent caries in children and adolescents. Outcome: Studies that evaluated the prevention of OIWSLs during multi-bracketed fixed orthodontic treatment or the reversal of OIWSLs were included. For studies assessing the prevention of OIWSLs, changes in the incidence of OIWSLs during multi-bracketed fixed orthodontic treatment was the primary outcome, and for studies assessing the reversal of OIWSLs after multi-bracketed fixed orthodontic treatment, a reduction in the size of OIWSLs or mean fluorescence values or the prevalence of OIWSLs were the primary outcomes. Study design: Randomized or quasi-randomized prospective controlled trials. Limitations: Only articles written in English were included, with no limitations concerning the publication year or status.
3	Sardana 2019 ⁴	Population: Patients undergoing multi-bracketed fixed orthodontic therapy, or patients having 1 or more OIWSLs after the completion of multi-bracketed fixed orthodontic therapy. Intervention: Professionally applied topical fluorides in the form of gels, foams or varnishes. Control: Placebo control or no control. Outcome: Changes in the incidence, a decrease in the prevalence or changes in the size of OIWSLs. Study design: Randomized or quasi-randomized prospective controlled trials, including only parallel designs. Limitations: Only articles written in English were included, with no limitations concerning the publication year or status.
4	Nascimento 2016 ¹³	Population: Patients using fixed orthodontic appliances. Intervention: The use of fluoride-containing dental materials. Control: A control group not using these materials. Outcome: Only studies evaluating the risk of OIWSLs in terms of a binary outcome (the presence or absence of lesions) were included. Study design: RCTs, including both parallel and split-mouth designs. Limitations: No limitations concerning the language, publication year or status were applied.
5	Lapenaite 2016 ¹⁷	Population: Patients of any age undergoing treatment with fixed orthodontic appliances. Intervention: Fluoride-containing products or casein derivatives used throughout appliance therapy or immediately after debonding. Control: Not provided. Outcome: The prevention of OIWSLs. Study design: Randomized or quasi-randomized controlled clinical studies. Limitations: Only articles written in English and published between 2008 and 2013 were included.
6	Sonesson 2016 ⁶	Population: Adolescents and young adults (<30 years) with OIWSLs registered and scored within 3 months after the debonding of fixed orthodontic appliances. Intervention: Any intervention, except laminate veneers, with the aim to reverse OIWSLs or to improve their esthetic appearance. Control: No treatment, placebo or best clinical practice. Outcome: The extent, hardness or appearance of OIWSLs with a follow-up period of at least 8 weeks, as assessed with visual clinical scores, photographs, caries detection devices, or patient/therapist satisfaction. Study design: CCTs (randomized or non-randomized) on >20 subjects, including parallel and split-mouth designs. Limitations: Only articles written in English and published between 2011 and Oct 31, 2015 were included.

Continued Supplementary Table 4

Given that different trials were included, did the included reviews use the same selection criteria?		
No.	Review	Studies included
7	Chen 2013 ¹⁸	<p>Population: Participants who completed fixed orthodontic treatment and had at least 1 clinically visible lesion on the labial enamel surface upon the removal of fixed orthodontic appliances.</p> <p>Intervention: Remineralizing agents for the treatment of OIWSLs (i.e., any fluoride- or CPP-ACP-based system).</p> <p>Control: Patients subjected to different agents or not subjected to any intervention (placebo or no intervention).</p> <p>Outcome: Studies in which the primary outcome was a change in the severity of OIWSLs between the experimental and control groups, and the severity was expressed macroscopically in terms of the area over the whiteness of the lesion or microscopically as the amount of mineral loss or the lesion depth.</p> <p>Study design: RCTs.</p> <p>Limitations: No limitations concerning the language, publication year or status were applied.</p>
8	Benson 2013 ⁸	<p>Population: Participants of any age undergoing orthodontic treatment with fixed braces in cases when DWLs were assessed on the teeth remaining in the mouth at the end of orthodontic treatment (at debonding, immediately after the active fixed brace was removed).</p> <p>Intervention: Topical fluorides in the form of toothpastes, mouth rinses, gels, varnishes, or dietary sources at any dose, frequency, duration, or method of administration, and with any of the following active agents/ingredients: NaF, SMFP, SnF₂, APF, and AmF.</p> <p>Control: Individuals not subjected to the fluoride intervention, but instead treated with a placebo, such as a non-fluoride toothpaste and mouth rinse, or given no intervention. Studies involving a control group subjected to an alternative fluoride intervention were also included.</p> <p>Outcome: The presence or absence of new lesions by participant, differences in the size and severity of OIWSLs between the experimental and control groups, any quantitative assessment of enamel mineral loss, such as fluorescent light techniques or microradiography, used with in situ caries models, any participant-assessed outcomes, such as the perception of the lesions and oral health-related quality of life data, or adverse effects.</p> <p>Study design: RCTs, including only parallel designs.</p> <p>Limitations: No limitations concerning the language, publication year or status were applied.</p>
9	Chadwick 2005 ¹⁹	<p>Population: Human subjects undergoing orthodontic treatment with fixed appliances.</p> <p>Intervention: Topical fluorides used throughout appliance therapy.</p> <p>Control: Not provided.</p> <p>Outcome: The outcome measure had to be clearly described and reproducible, i.e., the severity of WSLs or DMFS.</p> <p>Study design: RCTs, clinical trials, and prospective observational studies with concurrent or historical comparison groups.</p> <p>Limitations: No limitations concerning the language, publication year or status were applied.</p>
10	Derks 2004 ¹⁴	<p>Population: Orthodontic patients in whom demineralization-inhibiting measures were applied during orthodontic treatment.</p> <p>Intervention: Topical fluorides used throughout appliance therapy.</p> <p>Control: Not provided.</p> <p>Outcome: The preventive measure was used from the beginning of orthodontic treatment with bonded fixed appliances until debonding.</p> <p>Study design: RCTs.</p> <p>Limitations: Only articles written in English were included, with no limitations concerning the publication year or status.</p>

Given that different selection criteria were used, the Jadad algorithm would suggest assessing and comparing the publication status of primary studies, their methodological quality, language restrictions, and the analysis of data on individual patients.					
No.	Review	Publication status	Quality and quantity of primary studies	Language restrictions	Analysis of data on individual patients
1	Tasios 2019 ¹⁵	2019	4 trials: 1 – medium risk; 3 – high risk	no restrictions	aggregate data
2	Sardana 2019 ¹⁶	2019	3 trials: 1 – low risk; 2 – high risk	English-written only	systematic review
3	Sardana 2019 ⁴	Epub 2018	11 trials: 5 – low risk; 4 – medium risk; 2 – high risk	English-written only	aggregate data
4	Nascimento 2016 ¹³	2016	2 trials: all trials – high risk	no restrictions	aggregate data
5	Lapenaite 2016 ¹⁷	2016	7 trials quality not assessed	English-written only	systematic review
6	Sonesson 2016 ⁶	2016	4 trials: 1 – low risk; 3 – high risk	English-written only	systematic review
7	Chen 2013 ¹⁸	2013	4 trials: 1 – medium risk; 3 – high risk	no restrictions	systematic review
8	Benson 2013 ⁸	2013	3 trials: 1 – low risk, 1 – medium risk; 1 – high risk	no restrictions	systematic review
9	Chadwick 2005 ¹⁹	2005	6 trials quality not assessed	no restrictions	systematic review
10	Derks 2004 ¹⁴	2004	2 trials quality not assessed	English-written only	aggregate data

Accordingly, the study by Sardana et al.⁴ (Epub 2018), which included 11 trials, assessed the risk of bias appropriately, including 5 trials at a low risk of bias and 4 trials at a medium risk of bias, was chosen to be the best available evidence regarding the effectiveness of topical fluorides in the management of OIWSLs.

OIWSL – orthodontically induced white spot lesion; DWL – deep white lesion; SMFP – sodium monofluorophosphate; AmF – amine fluoride; WSL – white spot lesion; DMFS – decayed, missing, and filled teeth or surfaces.

Effect of casein phosphopeptide-amorphous calcium phosphate or other casein derivatives in the management of OIWSLs

Four systematic reviews appraised the outcomes from CPP-ACP application: Pithon et al. 2019,²⁰ Lape-naite et al. 2016,¹⁷ Sonesson et al. 2016,⁶ and Chen et al. 2013.¹⁸ Two out of the 4 reviews found a lack of reliable evidence supporting the effectiveness of CPP-ACP.^{6,18} Considering that these reviews were addressing the same question, using different trials and different selection criteria, the Jadad tool would once again suggest that the best available review be selected according to the superiority in its publication status, the methodological quality of its primary studies, language restrictions, and the analysis of data on individual patients. As a result, Pithon et al. 2019²⁰ was selected (Fig. 4). The detailed steps of the Jadad decision algorithm are provided in Supplementary Table 5.

Pithon et al. 2019²⁰ included 11 primary trials (9 RCTs and 2 CCTs) published between 2007 and 2016. The studies used either a parallel or cross-over design. The results indicated that CPP-ACP-containing products were effective in both preventing and reversing OIWSLs.

Effect of fluoride-releasing bonding materials in the management of OIWSLs

This outcome was addressed by 4 reviews: Tasios et al. 2019,¹⁵ Nascimento et al. 2016,¹³ Rogers et al. 2010,²¹ and Derks et al. 2004.¹⁴ The results of these reviews were inconsistent, indicating respectively that fluoride-releasing materials were not effective in the management of OIWSL; fluoride-releasing materials reduced the risk of lesion development; it was impossible to make recommendations on the use of fluoride-containing orthodontic adhesives; and the effect of fluoride-containing bonding materials was not statistically significant.

As in the previous situations, these reviews addressed the same question, but included different trials and utilized different selection criteria. Therefore, the best available review would be selected according to the superiority in its publication status, the methodological quality of its primary studies, language restrictions, and the analysis of data on individual patients. Accordingly, Tasios et al. 2019¹⁵ was selected (Fig. 4). The detailed steps of the Jadad decision algorithm applied from the beginning until the final decision are provided in Supplementary Table 6.

Tasios et al. 2019¹⁵ included 10 studies assessing the effectiveness of fluoride-containing bonding materials in the management of OIWSLs. All the studies had a split-mouth design. Data synthesis revealed that fluoride-releasing adhesives and glass-ionomer bracket adhesives showed no statistically significant differences in comparison with conventional and resin adhesives.

Effect of laser therapy in the management of OIWSLs

Only 1 systematic review was conducted to evaluate this outcome – Raghis et al. 2018,³ including 8 trials (5 RCTs and 3 CCTs) published between 2000 and 2015. Different laser types were utilized in an attempt to manage OIWSLs, including CO₂, neodymium-doped yttrium aluminum garnet (Nd:YAG), argon, and Optodan® lasers. All primary studies indicated that laser irradiation was effective in the management of OIWSLs, with the exception of an argon laser with parameters of 250 mW, 12 J/cm², a beam diameter of 5 mm, and a duration of 10 s. An argon laser within these particular parameters demonstrated a positive effect in a study by Blankenau et al.,²² whilst no effect was noticed in a study by Elaut and Wehrbein 2004.²³

Effect of resin infiltration and micro-abrasion in the management of OIWSLs

The only systematic review to be included which addressed the effect of resin infiltration and micro-abrasion on OIWSLs was by Sonesson et al. 2016.⁶ This review included 2 primary studies^{24,25} that evaluated the efficacy of resin infiltration and 1 primary study²⁶ that evaluated the efficacy of micro-abrasion. Although these studies revealed both strategies to be effective, the results of this review indicated a lack of reliable scientific evidence to support camouflaging strategies in managing OIWSLs due to the limited number of available studies.

Discussion

To the best of our knowledge, this review of reviews represents the first state-of-the-art appraisal of the efficacy of different adjunctive interventions in the management of OIWSLs. The adjunctive interventions in question were topical fluorides, the CPP-ACP products, fluoride-releasing adhesives, laser therapy, resin infiltration, and micro-abrasion. The best available evidence regarding these interventions was derived from 5 separate reviews.

Regarding topical fluoride application, 10 of the systematic reviews made an assessment, 3 of which found a lack of reliable evidence in support of fluoride. Indeed, discordant conclusions are likely due to the conflicting results of primary studies. Therefore, it is worth highlighting 2 gaps in the evidence base in order to interpret these results. Firstly, though many relevant reviews and original studies have been conducted, the best clinical fluoride concentration in the management of OIWSLs was deemed to be unclear; in other words, most primary studies used different fluoride concentrations with different forms of application. A study by Bailey et al. raised warnings against high concentrations of fluoride, which may arrest the remineralization of deeper layers through superficial hypermineralization, thus jeopardizing the esthetic treatment result.²⁷

Supplementary Table 5. Detailed comparison of the reviews assessing casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) or other casein derivatives according to the Jadad decision algorithm

Are the included reviews addressing the same question?		
No.	Review	Question
1	Pithon 2019 ²⁰	Is CPP-ACP application effective in the management of OIWSLs?
2	Lapenaite 2016 ¹⁷	Is CPP-ACP application effective in the management of OIWSLs?
3	Sonesson 2016 ⁶	Is CPP-ACP application effective in the management of OIWSLs?
4	Chen 2013 ¹⁸	Is CPP-ACP application effective in the management of OIWSLs?

Given that the included reviews were addressing the same question, did the reviews include the same trials?		
No.	Review	Studies included
1	Pithon 2019 ²⁰	1 – Akin and Basciftci 2012; 2 – Andersson et al. 2007; 3 – Bailey et al. 2009; 4 – Beerens et al. 2010; 5 – Bröchner et al. 2011; 6 – Heshmat et al. 2014; 7 – Huang et al. 2013; 8 – Robertson et al. 2011; 9 – Singh et al. 2016; 10 – Uysal et al. 2010; 11 – Wang et al. 2012
2	Lapenaite 2016 ¹⁷	1 – Huang et al. 2013; 2 – Robertson et al. 2011; 3 – Bailey et al. 2009; 4 – Beerens et al. 2010; 5 – Bröchner et al. 2011
3	Sonesson 2016 ⁶	1 – Akin and Basciftci 2012; 2 – Huang et al. 2013; 3 – Vashisht 2013
4	Chen 2013 ¹⁸	1 – Andersson et al. 2007; 2 – Bröchner et al. 2011; 3 – Bailey et al. 2009; 4 – Beerens et al. 2010

Given that different trials were included, did the included reviews use the same selection criteria?		
No.	Review	Selection criteria
1	Pithon 2019 ²⁰	Population: Orthodontic patients with labial fixed appliances. Intervention: The use of CPP-ACP-containing products. Control: Other oral agents or placebos. Outcome: The prevention or treatment of OIWSLs around orthodontic braces. Study design: CCTs (randomized or non-randomized). Limitations: No limitations concerning the language, publication year or status were applied.
2	Lapenaite 2016 ¹⁷	Population: Patients of any age undergoing treatment with fixed orthodontic appliances. Intervention: Fluoride-containing products or casein derivatives used throughout appliance therapy or immediately after debonding. Control: Not provided. Outcome: The prevention of OIWSLs. Study design: Randomized or quasi-randomized controlled clinical studies. Limitations: Only articles written in English and published between 2008 and 2013 were included.
3	Sonesson 2016 ⁶	Population: Adolescents and young adults (<30 years) with OIWSLs registered and scored within 3 months after the debonding of fixed orthodontic appliances. Intervention: Any intervention, except laminate veneers, with the aim to reverse OIWSLs or to improve their esthetic appearance. Control: No treatment, placebo or best clinical practice. Outcome: The extent, hardness or appearance of OIWSLs with a follow-up period of at least 8 weeks, as assessed with visual clinical scores, photographs, caries detection devices, or patient/therapist satisfaction. Study design: CCTs (randomized or non-randomized) on >20 subjects, including parallel and split-mouth designs. Limitations: Only articles written in English and published between 2011 and Oct. 31, 2015 were included.
4	Chen 2013 ¹⁸	Population: Participants who completed fixed orthodontic treatment and had at least 1 clinically visible lesion on the labial enamel surface upon the removal of fixed orthodontic appliances. Intervention: Remineralizing agents for the treatment of OIWSLs (i.e., any fluoride- or CPP-ACP-based system). Control: Patients subjected to different agents or not subjected to any intervention (placebo or no intervention). Outcome: Studies in which the primary outcome was a change in the severity of OIWSLs between the experimental and control groups, and the severity was expressed macroscopically in terms of the area over the whiteness of the lesion or microscopically as the amount of mineral loss or the lesion depth. Study design: RCTs. Limitations: No limitations concerning the language, publication year or status were applied.

Given that different selection criteria were used, the Jadad algorithm would suggest assessing and comparing the publication status of primary studies, their methodological quality, language restrictions, and the analysis of data on individual patients.					
No.	Review	Publication status	Quality and quantity of primary studies	Language restrictions	Analysis of data on individual patients
1	Pithon 2019 ²⁰	2019	11 trials: 9 – low risk; 2 – medium risk	no restrictions	systematic review
2	Lapenaite 2016 ¹⁷	2016	5 trials quality not assessed	English-written only	systematic review
3	Sonesson 2016 ⁶	2016	3 trials: 1 – low risk; 2 – high risk	English-written only	systematic review
4	Chen 2013 ¹⁸	2013	4 trials: all trials – high risk	no restrictions	systematic review

Accordingly, the study by Pithon et al.²⁰ (2019), which included 11 trials, where 9 trials were at a low risk of bias and 2 trials at a medium risk of bias, was chosen to be the best available evidence regarding the effectiveness of CPP-ACP-containing products in the management of OIWSLs.

Supplementary Table 6. Detailed comparison of the reviews assessing fluoride-containing bonding materials according to the Jadad decision algorithm

Are the included reviews addressing the same question?					
No.	Review	Question			
1	Tasios 2019 ¹⁵	Are fluoride-containing materials effective in the management of OIWSLs?			
2	Nascimento 2016 ¹³	Are fluoride-containing materials effective in the management of OIWSLs?			
3	Rogers 2010 ²¹	Are fluoride-containing materials effective in the management of OIWSLs?			
4	Derks 2004 ¹⁴	Are fluoride-containing materials effective in the management of OIWSLs?			

Given that the included reviews were addressing the same question, did the reviews include the same trials?		
No.	Review	Studies included
1	Tasios 2019 ¹⁵	1 – Allabdullah 2017; 2 – Banks et al. 1997; 3 – Gaworski 1999; 4 – Marcusson et al. 1997; 5 – Millett et al. 1999; 6 – Mitchell 1992; 7 – Trimpeneers and Dermaut 1996; 8 – Turner 1993; 9 – Adriaens 1990; 10 – van der Linden 1998
2	Nascimento 2016 ¹³	1 – Sonis and Snell 1989; 2 – Trimpeneers and Dermaut 1996; 3 – Marcusson et al. 1997; 4 – Millett et al. 2000
3	Rogers 2010 ²¹	1 – Sonis and Snell 1989; 2 – Marcusson et al. 1997; 3 – Millett et al. 1999; 4 – Gaworski 1999; 5 – Turner 1993; 6 – Banks et al. 1997; 7 – Mitchell 1992; 8 – Trimpeneers and Dermaut 1996; 9 – Millet et al. 2000; 10 – Gillgrass 2001
4	Derks 2004 ¹⁴	1 – Mitchell 1992; 2 – Turner 1993; 3 – Trimpeneers and Dermaut 1996; 4 – Marcusson et al. 1997; 5 – Banks et al. 1997; 6 – Millet et al. 1999; 7 – Millet et al. 2000

Given that different trials were included, did the included reviews use the same selection criteria?		
No.	Review	Selection criteria
1	Tasios 2019 ¹⁵	Population: Human patients of any age, sex, ethnicity, or malocclusion. Intervention: Any intervention administered at the beginning of treatment with the aim to prevent the development of OIWSLs. Control: A control/placebo group or other intervention. Outcome: The incidence and severity of OIWSLs. Study design: Randomized or quasi-randomized prospective controlled trials, including both parallel and within-person randomized trials. Limitations: No limitations concerning the language, publication year or status were applied.
2	Nascimento 2016 ¹³	Population: Patients using fixed orthodontic appliances. Intervention: The use of fluoride-containing dental materials. Control: A control group not using these materials. Outcome: Only studies evaluating the risk of OIWSLs in terms of a binary outcome (the presence or absence of lesions) were included. Study design: RCTs, including both parallel and split-mouth designs. Limitations: No limitations concerning the language, publication year or status were applied.
3	Rogers 2010 ²¹	Population: Patients who completed a full course of fixed orthodontic treatment. Intervention: Fluoride-containing adhesives. Control: Not provided. Outcome: Decalcification at the baseline and the end point of the study. When possible, the total number of OIWSLs, decalcifications as well as DMFT were recorded for the start and finish of the trial for both the subjects and the teeth. Study design: RCTs, clinical trials, and prospective observational studies with concurrent or historic comparison groups. Limitations: No limitations concerning the language, publication year or status were applied.
4	Derks 2004 ¹⁴	Population: Orthodontic patients in whom demineralization-inhibiting measures were applied during orthodontic treatment. Intervention: Topical fluorides used throughout appliance therapy. Control: Not provided. Outcome: The preventive measure was used from the beginning of orthodontic treatment with bonded fixed appliances until debonding. Study design: RCTs. Limitations: Only articles written in English were included, with no limitations concerning the publication year or status.

Given that different selection criteria were used, the Jadad algorithm would suggest assessing and comparing the publication status of primary studies, their methodological quality, language restrictions, and the analysis of data on individual patients.					
No.	Review	Publication status	Quality and quantity of primary studies	Language restrictions	Analysis of data on individual patients
1	Tasios 2019 ¹⁵	2019	10 trials: 3 – medium risk; 7 – high risk	no restrictions	aggregate data
2	Nascimento 2016 ¹³	2016	4 trials: all trials – high risk	no restrictions; however, only 1 database searched	aggregate data
3	Rogers 2010 ²¹	2010	10 trials quality not assessed	no restrictions	systematic review
4	Derks 2004 ¹⁴	2004	7 trials quality not assessed	English-written only	aggregate data

Accordingly, the study by Tasios et al.¹⁵ (2019), which included 10 trials, assessing fluoride-containing adhesives, was chosen to be the best available evidence regarding the effectiveness of fluoride-containing bonding materials in the management of OIWSLs.

DMFT – decayed, missing and filled teeth.

On the other hand, a study by Sonesson et al. indicated that high concentrations of fluoride could significantly manage OIWSLs.²⁸ Secondly, the inappropriate split-mouth design which was used by some primary studies might manipulate the outcomes, as fluorides could be distributed throughout the mouth by saliva and a carry-over or cross-contamination effect would be possible. Consequently, more robust, randomized, parallel-designed CCTs are still required.

As far as CPP-ACP-containing products are concerned, 2 out of 4 reviews found a lack of reliable evidence to support the effectiveness of CPP-ACP. Conflicts could be attributed to the application protocols, which differed with regard to application duration and frequency.^{27,29} The best current evidence, according to the Jadad decision algorithm, indicated that the release of phosphate and calcium ions from the CPP-ACP products led to the saturation of the medium and the re-establishment of oral pH, thereby achieving a remineralization effect.²⁰

Concerning the efficacy of fluoride-emitting adhesives, the best available evidence proposed that no statistically significant differences were found between conventional and fluoride-releasing adhesives¹⁵; however, these results have to be treated with considerable caution, because the primary studies included in all the reviews followed a split-mouth design, which also might result in a cross-contamination effect and incorrect data.

Regarding laser application, the only systematic review which was concerned in this intervention was from Raghis et al. 2018.³ Their results proposed that laser therapy was effective in preventing OIWSLs by assuming that laser application would lead to a higher enamel micro-hardness than in the case of the non-irradiated enamel.³

Resin infiltration and micro-abrasion have been recently proposed for camouflaging OIWSLs. Contemporary studies on etching and the development of a material with a high penetration coefficient, called an infiltrant, have expanded the use of the resin infiltration technique.³⁰ Regarding technical concerns, the application of resin infiltration must be repeated several times, while the micro-abrasion technique is normally administered at a single appointment.⁶ Although primary studies in the review by Sonesson et al. 2016⁶ revealed both techniques to be effective, a definite conclusion could not be drawn due to the limited number of studies. Perhaps more importantly, the long-term success rate of both techniques is still unknown; therefore, these methods should be used selectively on challenging cases.

Limitations

As with all reviews, this review has strengths and limitations. With regard to strengths, we followed the PRISMA checklist, applied an extensive electronic search, used the AMSTAR-2 tool in order to assess the quality of the selected reviews, and chose the best current evidence from among multiple reviews handling multiple methods of OIWSL management.

The review-of-reviews approach relies on 'second-hand' information, so it is potentially vulnerable to the interpretive biases of the previous reviewers. We attempted to control this using an objective method to choose the best available evidence, i.e., the Jadad decision algorithm. Additionally, all the included reviews ranged in quality between critically low to moderate and some results were ultimately drawn based on critically-low-quality reviews. The heterogeneity of the topical fluoride concentrations used in primary studies, the various CPP-ACP application protocols used and the inappropriate split-mouth design of many of primary studies assessing fluoride-releasing adhesives are considered to be the limitations of this review. Finally, as in all reviews of reviews, the most recent primary trials may not be covered.

Conclusions

Based on the currently available information and the Jadad decision algorithm criteria, topical fluorides yielded a 25–30% prevention of OIWSLs; however, their effect on reversing OIWSLs is unclear. The CPP-ACP products are effective in preventing and reversing OIWSLs. Fluoride-releasing adhesives offer no significant differences in comparison with conventional adhesives. Laser irradiation is effective in preventing OIWSLs, with some concerns regarding argon lasers. Finally, there is a lack of a reliable evidence to support resin infiltration and micro-abrasion due to the limited number of available studies.

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