Hussain et al. BMC Oral Health (2026) 26:358
https://doi.org/10.1186/s12903-026-07755-3

BMC Oral Health

RESEARCH

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Efficacy of various interventions for the management of white spot lesions associated with fixed orthodontic treatment: a systematic review and network meta-analysis of randomized controlled trials

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Abstract

Objective To synthesize the direct and indirect evidence on comparative effectiveness of various interventions for while spot lesions (WSLs) associated with fixed appliance treatment based on randomized clinical trials (RCTs).

Methods **Eligibility criteria**: RCTs evaluating agents for prevention, reduction, or reversal of WSLs in orthodontic patients with fixed appliances comparing them with placebo, no treatment, or another active agent

Information sources: Unrestricted literature search of six databases was conducted up to March 1, 2025

Risk of bias: was conducted using RoB-2

Synthesis of results: Pairwise and network meta-analyses used random-effects (REML) models. Networks (≥10 trials) included only RCTs with labial fixed brackets to ensure transitivity. Inconsistency was assessed via node-splitting; P-scores ranked interventions. Sparse data limited small-study effect assessment and reduced network size in sensitivity analyses. Confidence in NMA(CINeMA) rated confidence.

Results **Included studies**: Seventy RCTs involving 4,634 participants

Synthesis of results: For WSL score, self-assembling peptide, NovaMin, nano-agents, xylitol varnish, and casein phosphopeptide (CPP-ACP) showed the highest efficacy (SMD range: –1.38 to –0.94; P-scores: 0.71–0.86). Probiotics, fluoride combinations, and fluoride varnish also showed significant effects, while laser, chlorhexidine (CHX), and fluoride mouthwash/toothpaste did not. For WSL prevalence, fluoride varnish, fluoride combinations, and CPP-ACP were most effective (OR range: 0.25–0.32). Resin infiltration and fluoride toothpaste also showed benefit. No

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intervention significantly reduced WSL size. Networks were generally sparse. No major inconsistencies were detected. No small-study effects were found for WSL score (Egger's p = 0.45). CINeMA ratings ranged from high to low.

Discussion Limitations of evidence: Clinical heterogeneity, sparse network, moderate risk of bias, and exclusion of studies reporting non-standard outcomes limit the strength and generalizability of the findings.

Interpretation: Moderate-quality evidence suggests that CPP-ACP, self-assembling peptide, NovaMin, and nano-agents are effective for reducing WSL severity, while fluoride varnish is most effective for prevention.

Keywords Network meta-analysis, White spot lesions, Intervention, Orthodontic treatment, Fixed appliances

Introduction

Patients seek orthodontic treatment to enhance aesthetics and function. While orthodontic treatment can improve aesthetics, it may also have adverse effects. White spot lesions (WSLs) are initial carious lesions and are present as "subsurface enamel porosity due to demineralization", appearing milky white on the smooth surfaces of the teeth [1]. Fixed appliances create difficulty in maintaining good oral hygiene due to plaque accumulation, which results in these lesions [2]. Though these lesions are initially reversible, they can progress to cavitation if proper oral hygiene is not maintained and/or active intervention is not provided [3]. This unwanted side effect significantly affects dental health and aesthetics and remains challenging for orthodontists and patients. WSLs during orthodontic treatment occur in 2–97% of cases, and after appliance removal, they are not fully resolved and may need reversal or restorative treatment [4, 5].

Interventions for the prevention and reversal of WSLs include fluoride-containing products like varnish, mouthwashes, toothpastes, and fluoride-releasing adhesive [6–9]; remineralizing agents like Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) and tricalcium phosphate [10, 11]; bioglasses like calcium sodium phosphosilicate (NovaMin) [12]; antibacterial agents like chlorhexidine, ozone, and probiotics [12, 13]; bonding modifications like resin-modified glass inonomer, self-etching primer, and resin infiltration [14, 15]; and nano-agents like nanosilver and titanium oxide nanoparticles [16].

These agents prevent WSLs through various mechanisms. Fluoride can promote remineralization of enamel, inhibiting bacterial activity and enhancing enamel resistance to acid attacks.[6] CPP-ACP forms a reservoir of bioavailable calcium and phosphate ions on the tooth surface, promoting remineralization [17]. NovaMin promotes remineralization by releasing calcium and phosphate ions that bind to the tooth surface and initiate hydroxycarbonate apatite formation [18]. Antibacterial agents inhibit bacterial growth, disrupting biofilms, and allow remineralization of enamel from salivary minerals. Nano-agents allow greater contact with bacterial cells, enabling penetration and destruction due to their small size and their increased surface area. These agents exhibit strong anti-plaque and anti-cariogenic activity [4, 16]. A new treatment modality called self-assembling peptide (SAP) for WSLs, which promotes biomimetic mineralization, has been introduced. SAP works by infiltrating the subsurface lesion, which self-assembles into a nanofiber matrix [19]. This structure attracts calcium ions from saliva and templates hydroxyapatite formation, promoting natural enamel remineralization. By enhancing the inherent repair mechanisms of enamel, SAP offers a non-invasive treatment [20].

A previous network meta-analysis (NMA) aimed to compare various interventions for WSLs [21]; however, it was associated with several limitations and methodological flaws. In particular, their analysis included both orthodontic and non-orthodontic patients, as well as non-randomized and in-vitro studies, without acknowledging the implications of different study designs and population subgroups for the NMA results, introducing significant issues with transitivity and raising concerns about the quality of the conclusions. The authorsincluded only 15 studies involving participants with fixed orthodontic appliances, some of which were non-randomized. Moreover, the analysis combined different outcomes, such as Decayed, Missing, and Filled Teeth (DMFT) scores, WSL severity scores, and lesion size, which make the interpretation and comparison of results problematic. Additionally, the authors did not assess the certainty of the evidence, nor did they account for the clustering effect in split-mouth design studies.

There are no unified recommendations on the best treatment for WSLs associated with fixed appliance treatment, and comparing all modalities at once in primary studies and pairwise meta-analyses is not feasible. Traditional meta-analyses compare a few treatments, offering fragmented evidence about the investigated outcomes and treatments. Contrariwise, NMA assesses multiple interventions simultaneously, providing treatment effects for pairwise comparisons that are not directly investigated in any trial. Therefore, NMA allows for deriving a treatment hierarchy for each investigated outcome, with the validity of the results being subject to the consistency of the different evidence sources [22]. The present systematic review with NMA aims to uncover the comparative effectiveness of various interventions for WSLs associated with fixed appliance treatment based on randomized clinical trials. Furthermore, by assessing the quality of the available collated evidence, the present study will also uncover the extent to which recommendations can be currently made.

Methods

Protocol and registration

The protocol for this review was registered a priori with PROSPERO (CRDXXXXXX). All protocol deviations have been documented in Appendix 1 to aid transparency. This review was conducted and reported according to the guidelines set forth by the Cochrane Handbook [23] and the Preferred Reporting Items for Systematic Reviews with Network Meta-Analyses (PRISMA-NMA) statement [24]. The PRISMA-S was all considered to report the search strategy process [25].

Eligibility criteria

Inclusion criteria were based on the PICOS features referring to the target population, interventions, comparators, outcomes, and study designs. The target population was orthodontic patients who had been wearing fixed appliances for at least one month, regardless of total treatment duration, including those who had completed fixed-appliance therapy. Studies were eligible whether participants already had white spot lesions (WSLs) at baseline (therapeutic context) or were at risk of developing WSLs (preventive context); comparators were placebo, negative control, or another active agent aimed at reversing, preventing, or reducing WSL; primary outcomes included WSL prevalence/incidence and WSL score; secondary outcomes were WSL size and/or fluorescence loss; and eligible study designs included randomized controlled trials on humans with a split-mouth, parallel, or crossover design. The exclusion criteria were cleft lip and palate cases, removable appliances, clear aligners, patients with intellectual disabilities, and studies assessing WSL around molar bands only.

Search strategy

A systematic search was conducted in six databases (PubMed, Scopus, Web of Science, CENTRAL, Virtual Health Library, and LILACS) from inception to March 1, 2025, without language restrictions, using customized keywords (Table S1). Additionally, the reference lists of included studies and Google Scholar were searched manually to include any missed trials. Furthermore grey literature like ProQuest was also searched.

Study selection

Search results from all databases except Google Scholar were exported as CSV files and combined in a Microsoft Excel 2010 sheet. Using the built-in duplicate function, duplicates were identified by highlighting the font color of the title column, followed by deduplication. The first screening was conducted based on titles and abstracts by two independent authors (SSK and UWK) to exclude irrelevant papers. The remaining papers were accessed in full text and assessed against the eligibility criteria. Any discrepancies were resolved through discussion with the third author (UH).

Data extraction

Two authors (MAK and AC) independently extracted data on the first author, publication year, study design (parallel, split-mouth), country, number of participants, number of male and female participants, mean or range of participants' age, details of interventions and controls, follow-up time, the method used to record WSL, and outcomes measured (e.g., WSL score, size, prevalence, fluorescence loss). Any disagreements were resolved through discussion with the third author (UH). To allow synthesizing trials reporting the incidence with those reporting the prevalence of WSL, the incidence was converted into prevalence for certain outcomes, by multiplying the incidence with the follow-up duration reported in the corresponding trials.

Risk of bias assessment

After piloting and calibration, two authors (AR, OOA) independently assessed the risk of bias using the new Risk of Bias 2 (RoB-2) tool from the Cochrane Collaboration [26]. Any disagreements were resolved through discussion with the third author (UH).

Data synthesis

Effective sample size

Studies used a clustered split-mouth design to compare WSL prevalence between control and experimental groups. Clustering effects were adjusted using the design effect: $1 + (M - 1)*ICC$, where M is the average cluster size (teeth per cluster ~ 12) and ICC was set at 0.02 (Masood et al. [27]). The effective sample size was obtained by dividing participants and events by the design effect. For continuous data, only the sample size was adjusted; means and standard deviations remained unchanged [28]. This conservative approach accounts for the increased efficiency of the split-mouth design, which requires a sample size between that of purely clustered and unclustered designs.

There were some zero-event studies in the analysis; in such cases, we applied a continuity correction of 0.5 to enable the estimation of effect sizes.

Effect measures and data preparation

Since the included studies used different scales for measuring WSL scores (ICDAS, EDI, Gorelick et al. index) and lesion size (lesion width, lesion depth), a standardized mean difference (SMD) was used for pooling the data. The SMD allows comparison across studies despite differences in measurement scales by standardizing effect sizes. Means and standard deviations were imputed using Cochrane Handbook methods and Hozo et al. [29] when only medians, ranges, or sample sizes were reported. For binary outcomes, we estimated the odds ratio (OR) in the logarithmic scale and reported it on the original scale. For crossover trials included in the network meta-analysis, we extracted and analyzed only the data from the first treatment period to avoid potential carryover effects.

Pairwise and network meta-analysis

Analysis was done in R software 4.3.1 using the meta R package for the pairwise meta-analyses [30] and the *netmeta* package for network meta-analysis. For all outcomes, a pairwise meta-analysis was initially conducted for each pairwise comparison with at least two trials. Specifically, we opted for an inverse-variance random-effects model to account for the statistical heterogeneity manifesting from inherent clinical and methodological heterogeneity that stems from differences in the protocols and conduct of studies retrieved from literature searches [31]. Following recommendations from several empirical and simulation studies on the statistical properties of different heterogeneity estimators, we employed the restricted maximum likelihood (REML) estimator for having an overall good comparative performance [32, 33]. The between-trial standard deviation, τ, was reported and accompanied by a 95% confidence interval (CI) constructed using the Q-profile approach. The I^2 was also reported to gauge the relative statistical heterogeneity and was reported alongside a 95% CI. We planned to apply the Hartung-Knapp approach to obtain the 95% confidence intervals of the summary effects and also report the prediction intervals to communicate the implications of statistical heterogeneity; however, most comparisons included less than four trials, challenging the application of these approaches.

Transitivity

We constructed networks for outcomes with data from at least 10 trials. In sparse networks, the random-effects model may produce wide, non-credible confidence intervals, even when direct and indirect estimates are coherent [34, 35]. To satisfy the transitivity assumption, inclusion was limited to randomized clinical trials involving orthodontic patients wearing labial fixed metallic brackets, thereby ensuring a consistent patient population across studies. Each intervention (e.g., fluoride varnih, resin infiltration, chlorhexidine [CHX] mouthwash) was treated as a distinct node in the network to reflect differences in their mechanisms of action and application protocols. Inconsistency between direct and indirect evidence was evaluated using the node-splitting method (netsplit).

Treatment ranking and publication bias

A frequentist analogue of the surface under the cumulative ranking curve, the P-score metric was used to rank interventions hierarchically on a 0–1 scale, with higher values indicating better outcomes. We planned to assess small-study effects using comparison-adjusted funnel plots; however, it was not possible due to the sparsity of the networks [36].

Sensitivity analysis

We also planned to apply a sensitivity analysis by excluding trials with a high risk of bias; however, some comparisons were dropped, leading to networks that included a smaller set of treatments, compromising the comparison with the primary analysis results.

Confidence in network meta-analysis

We evaluated confidence in the network meta-analysis estimates for WSL score, WSL size and prevalence with the CINeMA (Confidence in Network Meta-Analysis) approach [37]. In case of spare connectedness in the network, imprecision domain was downgraded. Clinically important differences (CID) were not predefined for each variable due to heterogeneity in study populations, interventions, and outcome measures; instead, judgments were based on relative effect sizes, precision, and consistency across trials.

Results

Study search

The search yielded a total of 247 hits in PubMed, 519 in Scopus, 382 in CENTRAL, 22 in LILACS, and 295 in Web of Science after applying various filters. The comprehensive search strategy and detailed database results are provided in Table S1.

Study selection

A total of 1,466 records were identified from databases, with an additional two records obtained through manual citation searching. Following the removal of 517 duplicate records, 951 records were screened based on title and abstract, resulting in the exclusion of 752 records. Subsequently, 199 reports were sought for full-text retrieval, of which 120 were excluded for specific reasons, as detailed in Appendix II. Finally, 70 studies were included in the review, as illustrated in Fig. 1.

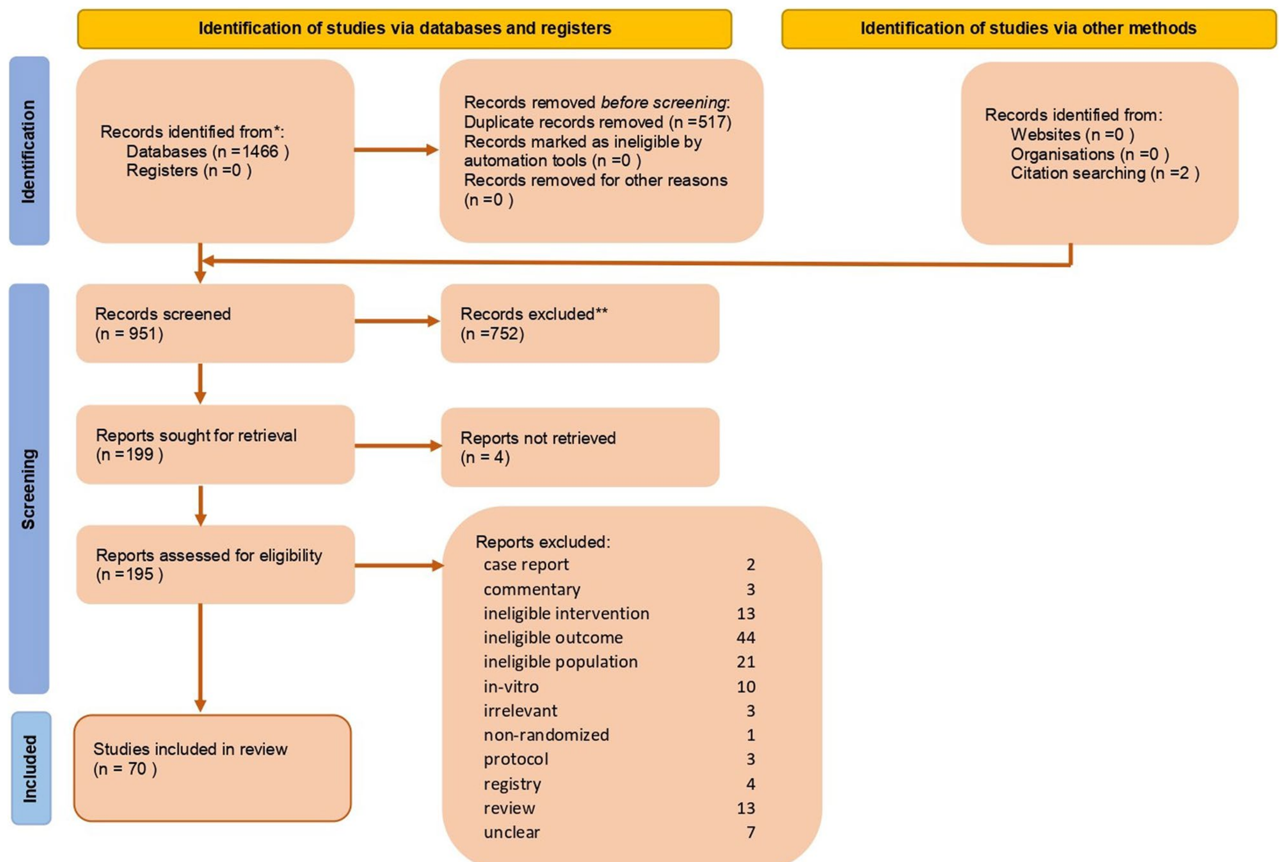

Fig. 1 PRISMA flowchart of the study selection process

Characteristics of included studies

The characteristics of the trials and participants are summarized in Table 1. The majority of the trials were parallel randomized controlled trials (RCTs), while 14 studies (20%) used a split-mouth design, and one study had a crossover design. A total of 4,634 participants were included across all studies. Gender distribution was reported in 61 studies, with male participants accounting for 1,879 (46.9%) of the total sample. The age of participants ranged from 12 to 50 years, with a mean age of 15.9 years. The included studies were conducted across 21 different countries, namely Australia, Belgium, Brazil, China, Egypt, Germany, Greece, India, Iran, Iraq, Italy, Jordan, the Netherlands, Poland, Saudi Arabia, Slovenia, Sweden, Switzerland, Turkey, the United Kingdom, and the United States. Among these, the most frequently represented country was India, accounting for 11 studies (15.71%), followed by Iran with 7 studies (10%), Germany and Turkey with 5 studies each (7.12%), and Sweden with 4 studies (5.71%). The included studies used various interventions, with fluoride varnish being the most common (16 studies, 22.9%), followed by CPP-ACP (12 studies, 17.1%), resin infiltration (7 studies, 10%), and nano-agents (6 studies, 8.6%). Chlorhexidine, fluoride in combination, fluoride mouthwash, and self-assembling peptides were each assessed in 3 studies (4.3%). Antibacterial adhesive, fluoride gel, NovaMin, probiotics, RMGIC varnish, and xylitol varnish were examined in 2 studies (2.9%), while microabrasion, fluoride film, laser treatment, ozone therapy, self-etch primer, and tri-calcium phosphate were each investigated in a single study (1.4%). The follow-up periods in the studies varied from as short as one month to as long as 36 months. Various methods were employed for WSLs detection in the included studies. DIAGNOdent was the most common ($n = 23$, 32.9%), followed by visual inspection ($n = 16$, 22.9%), intra-oral photographs ($n = 15$, 21.4%), and QLF ($n = 9$, 12.9%). Image software was used in ($n = 7$, 10%), while invasive methods used in four studies (5.7%). The outcome measures used for reporting initial carious lesions in the included studies were: "WSL Score" was the most frequently reported outcome ($n = 55$, 78.6%), followed by "Prevalence/Incidence" ($n = 29$, 41.4%) and "Lesion size" ($n = 10$, 14.3%). Less frequently reported outcomes included "DMFT" ($n = 4$, 5.7%), "Microhardness" ($n = 3$, 4.3%), "Fluorescence Loss" ($n = 2$, 2.9%), and "Mineral Content" ($n = 1$, 1.4%).

Table 1 Characteristics of the included studies

Study	Design; Country	Participants (M/F); Mean Age (years)	Interventions	Follow-up Time	Method to Record WSL/scale	Outcomes measured
Ali 2021[4]	RCT; Iraq	42 (16/26); 23.02	E1:Nanosilver MW($n=14$) E2: CHX MW ($n=14$) C: F MW $n=14$)	1,3,6 mo	visual inspection/ICDAS II score	-WSL score -No. of teeth with WSL
Vivaldi-Rodrigues 2006[51]	RCT(Split-mouth/cross over); Brazil	10 (5/5); 10–14	E: F^- varnish C: No intervention	12 mo	IOP/EDI	-WSL score
Shan 2021[52]	RCT; China	27 (10/17); ~17	E1: Resin infiltration ($n=9$) E2: Microabrasion ($n=9$) C: F TP ($n=9$)	6 mo	IOP/analyzed with ImageJ software	- WSL area/size - WSL optical density - WSL change in color
Kashash 2024[14]	RCT; Germany	36 (21/15); ~ 14	E: Resin infiltration ($n=18$) C: F^- varnish ($n=18$)	1, 3, 6 mo	IOP/ICDAS	- WSL change in color -WSL score
Willmot 2004[53]	RCT; UK	21 (10/11); 15.76	I: Low-F^- MR($n=12$) C: Placebo($n=9$)	12, 26 wk	IOP under polarized light	-WSL size reduction, -% lesion reduction
Benham 2009[54]	RCT (split-mouth): USA	60 (30/30); 11–16	E: Resin sealant($n=60$) C = No intervention($n=60$)	15–18 mo	DIAGNOdent	- WSL - WSL score
He 2016[55]	RCT: China	211 (94/17); 16.9	E1: F^- var ($n=69$) E2: F^- film ($n=70$) C: Placebo ($n=72$)	3, 6 mo	IOP/QLF	-WSL score - Fluorescence loss -Lesion area - lesion volume
Mollabashi 2023[56]	RCT (split-mouth design); Iran	35 (13/22); 17.9	E: Composite with TiO_2 nanoparticles ($n=35$) C: Conv. composite ($n=35$)	1, 3, 6 mo	DIAGNOdent	- WSL scores
Horan 2023[15]	RCT; Jordan	75 (31/44); ~19 yrs	E1: Self-etch primer($n=24$) E2: One-step adhesive system($n=24$) C: Conv. composite ($n=25$)	2,4 mo	IOP/QLF	Lesion area (pixels) - Fluorescence loss - WSL incidence
Garry 2017[57]	RCT(cross-over); UK	12 (8/4); ~15.2	E: CPP-ACP ($n=6$) C: Standard F^- TP ($n=6$)	1 mo	TMR	-Mineral loss -Lesion depth -Lesion width
Kirschneck 2016[58]	RCT; Germany	90 (44/46); 10–17	E1: Elmex® fluid var (10,000 ppm F−) ($n=30$) E2: Fluor Protector S var (7,700 ppm F−)($n=30$) C: Placebo ($n=30$)	1, 3, 4 mo	NR/ICDAS	-WSL score
Rajendran 2022[59]	RCT; India	90 (46/44); 15–25	E1: Strontium-doped nano-hydroxy-apatite paste($n=30$) E2: CPP-ACP cream($n=30$) C: Regular TP($n=30$)	1.5 mo	Visual inspection/Ekstrand	-WSL score
Gizani 2016[60]	RCT; Greece	85(29/56); 15.9	E: Probiotic lozenges ($n=42$) C: Placebo($n=42$)	17 mo	IOP/Gorelick et	-WSL score - WSL incidence
Sonesson 2014[8]	RCT; Sweden	424 (276/148);14.6	E: High F^- TP (5000ppm) ($n=188$) C: Regular TP($n=192$)	21.6 mo	IOP/Gorelick index	-WSL inidence -WSL score
Kannan 2023[61]	RCT; India	12(5/7):14–30	E: Resin Infiltration($n=6$) C = CPP-ACP($n=6$)	3,6 mo	DIAGNOdent	-Color change -Fluorescence loss

Table 1 (continued)

Study	Design; Country	Participants (M/F); Mean Age (years)	Interventions	Follow-up Time	Method to Record WSL/scale	Outcomes measured
Grocholewicz 2022[13]	RCT; Poland	150 (39/111); 16–50	E1: F^- (5% NaF) var ($n=30$) E2: F^- var + Ozone MR ($n=30$) E3: F^-(5% NaF) var + octenidine MR($n=30$) E4: : F^-(5% NaF) + ozone MR + octenidine MR ($n=30$) C: Regular TP ($n=30$)	12 mo	Visual inspection/Gorelick index	- WSL Incidence - DMF values
Kronenberg 2009[62]	RCT (split-mouth); Switzerland	20 (8/12); 15.0	E1: Ozone ($n=20$) E2: Cervitec(CHX/thymol) + Fluor Protector(F^-) var ($n=20$) C: No intervention ($n=20$)	26 mo	DIAGNOdent/visual/QLF index	-WSL DIAGNOdent score - WSL QLF score
Tiwari 2023[12]	RCT; India	93 (50/43); 13–35	E1: Probiotic TP($n=27$) E2: NovaMin (Na-Ca-phoshosilicate) TP($n=27$) C: Regular TP ($n=31$)	6 mo	Diagnodent	- WSL incidence - WSL scores
Stecksén-Blicks 2007[7]	RCT: Sweden	257 (85/172); 14.3	E: F^- (0.1%) Var ($n=132$) C: Placebo Var ($n=125$)	6–20 mo	IOP/Gorelick index	- WSL incidence - WSL Prevalence - WSL score
Jahanbin 2016[63]	RCT (split-mouth); Iran	20 (0/20); 15.5	E: NACP-contain composite ($n=20$) C: Conv. composite ($n=20$)	3, 6 mo	Vista Cam IX/Vista Cam IX scale	- Enamel mineral content
Sonesson 2020[9]	RCT; Sweden	148 (NR); ~14	E: F^- var ($n=75$) C: Placebo var ($n=73$)	20.4 mo	IOP/Gorelick index	- WSL Prevalence - WSL score
Belasic 2024[64]	RCT; Italy	64 (29/35); ~15	E1: 0.12% CHX ($n=21$) E2: F^- gel ($n=21$) C: Control ($n=22$)	1 mo	Visual inspection/non-specified WSL index	- WSL score
Sardana 2022[11]	RCT: Hong Kong	99 (36/63); ~18	E1: 5%NaF var($n=33$) E2: 5%NaF + TCP var($n=33$) C: Control ($n=33$)	18 mo	DIAGNOdent/ICDAS/Gorelick index	- WSL prevalence - WSL score
Mollabashi 2022[18]	RCT: Iran	36 (NR); 15–30	E: NovaMin TP ($n=18$) C: F^- TP ($n=18$)	1,3 mo	DIAGNOdent	- WSL score
Wierichs 2023[65]	RCT (split-mouth); Greece	15 (7/8); 14.3	E: Resin infiltration C: F^- var	3,6,9,12 mo	ICDAS/DIAGNOdent	- color change - WSL scores - Fluorescence score
Kaveh 2022[66]	RCT; Iran	60 (NR); 12–35	E1: MI Paste Plus (CPP-ACP + F^-+Xylitol) ($n=20$), E2: F^- Var ($n=20$), C: Control ($n=20$)	2, 4, 6 mo	Visual inspection/ICDAS	- WSLs score
Rohym 2021[67]	RCT (split-mouth); Egypt	6 (NR);15–25	E: RMGIC var C: Resin infiltration	3,6,12 mo	DIAGNODent	- Color change - WSL score
Øgaard 2005[68]	RCT; Sweden	97 (35/62); 14.4	E: AmF^- +Stannous F^- MR($n=50$) C: NaF MR($n=47$)	18 mo	Visual inspection/Gorelick index	- WSL incidence - WSL score
Enerbäck 2023[69]	RCT; Sweden	255(90/165):15.6	E1: F^- MR ($n=87$) E2: High F^- TP($n=81$); C: control ($n=87$)	24 mo	IOP/Gorelick index	- DiFS score - WSL incidence
Karabekiroğlu 2017[46]	RCT; Turkey	34 (18/16); 14–20	E: CPP-ACP paste ($n=16$) C: Regular toothpaste ($n=18$)	36 mo	DIAGNOdent/Gorelick Index/ICDAS II	- WSL Score -DMFT
Elaut 2004[70]	RCT(split mouth); Belgium	45 (17/28); 12.9	E: Argon laser curing C: Control	14 mo	IOP/Gorelick index like	- decalcification Incidence
Flynn 2022[71]	RCT; USA	40 (18/22); ~14	E: Resin sealant ($n=20$) E2: CPP-ACP var ($n=20$)	12 mo	IOP/Enamel Decalcification Index	- WSL incidence - EDI scores
Hammad 2016[72]	RCT; Egypt	42(22/20): 14.57	E: Sealant ($n=21$); C: Placebo($n=21$	12mo	IOP/modified scale	-WSL prevalence

Table 1 (continued)

Study	Design; Country	Participants (M/F); Mean Age (years)	Interventions	Follow-up Time	Method to Record WSL/scale	Outcomes measured
Trimpeneers 1996[73]	RCT (crossover); Belgium	50 (NR); 12.10	E: F^-releasing adhesive($n=50$) C: Control ($n=50$)	21 mo	IOP/yes or no	- WSL incidence
van der Kaaij 2015[74]	RCT; Netherlands	56(35/21); 13.3	E: F^-MR($n=26$); C: placebo ($n=30$)	24 mo	QLF/ICDAS	-WSL score -DMFS score
Pilli 2022[75]	RCT; India	90(44/46);~14	E: APF MR($n=45$) C: NaF MR($n=45$)	3, 6 mo	Visual inspection/ICDAS	- WSLs score
Bock 2016[76]	RCT; Germany	39(18/21);~15	E: F^- (1.25% NaF)gel($n=21$) C: placebo ($n=18$)	6 mo	IOP/software Image Pro Plus	-WSL size - WSL luminance (color change)
Shah 2017[6]	RCT (Split-mouth); India	22 (9/13); 16.3	E: Light-curable F^- (22.6 mg fluoride/ml NaF) var C: Conv. F^- (5% NaF) var	1.5, 3, 4mo	enamel section with Polarized light microscopy	- lesion depth
Badiee 2020[77]	RCT; Iran	50 (17/33); 10–35	E: Nano-hydroxyapatite TP($n=25$) C: F^- TP($n=25$)	1, 3, 6 mo	DIAGNOdent	- WSL score
Restrepo 2016[78]	RCT; Brazil	30 (18/12); 17.2	E1: 5% NaF var ($n=10$) E2: 2% CHX gel($n=10$) C: regular TP($n=10$)	1, 2, 3 mo	DIAGNOdent/Nyvad criteria	-WSL prevalence - WSL score
Jiang 2013[79]	RCT; China	100(50/50); 13.5	E: 1.23% APF foam ($n=53$) C: Placebo ($n=47$)	18 mo	Visual inspection/Gorelick index	-WSL prevalence - WSL score
Al Tuma 2023[16]	RCT(split mouth); Iraq	31 (7/24); 17.9	E: nCaF2-primer C: Conv. primer	1,3,6 mo	DIAGNOdent/Gorelick index	-WSL prevalence - WSL score
Mahmoudzadeh 2019[80]	RCT; Iran	95 (35/60); 21.0	E: CO2 Laser ($n=48$) C: Placebo ($n=47$)	6 mo	IOP/Enamel Decalcification Index	- WSL incidence
Benson 2019[81]	RCT (multicenter); UK, Ireland	197 (80/117); ~15.5	E: Resin-modified GIC ($n=96$) C: Conv. composite ($n=101$)	17.6 mo	IOP/Yes or no	-WSL Incidence -WSL color change
Bailey 2009[82]	RCT; Australia	45 (22/23); 15.5	E: CPP-ACP cream ($n=23$) C: Placebo cream ($n=22$)	1,2,3 mo	QLF/ICDAS II	- WSL prevalence - WSL scores
Baeshen 2011[83]	RCT; Saudi Arabia	37 (11/26); 17.2	E: Fluoridated (0.5% NaF) miswak ($n=19$) C: Control (only miswak) ($n=18$)	0.5, 1, 1.5 mo	DIAGNOdent/ICDAS II	- WSL score
Kau 2019[84]	RCT; USA	100 (35/32/33);	E1:1% NaF + TCP TP($n=35$); E2: 0.21% NaF + TCP cream ($n=32$) C: 0.2% NaF paste ($n=33$)	1,2,3, 4 mo	IOP/Enamel Decalcification Index	- WSL score
Mehta 2015[85]	RCT(split mouth); India	15 (NR); Mean age: 15.5	E: light-curable F^- var($n=15$) C: No treatment($n=15$)	0.5, 1, 1.5, 3, 4 mo	Polarized light microscopy	- Lesion depth
Uysal 2010[86]	RCT; Turkey	14 (6/8); 14.34	E: ACP-Containing Composite($n=7$) C: Control($n=7$)	1 mo	Microhardness test	-Microhardness score
Uysal 2011[87]	RCT; Turkey	16 (8/8); 12–17	E: Chitosan TP($n=8$) C: control ($n=8$)	2 mo	Microhardness test	-Microhardness score
Uysal a 2011[88]	RCT; Turkey	14 (8/6); 14.30	E: Antibacterial adhesive($n=7$) C: Control($n=7$)	1 mo	Microhardness test	-Microhardness score
Welk 2020[89]	RCT (Split-mouth); Germany	23 (13/10); 15.4	E: SAP P_{11}–4 C: Control	6 mo	Impedance scale	- WSL impedance - Lesion area(mm^2)
Gohar 2022[90]	RCT; Egypt	58 (25/33); ~21	E1: SAP var ($n=29$) C: F^- var ($n=29$)	3, 6 mo	DIAGNOdent/ICDAS	- WSL remineralizing score
Schlagenhauf 2022[91]	RCT; Germany	147 (NR);13.4	E: Hydroxyapatite TP ($n=75$) C: AmF/SnF2 TP ($n=72$)	6 mo	visual inspection/ICDAS	- WSL incidence (> ICDAS score 1)

Table 1 (continued)

Study	Design; Country	Participants (M/F); Mean Age (years)	Interventions	Follow-up Time	Method to Record WSL/scale	Outcomes measured
Silva 2021[92]	RCT; Brazil	55 (26/29); ~15	E1: F^- Var ($n=17$) E2: Xylitol Var ($n=19$) C: Control ($n=19$)	6 mo	QLF/ICDAS	- Fluorescence - WSL score
O'Reilly 2013[93]	RCT(split-mouth); USA	62 (19/43); 14.6	E: sealant C: control	26.6mo	Visual inspection/Gorelick	- WSL incidence -WSL score
Kiran 2023[94]	RCT; India	50 (26/24); 20	E: Amine F^- MW ($n=25$) C: Control($n=25$)	6 mo	IOP/ImageJ software	- WSL score
Beerens 2010[95]	RCT; Netherlands	54 (23/31); ~15	E: CPP-ACFP paste($n=28$) C: Control ($n=27$)	1.5, 3 mo	QLF	- Fluorescence loss - Lesion depth - Lesion area
Singh 2016[96]	RCT; India	45 (21/24); ~18	E1: F^- var($n=14$) E2: CPP-ACP C: Control ($n=14$)	1, 3, 6 mo	Visual inspection/DIAGNOdent	- WSL scores
Esenlik 2016[17]	RCT; Turkey	57 (28/29); ~17	E: CPP-ACP ($n=28$) C: Control ($n=29$)	25mo	IOP/Gorelick index	- WSL scores
Alshammari 219[97]	RCT(split mouth); Saudi Arabia	23(11/12);12–35	E: CPP-ACP ($n=23$) C: Control ($n=23$)	1, 6mo	DIAGNOdent	- WSL scores
Jena 2015[98]	RCT(split mouth); India	40(20/20);15.5	E: RMGIC var ($n=40$) C: Control ($n=40$)	6mo	Visual inspection/DIAGNOdent/Gorelick index	- WSL scores
Raghis 2018[99]	RCT(split mouth); Syria	26(8/18); 19.9	E: CO2 laser ($n=26$) C: Control ($n=26$)	6mo	DIAGNOdent/Geiger index	- WSL scores - WSL incidence - WSL area
Najafi 2022[45]	RCT; Iran	115(53/62); 15.9	E1: F^- Var ($n=29$) E2: Xylitol 10% Var ($n=27$) E2: Xylitol 20% Var ($n=30$) C: Control ($n=29$)	3, 6, 18 mo	DIAGNOdent	- WSL scores
Tomaževič 2022[100]	RCT; Slovenia	42(28/14);~17	E: 0.1% Flouride varnish ($n=21$) C: Control ($n=21$)	6 mo	DIAGNOdent/ICDAS	- WSL scores
Beerens 2018[101]	RCT; Netherlands	65(27/24);15	E: CPP-ACP containing paste ($n=25$) C: Control ($n=26$)	1.5, 6, 12 mo	QLF	- Lesion area - Fluorescence loss
Simon 2022[102]	RCT; India	60(25/35); 13–15	E: CPP-ACP ($n=30$) C: Resin infiltration ($n=30$)	1,3,6,12 mo	IOP/ICDAS II	- Lesion area
Du 2012[103]	RCT; India	96(31/65);3.2	E: Flouride varnish ($n=49$) C: Control ($n=47$)	3,6 mo	DIAGNOdent	- WSL scores
Hosseinpour-Nader 2022[104]	RCT; Iran	26(NR);15–30	E: Flouride varnish ($n=13$) C: Control ($n=13$)	1,2,3,4mo	visual inspection/ICDAS II	- WSL scores
Wang 2023 RCT[10]	RCT; China	79(NR); 15.9	E1: Flouride varnish ($n=20$) E2: ACP-CPP ($n=20$) E3: resin infiltration($n=20$) C: Control ($n=19$)	12 mo	ICDAS	- Lesion area

~ approximately, *APF* Acidulated Phosphate Fluoride, *Am* Amomium, *CHX* chlorhexidine, *Conv.* conventional, *CPP-ACP* Casein Phosphopeptide-Amorphous Calcium Phosphate, *DiFS* Decayed Initial Filled Surfaces, *E* Experimental, *EDI* enamel decalcification index, *F* female, *F* Fluoride, *d* days, *NR* not reported, *RCT* randomized clinical trial, *ICDAS* International Caries Detection and Assessment System score, *IOP* intraoral photograph, *M* male, *MW* Mouth wash, *mo* month, *NACP* nano-amorphous calcium phosphate, *nCaF2* nano-calcium fluoride, *TCP* tri-calcium phosphate, *RMGIC* Resin modified glass-ionomer, *SAP P11-4* self-assembling peptide P11-4, *TP* toothpaste, *TM* Transverse microradiography, *var* varnish, *WSL* white spot lesions, *wk* week

Risk of bias

In about one-third of the studies, there were issues with the randomization domain due to a lack of or inadequate allocation concealment ($n = 25$, 35.7%). Regarding deviations from intended interventions, some concerns arose in 3 trials (4.3%) due to the potential lack of blinding of the assessor. For missing outcome data, some concerns were identified in 7 trials (10.0%) primarily due to loss to follow-up. For the measurement of the outcome, some concerns were present in 3 trials (4.3%). About half of the trials ($n = 35$, 50.0%) had some concerns for the selective reporting domain due to a lack of trial registration. The overall risk of bias was 'some concerns' in 28 trials (40.0%), and a high risk in 4 trials (5.7%) (Tables 2 and Table S8).

Network meta-analysis

The network plot for WSL score showed moderate connectivity, with fluoride varnish and control being the most frequently compared interventions (12 studies). CPP-ACP, resin infiltration, and probiotic also had multiple connections. However, several treatments such as self-assembling peptide, RMGIC varnish, ozone, and laser were included in only a few studies, resulting in limited connectivity. In contrast, the WSL prevalence network was less well connected. Fluoride varnish, control, CPP-ACP, and chlorhexidine were the most studied interventions, while many others—such as probiotic, NovaMin, ozone, and self-etch primer—had minimal connections. Overall, the network was sparse, with limited comparisons among several treatments (Fig. 2) The network for lesion size was relatively sparse, with limited direct comparisons between treatments. The strongest connections were seen for CPP-ACP and control, both assessed in multiple studies. In contrast, several interventions—such as self-etching primer, resin infiltration, and microabrasion—were each evaluated in only one study, reducing the robustness of direct evidence for these treatments (Fig S1).

For WSL score, the NMA showed self-assembling peptide (SMD = −1.38, 95% CI −2.30 to −0.46; P-score = 0.86), NovaMin (SMD = −1.37, 95% CI −2.26 to −0.48; P-score = 0.86), Nano-agents (SMD = −1.16, 95% CI −1.79 to −0.53; P-score = 0.80), xylitol varnish (SMD = −0.99, 95% CI −1.84 to −0.15; P-score = 0.71), and CPP-ACP (SMD = −0.94, 95% CI −1.38 to −0.50; P-score = 0.71)

Table 2 Risk of bias summary for all included trials

Bias Domain	Category	No. of Trials(Percent)
Randomization Process	Low	41(58.6)
	Some Concerns	25(35.7)
	High	4(5.7)
Deviations from Intended Interventions	Low	67(95.7)
	Some Concerns	3(4.3)
	High	0(0)
Missing Outcome Data	Low	63(90)
	Some Concerns	7(10)
	High	0(0)
Measurement of the Outcome	Low	67(95.7)
	Some Concerns	3(4.3)
	High	0(0)
Selection of the Reported Result	Low	35(50)
	Some Concerns	35(50)
	High	0(0)
Overall Bias	Low	38(54.3)

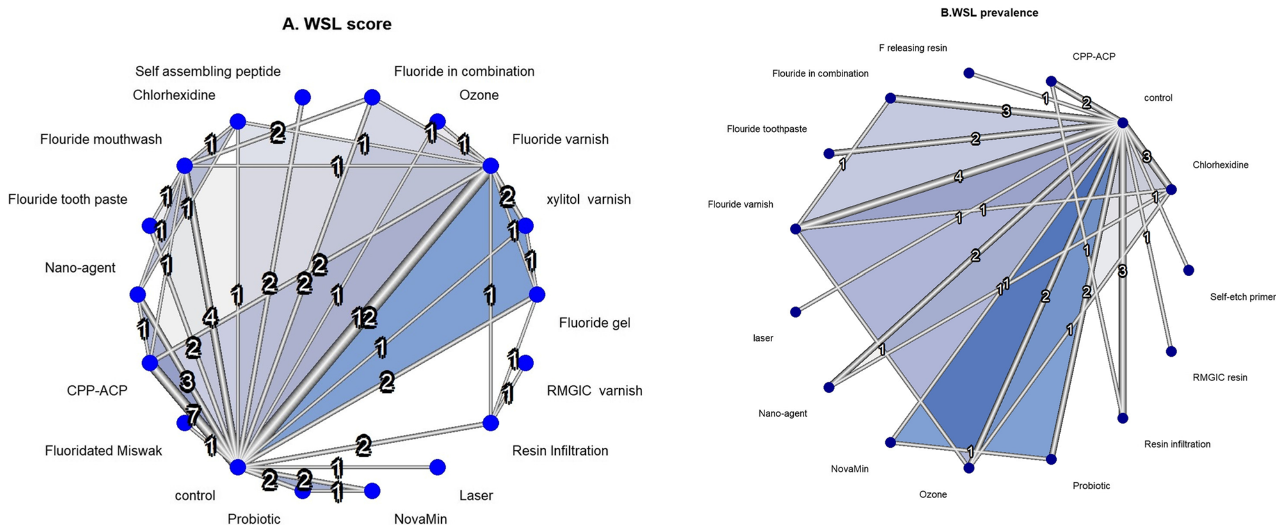

Fig. 2 Network plot for WSL score (right) and prevalence (left)

were most effective. Probiotics (SMD = −0.90, 95% CI −1.76 to −0.05; P-score = 0.66), fluoride in combination (SMD = −0.79, 95% CI −1.43 to −0.16; P-score = 0.62), and fluoride varnish (SMD = −0.67, 95% CI −1.01 to −0.34; P-score = 0.55) also showed statistically significant reductions compared to control. In contrast, laser and other fluoride-based interventions such as gel, toothpaste, mouthwash, as well as chlorhexidine and RMGIC varnish, showed statistically non-significant results with confidence intervals crossing zero (Fig. 3 & Table S2).

For WSL prevalence, fluoride varnish demonstrated the strongest and statistically significant reduction (OR = 0.25, 95% CI 0.14 to 0.45; P-score = 0.88), followed by fluoride in combination (OR = 0.31, 95% CI 0.16 to 0.59; P-score = 0.79), and CPP-ACP (OR = 0.32, 95% CI 0.13 to 0.82; P-score = 0.75). These three interventions statistically significantly reduced the odds of WSL occurrence compared to control. Additionally, resin infiltration (OR = 0.49, 95% CI 0.25 to 0.93) and fluoride toothpaste (OR = 0.61, 95% CI 0.40 to 0.93) also showed statistically significant effects. Other interventions, including ozone, laser, nano-agents, probiotics, and NovaMin, did not reach statistical significance (Fig. 3 & Table S3).

The NMA showed that none of the interventions statistically significantly reduced WSL size compared to control. Resin infiltration and microabrasion had the highest P-scores (0.68 and 0.65), but their effects were not statistically significant and showed wide confidence and

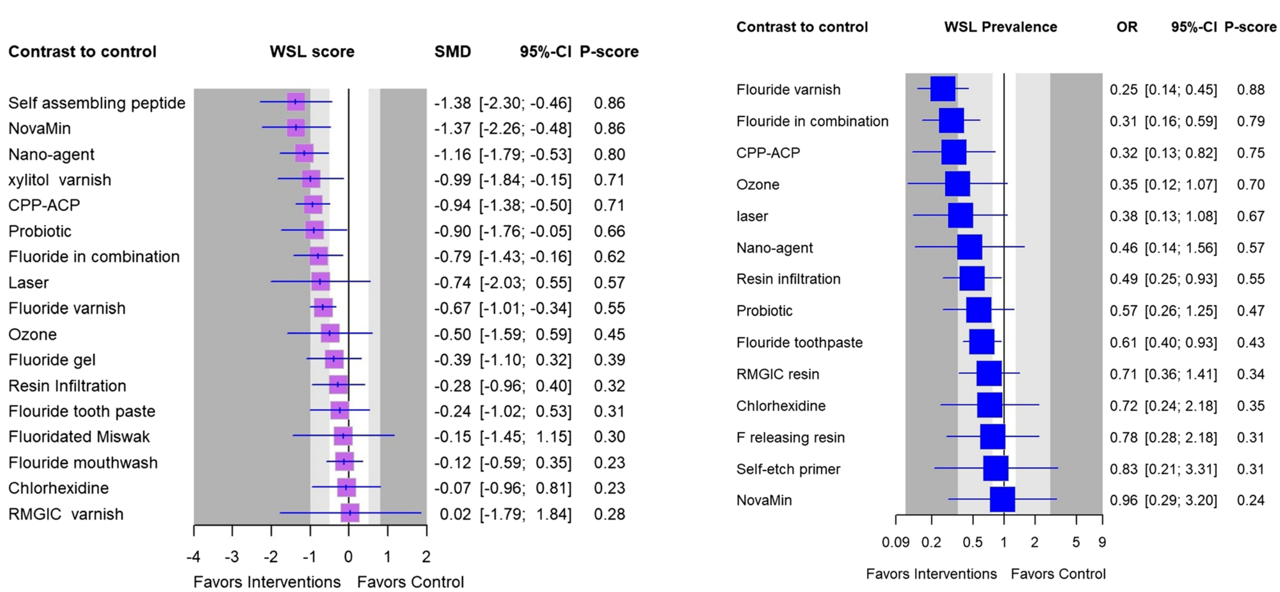

Fig. 3 Network meta-analysis results for reduction in WSL score (left side) and prevalence (right side) interventions compared to control

prediction intervals. Other treatments, including fluoride varnish, gel, film, CPP-ACP, and self-etching primer, also showed no statistically significant benefit. High heterogeneity (I^2 = 90.6%) indicated substantial variability among studies (Table S4 & Fig S2).

In the league table for treatment on WSL score reduction, CHX demonstrated no significant effect on WSL score reduction (SMD −1, 95% CI −2 to 1). In contrast, treatments such as self-assembling peptide (SAP), nano-agent, NovaMin, CPP-ACP, and xylitol varnish showed greater efficacy, with SMDs ranging from 1 to 2 and confidence intervals indicating statistically significant improvements. Fluoride-based interventions offered modest benefits, while ozone, fluoridated miswak, resin infiltration, and RMGIC varnish had limited or no effect. (Table S9) In Table S10, the league table shows CHX did not significantly reduce white spot lesion (WSL) prevalence compared with control (OR 0.6, 95% CI 0.2–2.1). Significant reductions were observed with fluoride combinations (OR 3.3, 95% CI 1.7–6.2), fluoride varnish (OR 3.9, 2.2–6.9), and resin infiltration (OR 2.1, 1.1–3.9). Other interventions such as nano-agents, NovaMin, probiotics, and ozone showed non-significant effects. In league table S11, none of the treatments showed statistically significant reductions in white spot lesion (WSL) size compared with control, as all standardized mean differences (SMD) had 95% confidence intervals crossing zero. These results suggest no clear evidence that any intervention is superior in reducing WSL size.

Consistency evaluation

There were no statistically significant differences between direct and indirect estimates for WSL score reduction across all comparisons. (Table S5) For CPP-ACP vs. Control, Resin Infiltration vs. Control, and Resin Infiltration vs. CPP-ACP, the differences between direct and indirect estimates were minimal and statistically non-significant (all $p > 0.05$). The only exception was the comparison of NovaMin vs. Control, which showed a statistically significant difference ($p = 0.01$), suggesting inconsistency between direct and indirect estimates for this comparison. The network meta-analysis showed mostly consistent direct and indirect estimates for WSL prevalence, with no significant differences ($p > 0.05$) except for fluoride varnish vs. fluoride in combination ($p = 0.03$), indicating possible inconsistency there..(Table S6) Other comparisons, including CHX, nano-agent, ozone, CPP-ACP, NovaMin, and resin infiltration, were associated with statistically non-significanr differences between direct and indirect evidence. Overall, due to sparsity of many comparisons in both networks, direct and indirect estimates were imprecise, leading to imprecise inconsistency estimates, and thus, large p-values, signifying inconclusive evidence regarding the plausibility of consistency.

The sensitivity analysis including only trials at low risk of bias showed that CPP-ACP (SMD = −1.72; 95% CI: −2.55 to −0.90; P-score = 0.91), self-assembling peptide (SMD = −1.38; 95% CI: −2.41 to −0.34; P-score = 0.81), NovaMin (SMD = −1.37; 95% CI: −2.37 to −0.38; P-score = 0.81), and nano-agent (SMD = −1.30; 95% CI: −2.04 to −0.56; P-score = 0.80) were significantly effective in reducing white spot lesion (WSL) scores, all showing large effect sizes. In terms of WSL prevalence, only fluoride varnish demonstrated a statistically significant reduction compared to control (OR = 0.08; 95% CI: 0.02 to 0.33; P-score = 0.98), indicating a strong preventive effect (Fig S3).

Publication bias

We planned to assess small-study effects using comparison-adjusted funnel plots; however, it was not possible due to the sparsity of the networks for WSL prevalence and Size. Publication bias was not detected for studies reporting WSL score ($p = 0.45$) indicated by symmetric funnel plots and non-significant Egger's tests (Fig S4).

Confidence in network meta-analysis

Using the CINeMA approach, the confidence in effect estimates for WSL outcomes—score, size, and prevalence—ranged from high to low, with most comparisons rated as moderate or low. For WSL score, high confidence was noted for fluoride mouthwash versus CHX, probiotics versus control, resin infiltration versus control, xylitol varnish versus control, and fluoride toothpaste versus FMW. Several fluoride-based interventions, including varnish, toothpaste, gel, and combinations, were generally supported by moderate confidence, though often limited by concerns related to within study bias or imprecision. Comparisons involving CHX, nano agents, and CPP-ACP commonly showed low confidence due to serious concerns related to imprecision or study limitations. In terms of WSL prevalence, only ozone versus control reached high confidence, while CHX, CPP-ACP, NovaMin, probiotics, and resin infiltration achieved moderate confidence. However, nano-agent and fluoride combination comparisons were often downgraded to low due to inconsistency or reporting bias. For WSL size, moderate confidence was observed for CPP-ACP and resin infiltration when compared with control or each other, while other interventions such as microabrasion, fluoride varnish, and resin infiltration versus control were rated low, primarily due to major concerns about imprecision and within study bias (Table S12).

Discussion

This systematic review and NMA assessed 70 randomized controlled trials searched in five major databases involving 4,634 participants from 21 different countries, reporting on the comparative effectiveness of various interventions for WSLs associated with fixed appliance treatment. This review overcomes the flaws of the previous NMA [21], which violated transitivity by including non-orthodontic patients, non-randomized and in-vitro studies, combining dissimilar outcomes (e.g., DMFT scores, WSL severity, lesion size), and lacking both certainty assessment and consideration of clustering effects in split-mouth design studies.

Results in context

The NMA revealed that self-assembling peptide, NovaMin, nano-agents, CPP-ACP, xylitol varnish, probiotics, fluoride combinations, and fluoride varnish significantly reduced WSL scores, with large to moderate effect sizes. For WSL prevalence, fluoride varnish, fluoride combinations, CPP-ACP, resin infiltration, and fluoride toothpaste showed significant reductions. However, no intervention showed a significant impact on WSL size. Sensitivity analysis confirmed large, significant effects for CPP-ACP, self-assembling peptide, NovaMin, and nano-agents, and a strong preventive effect of fluoride varnish. The overall consistency between direct and indirect estimates supports the robustness of findings, except for minor inconsistencies in a few comparisons.

In NMA, large and statistically significant effects can occur due to strong biological mechanisms, comparisons against placebo, or short-term outcomes where early improvements are more noticeable. This large effect has also been reported in previous NMAs, such as the study by Gianola et al. [38] on treatments for acute and subacute mechanical non-specific low back pain, where similarly large effects were observed.

Overall, the results show good coherence between the direct and indirect evidence for both WSL score and prevalence, as indicated by the non-significant differences between their effect estimates. This suggests that the findings from different types of comparisons align well, adding confidence to the results. The network for WSL score was moderately connected, with fluoride varnish, CPP-ACP, resin infiltration, and probiotics appearing as key interventions that linked the network and allowed for meaningful comparisons. Similarly, the network for WSL prevalence, though less densely connected, still included central treatments like fluoride varnish, control, CPP-ACP, and chlorhexidine, supporting a reasonable level of evidence consistency. However, the outcome related to WSL size was more challenging to analyze due to the limited number of studies and few direct comparisons. This resulted in a fragmented and weakly connected network, which reduces the reliability of indirect comparisons and makes it difficult to draw firm conclusions about the relative effectiveness of treatments for this outcome. The lack of data highlights the need for further research to fill these gaps.

The overall risk of bias across the included trials was generally low, supporting the reliability of the NMA findings. Most trials showed low risk in key domains such as deviations from intended interventions (95.7%), outcome measurement (95.7%), and missing data (90%). However, concerns were more notable in the randomization process, where 35.7% of studies had some concerns and 5.7% were at high risk, and in selective reporting, where 50% lacked trial registration. Overall, 54.3% of trials were rated low risk, with 40% having some concerns. While the evidence is largely robust, caution is advised when interpreting results from studies with unclear or unregistered protocols.

In this study, SAPs have demonstrated significant efficacy in remineralizing WSLs among orthodontic patients. A previous meta-analysis including 12 in-vitro studies and six RCTs on non-orthodontic patients found significant reduction in initial caries score (SMD [−0.61; 95%CI:−0.88, − 0.34]) [39]. SAPs function by self-assembling into nanofibers that mimic enamel matrix proteins, providing a scaffold for hydroxyapatite crystal formation, thereby promoting enamel remineralization [40].

The second most effective intervention to reduce the WSL score was NovaMin. NovaMin is a calcium sodium phosphosilicate, has shown promising results in remineralizing WSLs. The mechanism involves the release of calcium and phosphate ions upon contact with saliva, which then form a hydroxycarbonate apatite layer on the enamel surface, enhancing remineralization. Although no meta-analysis exists on the specific efficacy of NovaMin on orthodontic WSLs, several trials have demonstrated its effectiveness in reducing WSLs [12, 18, 41, 42].

In our network meta-analysis, nano-agents ranked as the third most effective intervention for reducing WSL scores (SMD = − 1.16; 95% CI: − 1.79 to − 0.53; P-score = 0.80), showing statistically significant improvements over controls. Their effectiveness is likely due to their ability to mimic natural enamel and facilitate remineralization by acting as nucleation sites for hydroxyapatite crystal growth. The nanoscale size allows deeper penetration into enamel lesions, enhancing mineral deposition. Additionally, some nano-agents possess antimicrobial properties, further contributing to WSL reduction by lowering bacterial activity [43]. These combined effects explain their strong performance in managing orthodontic WSLs. This is supported by a recent systematic review evaluating the effect of nano-hydroxyapatite (nano-HAP), with or without fluoride, on WSLs in terms of remineralization and colour change. Fourteen studies were included, of which 12 contributed to the meta-analysis. Nano-HAP significantly improved enamel surface microhardness (MD = 9.29; 95% CI: 7.74–10.84), mineral content (MD = 0.09; 95% CI: 0.05–0.13), and showed comparable remineralization ability to fluoride based on

DIAGNOdent™ (DD) scores (MD = 0.09; 95% CI: 0.05–0.13; $p < 0.001$) [44].

Several interventions included in our network meta-analysis demonstrated notable effectiveness in reducing (WSLs among orthodontic patients. Xylitol varnish, for instance, showed promising results likely due to its dual role in reducing cariogenic bacteria—particularly Streptococcus mutans—and enhancing salivary flow. These effects help create a more favorable oral environment for natural remineralization [45]. CPP-ACP also emerged as an effective option. It works by delivering bioavailable calcium and phosphate ions to the enamel surface, facilitating their diffusion into subsurface lesions. This process helps to rebuild the enamel structure and halt lesion progression, especially in areas affected by plaque accumulation due to orthodontic appliances [17, 46]. These findings align with a systematic review of 13 randomized controlled trials evaluating the clinical efficacy of CPP-ACP in orthodontic patients. The review concluded that CPP-ACP can reduce the prevalence of WSLs and enhance their remineralization during or after orthodontic treatment [47].

Probiotics, though relatively new in the context of WSL management, also demonstrated a beneficial impact. Their effectiveness may stem from their ability to restore microbial balance by outcompeting harmful bacteria and reducing acidogenic biofilm activity, thereby lowering the risk of enamel demineralization. A recent systematic review published in 2023, involving patients undergoing fixed orthodontic therapy, found that probiotics significantly reduced mutans streptococci counts—key bacteria associated with the development of white spot lesions (WSLs) [48]. However, only one of the included studies directly assessed WSLs and reported no clear clinical benefit from probiotic use. In contrast, our network meta-analysis (NMA), which included two randomized controlled trials (RCTs) specifically measuring WSL scores, demonstrated that probiotics significantly reduced WSL severity. This discrepancy may be attributed to the methodological strength of NMA, which combines both direct and indirect comparisons to enhance statistical power and detect subtle treatment effects.

Fluoride—both in combination with other agents and as a standalone varnish—was effective intervention in WSL score and prevalence reduction. Fluoride helps by enhancing enamel resistance through the formation of fluorapatite and promoting remineralization of early lesions. These findings are corroborated by a systematic review conducted by Sonesson et al. [49] which evaluated the preventive effect of fluoride varnish (FV) when applied regularly during orthodontic treatment. Including seven randomized controlled trials (n = 666), the review reported that all studies favored the FV intervention, with a pooled risk ratio of 0.64 (95% CI: 0.42–0.98), indicating a statistically significant reduction in WSL prevalence.

In this study, resin infiltration significantly reduced the prevalence of white spot lesions (WSLs) compared to the control group (OR = 0.49, 95% CI: 0.25 to 0.93), indicating a 51% lower likelihood of WSLs. This effect is likely due to resin infiltration's ability to penetrate and seal porous enamel, blocking acid diffusion and halting lesion progression. Its dual function—both preventive and aesthetic—makes it a valuable option, especially for managing early WSLs during orthodontic treatment. This is supported by a systematic review that included 11 studies and found a significantly greater optical improvement in WSLs treated with resin infiltration compared to untreated controls (SMD = 1.24, 95% CI: 0.59 to 1.88) [50].

The reliability a NMA depends on study quality and consistency of evidence. To assess this, we used the CINeMA tool and performed a sensitivity analysis including only low-risk-of-bias studies to confirm the robustness of our findings [37]. High confidence was noted in key comparisons for WSL score, including fluoride mouthwash versus CHX, probiotics versus control, resin infiltration versus control, xylitol varnish versus control, and fluoride toothpaste versus fluoride mouthwash—supporting some nontraditional interventions. However, many comparisons, particularly those involving CHX, nano agents, and CPP ACP, had low confidence due to imprecision, reporting bias, and limited direct evidence. Most fluoride based interventions were rated with moderate confidence, often affected by within study bias and inconsistency. For WSL prevalence, high confidence was seen only for ozone versus control, while moderate confidence was found for CHX, CPP ACP, NovaMin, probiotics, and resin infiltration. Most other comparisons were rated low due to inconsistency and reporting bias. For WSL size, no intervention reached high confidence. Only CPP ACP and resin infiltration showed moderate confidence, while others, such as fluoride varnish and microabrasion, were downgraded due to imprecision and study bias.

The sensitivity analysis, limited to trials with low risk of bias, provided meaningful findings. CPP ACP, self assembling peptide, NovaMin, and nano agents consistently showed significant and large effects in reducing WSL scores, confirming their effectiveness even under stricter methodological conditions. This strengthens their clinical relevance in managing or reversing early enamel demineralization. For WSL prevalence, the analysis further supported the effectiveness of fluoride varnish, showing a substantially lower odds ratio compared to control and a high P score of 0.98. These results reinforce its role in preventive care protocols for white spot lesions.

It was not possible to distinctly analyze and draw separate conclusions for the prevention or treatment of WSLs through various interventions. This is due to the complex nature of the condition, as new lesions may develop during active fixed appliance therapy while existing ones are being managed. However, all included studies were randomized controlled trials with a control group, and outcomes such as WSL score, prevalence, or lesion size were assessed at the end of a defined follow-up period. This allowed us to evaluate the overall efficacy of interventions in both preventing the occurrence of new lesions and reducing the severity of existing ones.

Strengths

This study has several strengths. First, it included only randomized clinical trials involving patients with fixed orthodontic appliances, which improves the reliability and direct relevance of the findings to clinical practice. Second, by excluding laboratory studies, non-randomized studies, and studies on non-orthodontic patients, consistency in study design and patient characteristics was improved. Third, the clustering effect in split mouth study designs was accounted for, which is often overlooked but essential for producing accurate effect estimates. Fourth, both pairwise and network meta-analyses were conducted, allowing for a comprehensive comparison of all available interventions and enabling treatment ranking. A sensitivity analysis including only studies with low risk of bias was also performed, supporting the stability and credibility of the results. Finally, the certainty of the evidence was assessed using the CINeMA approach, providing valuable guidance for evidence-based clinical decision making.

Limitations

This network meta-analysis has several limitations. First, there was substantial clinical heterogeneity among the included studies, particularly due to variations in the concentration or dosage of interventions, differences in follow-up durations, and variability in patients' oral hygiene status. To account for this, we employed a random-effects model and used the CINeMA approach to assess the quality of evidence.

Second, the network for the outcome of white spot lesion (WSL) size was sparsely connected due to the limited number of direct comparisons, which may affect the robustness of the results for this specific outcome.

Third, although we included only randomized controlled trials (RCTs), many of the included studies had a moderate risk of bias, especially related to the randomization process and selective reporting.

Fourth, the clinical the large effect sizes should be interpreted with caution, as most included studies reported short-term outcomes without long-term follow-up.

Finally, a number of eligible studies could not be included in the NMA because they did not report the three common outcomes (WSL score, size, and prevalence). Instead, they reported other outcomes such as DMFT, microhardness, fluorescence loss, or mineral content. Outcomes reported by fewer than 10 studies were not pooled to avoid generating wide and non-credible confidence intervals.

Future directions

There is a need to conduct:

- Well-designed, multicenter RCTs with large sample sizes using standardized and validated outcome measures.
- Standardized intervention protocols and follow-up durations to reduce clinical heterogeneity.
- Long-term follow-up studies to assess the durability of treatment effects.
- Evaluations of patient-reported outcomes and esthetic satisfaction, which are currently underrepresented.
- Future research should prioritize well-designed head-to-head RCTs, especially for NovaMin, ozone, xylitol varnish, probiotics, nano-agents, and resin infiltration versus fluoride-based strategies, to confirm treatment rankings and strengthen clinical recommendations.

Conclusion

Fluoride-based interventions, particularly varnish and combination therapies, showed the most consistent effectiveness in preventing white spot lesions during fixed orthodontic treatment. Resin infiltration demonstrated moderate confidence for improving lesion size and appearance, whereas other agents such as CPP-ACP, NovaMin, self-assembling peptide, and nano-agents showed variable or limited evidence. Overall, fluoride-based strategies and resin infiltration remain the most reliable options, but further high-quality trials are needed to strengthen the evidence base. Treatment choice should be individualized, considering lesion severity, oral hygiene, patient age, caries risk, and aesthetic expectations. Evidence gaps, especially regarding long-term outcomes and comparative effectiveness, highlight the need for further high-quality trials.

Abbreviations

CHX	Chlorhexidine
CI	Confidence Interval
CINeMA	Confidence in Network Meta–Analysis
CPP	ACP–Casein Phosphopeptide–Amorphous Calcium Phosphate
DMFT	Decayed, Missing, and Filled Teeth
ICC	Intraclass Correlation Coefficient
NMA	Network Meta–Analysis
OR	Odds Ratio
PICOS	Population, Intervention, Comparator, Outcomes, Study design
PRISMA	NMA–Preferred Reporting Items for Systematic Reviews with Network Meta–Analyses
PRISMA	S–Preferred Reporting Items for Systematic Reviews and Meta–Analyses–Search Extension
PROSPERO	International Prospective Register of Systematic Reviews
QLF	Quantitative Light–Induced Fluorescence
RCTs	Randomized Controlled Trials
REML	Restricted Maximum Likelihood
RMGIC	Resin–Modified Glass Ionomer Cement
RoB	2–Risk of Bias 2 Tool
SAP	Self–Assembling Peptide
SMD	Standardized Mean Difference
WSLs	White Spot Lesions

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-026-07755-3.

Supplementary Material 1.

Acknowledgements

We are thankful to Nikolaos Pandis editor-in-chief Progress Orthodontics for his valuable help at protocol level.

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Funding

This research received no external funding.

Data availability

Data are available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable. This study is a systematic review and does not involve human participants, patient data, or animal subjects.

Consent for publication

Not applicable, as this meta-analysis is based solely on previously published data and does not involve human participants.

Competing interests

The authors declare no competing interests.

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Received: 1 September 2025 / Accepted: 19 January 2026
Published online: 21 February 2026

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