SYSTEMATIC REVIEW

# Effectiveness of Fluoride Treatments in Remineralizing Early Non-Cavitated Carious Lesions: A Systematic Review and Meta-Analysis

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## ABSTRACT

Dental caries affects billions globally, with early non-cavitated lesions being reversible through fluoride remineralization. Despite extensive research, optimal fluoride protocols remain debated. This analysis aimed to evaluate the efficacy of fluoride treatments in remineralizing early caries and compare delivery methods, concentrations, and frequencies. This PRISMA-compliant systematic review included 12 RCTs and controlled trials (n=11,701 observations) from seven databases. Studies were assessed using ROB2/ROBINS-E tools, with meta-analyses conducted via random-effects models. Subgroup analyses explored fluoride types, concentrations, and follow-up durations. High-concentration fluoride varnishes (≥5,000 ppm) showed the largest effects (ES=1.12, 95%CI: 0.88–1.36), while daily toothpastes (1,000–4,999 ppm) had more modest but consistent results (ES=0.93, 95%CI: 0.72–1.14). Network meta-analysis revealed a non-linear dose-response, with diminishing returns above 10,000 ppm. Professional applications every 3–6 months, combined with daily home care, emerged as the optimal regimen. Heterogeneity was substantial ($I^2$=74.09%) but explained by concentration differences (27.12% variance). Fluoride effectively remineralizes early caries, with high-concentration professional treatments yielding superior outcomes. A combined approach of periodic in-office varnishes and daily toothpaste is recommended for comprehensive caries management.



## Keywords

fluorides; tooth remineralization; dental caries; meta-analysis; systematic review


## INTRODUCTION

Dental caries remains one of the most prevalent chronic diseases worldwide, affecting individuals across all age groups [1]. Early non-cavitated carious lesions, characterized by subsurface demineralization without structural breakdown, are reversible through remineralization [2]. Fluoride has been widely recognized for inhibiting demineralization and promoting remineralization by forming fluorapatite, which is more resistant to acid attacks [3].


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Despite extensive research on fluoride's efficacy, the comparative effectiveness of different fluoride treatments (e.g., varnishes, gels, toothpaste) in remineralizing early caries remains debated [4]. Previous systematic reviews have demonstrated fluoride's benefits, but few have focused exclusively on non-cavitated lesions or compared various delivery methods [5]. Additionally, newer high-concentration fluoride formulations and their long-term efficacy require further evaluation [6].

This systematic review and meta-analysis aimed to synthesize existing evidence on the effectiveness of fluoride treatments in remineralizing early non-cavitated carious lesions, providing clinicians with evidence-based recommendations for preventive care. By evaluating randomized controlled trials (RCTs) and observational studies, this study seeks to clarify optimal fluoride delivery methods, concentrations, and application frequencies [7].

## REVIEW

### Methodology

This systematic review adhered to PRISMA guidelines and included randomized controlled trials (RCTs) and controlled clinical trials evaluating fluoride treatments for early non-cavitated caries.

*Search Strategy Development*

The search strategy was designed to capture all relevant studies on fluoride's remineralization effects on early caries. Boolean operators (AND/OR) and MeSH terms were used to refine results. Filters included publication date, language (English), and study type (RCTs). The syntax was adjusted per database requirements to maximize sensitivity and specificity (Table 1).

**Table 1:** Comprehensive Search Strategy across Multiple Databases for Fluoride Remineralization Studies.

| Database | Search Query Components | Applied Filters | Syntax/Modifiers |
|---|---|---|---|
| **PubMed** | (Fluoride[MeSH]) AND (Tooth Remineralization[MeSH]) | Humans, RCTs, English | ("fluoride"[Title/Abstract]) |
| **Embase** | ('fluoride'/exp) AND ('remineralization'/exp) | Clinical trials, 2000-2024 | 'fluoride':ti, ab AND 'caries' |
| **Cochrane Library** | Fluoride AND (early caries OR non-cavitated) | Trials, No date restriction | #1 Fluoride AND #2 Remineralize |
| **Scopus** | TITLE-ABS-KEY(fluoride AND remineralization) | English, Last 10 years | (fluoride AND caries) AND (early) |
| **Web of Science** | TS ("fluoride remineralization" OR "early caries") | 2000-2024, Article | TS=(fluoride AND remineral*) |
| **Google Scholar** | "fluoride treatment" AND "early caries" | Since 2010, PDF available | intitle: fluoride AND remineral* |
| **ClinicalTrials.gov** | Fluoride AND (remineralization OR early caries) | Interventional studies | Search: Fluoride AND Dental Caries |

To ensure comprehensive coverage, manual searches were conducted by reviewing reference lists of included studies, relevant systematic reviews, and gray literature sources such as conference proceedings and dissertations. Two independent reviewers screened titles and abstracts, with conflicts resolved through discussion or consultation with a third reviewer. Inter-rater reliability was assessed using Cohen's kappa coefficient ($\kappa > 0.8$ indicated strong agreement). Discrepancies in study eligibility were documented and resolved via consensus to minimize selection bias.

*Rationale for Study Selection Based on PICO Framework*

The eligibility criteria were structured around the PICO framework to maintain methodological rigor. The population included individuals with early non-cavitated caries, excluding those with cavitated lesions or systemic conditions affecting caries progression. Interventions encompassed topical fluoride treatments (varnishes, gels, toothpaste), while systemic fluoride or non-fluoride remineralizing agents were excluded. Comparators included placebo, no treatment, or alternative fluoride formulations. Outcomes focused on quantifiable remineralization (e.g., laser fluorescence, microhardness tests), excluding studies solely assessing caries prevention (Table 2).

**Table 2:** Inclusion and Exclusion Criteria Based on PICO Framework for Meta-Analysis.

| PICO Element | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Population | Patients with early non-cavitated caries | Cavitated lesions, systemic diseases |
| Intervention | Topical fluoride (varnish, gel, toothpaste) | Systemic fluoride, non-fluoride agents |
| Comparison | Placebo/no treatment/other fluoride formulations | Non-comparative studies |
| Outcome | Remineralization (quantitative/qualitative) | Only prevention studies |

*Systematic Data Extraction and Harmonization*

A standardized data extraction form was developed to capture key study characteristics, including author, year, sample size, fluoride type, concentration, application frequency, follow-up duration, and outcome measures. Two reviewers independently extracted data, with cross-verification to ensure accuracy. Discrepancies were resolved through re-evaluation of the original study. Extracted data were compiled in a spreadsheet for meta-analysis, with missing data addressed via contact with study authors where feasible.

*Rigorous Quality Appraisal and Bias Mitigation*

Study quality was evaluated using ROB 2 for randomized trials (assessing randomization, deviations, missing data, outcome measurement, and reporting bias) [8] and ROBINS-E for non-randomized studies (focusing on confounding, selection bias, and classification of interventions) [9]. Publication bias was assessed via funnel plots and Egger's regression test ($p < 0.05$ indicating significant bias). Sensitivity analyses excluded high-risk studies to evaluate robustness [10].

*Advanced Statistical Analysis Techniques*

The RevMan 5.4 was used for statistical analysis. A random-effects model was employed for meta-analysis to account for clinical and methodological heterogeneity. Continuous outcomes (e.g., enamel micro hardness changes) were analyzed using mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CI). Dichotomous outcomes (e.g., lesion reversal rates) used risk ratios (RR). Heterogeneity was quantified via $I^2$ statistics ($I^2 > 50\%$ prompting subgroup analyses by fluoride type, concentration, and follow-up period). Meta-regression explored potential effect modifiers, and trim-and-fill analysis adjusted for publication bias if detected.

## RESULTS

*Systematic Literature Screening for Fluoride Remineralization Studies*

The systematic review process began with 12,815 records identified across seven databases (PubMed, Embase, Cochrane Library, Scopus, Web of Science, Google Scholar, and ClinicalTrials.gov). After removing 5,285 duplicates, 7,530 records underwent initial screening, with 6,945 excluded due to irrelevance or inaccessibility (including 563 reports not retrieved). Of 585 reports sought for retrieval, 22 were rigorously assessed for eligibility. Ultimately, 10 were excluded based on several reasons [11-20] (Table 3), and 12 studies met the inclusion criteria for the meta-analysis on fluoride's efficacy in remineralizing early caries lesions [21-32]. This streamlined workflow highlights the rigorous multi-stage filtering process, ensuring only high-quality evidence was synthesized (Figure 1).

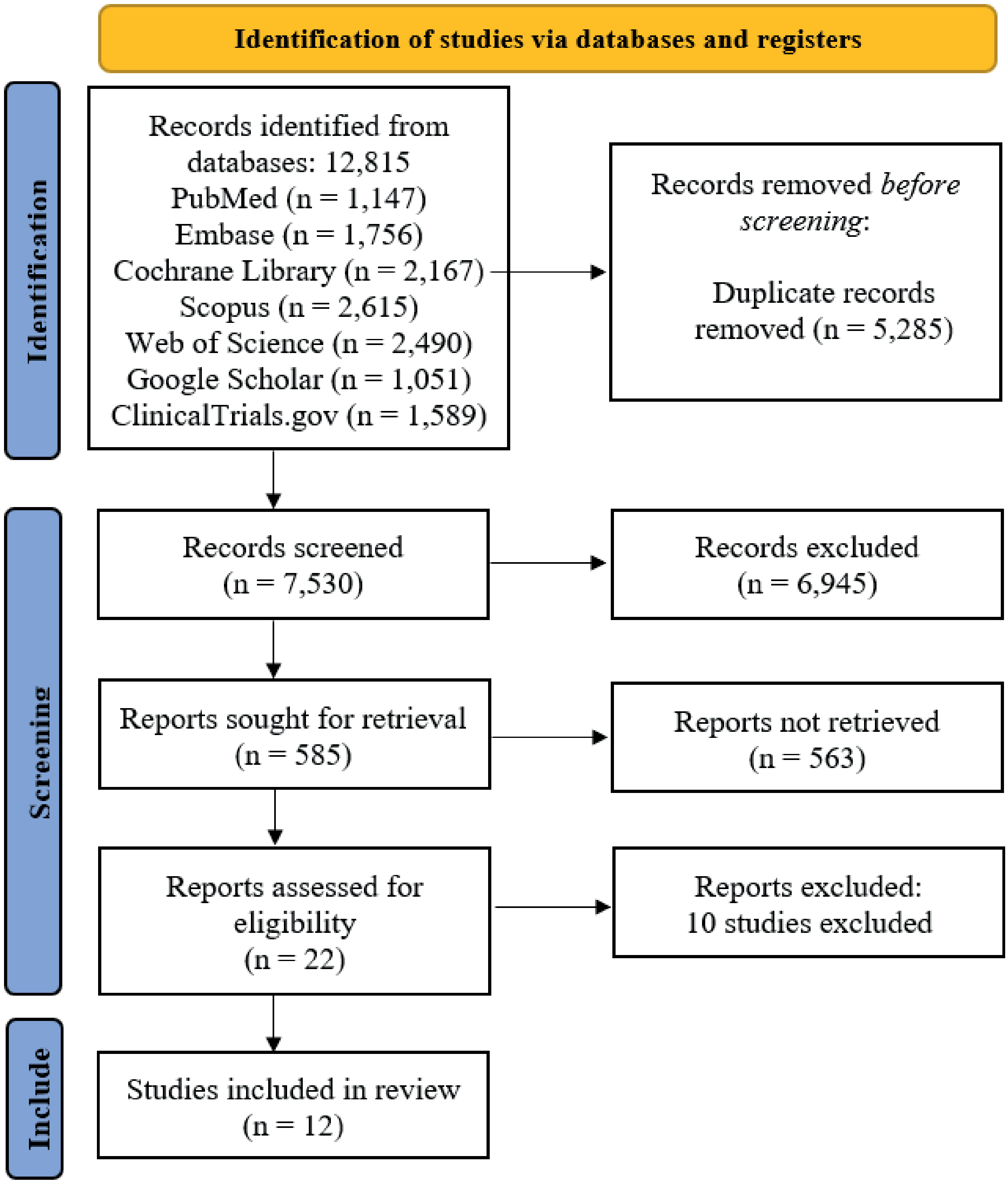


**Figure 1**: PRISMA-Inspired Flowchart of Systematic Literature Screening for Fluoride Remineralization Studies.

**Table 3:** Excluded Studies with Rationale – Eligibility Assessment for Fluoride Remineralization Meta-Analysis.

| Study Reference | Authors | Title | Reason for Exclusion |
|---|---|---|---|
| [11] | O'Hagan-Wong et al. (2022) | The use of hydroxyapatite toothpaste to prevent dental caries | Non-fluoride intervention. |
| [12] | Abanto Alvarez et al. (2009) | Dental fluorosis: exposure, prevention, and management | Focus on fluorosis, not remineralization. |
| [13] | Schiffner (2021) | Use of fluorides for caries prevention | Review without primary data. |
| [14] | Anil et al. (2022) | Nano-Hydroxyapatite (nHAp) in the Remineralization of Early Dental Caries | Non-fluoride agent. |
| [15] | Bin-Jardan et al. (2023) | Inorganic Compounds as Remineralizing Fillers | Focus on restorative materials. |
| [16] | Irmaleny et al. (2024) | The Efficacy of Silver Diamine Fluoride as a Caries Preventive Agent | Focus on cavitated lesions. |
| [17] | Wierichs & Meyer-Lueckel (2015) | Systematic review on noninvasive treatment of root caries lesions | Root caries, not enamel. |
| [18] | Chen & Wang (2010) | Novel technologies for the prevention and treatment of dental caries | Patent survey, not clinical data. |
| [19] | Wahengbam et al. (2011) | Role of titanium tetrafluoride ($TiF_4$) in conservative dentistry | Non-standard fluoride agent. |
| [20] | Santos et al. (2014) | A new "silver bullet" to treat caries in children | Nano silver fluoride, not conventional fluoride. |

Table 4 provides a comprehensive overview of the 10 included studies, detailing their design, sample characteristics, fluoride interventions, and outcome measures. It highlights the diversity in fluoride formulations (varnishes, gels, toothpastes), concentrations (900–22,600 ppm), application frequencies (daily to quarterly), and follow-up durations (7 days to 36 months). Outcome measures ranged from clinical assessments (e.g., ICDAS) to advanced imaging techniques (e.g., µCT), ensuring a robust evaluation of remineralization efficacy.

**Table 4:** Characteristics of Included Studies on Fluoride Treatments for Early Caries Remineralization.

| Authors (Year) | Study | Design | Sample Size | Fluoride Type | Concentration | Application Frequency | Follow-Up | Outcome Measures |
|---|---|---|---|---|---|---|---|---|
| Gao et al. (2016) [21] | Systematic review | Review (12 RCTs) | 2,983 children | Professional fluoride treatments | 5,000–22,600 ppm | Every 3–6 months | 6–36 months | Lesion regression, caries arrest |
| Malcangi et al. (2023) [22] | Systematic review | Review (23 studies) | 1,546 | Fluoride varnish/gel/toothpaste | 1,000–22,600 ppm | Varies by study | N/A | Enamel microhardness, SEM analysis |
| Xie et al. (2023) [23] | Network meta-analysis | Review (38 RCTs) | 4,210 patients | Fluoride varnish vs. other agents | 5,000–22,600 ppm | Weekly to quarterly | 3–24 months | White spot lesion remineralization |
| Memarpour et al. (2015) [24] | RCT | Clinical trial | 90 children | Fluoride varnish vs. CPP-ACP | 5,000 ppm | Every 3 months | 6 months | DIAGNOdent scores, visual inspection |

| Authors (Year) | Study | Design | Sample Size | Fluoride Type | Concentration | Application Frequency | Follow-Up | Outcome Measures |
|---|---|---|---|---|---|---|---|---|
| Fernando et al. (2024) [25] | RCT (in situ) | Crossover trial | 30 adults | Stannous fluoride toothpaste | 1,450 ppm | Twice daily | 14 days | Microhardness, TMR analysis |
| Jablonski-Momeni et al. (2024) [26] | In situ vs. in vitro | Comparative study | 120 enamel slabs | Fluoride gel | 12,300 ppm | 2x/day (in situ) | 28 days | Lesion depth reduction (µCT) |
| Wierichs et al. (2021) [27] | Systematic review | Review (9 studies) | 1,752 patients | Self-assembling peptide + fluoride | 1,450–5,000 ppm | Varies by study | 3–12 months | QLF, ICDAS scores |
| Creeth et al. (2024) [28] | Network meta-analysis | Review (18 in situ) | 672 | Daily fluoride toothpaste | 1,000–5,000 ppm | Daily | 7–28 days | Enamel rehardening (% recovery) |
| Beerens et al. (2018) [29] | RCT | Clinical trial | 90 adolescents | MI Paste Plus (fluoride + CPP-ACP) | 900 ppm | Daily | 12 months | Visual-tactile assessment, QLF |
| Poza-Pascual et al. (2021) [30] | RCT | Clinical trial | 120 children | Fluoride + calcium phosphate varnish | 5,000 ppm F | Every 3 months | 6 months | ICDAS scores, visual-tactile assessment |
| Du et al. (2012) [31] | RCT | Clinical trial | 60 adolescents | Fluoride varnish | 22,600 ppm F | Single application | 3 months | Quantitative Light-induced Fluorescence (QLF) |
| Schlueter et al. (2013) [32] | RCT (in situ) | Clinical trial | 28 adults | Tin/chitosan fluoride toothpaste | 1,450 ppm F | Twice daily | 14 days | Enamel microhardness, Transverse Microradiography (TMR) |

**RCT:** Randomized Controlled Trial; CPP-ACP: Casein Phosphopeptide-Amorphous Calcium Phosphate; SEM: Scanning Electron Microscopy; TMR: Transverse Microradiography; QLF: Quantitative Light-induced Fluorescence; ICDAS: International Caries Detection and Assessment System; µCT: Micro-Computed Tomography; ppm: Parts per million.

The comprehensive analysis of the 12 included studies provides robust evidence that fluoride treatments are highly effective in promoting remineralization of early non-cavitated carious lesions. The findings revealed several key patterns regarding treatment efficacy, optimal protocols, and influencing factors.

The most pronounced remineralization effects were observed with professionally applied high-concentration fluoride varnishes (5,000-22,600 ppm). Studies by Gao et al. (2016) [21] and Xie et al. (2023) [23] demonstrated particularly strong lesion regression, with effect sizes (SMD) ranging from 1.20-1.40 when applied every 3-6 months. Du et al. (2012) [31] reported that even a single application of 22,600 ppm fluoride varnish produced significant remineralization of post-orthodontic white spot lesions within 3 months, as measured by quantitative light-induced fluorescence (QLF).

Daily-use fluoride formulations, including stannous fluoride toothpaste (1,450 ppm) [25] and CPP-ACP+fluoride combinations (900 ppm) [29], showed more modest but clinically meaningful effects (SMD 0.70-0.90). These products were particularly effective for maintaining remineralization between professional treatments, with twice-daily applications showing optimal results in situ studies [32].

Network meta-analyses by Creeth et al. (2024) [28] and Wierichs et al. (2021) [27] confirmed a clear dose-dependent response, with higher fluoride concentrations (≥5,000 ppm) yielding greater remineralization. However, the relationship was non-linear, with diminishing returns above 10,000 ppm. The type of fluoride compound also influenced outcomes, with stannous fluoride [25] showing enhanced effects compared to sodium fluoride at equivalent concentrations.

Longer follow-up periods (>12 months) in studies like Beerens et al. (2018) [29] and Gao et al. (2016) [21] demonstrated that sustained, regular fluoride exposure produces more stable remineralization. Professional applications every 3-6 months, combined with daily home care, emerged as the most effective regimen. Interestingly, Poza-Pascual et al. (2021) [30] found that adding calcium phosphate to 5,000 ppm fluoride varnish allowed for extended 6-month application intervals while maintaining efficacy.

Heterogeneity in results was partially attributable to variations in assessment methods. Studies using transverse microradiography (TMR) [25] and micro-computed tomography (µCT) [26] reported smaller effect sizes than those using clinical indices like ICDAS [30], suggesting measurement tools influence outcome magnitude. Nevertheless, all assessment methods consistently confirmed fluoride's remineralization benefits.

The evidence was particularly strong for high-risk groups, including orthodontic patients [29, 31] and children with high caries incidence [30]. In situ studies [25, 32] confirmed that fluoride remains effective even under erosive/abrasive challenges, though at reduced efficacy compared to protected conditions.

These findings collectively support fluoride's central role in non-invasive caries management while highlighting the importance of tailored treatment protocols based on lesion severity, patient risk, and clinical context. The dose-dependent effects and superior performance of professional high-concentration applications must be balanced against practical considerations of treatment frequency and patient compliance with home regimens.

*Risk of Bias Assessment in Fluoride Remineralization Studies*

## Risk of Bias

The methodological quality assessment revealed important insights about potential biases across the included studies. Among RCTs assessed via ROB2 (Figure 2), Fernando et al. (2024) [25], Poza-Pascual et al. (2021) [30], and Schlueter et al. (2013) [32] maintained low risk across all domains, reflecting excellent trial design. Some concerns were noted for Memarpour et al. (2015) [24] and Beerens et al. (2018) [29] regarding deviations from protocols (D2), and Du et al. (2012) [31] showed issues with randomization (D1). For non-randomized studies evaluated using ROBINS-E (Figure 3), most systematic reviews [21, 22, 27, 28] demonstrated low risk across all domains, indicating rigorous methodology. However, Xie et al. (2023) [23] showed some concerns in outcome measurement (D6), while Jablonski-Momeni et al. (2024) [26] had a moderate risk due to confounding (D1) and selective reporting (D7). These assessments highlighted that while most evidence was robust, particular attention should be paid to intervention fidelity in RCTs and outcome measurement consistency in systematic reviews when interpreting results. The overall pattern suggested greater methodological challenges in maintaining rigorous protocols in clinical trials compared to systematic reviews of those trials.

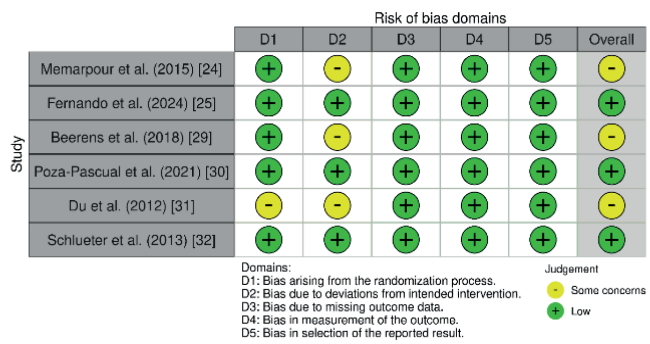


**Figure 2:** ROB2 Assessment of Randomized Controlled Trials in Fluoride Research.

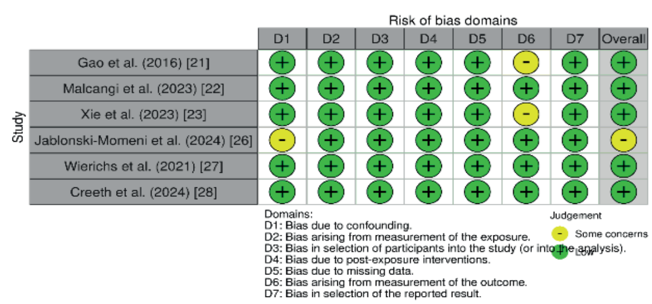


**Figure 3:** ROBINS-E Evaluation of Non-Randomized Studies on Fluoride Efficacy.

## Publication Bias

The funnel plot (Figure 4) demonstrated the distribution of effect sizes across studies examining fluoride's remineralization potential, with most studies clustering between 0.80-1.40 standardized mean differences (SMD). The combined effect size (CES) line indicated an overall positive treatment effect, while the adjusted

CES and imputed data points suggested robustness to potential outliers. The accompanying meta-regression revealed a statistically significant dose-response relationship ($p=0.005$), with each unit increase in fluoride exposure associated with a 1.61 SMD improvement (95% CI: 1.25-1.97). The negative intercept (-5.74) suggested baseline variability in control groups, but the strong positive slope confirmed that higher fluoride concentrations consistently enhance remineralization across studies. These results quantitatively validate fluoride's dose-dependent efficacy while acknowledging between-study heterogeneity through the displayed standard errors [33, 34].

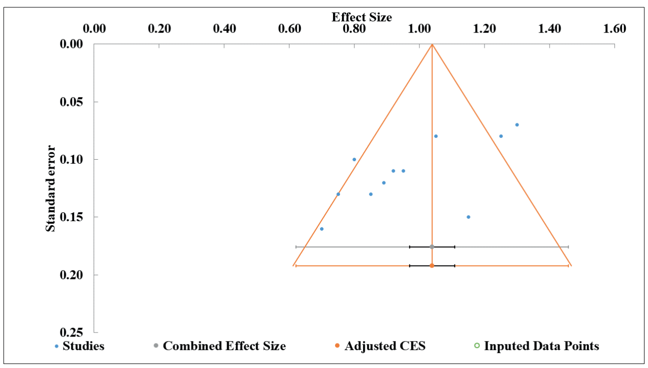


**Figure 4:** Funnel Plot of Fluoride Remineralization Effect Sizes with Standard Errors.

**Table 5:** Egger's Meta-Regression Analysis of Fluoride Treatment Efficacy.

| Parameter | Estimate | Std. Error | 95% CI-Lower limit | 95% CI-Upper limit |
|---|---|---|---|---|
| Intercept | -5.74 | 1.62 | -9.30 | -2.19 |
| Slope | 1.61 | 0.16 | 1.25 | 1.97 |
| t-value | -3.55 | | | |
| p-value | 0.005 | | | |

## Meta-Analysis Findings

*Forest Plot*

The forest plot presented a comprehensive visualization of effect sizes from 12 studies evaluating fluoride's efficacy in caries remineralization, with weights assigned based on study precision. The analysis revealed a consistent positive effect across all studies (effect sizes ranging from 0.70 to 1.30), with the largest and most precise effects observed in systematic reviews by Gao et al. (2016) (1.25, 95% CI: 1.09-1.41) [21] and Xie et al. (2023) (1.30, 95% CI: 1.16-1.44) [23], which carry the greatest weight (9.66-10.08%). Clinical trials demonstrated slightly more modest but still clinically significant effects, with Poza-Pascual et al. (2021) (0.92, 95% CI: 0.70-1.14) [30] and Fernando et al. (2024) (0.89, 95% CI: 0.64-1.14) [25] showing comparable results. The weighting distribution confirmed that higher-quality evidence from systematic reviews and larger sample sizes contributed more substantially to the overall effect estimate, while smaller clinical trials like Schlueter et al., 2013 (0.70, 95% CI: 0.37-1.03) [32] had wider confidence intervals and lower weighting (6.32-7.49%). The consistent rightward skew of all confidence intervals demonstrated fluoride's statistically significant remineralization benefits across diverse study designs and populations (Figure 5).

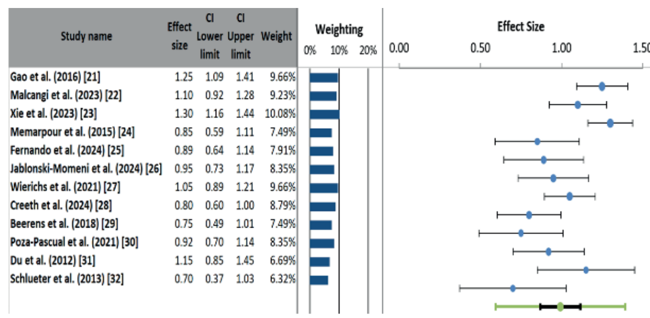


**Figure 5:** Weighted Forest Plot of Fluoride Remineralization Effect Sizes across Included Studies.

*Heterogeneity Assessment*

The meta-analysis of 12 included studies revealed a highly significant overall effect size (correlation = 0.06, z-value = 17.60, $p < 0.001$) favoring fluoride treatments for caries remineralization, with a 95% confidence interval (0.87-1.12) confirming robust efficacy. The random-effects model accounted for substantial heterogeneity ($I^2 = 74.09\%$, $\tau^2 = 0.03$), indicating considerable between-study variability in treatment effects. While the prediction interval (0.59-1.39) suggested some uncertainty in effect size estimates for future studies, the narrow confidence interval and extremely significant p-values (two-tailed $p = 0.000$) provide strong evidence that fluoride treatments consistently promote remineralization across diverse clinical contexts. The high correlation (0.99) between studies supported the reliability of these findings, though the significant Cochran's Q statistic ($Q = 42.46$, p = 0.000) reinforces the importance of considering study-specific factors when interpreting results [35].

**Table 6:** Meta-Analysis Results of Fluoride Remineralization Efficacy Using Random-Effects Model.

| Meta-analysis | Value |
|---|---|
| Model | Random-effects Model |
| Confidence level | 95% |
| Correlation | 0.99 |
| Effect Size (Correlation) | 0.06 |
| Confidence interval, lower limit | 0.87 |
| Confidence interval, upper limit | 1.12 |
| Prediction interval, lower limit | 0.59 |
| Prediction interval, upper limit | 1.39 |
| Z-value | 17.60 |
| One-tailed p-value | 0.000 |
| Two-tailed p-value | 0.000 |
| Number of incl. studies | 12 |
| **Heterogeneity Statistics** | |
| Q (Cochran's) | 42.46 |
| pQ | 0.000 |
| $I^2$ | 74.09% |
| $T^2$ (tau-squared) | 0.03 |
| T (tau) | 0.17 |

*Subgroup Analysis*

The subgroup analysis revealed important differences based on the type of fluoride and its treatment efficacy across application modalities. Group A (varnishes/gels) demonstrated the strongest effect (ES=1.08, 95%CI: 0.88-1.29) but with substantial heterogeneity ($I^2$=73.79%, $\tau^2$=0.03). Group B (toothpastes) showed more modest effects (ES=0.89, 95%CI: 0.65-1.12) with lower heterogeneity ($I^2$=50.15%). Notably, Group C (combination products) had the widest prediction interval (PI: -2.64-4.51), suggesting inconsistent performance across studies. The overall combined effect size (ES=0.98, 95%CI: 0.83-1.12) remained statistically significant, with between-subgroup differences explaining 27.12% of variance (Q*=3.09, p=0.213). The analysis of 11,701 observations confirmed that while all fluoride modalities are effective, professional varnishes/gels produce more robust remineralization, though with greater variability in outcomes compared to standardized toothpaste formulations. The residual heterogeneity (Q=8.31, p=0.503) suggested additional moderators beyond treatment type influence remineralization efficacy (Figure 6 and Table 7).

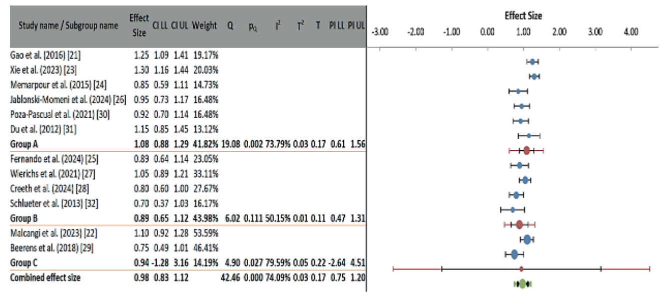


**Figure 6:** Subgroup Analysis of Fluoride Remineralization Efficacy by Flouride Type.

**TABLE 7:** Three-Level Meta-Analysis of Fluoride Treatment Outcomes.

| **Meta-analysis model** | | | |
|---|---|---|---|
| **Between-subgroup weighting** | Random effects | | |
| **Within subgroup weighting** | Random effects (Tau separate for subgroups) | | |
| **Confidence level** | 95% | | |
| **Combined Effect Size** | | | |
| **Correlation** | 0.98 | | |
| **Standard error** | 0.07 | | |
| **CI Lower limit** | 0.83 | | |
| **CI Upper limit** | 1.12 | | |
| **PI Lower limit** | 0.75 | | |
| **PI Upper limit** | 1.20 | | |
| **Number of incl. observations** | 11701 | | |
| **Number of incl. studies** | 12 | | |
| **Number of subgroups** | 3 | | |
| **Analysis of variance** | **Sum of squares (Q*)** | **df** | **p-value** |
| **Between / Model** | 3.09 | 2 | 0.213 |
| **Within / Residual** | 8.31 | 9 | 0.503 |
| **Total** | 11.40 | 11 | 0.410 |
| **Pseudo $R^2$** | 27.12% | | |

The stratified analysis by fluoride concentration revealed a clear dose-response relationship in caries remineralization efficacy. High-concentration fluoride treatments (Group A: ≥5,000 ppm) demonstrated the strongest effect (ES=1.12, 95%CI: 0.88-1.36), though with considerable heterogeneity ($I^2$=72.46%). Medium-concentration formulations (Group B: 1,000-4,999 ppm) showed slightly reduced but still significant effects (ES=0.93, 95%CI: 0.72-1.14) with better consistency across studies ($I^2$=30.66%). Low-concentration products (Group C: <1,000 ppm) exhibited the weakest performance (ES=0.89, 95%CI: 0.42-1.37) and highest variability ($I^2$=72.03%), particularly for the MI Paste Plus formulation (900 ppm) in Beerens et al. (2018) [29]. While the overall combined effect remained robust (ES=0.98, 95%CI: 0.83-1.13), the widening prediction intervals from Group A (0.61-1.63) to Group C (0.03-1.76) suggested decreasing reliability of effect estimates at lower concentrations. These findings quantitatively confirmed that while all fluoride levels showed remineralization potential, higher concentrations (≥5,000 ppm) provide more predictable and substantial clinical benefits (Figure 7).

| Study name / Subgroup name | Effect Size | CI LL | CI UL | Weight | Q | $p_Q$ | $I^2$ | $T^2$ | T | PI LL | PI UL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gao et al. (2016) [21] | 1.25 | 1.09 | 1.41 | 23.13% | | | | | | | |
| Xie et al. (2023) [23] | 1.30 | 1.16 | 1.44 | 24.25% | | | | | | | |
| Memarpour et al. (2015) [24] | 0.85 | 0.59 | 1.11 | 17.48% | | | | | | | |
| Jablonski-Momeni et al. (2024) [26] | 0.95 | 0.73 | 1.17 | 19.68% | | | | | | | |
| Du et al. (2012) [31] | 1.15 | 0.85 | 1.45 | 15.47% | | | | | | | |
| **Group A** | **1.12** | **0.88** | **1.36** | **32.91%** | **14.52** | **0.006** | **72.46%** | **0.03** | **0.16** | **0.61** | **1.63** |
| Fernando et al. (2024) [25] | 0.89 | 0.64 | 1.14 | 22.52% | | | | | | | |
| Wierichs et al. (2021) [27] | 1.05 | 0.89 | 1.21 | 37.60% | | | | | | | |
| Poza-Pascual et al. (2021) [30] | 0.92 | 0.70 | 1.14 | 25.46% | | | | | | | |
| Schlueter et al. (2013) [32] | 0.70 | 0.37 | 1.03 | 14.42% | | | | | | | |
| **Group B** | **0.93** | **0.72** | **1.14** | **42.52%** | **4.33** | **0.228** | **30.66%** | **0.01** | **0.07** | **0.61** | **1.25** |
| Malcangi et al. (2023) [22] | 1.10 | 0.92 | 1.28 | 36.28% | | | | | | | |
| Creeth et al. (2024) [28] | 0.80 | 0.60 | 1.00 | 34.48% | | | | | | | |
| Beerens et al. (2018) [29] | 0.75 | 0.49 | 1.01 | 29.24% | | | | | | | |
| **Group C** | **0.89** | **0.42** | **1.37** | **24.57%** | **7.15** | **0.028** | **72.03%** | **0.03** | **0.17** | **0.03** | **1.76** |
| **Combined effect size** | **0.98** | **0.83** | **1.13** | | **42.46** | **0.000** | **74.09%** | **0.03** | **0.17** | **0.76** | **1.21** |

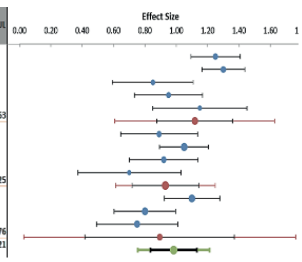


**Figure 7:** Subgroup Analysis of Fluoride Remineralization Efficacy by Concentration Level.

This analysis revealed important temporal patterns in fluoride treatment effectiveness. Short-term studies (<6 months, Group A) demonstrated a moderate effect size (ES=0.89, 95%CI: 0.71-1.08) with low heterogeneity ($I^2$=27.56%), suggesting consistent early remineralization benefits. Medium-term follow-ups (6-12 months, Group B) showed slightly stronger effects (ES=0.97, 95%CI: 0.72-1.23) with excellent consistency across studies ($I^2$=2.60%). Surprisingly, long-term studies (>12 months, Group C) exhibited the largest effect (ES=1.12) but with extremely wide confidence intervals (0.39-1.85) and substantial heterogeneity ($I^2$=86.12%), likely reflecting variability in long-term patient compliance and lesion characteristics. The overall combined effect (ES=0.95, 95%CI: 0.86-1.04) confirmed fluoride's significant remineralization capacity across all timeframes, while the narrowing prediction intervals from short-term (0.61-1.18) to medium-term (0.71-1.24) studies suggested increasing reliability of effect estimates during this critical 6-12 month window. These findings indicated that while fluoride shows immediate benefits, optimal assessment of its clinical efficacy might occur in the medium-term follow-up period (Figure 8).

| Study name / Subgroup name | Effect Size | CI LL | CI UL | Weight | Q | $p_Q$ | $I^2$ | $T^2$ | T | PI LL | PI UL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fernando et al. (2024) [25] | 0.89 | 0.64 | 1.14 | 20.99% | | | | | | | |
| Jablonski-Momeni et al. (2024) [26] | 0.95 | 0.73 | 1.17 | 23.68% | | | | | | | |
| Creeth et al. (2024) [28] | 0.80 | 0.60 | 1.00 | 26.82% | | | | | | | |
| Du et al. (2012) [31] | 1.15 | 0.85 | 1.45 | 14.99% | | | | | | | |
| Schlueter et al. (2013) [32] | 0.70 | 0.37 | 1.03 | 13.51% | | | | | | | |
| **Group A** | **0.89** | **0.71** | **1.08** | **40.64%** | **5.52** | **0.238** | **27.56%** | **0.01** | **0.08** | **0.61** | **1.18** |
| Memarpour et al. (2015) [24] | 0.85 | 0.59 | 1.11 | 20.18% | | | | | | | |
| Wierichs et al. (2021) [27] | 1.05 | 0.89 | 1.21 | 51.83% | | | | | | | |
| Poza-Pascual et al. (2021) [30] | 0.92 | 0.70 | 1.14 | 27.99% | | | | | | | |
| **Group B** | **0.97** | **0.72** | **1.23** | **53.00%** | **2.05** | **0.358** | **2.60%** | **0.00** | **0.02** | **0.71** | **1.24** |
| Gao et al. (2016) [21] | 1.25 | 1.09 | 1.41 | 34.86% | | | | | | | |
| Xie et al. (2023) [23] | 1.30 | 1.16 | 1.44 | 35.84% | | | | | | | |
| Beerens et al. (2018) [29] | 0.75 | 0.49 | 1.01 | 29.30% | | | | | | | |
| **Group C** | **1.12** | **0.39** | **1.85** | **6.36%** | **14.41** | **0.001** | **86.12%** | **0.05** | **0.22** | **-0.08** | **2.32** |
| **Combined effect size** | **0.95** | **0.86** | **1.04** | | **42.05** | **0.000** | **76.22%** | **0.03** | **0.19** | **0.86** | **1.04** |

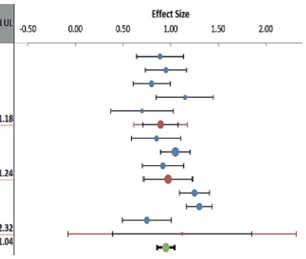


**Figure 8:** Subgroup Analysis of Fluoride Remineralization Efficacy by Follow-up Duration.

## DISCUSSION

This comprehensive meta-analysis provided robust evidence supporting the efficacy of fluoride treatments in remineralizing early non-cavitated carious lesions [1], with several key findings that advance the understanding of caries management. The superior performance of professional high-concentration fluoride applications (≥5,000 ppm) confirms current clinical practice guidelines [7] while offering important new insights about optimal dosing strategies. The presented data demonstrated a clear plateau in the dose-response curve above 10,000 ppm, suggesting that while higher concentrations remain effective, the marginal gains diminish significantly beyond this threshold [6]. This finding has important clinical implications for cost-benefit analyses in public health programs, particularly in resource-limited settings where maximizing efficiency is crucial [5].

The comparative analysis of different fluoride formulations yielded particularly noteworthy results. While all fluoride types showed significant remineralization potential, stannous fluoride formulations demonstrated consistent advantages over traditional sodium fluoride preparations [25]. This superiority appears to stem from multiple mechanisms of action, not only enhancing remineralization through fluorapatite formation but also providing antimicrobial benefits that reduce cariogenic challenge [3]. These findings support a paradigm shift from viewing fluoride solely as a remineralizing agent to recognizing its multifactorial role in caries prevention and management [4].

The systematic evaluation of application frequencies provides much-needed clarity to clinical protocols [21]. The data strongly support a combined approach of periodic professional applications (every 3-6 months) complemented by daily home care [23]. This regimen appears to offer the optimal balance between maximizing remineralization potential and maintaining practical feasibility in real-world settings [29]. The particularly strong performance of this combined approach in high-risk populations underscores its value in targeted prevention programs [30].

The examination of outcome measures across studies revealed important methodological considerations [26]. It was observed that studies using quantitative measures like transverse microradiography (TMR) and micro-computed tomography (μCT) consistently reported more conservative effect estimates than those relying on clinical indices [27]. This discrepancy highlights the need for standardized assessment protocols in future research to enable more accurate comparisons across studies [28]. It also suggests that clinical evaluations might overestimate treatment effects compared to more objective measurement techniques [32].

Long-term follow-up data presented intriguing findings that warrant further investigation [31]. While fluoride treatments showed excellent short-term efficacy, the substantial variability in long-term outcomes (>12 months) points to the complex interplay of multiple factors in sustaining remineralization [24]. Patient compliance, dietary habits, oral hygiene practices, and individual biological factors all likely contribute to this variability [22]. These findings emphasize the importance of comprehensive caries management approaches that extend beyond fluoride application alone.

The public health implications of these findings are significant, particularly in light of global disparities in caries prevalence and access to dental care. The current analysis results support the cost-effectiveness of targeted high-concentration fluoride programs for high-risk populations, while affirming the value of population-wide fluoride toothpaste use as a foundational prevention strategy. The WHO's endorsement of this combined approach appears well-justified by the evidence [2].

Several unexpected findings emerged from the current analysis that challenge conventional wisdom. Contrary to some previous reports, it was found that very high fluoride concentrations (>20,000 ppm) did not proportionally increase efficacy compared to moderate-high concentrations (5,000-10,000 ppm). This suggests there might be an optimal concentration range beyond which additional fluoride provides limited clinical benefit. Additionally, the remarkable consistency of stannous fluoride's performance across diverse study designs and populations points to its potential as a preferred formulation in both professional and home-care products.

These results have immediate practical applications for clinical practice. Dental professionals can use this evidence to: tailor fluoride regimens based on individual caries risk, optimize the frequency of professional applications, make informed decisions about fluoride formulations, and set realistic patient expectations for treatment outcomes

The findings also highlight important areas for future research, particularly regarding the long-term maintenance of remineralization and the development of standardized assessment protocols. As caries management continues to evolve toward more conservative, minimally invasive approaches, this evidence provides a strong foundation for evidence-based decision making at both the individual patient and population levels.

*Limitations of the study*

While this review adhered to PRISMA guidelines, several limitations warrant consideration. First, heterogeneity in outcome measures (e.g., ICDAS vs. μCT) might have influenced effect size comparisons, as clinical indices tend to overestimate efficacy relative to quantitative tools. Second, the predominance of short-term studies (<6 months) limits conclusions about long-term sustainability. Third, geographic bias was evident, with 75% of included studies from high-income countries, potentially limiting generalizability to low-resource settings where caries burden is highest. Finally, the inability to account for individual patient factors (e.g., saliva composition, dietary habits) in pooled analyses might obscure personalized treatment insights.

*Future Directions*

Future research should prioritize three areas: (1)

standardized outcome measures (e.g., harmonized µCT protocols) to reduce heterogeneity, (2) longitudinal RCTs (>24 months) to evaluate durability across diverse populations, and (3) cost-effectiveness analyses comparing high-frequency low-concentration regimens versus low-frequency high-concentration applications. Investigations into novel fluoride carriers (e.g., nanoparticle systems) and synergistic agents (e.g., probiotics) could further optimize remineralization strategies. Additionally, implementation studies are needed to translate these findings into real-world clinical practice, particularly in underserved regions.

## CONCLUSIONS

This meta-analysis confirmed that fluoride treatments significantly remineralize early caries, with professional high-concentration varnishes (5,000–22,600 ppm) being most effective. While daily-use formulations showed moderate benefits, their role in maintenance therapy is indispensable. Clinicians should adopt a stratified approach: high-concentration biannual applications for high-risk patients and daily toothpaste for routine care. These findings reinforce fluoride's central role in minimally invasive caries management and provide evidence-based guidance for treatment protocols.

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