Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents (Review)

Walsh T, Worthington HV, Glenny AM, Appelbe P, Marinho VCC, Shi X

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[Intervention Review]

Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents

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ABSTRACT

Background

Caries (dental decay) is a disease of the hard tissues of the teeth caused by an imbalance, over time, in the interactions between cariogenic bacteria in dental plaque and fermentable carbohydrates (mainly sugars). The use of fluoride toothpaste is the primary intervention for the prevention of caries.

Objectives

To determine the relative effectiveness of fluoride toothpastes of different concentrations in preventing dental caries in children and adolescents, and to examine the potentially modifying effects of baseline caries level and supervised toothbrushing.

Search methods

A search was undertaken on Cochrane Oral Health Group's Trials Register, CENTRAL, MEDLINE and several other databases. Reference lists of articles were also searched.

Date of the most recent searches: 8 June 2009.

Selection criteria

Randomised controlled trials and cluster-randomised controlled trials comparing fluoride toothpaste with placebo or fluoride toothpaste of a different concentration in children up to 16 years of age with a follow-up period of at least 1 year. The primary outcome was caries increment in the permanent or deciduous dentition as measured by the change in decayed, (missing), filled tooth surfaces (D(M)FS/d(m)fs) from baseline.

Data collection and analysis

Inclusion of studies, data extraction and quality assessment were undertaken independently and in duplicate by two members of the review team. Disagreements were resolved by discussion and consensus or by a third party. The primary effect measure was the prevented fraction (PF), the caries increment of the control group minus the caries increment of the treatment group, expressed as a proportion

of the caries increment in the control group. Where it was appropriate to pool data, network meta-analysis, network meta-regression or meta-analysis models were used. Potential sources of heterogeneity were specified a priori and examined through random-effects meta-regression analysis where appropriate.

Main results

75 studies were included, of which 71 studies comprising 79 trials contributed data to the network meta-analysis, network meta-regression or meta-analysis.

For the 66 studies (74 trials) that contributed to the network meta-analysis of D(M)FS in the mixed or permanent dentition, the caries preventive effect of fluoride toothpaste increased significantly with higher fluoride concentrations (D(M)FS PF compared to placebo was 23% (95% credible interval (CrI) 19% to 27%) for 1000/1055/1100/1250 parts per million (ppm) concentrations rising to 36% (95% CrI 27% to 44%) for toothpastes with a concentration of 2400/2500/2800 ppm), but concentrations of 440/500/550 ppm and below showed no statistically significant effect when compared to placebo. There is some evidence of a dose response relationship in that the PF increased as the fluoride concentration increased from the baseline although this was not always statistically significant. The effect of fluoride toothpaste also increased with baseline level of D(M)FS and supervised brushing, though this did not reach statistical significance. Six studies assessed the effects of fluoride concentrations on the deciduous dentition with equivocal results dependent upon the fluoride concentrations compared and the outcome measure. Compliance with treatment regimen and unwanted effects was assessed in only a minority of studies. When reported, no differential compliance was observed and unwanted effects such as soft tissue damage and tooth staining were minimal.

Authors' conclusions

This review confirms the benefits of using fluoride toothpaste in preventing caries in children and adolescents when compared to placebo, but only significantly for fluoride concentrations of 1000 ppm and above. The relative caries preventive effects of fluoride toothpastes of different concentrations increase with higher fluoride concentration. The decision of what fluoride levels to use for children under 6 years should be balanced with the risk of fluorosis.

PLAIN LANGUAGE SUMMARY

Comparison between different concentrations of fluoride toothpaste for preventing tooth decay in children and adolescents

Many children experience painful tooth decay which can lead to the tooth/teeth being extracted. Even if teeth are not extracted the tooth decay may be distressing, be expensive to treat and may involve children and their carers having time off school and work.

Another Cochrane review showed that fluoride toothpastes do reduce dental decay, by about 24% on average, when compared with a non-fluoride toothpaste. This review compares toothpastes with different amounts of fluoride.

This review includes 79 trials on 73,000 children. As expected the use of toothpaste containing more fluoride is generally associated with less decay. Toothpastes containing at least 1000 parts per million (ppm) fluoride are effective at preventing tooth decay in children, which supports the current international standard level recommended.

Although none of the trials included in the review looked at fluorosis or mottling of the children's teeth, fluorosis may be an unwanted result of using fluoride toothpaste in young children and a Cochrane review on this topic has also been published. The possible risk of fluorosis should be discussed with your dentist who may recommend using a toothpaste containing less than 1000 ppm fluoride.

BACKGROUND

Description of the condition

Tooth mineral is lost and gained in a continuous process of de- and re-mineralization. Caries (dental decay) is a disease of the hard tissues of the teeth caused by an imbalance in this process over time, from the interactions between cariogenic bacteria in dental plaque

and fermentable carbohydrates (mainly sugars). Aside from the pain arising from the carious lesions themselves, there is also the emotional distress of the disease and the potential consequences of medical intervention. Affected teeth cannot always be saved and may have to be extracted. This has particular consequences for young children, for whom general anaesthesia may be required. There is an associated social impact of this disease in terms of absence from school for the children and absence from work for their carers. There are also important financial implications for this disease with a substantial proportion of healthcare budgets being spent every year on treating caries.

Whilst in some areas of the developed world there has been evidence of a reduction in the prevalence and severity of dental caries in recent years, social inequalities in dental health exist, with many individuals and communities having a clinically significant burden of preventable dental disease. Whilst some success has been achieved in a reduction in caries in adults, challenges remain in the prevention of caries in young children, and in reducing inequalities in this population.

The link between fluoride and oral health dates back to the 1930s. Nearly 80 years on and fluoride remains one of dentistry's key strategies for the prevention of dental caries. At the 8th World Congress on Preventive Dentistry (Liverpool, 2005) members of the International Association for Dental Research, the World Health Organization (WHO), the European Association of Dental Public Health and the British Association for the Study of Community Dentistry put forward a call for action in the 'Liverpool Declaration' (IADR/WHO/BASCD 2005). They outlined nine areas of work that should be addressed by the year 2020, one of which was the need for countries to ensure the availability of appropriate and affordable fluoride programmes for the prevention of tooth decay. This has recently been reinforced by the findings of a Global Consultation on Oral Health through Fluoride (2006) which suggests that promoting dental health by using fluoride will "improve quality of life and enhance achievement of the Millennium Development Goals by reducing the high dental disease burden of populations, especially children in disadvantaged populations" (FDI World Dental Federation 2006).

Description of the intervention

There are many methods of fluoride delivery e.g. fluoridated water, milk, toothpaste, gels, varnish etc. The beneficial effects of topical fluoride agents have been examined in a series of high quality Cochrane systematic reviews (Marinho 2002; Marinho a 2002; Marinho 2003; Marinho a 2003; Marinho b 2003; Marinho 2004; Marinho a 2004). In particular, evidence for the use of fluoride toothpastes is unequivocal (Marinho b 2003). Summarising all available placebo-controlled evidence from randomised controlled trials (RCTs), the review concluded that fluoride toothpastes are effective in preventing caries when compared to non-fluoride toothpastes in children and adolescents and that the effect of fluoride toothpaste on caries prevention increased according to some factors, which included higher fluoride concentration. However, comparisons of toothpastes of differing fluoride concentration were not explicitly (directly) evaluated. This review aims to evaluate the relative caries preventive effects of toothpastes of different fluoride concentrations with a view to establishing the benefits of different concentrations for children and adolescents. This review has been conducted alongside a Cochrane review evaluating the effect of topical fluoride (including that from toothpaste of different concentrations) on dental fluorosis (Wong 2010). To be fully informed of the potential caries preventive benefits of fluoride toothpastes of different concentrations and the potential risks of fluorosis arising from fluoride toothpaste use both reviews should be read.

Why it is important to do this review

The objectives of the WHO Global Oral Health Programme are detailed in a WHO report (Petersen 2003) and summarised in a global policy document (Petersen 2009) with one of the priority action areas being the effective use of fluoride. Prevention and effective use of fluoride toothpaste is the recommended strategy for oral health in children and adolescents in a recent Lancet editorial (Lancet 2009), although it is acknowledged that its cost prohibits its widespread use in many low-income and middle-income countries.It is important that recommendations concerning the use of fluoride toothpaste are evidence based. The recently published document 'Delivering Better Oral Health: An Evidence-Based Toolkit' from the Department of Health in the UK (DoH 2007) on fluoride concentration in toothpaste has cited evidence from the Cochrane systematic review (Marinho b 2003), a single RCT (Davies 2002) and three published reviews of fluoride toothpastes for caries prevention in children and adolescents (Ammari 2003; Steiner 2004; Twetman 2003). This toolkit recommends that for preventing caries in children aged up to 3 years "only a smear of toothpaste containing no less than 1000 ppm fluoride" be used, and for all children aged 3 to 6 years "a pea-sized amount of toothpaste containing 1350-1500 ppm fluoride" be used. For children older than 6 years, fluoridated toothpaste of 1350 ppm or above is recommended. The table of key references cited in the toolkit provides "further relevant references" pertaining to fluoride concentration:

- "Toothpastes containing 1450 ppm fluoride offers more caries-preventive effect than toothpaste containing 440 ppm fluoride" and
- "Toothpastes containing 1450 ppm fluoride offers more caries-preventive effect than toothpaste containing 1000 ppm fluoride."

Evidence to support the former recommendation is the Cochrane systematic review of placebo-controlled trials (Marinho b 2003) and a single long-term RCT based in deprived areas of the North

of England (Davies 2002). Whilst the Cochrane systematic review concluded that the effect of fluoride toothpaste on caries prevention increased according to higher fluoride concentration amongst other factors, this was not explicitly evaluated and no optimum level of fluoride concentration for caries prevention was given.

Evidence to support the second recommendation comes from meta-analyses in reviews carried out in 2003 and 2004 (Ammari 2003; Steiner 2004; Twetman 2003). The reviews differ in their methods, though none have been undertaken as Cochrane systematic reviews. Not all reviews have included an assessment of the quality of trials, and some of the included studies are cluster-randomised, with no evidence that this has been taken into account in the analysis. Many important details of the review research process go unreported in these publications. For instance, it is unclear whether a protocol was written prior to undertaking the review, and search criteria are not fully documented. Additionally, important information on methods of analysis of the concentration-response effectiveness has been omitted or has been undertaken sometimes narratively. The comparisons made in the reviews are:

- 250 ppm relative to 1000 ppm (n = 4 trials) (Steiner 2004);
- 250 ppm relative to 1000 ppm (n = 6 trials) and 500-550 ppm relative to 1000-1055 ppm (n = 2 trials narrative only) (Ammari 2003);
- fluoride toothpaste compared to placebo, <1000 ppm relative to 1000-1100 ppm (n = 4 trials), 1500 ppm relative to 1000-1100 ppm (n = 9 trials) (Twetman 2003).

A further published meta-analysis examined the caries preventive effect of higher level fluoride toothpastes of 1700 ppm, 2200 ppm, 2800 ppm relative to 1100 ppm (Bartizek 2001). This meta-analysis was based on a single multicentre randomised controlled trial. No Cochrane systematic review including trials of active interventions, i.e. fluoride toothpastes of different concentrations, and placebo-controlled trials has been undertaken.

Recently revised guidelines (EAPD 2009) from the European Academy of Paediatric Dentistry on the use of fluoride in children have provided recommendations which include fluoride concentration, frequency of daily toothbrushing and amount of toothpaste to be used, for children from the ages of 6 months through to 6 years and over. Whilst fluoride concentrations have been recommended for the different age groups, based on previous reviews (Steiner 2004; Twetman 2003) the authors of the guidelines state that "a children's toothpaste with a lower concentration of fluoride may be indicated although the evidence for a caries preventive effect of formulas with less than 500 ppm fluoride are insufficient." Further, in considering the potential caries preventive benefit of fluoridated toothpaste against the potential risks of fluorosis before the age of 6 years the authors state that "care must be taken to ensure that a balance is maintained between maximising the protective effect against dental caries and minimising the risk of dental fluorosis."

A systematic review addressing all the available evidence on the concentration of fluoride in toothpastes using appropriate statistical methodologies will identify the relative caries preventive effects of toothpastes of different fluoride concentrations in children and adolescents. Effects on the deciduous and mixed/permanent dentition will be assessed separately.

Traditional approaches to meta-analysis have focused on direct (head to head) pairwise comparisons within RCTs. However, when many different interventions exist, the number of pairwise comparisons becomes prohibitive and interpretation difficult. For example when there are six interventions to be compared, this will result in 15 distinct pairwise combinations. Combining similar fluoride levels may be a solution, but this runs the risk of obscuring subtle concentration-related differences in effect. Adjusted indirect comparisons can be made between trials with a common comparator. Further, with advances in statistical methodologies, it is possible to combine both direct and indirect evidence from RCTs in what the *Cochrane Handbook for Systematic Reviews of Interventions* refers to as multiple treatments meta-analysis (Higgins 2008). This methodology is sometimes known in the literature as network meta-analysis or mixed treatment comparisons (MTC). Such a technique refers to a meta-analysis of multiple interventions, and can involve both direct and indirect treatment comparisons. This has been used to evaluate many different interventions including for example self monitoring of diabetes (Jansen 2006) and stroke prevention treatments (Cooper 2006), and is suitable for both binary and continuous outcome measures. The research will therefore incorporate a substantial statistical and methodological component and will advance knowledge in this area. A systematic review addressing all the available evidence on the concentration of fluoride in toothpastes will help to identify the relative caries preventive effects of fluoride toothpastes of different concentrations. This is important as fluoride has been identified as a causative factor in objectionable enamel fluorosis in children. Other factors which may modify the influence of fluoride concentration on caries prevention will also be evaluated, based on previously published literature. Baseline caries level and whether toothbrushing is supervised or not have been identified as potential effect modifiers in a previous review (Marinho b 2003). Compliance with the intervention could also be proposed to influence any treatment effect. Possible differential effects on the deciduous and mixed or permanent dentition will be evaluated by undertaking separate analyses.

The primary aim of this review is to provide a clear and robust summary of the research evidence on the relative caries preventive effects of fluoride toothpastes of different concentrations for dental health in children and adolescents.

OBJECTIVES

To determine the relative effectiveness of placebo and fluoride toothpastes of different concentrations in preventing dental caries

in children and adolescents, and to examine the potentially modifying effects of baseline caries level and supervised toothbrushing.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and cluster-randomised trials (CRCTs) comparing fluoride toothpaste with placebo or fluoride toothpaste of a different concentration with a follow-up period of at least 1 year. Studies where random allocation was not used or indicated were excluded, as were split-mouth studies.

Types of participants

Children and adolescents. Studies where the majority of participants were aged 16 years or less at the start of the study were included (irrespective of initial level of dental caries, background exposure to fluorides, dental treatment level, nationality, setting where the intervention is received or time when the intervention started). Studies where the participants were selected on the basis of special (general or oral) health conditions were excluded.

Types of interventions

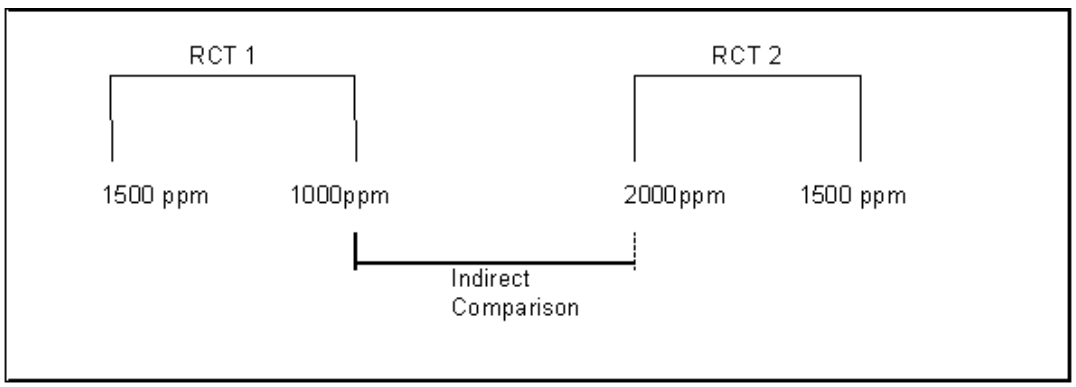
Studies making a comparison between at least two fluoride toothpastes of differing concentrations, or fluoride toothpaste and placebo toothpaste. Fluoride agents combined or not in the following formulations:

- Sodium fluoride (NaF)
- Sodium monofluorophosphate (SMFP)
- Stannous fluoride (SnF_2)
- Acidulated phosphate fluoride (APF)
- Amine fluoride (AmF).

These may be formulated with any compatible abrasive system and are considered at any fluoride concentration (parts per million (ppm)), frequency of use, amount or duration of application, and with any technique of toothbrushing or post-toothbrushing procedure. Studies where the intervention group alone or both the intervention and control groups received any additional active agent(s) or caries preventive measure(s) as part of the study (e.g. chlorhexidine agent, other fluoride-based procedures, oral hygiene procedures, sealants, xylitol chewing gums, glass ionomers) in addition to the fluoride or placebo toothpaste were excluded. Studies that included participants receiving additional measures as part of their routine oral care such as oral hygiene advice, supervised brushing, fissure sealants etc. were included.

It was acknowledged in advance that the comparison of certain fluoride toothpaste concentrations may be sparse, and direct and indirect comparisons were undertaken where appropriate (Figure 1).

Figure 1. Illustration of potential indirect comparison, using placebo toothpastes as common comparator, and fluoride toothpastes of 1000 ppm and 1500 ppm.



Types of outcome measures

Primary outcomes

The primary outcome measure is caries increment as measured by

either:

- change from baseline in the decayed, (missing) and filled surface (D(M)FS) index, in all permanent teeth erupted at the start and erupting over the course of the study (dental caries is defined here as being clinically and radiologically recorded at the dentine level of diagnosis);
- change from baseline in the decayed, (missing/extraction indicated), and filled surface d(e/m)fs index, in deciduous tooth surfaces;
- change in the proportion developing new caries.

Secondary outcomes

The secondary outcome will be side effects such as irritation, dental staining/discolouration etc.

Search methods for identification of studies

The searches attempted to identify all relevant studies irrespective of language until June 2009. We aimed to have all papers not published in English translated. There was no restriction with regard to status of publication and both published and unpublished studies were sought.

Electronic searches

The following databases were searched:

- Cochrane Oral Health Group's Trials Register (8 June 2009)
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 2)
- MEDLINE (OVID) (from 1950 to 8 June 2009)
- EMBASE (OVID) (from 1980 to 8 June 2009).

Sensitive search strategies were developed using a combination of free text and controlled vocabulary. The strategy for MEDLINE (OVID) is presented in Appendix 1. This was run with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.1 (updated September 2008) (Higgins 2008).

Searching other resources

Reference searching

Previously published systematic reviews of fluoride toothpastes were also screened to identify any reports that met the inclusion criteria (Ammari 2003; Bartizek 2001; Clarkson 1993; Steiner 2004; Twetman 2003). The Cochrane fluoride toothpaste systematic review (Marinho b 2003) has recently been updated and relevant trials located through the update were incorporated into this review.

Searching for ongoing trials

The trial databases ClinicalTrials.gov (www.clinicaltrials.gov) and The *meta*Register of Controlled Trials (www.controlled-trials.com) were searched to identify any ongoing studies of relevance.

Data collection and analysis

Identification of studies

The downloaded set of records from each database were imported into the bibliographic software package EndNote. Duplicate records were identified and removed. All records were independently scanned for relevance by two of the review authors on the basis of title and abstract (where available). Irrelevant records were discarded and the full text of the remaining records was obtained for further evaluation. Relevancy was assessed according to the characteristics of the participants, nature of the intervention, comparison and outcome as stated in the review title.

Selection of studies

Following the initial screening, for studies appearing to meet the inclusion criteria, or for which there was insufficient information in the title and abstract to make a clear decision, the full report was obtained. These reports were assessed independently and in duplicate by the review authors to establish whether the studies met the inclusion criteria. Disagreements were resolved by discussion. Studies written in a language not known by the review team were translated by members of the Cochrane Oral Health Group and included/excluded as appropriate. Those studies awaiting translation are presented in the Studies awaiting classification section of the review.

Studies rejected at this or subsequent stages were recorded in the Characteristics of excluded studies section with the reason for exclusion.

Data extraction and management

Data extraction was undertaken for all studies meeting the inclusion criteria independently and in duplicate by four review authors (Helen Worthington (HW), Priscilla Appelbe (PA), Valeria Marinho (VM) and Tanya Walsh (TW)) using a piloted data extraction form. Information on study design, participants, intervention(s) and comparator, and outcomes were extracted, specifically:

- Article information: author, journal, year of publication
- Study information: location, duration of data collection (months), date of baseline collection[1], dates of data collection, number of centres, location setting where participants were recruited (e.g. school), other sources of fluoride exposure[2], duration of intervention, individual or cluster-randomisation

- Participant information: age at baseline, initial number, baseline caries[3], mean decayed missing and filled surfaces/teeth (standard deviation (SD)/standard error (SE)) for deciduous or permanent dentition or both
- Intervention: concentration and formulation of fluoride, abrasive system, frequency of brushing, supervised brushing, duration of intervention
- Assessment: teeth included, criteria for clinical diagnosis, calculation of change/increment, diagnostic threshold, net or crude caries increment
- Outcome information: final caries and number, proportion of children developing new caries, mean DMFS/dmfs (SD/SE) increment, mean DMFT/dmft (SD/SE) increment, level of compliance
- Reliability of primary outcome measurement: number of examiners and calibration details, method of clinical assessment
- Side effects: e.g. soft tissue damage, dental stain, irritation.

[1] When data on the study start were not provided a 'probable date' was calculated by subtracting the duration of the study (in years) plus 1 extra year, from the publication date of the study.
[2] Background exposure to other fluoride sources encompassed data on the use (outside the trial) of topical fluorides/fluoride rinses or even fluoride toothpastes (in studies where the intervention was tested under supervision at school and no supply of any toothpaste had been provided for home use) and the consumption of fluoridated water/salt/tablets. Background use of other fluorides (rinses, gels, tablets, etc) should be clearly reported as used by the majority in a study to be considered as such, and exposure to water/salt fluoridation should be above 0.3 ppm fluoride.
[3] From the study sample analysed (final sample) and in connection with the caries increment index chosen.
It is acknowledged that caries increment could be reported differently in different trials. To account for this the choice of primary outcome will follow the hierarchy presented in the Cochrane systematic review of placebo-controlled trials (Marinho b 2003):
- data on surface level will be chosen over data on tooth level
- DFS data will be chosen over DMFS data, and these will be chosen over DS or FS
- data for 'all surface types combined' will be chosen over data for 'specific types' only
- data for 'all erupted and erupting teeth combined' will be chosen over data for 'erupted' only, and these over data for 'erupting' only
- data from 'clinical and radiological examinations combined' will be chosen over data from 'clinical' only, and these over 'radiological' only
- data for dentinal/cavitated caries lesions will be chosen over data for enamel/non-cavitated lesions
- net caries increment data will be chosen over crude (observed) increment data
- follow-up nearest to 3 years (often the one at the end of the study period) will be chosen over all other lengths of follow-up, unless otherwise stated.

Assessment of risk of bias in included studies

All trials included in the review were assessed for risk of bias independently and in duplicate as part of the data extraction process, with reference to the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.1 (Higgins 2008). A specially designed and piloted form was used for this purpose. Included trials were assessed on the following:
- Adequate sequence generation: Yes, No, Unclear
- Allocation concealment: Yes, No, Unclear
- Blinding: Yes, No, Unclear
- Incomplete outcome data addressed: Yes, No, Unclear
- Free of selective outcome reporting (e.g. DMFT or DMFS or both reported?): Yes, No, Unclear
- Free from baseline imbalance: Yes, No, Unclear
- Free of contamination/co-intervention: Yes, No, Unclear.

'Yes' indicates a low risk of bias, 'No' indicates high risk of bias and 'Unclear' indicates either lack of information or uncertainty over the potential for bias. A risk of bias table was completed for each included study (*see* Risk of bias in included studies and Characteristics of included studies). Results are presented graphically by study (Figure 2) and by domain over all studies (Figure 3).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

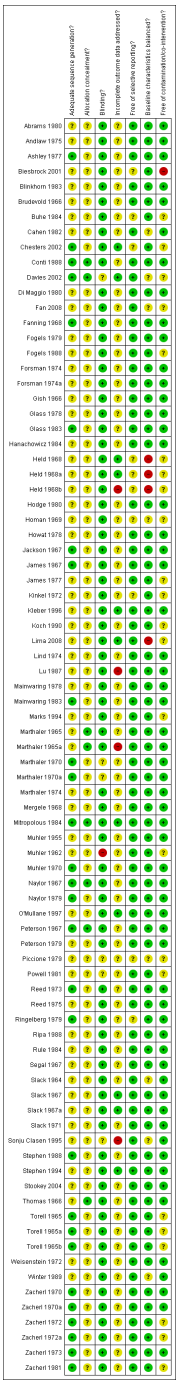
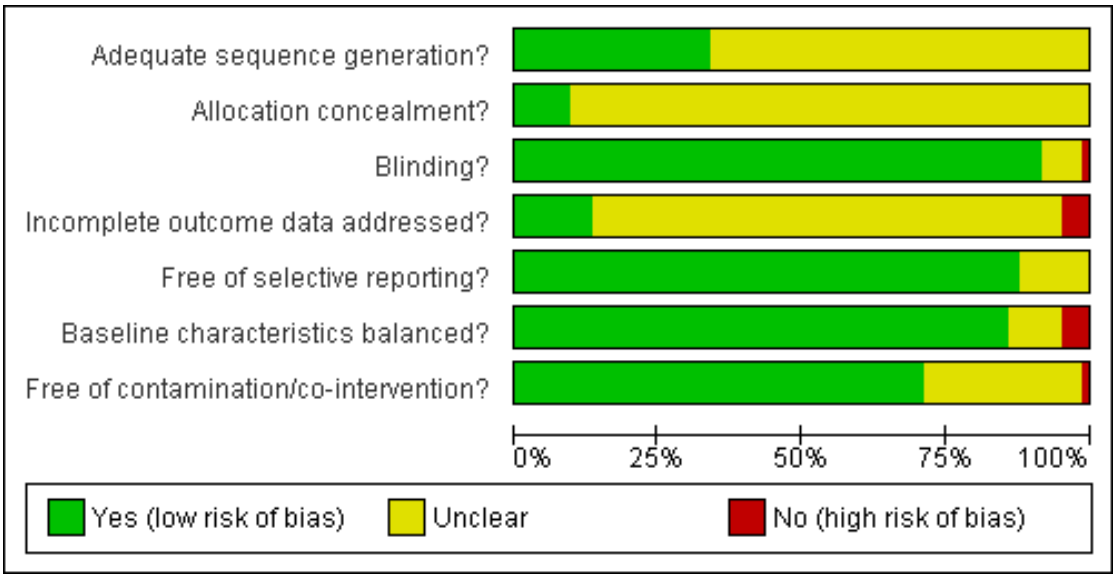


Figure 3. Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.



Measures of treatment effect

The prevented fraction (PF) was the primary estimate of effect. The PF is expressed as the mean increment in the control group minus the mean increment in the intervention group divided by the mean increment in the control group i.e. the caries increment in the treatment group expressed as a percentage of the control group. The PF is considered to be more appropriate than the absolute mean difference or standardized mean difference as it allows for the combination of different ways in which caries increments are measured across studies and is simple to interpret. Variances and confidence intervals were estimated using the Stata user written program fielleri.ado (version 1.0 2004-12-07, Joseph Coveney), following the formula of Fieller (Abrams 1972). The PF was calculated at both a surface level and a tooth level, and deciduous and permanent dentition were analysed throughout.

For completeness and to compare results with earlier publications, raw values (mean, standard deviation (SD), n) are presented along with the standardized mean difference (SMD) (Cohen's d).

For the proportion of children developing new caries, data were analysed using risk ratios (RR). Review Manager (RevMan) 5 was used for estimation of treatment effects using a fixed-effect model for the pooled estimate.

Dealing with missing data

For the main outcome data, missing standard deviations for caries increments not revealed through contact with the original researchers was imputed through linear regression of log (standard deviations) on log (mean caries) increments as per the Cochrane systematic review of placebo-controlled trials (Marinho b 2003).

Data synthesis

A graphical representation of the taxonomy of interventions to determine the nature of the network was undertaken. Estimates of treatment effects (PF and SMD) were calculated through the Stata software package. Network meta-analysis and meta-regression were carried out using the WinBugs package using a random-effects model for the multiple treatments meta-analysis for the prevented fraction data and standardized mean difference, taking into account the correlation between multi-arm trials where appropriate. This was undertaken at both a surface level and a tooth level, and deciduous and permanent dentition were analysed separately throughout. PF estimates of effect were calculated and entered into the WinBugs package using the contrast approach for trial level data to estimate direct and indirect effects. The network meta-analysis method enables the comparison of in-

direct effects, treatment comparisons not addressed within the primary trials. Such network analysis can only be applied to connected networks of trials (*see* Figure 4; Figure 5). The random-effects network meta-analysis on which this analysis was based can be downloaded from www.bris.ac.uk/cobm/research/mpes/mixed-treatment-comparisons.html.

Figure 4. D(M)FS network diagram.

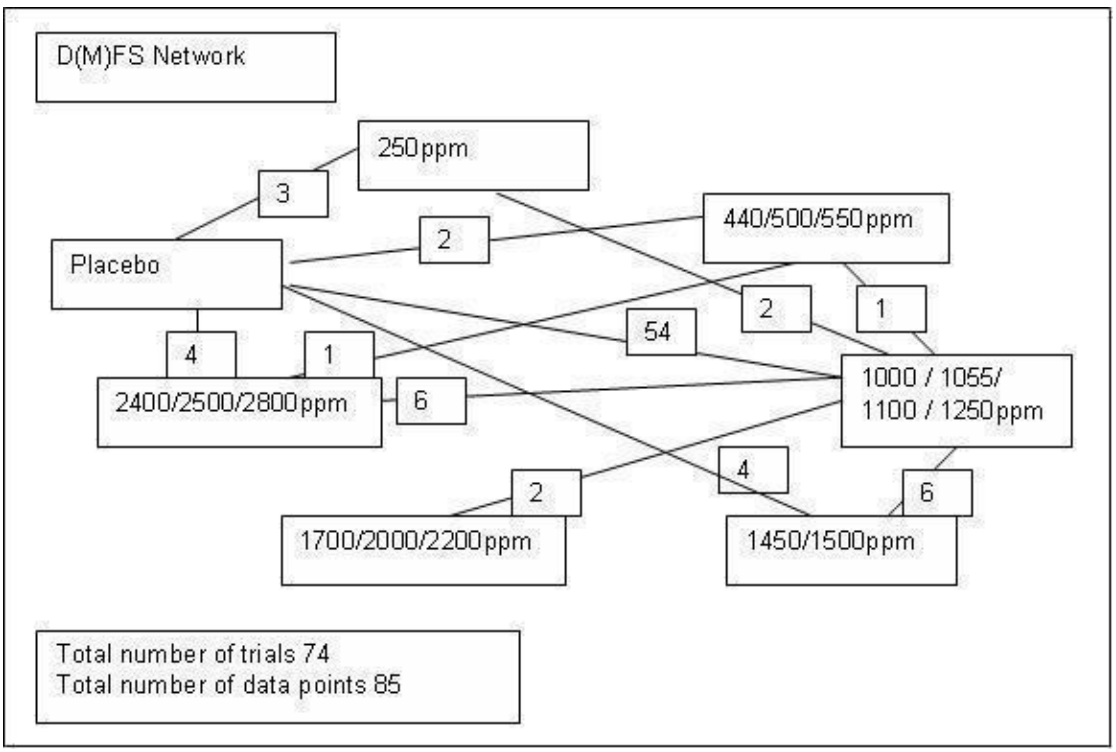
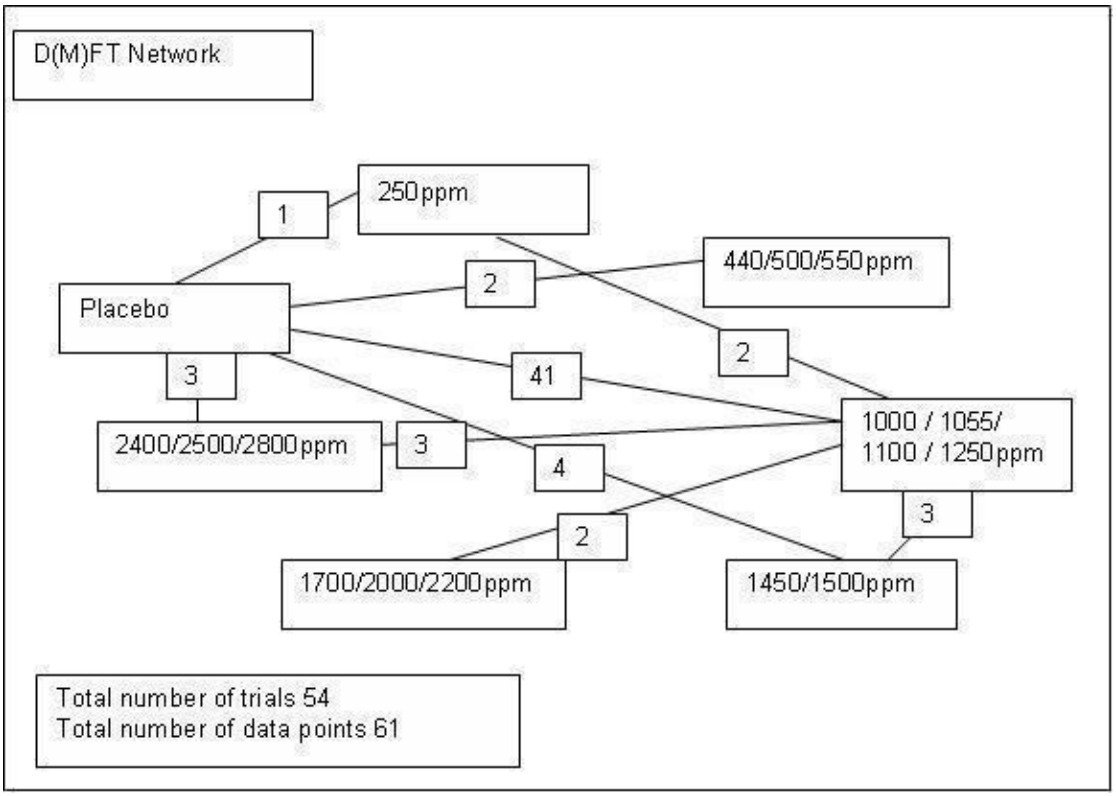


Figure 5. D(M)FT network diagram.



The goodness of fit of the models was assessed by calculating the residual deviance. This is defined as the difference between the deviance for the fitted model and the difference between the saturated model, where the deviance measures the fit of the model to the data points using the likelihood function. Under the null hypothesis that the model provides an adequate fit to the data, the mean residual deviance will approximately equal the number of unconstrained data points in the analysis.

For the proportion of participants developing new caries, data were analysed by calculating risk ratios. RevMan was used for estimation of overall treatment effects using a fixed-effect model for the pooled estimate. Studies reporting compliance with the treatment regimen or any side effects of toothpaste use were noted.

Subgroup analysis and investigation of heterogeneity

Heterogeneity was assessed by inspection of forest plots of the estimates and confidence intervals of treatment effects.

Two potential sources of heterogeneity were specified a priori: baseline caries level and toothbrushing (supervised or not), and were an important aspect of the review. To this end, a random-effects network meta-regression was proposed where there were sufficient trials for this to be undertaken. Data from 'baseline caries level' were calculated from the study sample analysed and in accordance with the chosen caries increment index.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Following the removal of duplicates, 1563 records were retrieved from the electronic database search. After applying the Cochrane RCT filter and removing duplicates, this number was reduced to 535.

The search for ongoing trials yielded no additional reports, as did the search of non-electronic resources.

Following screening, 129 records were considered to be potentially eligible, and sought for further detailed assessment. This resulted

in 75 included studies, 51 excluded studies and 3 reports awaiting assessment (either awaiting translation or insufficient information following translation to enable an inclusion/exclusion assessment to be made).

Included studies

See Characteristics of included studies table for details of included studies.

There are 75 studies included in the review, of which 35 have more than one publication. The following studies have been treated as independent sources as they contain more than one trial with either different age groups (Marthaler 1965; Marthaler 1970; Zacherl 1970) or report results separately from different locations (Forsman 1974; Held 1968) or both (Torell 1965). There are also distinct studies published in the same year by the same author (Slack 1967; Slack 1967a; Zacherl 1972; Zacherl 1972a). This results in 83 independent trials.

All reports were published between the years 1955 and 2008.

Trials were conducted mainly in the USA and UK, but also in the following locations: France, Lithuania, Germany, Italy, Australia, Sweden, Switzerland, Iceland, Denmark, China, Puerto Rico, Brazil and Canada.

Design and methods

The review includes both placebo-controlled trials and trials comparing one active intervention to at least one other active intervention. The review includes two, three, four and five arm trials.

The minimum duration of the study for inclusion in the review was 12 months, and the longest reported follow-up period was 7 years. Analysis was undertaken on results nearest to 3 years follow-up.

One trial was cluster randomised (Sonju Clasen 1995) though reported as an individual randomised trial.

Participants

The minimum age of participants in studies of effects on the deciduous dentition was 12 months; the minimum age for the studies of effects on the mixed and permanent dentition was 5 years. Data on baseline caries level in the mixed and permanent dentition was reported in all but five trials (D(M)FS) and nine trials (D(M)FT) and ranged from 1.4 to 23.5 DMFS. For trials including participants with deciduous teeth, the maximum reported baseline dfs was 3.6 dfs.

Interventions

The review included 58 placebo-controlled studies and 17 studies making a comparison between active interventions. For the purposes of analysis, fluoride (F) concentration was grouped into the following categories and these numbers are used to designate the specific comparisons in the Additional tables:

1. Placebo 0 ppm F
2. 250 ppm F
3. 440/500/550 ppm F
4. 1000/1055/1100/1250 ppm F
5. 1450/1500 ppm F
6. 1700/2000/2200 ppm F
7. 2400/2500/2800 ppm F.

Interventions for the majority of trials specified unsupervised brushing.

Outcome measures

The primary outcome measure was caries increment measured at surface level, and this was included in all studies. Caries increment at tooth level, percentage caries free, proportion developing new caries were also measured. The majority of studies presented results for the permanent dentition; only five trials reported on caries levels in the deciduous dentition; two trials reporting d(m)fs and d(m)ft, one study reporting d(m)ft alone, one study reporting dfs alone and one study reporting caries progression and arrest. One trial reporting effects on the permanent dentition also assessed effects on the deciduous dentition. Adverse effects of the intervention were unreported in the majority of studies, but when reported included oral (soft tissue) damage and tooth staining. No trials reported on fluorosis.

Excluded studies

Reasons for exclusion of a trial from the review are given in the Characteristics of excluded studies table. The 51 studies were excluded for the following reasons: Non-random or systematic allocation, randomisation not stated or indicated, inappropriate randomisation (randomising two clusters, one to each of the groups compared), additional active agents or other fluoride-based interventions in addition to fluoride toothpaste or where participants were institutionalised children or adolescents with specific health problems. A trial could be excluded for more than one reason.

Risk of bias in included studies

Adequate sequence generation

Adequate sequence generation was observed in 28 trials (34%), where a clear statement of the method of randomisation was reported. In the remainder of trials a judgment of 'unclear' was given as reporting lacked description with such statements as 'were randomised' or 'were stratified' appearing most commonly.

Allocation

Adequate allocation concealment was observed in eight trials (10%). The remainder failed to indicate whether the generated randomisation sequence was concealed from individuals involved in the enrolment and assignment of participants.

Blinding

In 76 trials (92%), both participants and clinical examiners were blinded to the allocated intervention. There was high risk of bias for this domain in only one trial (1%), where the placebo and fluoride toothpastes were packaged differently and hence blinding of participants was not achieved.

Incomplete outcome data

In four trials (5%), attrition rates were unduly high given the length of follow-up e.g. over 50% in 3 years, over 40% in 2 years, over 30% in 1 year resulting in a judgment of high risk of bias. In 68 trials (81%) there was insufficient information to determine a judgment of high or low risk of bias. The principal reasons for judgments of 'unclear' on this domain were lack of reporting of this information or information reported but differential losses not assessable. The remainder of the trials fully reported on attrition rates by groups with reasons for attrition.

Selective reporting

73 trials (88%) were free of selective reporting in that all pre-specified outcomes caries indices were reported according to the different units measured, methods of examination, diagnostic thresholds for caries and approaches for reversals, with 10 (12%) trials providing insufficient information for a judgment of high or low risk of bias.

Other potential sources of bias

Baseline characteristics

Baseline characteristics were reported and comparable between groups in 71 (86%) of trials, with a high risk of bias through baseline imbalance of caries levels in the different fluoride groups for 4 (5%) trials. Baseline similarity was achieved through stratification by important prognostic variables. An unclear judgment was given for 8 (9%) trials when not reported or not reported by group.

Free of contamination or co-intervention

One study was judged to be at high risk of bias from contamination, when a concurrent fluoride rinse programme was introduced to trial participants. 59 trials (71%) were judged free from the possibility of any inadvertent application of the intervention being evaluated to people in the control group (contamination) and/or any additional treatment being given to one of the groups differentially (co-intervention), and hence were judged to be at low risk of bias. In 23 trials (28%) there was insufficient information to enable a judgment to be made.

Effects of interventions

Effect of fluoride toothpaste on dental caries increment

In accordance with the objectives of the review, and in line with the information given in the methods section, the results are reported separately for:

(1) Decayed, (Missing) and Filled Surfaces prevented fraction (D(M)FS PF)

(2) Decayed, (Missing) and Filled Teeth prevented fraction (D(M)FT PF)

(3) D(M)FS and D(M)FT pooled using a standardized mean difference (SMD)

(4) decayed, (missing) and filled surfaces/teeth prevented fraction (d(m)fs PF and d(m)ft PF). Estimates of the effects on caries increments in the deciduous dentition

(5) Proportion developing new caries in the permanent or deciduous dentition

(6) Compliance with toothbrushing and side effects of toothpaste.

Four studies did not report data necessary for inclusion in the analysis but are retained in the review. Either caries increment data were not reported or obtainable (Powell 1981 placebo versus 1000 ppm; Slack 1964 placebo versus 1000 ppm), fluoride concentration was not stated (Kinkel 1972 study states only fluoride versus placebo), or a combination of both (Homan 1969 fluoride toothpaste (three groups SnF_2 and APF) versus placebo).

Standard deviations were missing or not obtainable and subsequently imputed for the following studies: Abrams 1980; Fogels 1979; Forsman 1974; Forsman 1974a; Held 1968; Held 1968a; Held 1968b; James 1977; Muhler 1955; Piccione 1979.

Based on the available data from trials reporting standard deviations of the caries increments, a regression equation to estimate the missing standard deviations was derived for the caries increment D(M)FS and D(M)FT indices. The equations were:

D(M)FS log(sd caries increment) = 0.7574 + 0.491 * log(mean caries increment)

D(M)FT log(sd caries increment) = 0.5264 + 0.3811 * log(mean caries increment).

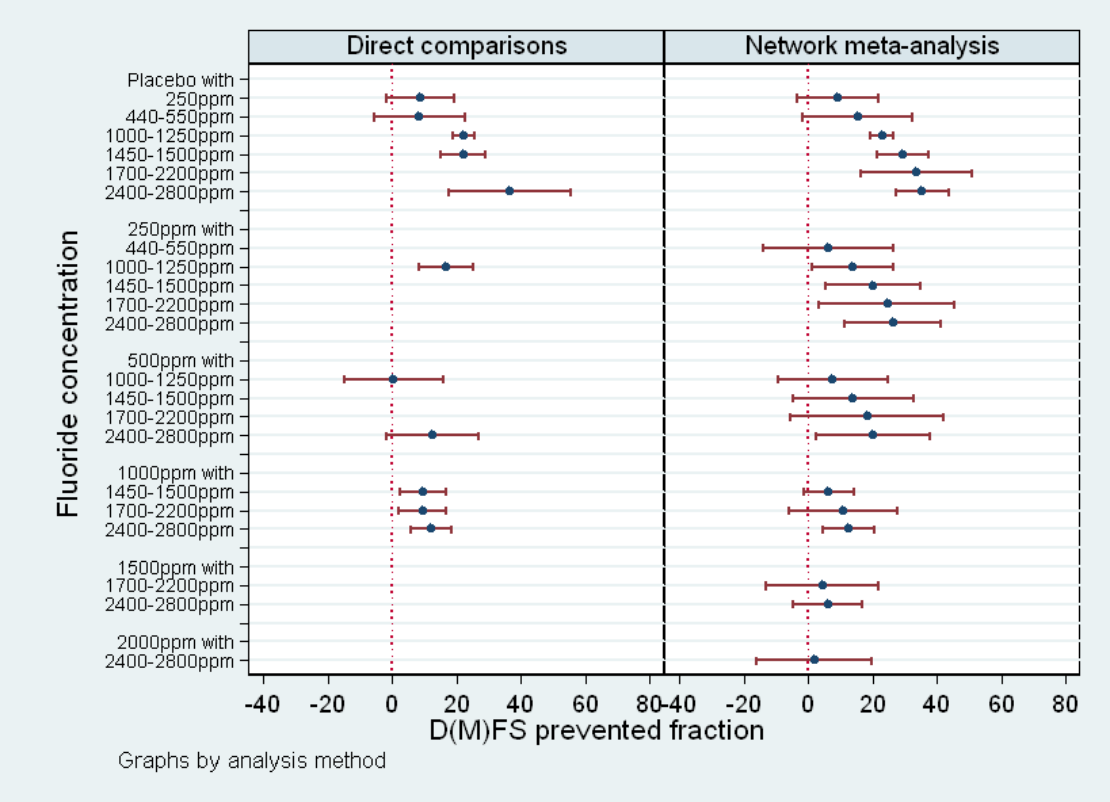
(1) Effect on tooth surfaces: D(M)FS PF

Estimates of effect and standard error for pairwise difference(s) with respect to fluoride concentration were calculated in Stata. The

pooled analysis comprised 85 pairwise comparisons resulting from 74 trials with available D(M)FS data. For the purposes of analysis there were 65 comparisons of two fluoride concentrations, seven comparisons of three fluoride concentrations and two comparisons of four fluoride concentrations. Interventions are displayed as a network meta-analysis diagram in Figure 4, where the different interventions are represented as nodes in the network and the links between them represent the pairwise treatment comparisons. The trials formed a connected network. There were 67 placebo-controlled trials, two trials with 250 ppm as baseline, two trials with 440/500/550 ppm as baseline, and 14 trials with 1000/1055/1100/1250 ppm as baseline. The model indicated a good fit with a median summary deviation of 80.00 (95% credible interval (CrI) 58.36 to 106.70). Tau was 68.52 (95% CrI 46.15 to 100.30).

For each direct comparison the D(M)FS PF and 95% confidence interval (CI) can be viewed in Analysis 1.1 D(M)FS increment (prevented fraction) of the Data and analyses section. Additional Table 1 gives the results of both the direct comparison and network meta-analysis. These are depicted graphically by means of a caterpillar plot (Figure 6) for all the possible pairwise comparisons. The pooled PF increases in favour of higher fluoride as the difference in fluoride concentration increases. For the comparisons with placebo it can be seen from the caterpillar plot that concentrations of 440/500/550 ppm and below show no statistically significant effect when compared to placebo, attaining statistical significance thereafter at concentrations of 1000/1055/1100/1250 ppm with median PF of 23% when compared to placebo (95% CrI 19% to 27%) rising to 36% (95% CrI 27% to 44%) with the highest fluoride concentration. For the active interventions, PF for comparisons of 440/500/550 ppm with higher concentrations only attained statistical significance (PF 20%, 95% CrI 2% to 38%) when compared to 2400/2500/2800 ppm fluoride. All pairwise comparisons are shown in Additional Table 1.The 95% CrIs are relatively wide indicating uncertainty in many of the comparisons, and reflecting the small number of trials for some of the comparisons.

Figure 6. Caterpillar plot D(M)FS PF.



There is evidence of a dose response effect, indicated by the network meta-analysis results in the caterpillar plot, with the magnitude of the prevented fraction increasing as the distance between baseline and higher fluoride concentration increases, though this is not always statistically significant, particularly when fluoride concentrations are lower and similar to baseline concentration.
In terms of the optimum fluoride concentration with greatest prevented fraction, the highest probability of caries preventive benefit was associated with the greater fluoride concentration: the probability was 0.53 for toothpastes containing 2400/2500/2800 ppm fluoride followed by 0.40 for toothpastes containing 1700/2000/2200 ppm fluoride.

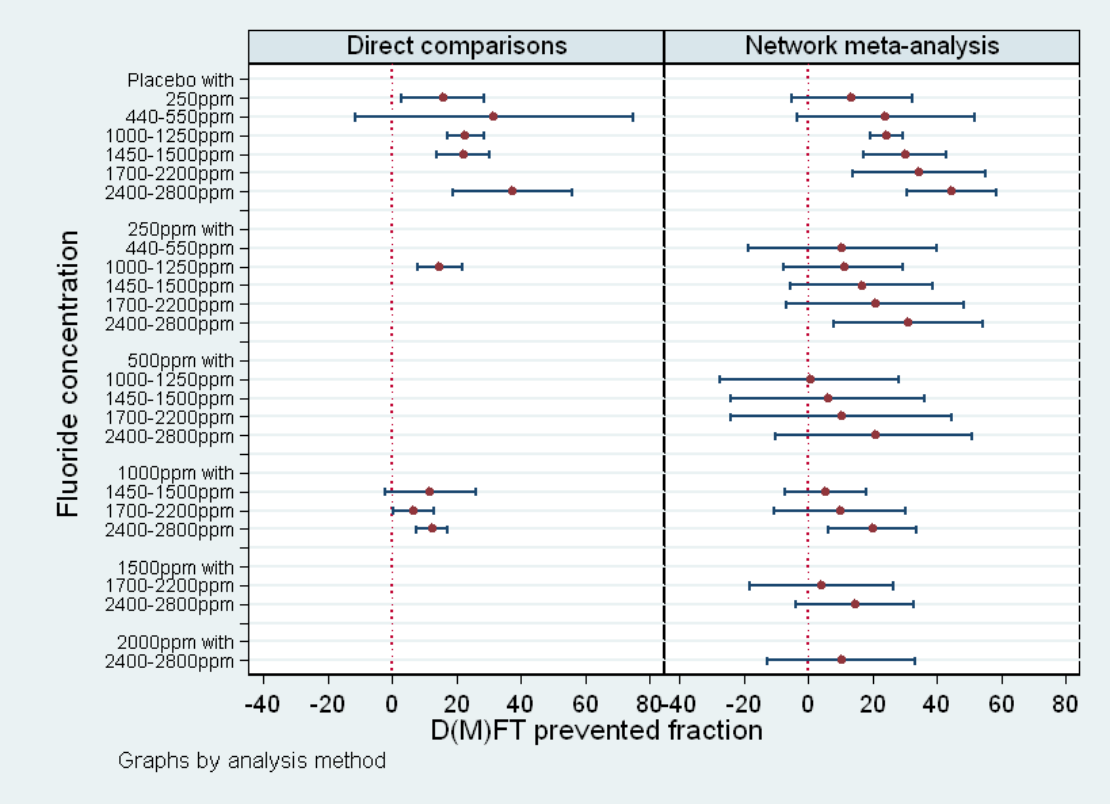
Meta-regression

Two studies did not include data on baseline levels of caries (Chesters 2002; Segal 1967). The pooled analysis comprised 83 pairwise comparisons resulting from 72 trials. There was very little difference in the fit for this model: median summary deviation of 78.43 (95% CrI 56.99 to 104.60). Tau was 78.43 (95% CrI 44.6 to 99.33). Univariate meta-regression indicated a small association with estimates of D(M)FS PF with baseline level of caries (coefficient 0.38%, 95% CrI -0.23% to 0.99%), though this was not statistically significant.
All studies reported on whether brushing was supervised or not. The pooled analysis comprised 85 pairwise comparisons resulting from 74 trials. The model fit was similar: median summary deviation of 80.38 (95% CrI 58.31 to 107.00). Tau was 71.25 (95% CrI 47.39 to 105.80). Univariate meta-regression indicated an association of D(M)FS PF with supervised brushing (coefficient 5.98%, 95% CrI -0.59% to 12.55%), though this was not statistically significant.

(2) Decayed, (Missing) and Filled Teeth prevented fraction (D(M)FT PF)

Estimates of effect and standard error for pairwise differences with respect to fluoride concentration were calculated in Stata. The pooled analysis comprised 61 pairwise comparisons resulting from 54 trials with available D(M)FT data. For the purposes of analysis there were 49 comparisons of two fluoride concentrations, three comparisons of three fluoride concentrations and two comparisons of four fluoride concentrations). Interventions are displayed as a network meta-analysis diagram in Figure 5, where the different interventions are represented as nodes in the network and the links between them represent the pairwise treatment comparisons. The trials formed a connected network. There were 51 placebo-controlled trials, two trials with 250 ppm as baseline, and eight trials with 1000/1055/1100/1250 ppm as baseline. The model indicated a good fit with a median summary deviation of 57.08 (95% CrI 39.06 to 79.81). Tau was 44.20 (95% CrI 27.27 to 68.85).
For each direct comparison the D(M)FT PF and 95% CI can be viewed in Analysis 1.2 D(M)FT increment (prevented fraction) of the Data and analyses section. Additional Table 2 gives the results of the direct comparison and network meta-analysis. These are depicted graphically by means of a caterpillar plot (Figure 7) for all the possible pairwise comparisons. The PF pooled increases as the difference in concentration increases. For the comparisons with placebo, concentrations of 440/500/550 ppm fluoride and below show no statistically significant effect, attaining statistical significance thereafter with median PF of 25% (95% CrI 19% to 30%) when compared to 1000/1055/1100/1250 ppm fluoride rising to 45% (95% CrI 31% to 58%) when compared to the highest fluoride concentration. For the active comparisons, the magnitude of the differences in fluoride concentration required to attain statistical significance are greater than those of D(M)FS, the more sensitive index. For the active interventions, only the PF for comparisons of 250 ppm with 2400/2500/2800 ppm (PF 31% 95% CrI 8% to 54%) and 1000/1055/1100/1250 ppm fluoride with 2400/2500/2800 ppm (PF 20% 95% CrI 6% to 34%) attain statistical significance. The 95% CrIs are relatively wide indicating uncertainty in many of the comparisons, and reflecting the small number of trials for some of the comparisons.

Figure 7. Caterpillar plot D(M)FT PF.



There is evidence of a dose response effect, with the magnitude of the prevented fraction increasing as the distance between baseline and higher fluoride concentration increases, though this is rarely statistically significant, other than for the placebo-controlled trials at concentrations greater or equal to 1000 ppm.

In terms of the optimum fluoride concentration for greatest prevented fraction, the highest probability of caries preventive benefit was associated with the greater fluoride concentration: the probability was 0.72 for toothpastes containing 2400/2500/2800 ppm fluoride followed by 0.17 for toothpastes containing 1700/2000/2200 ppm fluoride.

Meta-regression

Eight studies did not include data on baseline level of caries: Abrams 1980; Fogels 1979; Gish 1966; Hanachowicz 1984; Muhler 1955; Muhler 1962; Muhler 1970; Koch 1990. The pooled analysis comprised 53 pairwise comparisons resulting from 46 trials.The model fit was good with a median summary deviation of 49.31 (95% CrI 32.75 to 70.86). Tau was 37.73 (95% CrI 22.20 to 60.95). Univariate meta-regression indicated a small association of D(M)FT PF with baseline level of caries (coefficient -0.93% 95% CrI -3.21% to 1.36%), though this was not statistically significant.

All studies reported on whether brushing was supervised or not. The pooled analysis comprised 61 pairwise comparisons resulting from 54 trials. The model fit was good with a mean summary deviation of 56.66 (95% CrI 38.66 to 79.56). Tau was 46.73 (95% CrI 28.70 to 72.65). Univariate meta-regression indicated an association with estimates of D(M)FT PF with supervised brushing (coefficient 8.67%, 95% CrI -0.45% to 17.94%), though this was not statistically significant.

(3) D(M)FS and D(M)FT pooled using a standardized mean difference (SMD)

Estimates of effect and standard error for pairwise differences with respect to fluoride concentration for both indices were calculated in Stata using Cohen's D.

For each direct comparison the SMD of the two indices and 95% CrIs can be viewed in Analysis 1.3 D(M)FS increment (SMD) and Analysis 1.4 D(M)FT increment (SMD) in the Data and analyses section. Additional Table 3 and Table 4 give the results of the direct comparison and network meta-analysis for D(M)FS and D(M)FT

with SMD. Results from the SMD pooled were materially similar to those obtained from the analysis of PF, with the exception of the placebo versus the highest fluoride concentration. Model fit for these data was relatively poor (D(M)FS 128.7 95% CrI 102.6 to 159.1, Tau 90.27 95% CrI 50.7 to 170.3; D(M)FT 108.60 95% CrI 85.24 to 135.5, Tau 107.4 95% CrI 47.82 to 279.6).

(4) decayed, (missing) and filled surfaces/teeth prevented fraction (d(m)fs PF and d(m)ft PF). Estimates of the effects on caries increments in the deciduous dentition

Two studies provided data for caries increments in both d(m)fs and d(m)ft; two studies provided data for analysis of d(m)ft alone and one study provided data for analysis of dfs alone. One study reporting D(M)FT as the primary outcome also reported the 'df-rate' of deciduous teeth.

d(m)fs comparison 1.5

(Analysis 1.5.)

To evaluate the caries preventive effects of fluoride toothpastes of different concentrations on tooth surfaces of the deciduous dentition one trial compared fluoride toothpaste to placebo and three trials compared toothpastes of different concentrations. The placebo-controlled trial compared a non-fluoridated toothpaste with a toothpaste containing 1500 ppm fluoride (Fan 2008). The PF was 39% (95% CI 29% to 49%) in favour of the fluoride toothpaste. The first compared the caries preventive effects of brushing with toothpaste containing fluoride concentrations of 250 ppm or 1450 ppm (Sonju Clasen 1995). This trial was of a cluster-randomised trial analysed and reported as an individual randomised trial. Using an intra-cluster coefficient of 0.05 with the average cluster size of 17.2, a design effect of 1.81 was calculated (Higgins 2008) and the standard error of the PF adjusted accordingly. This resulted in an increased standard error from 18.3 ignoring clustering to 24.6. The PF was 41.4% (95% CI -6.87% to 89.67%) in favour of the 1450 ppm fluoride toothpaste. A second trial compared the effects of brushing with toothpaste containing fluoride concentrations of 550 ppm versus 1055 ppm (Winter 1989). The PF was 9% (95 % CI -15% to 33%). Lima 2008 evaluated caries progression/arrest by initial caries status and reported no statistically significant difference in the mean number of new lesions in the caries inactive group but a highly statistically significant difference in net caries increment for the caries active group in favour of 1100 ppm fluoride toothpaste when compared to 500 ppm fluoride toothpaste.

Due to the small number of trials for this outcome a meta-regression was not undertaken.

d(m)ft comparison 1.6

(Analysis 1.6.)

These trials reported caries increment at the d(m)ft level. For the Sonju Clasen 1995 study, the high PF of 33.3% failed to reach statistical significance (95% CI -21.77% to 88.37%) as did the study by Winter 1989 with a PF of 16% (95 % CI -2% to 34%). In contrast, the study by Davies 2002 comparing the effects of brushing with fluoride concentrations of 440 ppm or 1450 ppm resulted in a statistically significant PF of 11% (95% CI 3% to 19%) in favour of the higher fluoride toothpaste.

In a placebo-controlled trial of 1500 ppm fluoride toothpaste, Cahen 1982 calculated the 'df-rate', denoted as the number of decayed or filled teeth per 100 observed primary teeth. In the placebo group this df-rate was 18.25, with a lower 'df-rate' of 11.45 in the combined fluoride groups.

Due to the small number of trials for this outcome a meta-regression was not undertaken.

(5) Proportion developing new caries in the permanent or deciduous dentition

Seven studies (eight trials) contributed data for the analysis of the proportion of children developing new caries in the permanent dentition; three studies contributing data for the effect on the deciduous dentition. To evaluate the caries preventive effects on the permanent dentition, seven trials utilised a placebo toothpaste. Plotting the pairwise treatment comparisons with respect to fluoride concentration revealed a radial pattern rather than a connected network and so for this outcome direct effects only were compared using the risk ratio. Pooled estimates of effect using a fixed-effect model were calculated for each pairwise comparison. The effect estimates (RR) and 95% CI can be viewed in comparisons 1.7 and 1.8 of the Data and analyses section. The results of the trials were equivocal with two of the pairwise comparisons reaching statistical significance in favour of the fluoride toothpaste: placebo versus 1000/1055/1100/1250 ppm RR(fixed) 0.88 (95% CI 0.82 to 0.95) and placebo versus 1450/1500 ppm RR(fixed) 0.95 (95% CI 0.91 to 0.98). The direct comparison of 1000/1055/1100/1250 ppm with 1450/1500 ppm did not reach statistical significance RR(fixed) 1.07 (95% CI 1.00 to 1.14) and overall, the pooled effect was not statistically significant RR 0.98 (95% CI 0.94 to 1.02).

Three studies of fluoride toothpastes of different concentrations presented data on the proportion of children developing new caries in the primary dentition (Davies 2002; Sonju Clasen 1995; Winter 1989). For this outcome direct effects only were compared using the risk ratio. Pooled estimates of effect using a fixed-effect model were calculated for the three direct pairwise comparisons. The effect estimates (RR) and 95% CI can be viewed in comparison 1.8 of the Data and analyses section. For the 250 ppm versus 1450 ppm comparison (Sonju Clasen 1995), there was no statistically significant difference in the proportion of children developing new caries (RR 1.01, 95% CI 0.63 to 1.62). The remaining comparisons were statistically significant, favouring higher fluoride con-

centrations (550 ppm compared with 1055 ppm RR(fixed) 0.89, 95% CI 0.80 to 0.99 and 440 ppm compared with 1450 ppm RR(fixed) 0.85, 95% CI 0.78 to 0.93). Overall, the pooled estimate was statistically significant in favour of a higher fluoride concentration (RR 0.87, 95% CI 0.81 to 0.93).

(6) Compliance with toothbrushing and side effects of toothpaste

Sixteen trials assessed possible side effects arising from toothpaste use, principally in terms of oral (soft tissue) pathologies and tooth staining. For the soft tissue findings, six trials reported either no untoward events or no untoward events which could be attributed to the use of the toothpaste (Conti 1988; Fogels 1979; Fogels 1988; Koch 1990; Rule 1984; Stephen 1994). For staining, six trials reported a greater incidence of staining in the stannous fluoride group (Fanning 1968; James 1967; Naylor 1967; Slack 1964; Slack 1967; Slack 1967a). One trial (Jackson 1967) reported no differential staining between the groups (2.5% fluoride group versus 1% placebo group) and no staining was found in another (Fogels 1979).

No side effects were observed or reported in three trials (Fan 2008; Glass 1983; Kleber 1996).

Compliance with toothbrushing was assessed in 21 trials and evaluated either as brushing frequency (<1 per day, 1 per day or >1 per day; average number of (supervised) brushings, attendance at >75% of brushing sessions per week), assessment of toothpaste consumption, or general compliance or co-operativeness with the treatment regimen.

When results were reported by group, two trials found no differential in compliance with regard to toothbrushing frequency (Conti 1988 (374.1 brushings 1000 ppm fluoride group, 370.4 1500 ppm fluoride group out of maximum 450 brushings over a 3-year period); Marks 1994 (ranged from 352 to 354 brushings with no statistical significance in mean number of brushing sessions). The proportion of co-operative children was reported in one trial (James 1967) with no differential between the groups (8% versus 6% control).

Some trials reported no problems with compliance and no differential compliance but results were not reported and/or not reported by group. For brushing frequency, Ashley 1977 reported that the mean number of attendances at school brushing sessions did not differ by group; Hanachowicz 1984 reported that 11% of children brushed less than 5 times per week with no differential between the groups. Hodge 1980 reported that 85% of subjects attended >75% of brushing sessions and that less regular attenders distributed evenly between the groups as did Howat 1978 where 58% of subjects attended >75% of brushing sessions. Koch 1990 reported that 65% of participating children brushed more than twice per day when self-reported frequency of brushing was evaluated. Marthaler 1970 reported 680 brushings per year on average, and Marthaler 1970a, Muhler 1962 reported that the average participant brushed 0.9 times per day. O'Mullane 1997 reported similar brushing frequency across the 1000 and 1500 groups, and Stephen 1994 found that 51% brushed more than once per day. Three trials reported that toothpaste usage was virtually similar in each group (Jackson 1967; Marthaler 1965; Marthaler 1965a). Ripa 1988 assessed compliance to the trial regimen by a telephone call to a sample of 150 homes of participating children and found the pattern of compliance "similar for all groups". Likewise, Kleber 1996 reported "no compliance problems". Piccione 1979 reported no differential results.

Results on participant compliance were "reported elsewhere" for one trial (Winter 1989) and not reported at all in another (Fan 2008).

DISCUSSION

Summary of main results

The principal focus of this review was to evaluate the relative effect of toothpastes containing fluoride of different concentrations for preventing caries in children and adolescents. Following a thorough literature search, the number of studies included in the review was 75 (83 trials).

Study results: There is a caries preventive beneficial effect of fluoride toothpastes when used by children and adolescents but not at all concentrations. Using the prevented fraction (PF) as the primary measure of effect, in the placebo-controlled trials, the benefits of increasing fluoride concentration in preventing caries was only statistically significant different from concentrations of 1000/1055/1100/1250 ppm and above (D(M)FS PF 23%, 95% credible interval (CrI) 19% to 27%; D(M)FT PF 25%, 95% CrI 19% to 30%) with the PF increasing thereafter. In subjective terms, this may be considered to be of relatively small magnitude but of clinical importance. For the active comparisons, using 250 ppm as the baseline, comparisons with fluoride concentrations of 1000/1055/1100/1250 ppm and above are statistically significant, ranging from D(M)FS PF 14%, (95% CrI 1% to 27%); through to 26% (95% CrI 11% to 41%) at concentrations of 2400/2500/2800 ppm. There is a greater caries preventive benefit of brushing with a toothpaste containing fluoride concentration of 1000 ppm and higher when compared to brushing with toothpaste containing 250 ppm fluoride. Pairwise comparisons using fluoride concentrations of 440/500/550 ppm and 1000/1055/1100/1250 ppm as a baseline were only statistically significant at the highest level 2400/2500/2800 ppm. Using fluoride concentrations of 1450/1500 ppm or 1700/2000/2200 ppm as a baseline there were no statistically significant benefits of the higher concentrations. There is some evidence of dose response relationship in that the prevented fraction increases as the fluoride concentration increases from the baseline. However the increase in prevented fraction is not always statistically significant. Whilst levels of caries at baseline

and supervised brushing have been previously cited as important effect modifiers, they were not found to be statistically significant in this review.

For the deciduous dentition, two placebo-controlled trials and four trials comparing effects of different fluoride concentrations were included in the review. For both d(m)fs and d(m)ft PF, results of the trials were equivocal. This is not surprising given the different concentrations compared.

In terms of the proportion of children and adolescents developing new caries during the trial, seven studies (eight trials) reported on new caries in the permanent dentition, with three trials reporting new caries in the deciduous dentition. For the permanent dentition the results of the trials were equivocal with two of the three pairwise comparisons reaching statistical significance in favour of the fluoride toothpaste. The direct comparison of 1000/1055/1100/1250 ppm with 1450/1500 ppm did not reach statistical significance and overall the pooled effect was not statistically significant risk ratio (RR) 0.98 (95% confidence interval (CI) 0.94 to 1.02). For the deciduous dentition which compared different fluoride concentrations the results were again equivocal, dependent upon the concentrations being compared. Direct pairwise comparisons of fluoride of similar concentrations yielded difference in caries preventive benefit between the different concentrations, though overall, the pooled estimate was statistically significant in favour of a higher fluoride concentration (RR 0.87, 95% CI 0.81 to 0.93).

Overall completeness and applicability of evidence

The review aimed to identify all randomised controlled trials (RCTs) evaluating the use of fluoride toothpastes in the prevention of caries. The present review has explicitly evaluated the preventive effect of fluoride at different levels. However, the review is dominated by studies comparing fluoride concentrations of 1000/1055/1100/1250 ppm to placebo. Whilst trials comparing other fluoride concentrations, from 250 ppm to 2500 ppm and which are of importance to clinical practice and policy are included in this review, they are less commonly undertaken. Though the explicit pairwise comparisons of different fluoride concentrations addresses issues important to clinical practice and policy, the lack of trials of different fluoride concentrations and in the different dentitions can be cited as a limitation of the review. The lack of trials in the deciduous dentition, where the potential for harm as a result of caries or fluoride exposure compared to the mixed or permanent dentition is of particular concern.

This review was intended to evaluate the relative caries preventive effect of fluoride toothpastes of different concentrations. Where stated in the trial report, adverse effects such as oral (soft tissue) damage and staining have been documented in the characteristics of included studies table. An important consideration when advocating the use of topical fluoride in children and adolescents in different treatment modalities such as toothpastes, gels varnishes etc. and at different concentrations is the potential for fluorosis arising from fluoride application. A recently published Cochrane review (Wong 2010) concluded that there was no significant association between frequency of toothbrushing and amount of toothpaste used (imperfect proxies for the amounts of fluoride ingested) and fluorosis. With reference to fluoride toothpaste concentration in the deciduous dentition, a meta-analysis of two studies found no statistically significant association between fluoride concentration and fluorosis (RE OR = 0.79, 95% CI 0.61 to 1.02). This result should be interpreted cautiously as the meta-analysis included only two studies and differed in terms of fluoride concentrations being compared (440 ppm with 1450 ppm and 550 ppm with 1000 ppm), duration of exposure and age of initiation of fluoride toothbrushing. To be fully informed of the potential caries preventive benefits of fluoride toothpastes of different concentrations and the potential risks of fluorosis arising from fluoride use both reviews should be read.

The prevented fraction (PF) was chosen to be the primary estimate of effect. The PF was considered to be more appropriate than the absolute mean difference or standardized mean difference as allowed for the combination of different ways in which caries increments are measured across studies, has clinical relevance to researchers as evidenced by its use in caries trials and is simple to interpret by clinicians. The review does not address cost effectiveness in terms of the potential reduction in financial cost associated with caries diagnosis prevention and treatment. However, it should be noted that for constant PF values across different populations the burden of disease (mean number of carious lesions) 'saved' by a higher level of fluoride toothpaste will increase as the underlying amount of disease in the population increases.

In 10 studies, treatment groups receiving additional non-fluoride agents with potential anticaries benefit as part of the intervention were excluded from the analysis if the additional agent was tested in isolated groups for their potential anticaries effect in comparison with either fluoride or placebo groups. Agents identified in trials in this review included secondary calcium pyrophosphate (one trial), heat-treated calcium orthophosphate (one trial), Na N-lauroyl sarcosinate (five trials), calcium phosphate/glycerophosphate (two trials), additional anticalculus agents (one trial). These groups were excluded as their anticaries effects had yet to be established and it is plausible that their addition to toothpaste could exert an additional preventive benefit when compared to formulations which did not receive such additional benefits. However, the influence of such additional agents could have been established through a sensitivity analysis. This will be considered in the review update.

Whilst an indication of the background exposure to fluoride for each of the studies is provided in the characteristics of included studies tables, it is clear that information regarding background exposure is not reported for many. Such a potential effect modifier could have been included in the analysis but due to insufficient information in many of the trial reports this was not undertaken,

and could be identified as a limitation of the review. Nevertheless, potential misclassification, especially due to the incomplete reporting of data for exposure to fluorides other than water (Marinho b 2003) would call for a cautious interpretation of the results of such an analysis.

Quality of the evidence

The included studies range in publication date from 1955 to 2008. The quality of conduct and reporting of RCTs has improved greatly during that time, and that is reflected in the studies included in the review. Many earlier studies lacked information on the methods of randomisation and the process of treatment allocation, hence the large number of studies classified as 'unclear' for these domains. Many studies used stratified randomisation to ensure as far as possible comparable baseline values in terms of unknown and known prognostic indicators, though failing to state the explicit method of randomisation. In terms of allocation concealment, participants were allocated different toothpastes without the involvement of the assessors, with a minimal risk of bias occurring. Of the other key quality domains assessed, the risk of bias is relatively low in trials of toothpastes such as these. Blinding of participants to the allocated toothpaste was done in all but one trial, by ensuring that the products were similarly packaged with taste and appearance, and assessment was carried out by examiners blinded to treatment allocation. Aside from a possible objection to taste, or tooth staining as a result of toothpaste use, lack of blinding would have been of minimal consequence to compliance or outcome assessment. All studies reported caries increment at a surface level as the outcome measure, the primary outcome measure expected to be reported in toothpaste trials, with the majority of studies additionally reporting on caries increment at the tooth level. Risk of bias arising from imbalance of baseline caries levels across groups was low. Stratification according to at least initial caries level was employed and reported in most trials.

The minimally accepted length of follow-up for trials where the outcome is caries increment is 12 months. This minimum duration was an inclusion criterion for the review. A preferred follow-up period is closer to 3 years, and the caries increment reported closest to this time was chosen as the outcome measure for this review. With such a duration some degree of attrition is to be expected, and largely unrelated to the allocated toothpaste. Reasons reported for attrition were principally due to participants moving schools, or absent from school on the day of the examination. Where participants were reported to be explicitly excluded from participation this was noted, but reflected only a very small proportion of the participants studied. The risk of bias of this domain was unclear for the majority of studies as reasons for drop out and differential losses were not reported. Only four trials were at high risk of bias on this domain as a result of high levels of attrition.

A potential source of bias in the review is contamination from other sources of fluoride (toothpaste or otherwise) or co-intervention. If the intervention took place within a school setting contamination is ordinarily unlikely to have occurred, and extremely unlikely to have occurred if the toothbrushing session was carefully supervised or the toothpaste carried the child's name on tube. A possible source of contamination was the use of family toothpaste but this was reduced in studies where sufficient toothpaste was provided for the entire family's use. The risk of bias in this domain was low. In general the studies can be considered to be largely free from bias in terms of the key domains identified, with the exception of randomisation, allocation concealment and incomplete outcome data as discussed above, where the majority of studies received a judgement of 'unclear'.

Potential biases in the review process

There was a single departure from the protocol: the outcome measure proportion of children developing new caries was felt to be a more appropriate measure of prevention than per cent remaining caries free. The latter measure would have excluded all those participants with caries at the commencement of the trial. The proportion of children remaining caries free was therefore removed from the list of outcomes.

No shortcomings in the search strategy were identified by the review authors.

Only three studies are awaiting retrieval or translation (and hence classification).

A limitation of the review in terms of absence of data results from incomplete study characteristics, baseline level of covariates and summary estimates and can be traced back in most cases to the number of years since publication. The review included papers published since 1955, well before the publication of the CONSORT Statement, and as such important data were omitted in some instances. The many years since publication precluded trying to contact authors for further information. In terms of evaluating the quality of studies, the lack of important information in some of the trial reports has resulted in categorisations of 'unclear'.

The external validity of the review is good, in that the baseline level of caries in the included studies is wide ranging, as is the age of participants at commencement of the studies, and gender is often used as a stratifying factor in the randomisation method. The review includes studies incorporating interventions for use at home and under supervised conditions, usually in a school setting. Meta-regression addressed whether such differences in intervention had an effect. The PF was used as the primary outcome measure to ensure that measurements at different indices can be appropriately combined, in an effect measure that is easy to understand and interpret clinically.

For the primary outcome measure PF D(M)FS, there was little evidence of heterogeneity between trials comparing similar levels of fluoride concentration. A meta-regression was formally undertaken with baseline caries and supervised brushing as possible effect modifiers. There was an effect of baseline caries and supervised

brushing on D(M)FS PF (coefficient 0.38%, 95% CrI -0.23% to 0.99% and coefficient 5.98%, 95% CrI -0.59% to 12.55% respectively), though this was not statistically significant, suggesting an anticaries effect of fluoride toothpaste irrespective of initial caries level and supervision of brushing.

Agreements and disagreements with other studies or reviews

Whilst placebo-controlled trials were covered in a previous review (Marinho b 2003), the effect of fluoride toothpastes of different concentrations was only evaluated indirectly, through meta-regression analysis. The review showed an unequivocal effect of fluoride when compared to placebo, and the results of meta-regression analysis suggested a greater treatment effect with increased fluoride concentration, but it drew no firm conclusions as to the relative effectiveness of fluoride toothpastes of different concentrations in preventing dental caries in children and adolescents.

For completeness, comparisons with published reviews will be made but it should be borne in mind that differences in the review process are likely to impact on the results. The present review found evidence of a statistically significant benefit of 250 ppm fluoride toothpaste relative to 1000 ppm fluoride toothpaste for caries prevention in the mixed/permanent dentition (PF D(M)FS 14% 95% CrI 1% to 26%). This result was also found in the two reviews comparing fluoride toothpastes at these concentrations (Ammari 2003; Steiner 2004).

In a review comparing the effects of fluoridated toothpaste compared to placebo and toothpaste of different concentrations, a quality assessment was undertaken and the results were reported narratively (Twetman 2003). An overall effect of fluoride toothpaste when compared to placebo (simple average) was reported in the review comprising 26 trials (Twetman 2003). In the comparison of toothpastes with a fluoride concentration of less than 1000 ppm fluoride relative to 1000-1100 ppm results of four trials were presented narratively indicating either a benefit or no effect of higher fluoride levels. The analysis undertaken in this review suggests that when compared to placebo, fluoride toothpastes of 1000 ppm and above are of benefit (PF D(M)FS 23%, CrI 19% to 27%), and that there is a significant benefit of 1000 ppm fluoride toothpastes when compared to 250 ppm fluoride toothpastes (PF D(M)FS 14%, CrI 1% to 26%). There is no statistically significant additional benefit of 500 ppm fluoride toothpastes compared to 250 ppm fluoride toothpastes (PF D(M)FS 6%, CrI -14% to 26%) or of 1000 ppm fluoride toothpaste compared to 500 ppm fluoride toothpaste (PF D(M)FS 8%, CrI -10% to 25%). The caries preventive effect of fluoride toothpaste containing 1500 ppm fluoride relative to 1000-1100 ppm fluoride was also reported (simple average, n = 9 trials) in favour of higher fluoride concentrations. Whilst the magnitude of effect was similar in this review and also in favour of higher fluoride concentration, this was not statistically significant (PF D(M)FS 6%, 95% CrI -2% to 14%).

Finally, a meta-analysis of standard and experimental toothpastes at fluoride concentrations ranging from 1700 ppm, 2200 ppm and 2800 ppm fluoride relative to 1000 ppm fluoride reported a caries preventive effect of higher fluoride concentration, though this was only statistically significant at the 2800 ppm fluoride level (Bartizek 2001). This pattern of results with similar fluoride concentrations was observed in this review (1000/1055/1100/1250 ppm relative to 1700/2000/2200 ppm relative PF D(M)FS 11%, CrI -6% to 28%; 1000/1055/1100/1250 ppm relative to 2400/2500/2800 ppm PF D(M)FS 13%, CrI 5% to 20%).

AUTHORS' CONCLUSIONS

Implications for practice

Using the prevented fraction (PF) as the primary measure of effect, in the placebo-controlled trials, the benefits of increasing fluoride concentration in preventing caries was only statistically significant different from concentrations of 1000/1055/1100/1250 ppm and above (D(M)FS PF 23%, D(M)FT PF 25% with the PF increasing thereafter, but concentrations of 440/500/550 ppm and below showed no statistically significant effect when compared to placebo). Based on these results, it may not be appropriate to recommend the use of 440/500/550 ppm fluoride toothpaste for the prevention of caries in the deciduous dentition, whilst acknowledging that there is considerable uncertainty surrounding the estimates at these levels. The use of 1000 ppm or higher in children under 6 years must be made taking into account the risk of fluorosis. The results support the international standard level of 1000 ppm fluoride for younger children and up to 1500 ppm for older children.

Implications for research

More research into the effects of fluoride toothpastes at lower levels of fluoride concentration is needed. Given the current recommended fluoride concentration level in the United Kingdom is around 1500 ppm and around 1000 ppm internationally, studies to evaluate the potential anticaries effects of toothpastes containing lower fluoride concentrations may face ethical difficulties. The majority of studies included in this review come from older, placebo-controlled studies carried out before fluoride was commonly used. As fluoride has become an accepted caries preventive measure then studies directly comparing different fluoride concentrations would be a good addition to the literature. In particular the number of studies evaluating the effects on the deciduous dentition small (six studies), and potential adverse effects of toothpaste use.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abrams 1980

Methods	Stratified random allocation; double-blind; placebo-controlled; 48% drop out after 3 years (study duration = 3 years). Reasons for high drop out described: change of residence, absenteeism, non-adherence to study protocol; no differential group losses
Participants	1141 children analysed at 3 years (available at final examination). Age range at start: 5-12 years. Surfaces affected at start: 3.2 DFS. Background exposure to fluoride: none reported. Year study began: in/before 1976. Location: USA.
Interventions	FT (2 groups) versus PL (both SnF_2 groups = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: silica gel in one SnF_2 and placebo toothpaste, Ca pyrophosphate in the other SnF_2 toothpaste.
Outcomes	3yNetDFS increment - (E+U) (CA)cl+(ER)xr. Reported at 1, 2 and 3 years follow-ups. DMFT. DMFS. DFT. MD-DFS. DFT rate. DFS rate.
Notes	Participants randomised (n = 2210). Baseline characteristics (DFS) 'balanced' . Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment (postBW) by 2 examiners; diagnostic threshold = ER. State of tooth eruption included = E/U. Intra- and inter-examiner reproducibility of clinical caries diagnosis (DFS) assessed annually by duplicate examination of 10% random sample (percentage of times diagnosis replicated in all 3 examinations ranged 42% to 97% and 77% to 92% for both examiners and for each respectively)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Children were randomly assigned to one of 3 treatment groups. A stratified sequential sampling technique was used within each school to balance the sample size with respect to sex and grade level for

Abrams 1980 (*Continued*)

		each dentifrice." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "A 3 year double-blind study of a dentifrice containing 0.4% stannous fluoride and a placebo..." "The examiners at all times were unaware of the children's dentifrice assignment." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 48% in 3 years. Drop out by group: 357/740 FD1, 343/721 FD2, 369/749 PL. Reasons for losses: Change of residence, absenteeism, exclusion due to non-adherence to study requirements Comment: Numbers lost were high for the length of follow-up. No differential loss between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E+U) (CA)cl+(ER)xr, reported at 1, 2 and 3 years follow-ups. DMFT. DMFS. DFT. MD-DFS. DFT rate. DFS rate. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 2.90 FD1, 3.28 FD2, 2.94 PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quotes: "Provisions were made ensuring the randomization process to assure that only one dentifrice code would be available

Abrams 1980 (*Continued*)

		in each household....A letter to parents was attached, giving brushing instructions and urging use of only the assigned dentifrice." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Andlaw 1975

Methods	Stratified random allocation; double-blind; placebo-controlled; 13% drop out after 3 years (study duration = 3 years). Main reasons for attrition described: moved away, absent at final examination; no differential group losses
Participants	740 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 6.9 DFS. Background exposure to fluoride: none reported. Year study began: 1970. Location: UK.
Interventions	FT versus PL (SMFP group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Al oxide trihydrate.
Outcomes	3yNetDFS increment - (E+U)(CA)cl+(ER)xr. Reported at 3 years follow-up. DMFS. DFT. DMFT. PF-DMFS. MD-BL-DMFS. MD-DMFS. O-DMFS. ECSI.
Notes	Participants randomised (n = 846). Baseline characteristics (age, dental age, TAR, DFS, DMFS, DFT, DMFT, ECSI) 'balanced'. Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA. Radiographic assessment (2 postBW) by 2 examiners; diagnostic threshold = ER. State of tooth eruption included = E/U. Reproducibility ratio was less than 0.22 for intra-examiner reproducibility of clinical and radiographic caries diagnosis; "significant differences between examiners could not have affected caries increment figures since each examined same children annually."

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Unclear	Quote: "Following baseline examinations, the children were grouped on the basis of age, sex, previous caries experience and the number of erupted 2^{nd} permanent molars; they were then randomly assigned to either the test or control group." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "Radiographs were examined ..... without reference to the clinical examination data." "The test dentifrice contained MFP....The toothpastes were packed in similar but distinguishable tubes. The investigators did not know which of the tubes contained the test paste nor which of the pastes any child was using." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 13% in 3 years. Drop out by group: 54/418 FD, 52/428 PL. Reasons for losses: Did not like taste of paste (1 from control group), changed school or moved away (63), exclusion due to absence at last examination Comment: Numbers lost were not unduly high for the length of follow-up, with no differential loss between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E+U) (CA)cl+(ER)xr, reported at 3 years follow-up. DMFS. DFT. DMFT. PF-DMFS. MD-BL-DMFS. MD-DMFS. O-DMFS. ECSI.

Andlaw 1975 (*Continued*)

		Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 6.30 (4.04) FD, 6.43 (4.31) PL. Age (years): 11.73 (0.33) FD, 11.69 (0.32) PL. TAR: 17.25 (4.35) FD, 17.35 (4.40) PL. Dental age: 21.75 (4.51) FD, 21.77 (4.47) PL. DFT: 4.52 (2.56) FD, 4.42 (2.66) PL. DMFT: 5.04 (2.68) FD, 4.96 (2.99) PL. DMFS: 8.80 (6.55) FD, 9.10 (7.25) PL. ECSI: 12.03 (8.34) FD, 12.41 (8.66) PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "The distribution of toothpastes and toothbrushes was the responsibility of two ladies called 'home visitors', whose duties were to visit each home every 5 weeks to supply enough of the appropriate toothpaste for the needs of the whole family.... and maintaining the interest and co-operation of participants throughout the trial." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Ashley 1977

Methods	Stratified random allocation; double-blind; placebo-controlled; 12% drop out (for all study groups combined) after 2 years (study duration = 2 years). Natural losses; any differential group losses not assessable
Participants	489 children analysed at 2 years (available at final examination). Average age at start: 12 years. Surfaces affected at start: 9.1 DFS. Background exposure to fluoride: none. Year study began: 1973. Location: UK.
Interventions	FT versus PL (SMFP group = 1000 ppm F). School use/supervised, daily, 1 g applied for 1 min, post-brushing water rinse done (non-fluoride toothpaste provided to all for home use). Abrasive system: IMP (main abrasive).

Ashley 1977 (*Continued*)

Outcomes	2yNetDFS increment - (E+U) (NCA)cl+(ER)xr. Reported at 2 years follow-up. PF-DFS. MD-BL-DFS. MD-DFS. DFS (U). Compliance.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, DFS, DMFS, DMFT) 'balanced'. Clinical (V) caries assessment by 1 examiner (FOTI used); diagnostic threshold = NCA. Radiographic assessment (postBW) by 1 examiner; diagnostic threshold = ER. State of tooth eruption included = E/U. Intra-examiner reproducibility checks for incremental caries data (ICC for clinical 0.95, for radiographic 0.8); reversal rate between 12% and 7% of observed DFS increment in study groups

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Using a table of random numbers, subjects were allocated within each school to one of four study groups."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The control dentifrice was identical, except that it did not contain sodium MFP." "The study was organised on a double-blind basis..." "Records of earlier examinations were not available at the subsequent examination sessions." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 12% in 2 years (133/1135, all 4 groups combined). Drop out by group: Not reported. Reasons for losses: Mainly due to moving from the area Comment: Numbers lost were not unduly high given length of follow-up; it is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present

Ashley 1977 (*Continued*)

		at baseline and final exams.
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E+U) (NCA)cl+(ER)xr, reported at 2 years follow-up. PF-DFS. MD-BL-DFS. MD-DFS. DFS (U). Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 8.44 (5.58) FD, 9.79 (7.28) PL. DMFT: 5.35 (3.03) FD, 6.06 (3.66) PL. DMFS: 9.89 (6.94) FD, 11.05 (7.98) PL. Age: 12.33 FD, 12.28 PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "...all subjects received ample supplies of the non-fluoride control toothpaste and toothbrushes. This ensured that the exposure of the subjects to fluoride dentifrice or rinse was restricted to the experimental regime." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Biesbrock 2001

Methods	Stratified random allocation; double-blind; 18.5% drop out (for all groups combined) after 1 year (study duration = 3 years). Reasons for attrition not reported
Participants	4431 children analysed at 1 year (available at examination). Age range at start: 6-15 years (average = 9). Surfaces affected at start: 5.3 DMFS. Background exposure to fluoride: water <0.3 ppm F in community. Year study began: in/before 2001. Location: USA.
Interventions	FT (4 groups) (all groups NaF: 1100 ppm F, 1700 ppm F, 2200 ppm F, 2800 ppm F) Home use/unsupervised, daily frequency assumed. Abrasive system: silica abrasive.

Biesbrock 2001 (*Continued*)

Outcomes	1yNet DMFS increment cl+xr, reported at 1 year follow-up. DMFS increment. DMFS increment by surface. DMFT increment. Reported at 1 year follow-up. DMFS increment at years 1, 2 and 3 from baseline exam.
Notes	Participants randomised (n = 5439). Baseline characteristics (age, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment and radiographic assessment carried out by a single examiner established as "repeatably sensitive" based on prior trial experience Results at years 2 and 3 confounded by a concurrent fluoride rinse programme, which involved half of the study population

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "randomly assigned to one of the four dentifrice groups."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quote: "...double-blind study." Quote: "They [dentifrices] were supplied in plain white 2.7 oz tubes." Quote: "Subject and examiner blindness to treatment were maintained throughout the study."
Incomplete outcome data addressed? All outcomes	Unclear	Comment: 38% drop out at 3 years. No reasons are given for those not examined but similar attrition rate in each of the 4 groups. Not stated but assumed that ITT analysis carried out for those present at exam. No imputation carried out
Free of selective reporting?	Unclear	Comment: Unclear but DMFS data not presented by surface for years 2 and 3, unlike year 1
Baseline characteristics balanced?	Yes	Quote: "..well balanced with respect to . ...mean caries experience as measured by DMFS and DMFT at baseline."
Free of contamination/co-intervention?	No	Quote "Results at years 2 and 3 confounded by a concurrent fluoride rinse programme.

		" Comment: After 1 year schools participated to varying degrees in a fluoride rinse programme. Only results for 1 year follow-up analysed in review

Blinkhorn 1983

Methods	Stratified random allocation; double-blind; placebo-controlled; 10% drop out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers: 57 left school, 12 withdrawn by parents, 6 absent at final examination; no differential group losses
Participants	368 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 8.2 DMFS. Background exposure to fluoride: none reported. Year study began: 1972. Location: UK.
Interventions	FT versus PL (SMFP group = 1000 ppm F). School use/supervised, daily, for 1 min, post-brushing water rinse done (appropriate toothpastes also provided for home use). Abrasive system: IMP (main abrasive).
Outcomes	3yNetDFS increment - (E+U) (CA)cl+(DR)xr. Reported at 3 years follow-up. PF-DFS. MD-BL-DFS. MD-DFS. postMD-DFS. DFS (U). DMFT. anterior DMFT. posterior DMFT. DMFT (U).
Notes	Participants randomised (n = 410). Baseline characteristics (DMFS, DMFT, SAR) 'balanced' (DFS baseline data not reported). Clinical (V) caries assessment by 1 examiner, diagnostic threshold = CA. Radiographic assessment (1 postBW) by 1 examiner; diagnostic threshold = DR. State of tooth eruption included = E/U. Intra-examiner reproducibility checks for incremental clinical and radiographic caries data in 10% sample (ICC score 0.9)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "The children were allocated to four groups by stratified random sampling at two levels: school and dental age." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The trial was organized on a double-blind basis, neither the children nor the examiner being aware of who was receiving test or control products." "...another group used the fluoride dentifrice..... and a fourth group....a placebo dentifrice." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 10% in 3 years. Drop out by group: 21/ 205 FD, 21/205 PL. Reasons for losses: Left school (57), withdrawn by parents (12) , absent at final examination (6) (not reported by group) Comment: Numbers lost were not unduly high for the length of follow-up with no differential loss between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination.
Free of selective reporting?	Yes	Outcomes reported: DFS increment (E+U) (CA)cl+(DR)xr, reported at 3 years follow-up. PF-DFS. MD-BL-DFS. MD-DFS. postMD-DFS. DFS (U). DMFT. Anterior DMFT. Posterior DMFT. DMFT (U). Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way

Blinkhorn 1983 (*Continued*)

Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFT: 4.94 (2.86) FD, 5.26 (3.47) PL. DMFS: 7.83 (5.17) FD, 8.48 (6.29) PL. SAR: 93.41 (21.30) FD, 93.61 (20.43) PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "..both dentifrice tubes and rinse bottles were colour coded so that the children received the correct products. Independent laboratory checks of the dispensed rinse and dentifrice were made at regular intervals to assess the reliabilty of the supervisors who dispensed agents. The coded dentifrice and rinse was dispensed in the school..." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Brudevold 1966

Methods	Stratified random allocation; double-blind; placebo-controlled; 25% drop out (for all study groups combined) after 2 years (study duration = 2 years). Reasons for attrition not reported; any differential group losses not assessable
Participants	1278 children analysed at 2 years (present for the entire trial period). Average age at start: 7-16 years (average = 12). Surfaces affected at start: 15.7 DFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: 1961. Location: USA.
Interventions	FT (3 groups)** versus 'PL' (both SnF_2 groups = 1000 ppm F, APF group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in one SnF_2 toothpaste, IMP in the other SnF_2 and in the APF toothpaste, control toothpaste abrasive not reported
Outcomes	2yDFS increment - cl+xr. Reported at 2 years follow-up. DMFS. DMFT. DFT.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (dental age, DFS, DFT, DMFS, DMFT, gender) 'balanced'. Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA. Radiographic

Brudevold 1966 (*Continued*)

	assessment (10 BW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported. **NaF-secondary Ca pyrophosphate toothpaste group not considered (abrasive system known to be incompatible with NaF)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "At the initial exam, the record cards of these youngest, or master, siblings were stratified (ordered) simultaneously according to 12 characteristics....The ordered cards of the 'master' siblings were then divided into 5 dentifrice groups by superimposing the numbers 1 through 5 in random sequence. The same dentifrice was assigned automatically to the other, or "trailing", siblings in his household." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "Each (of 2) examiner assessed about half of the subjects in each group, and each subject had the same dentist-examiner throughout the study. Separate records were used for each examination, and previous records were never available to the examiner. All observations were recorded in code for subsequent transfer to machine data processing. The radiographs were read and recorded independently by a third dentist. At no time was it possible for the examiners to identify a subject with a dentifrice group." "An independent laboratory was assigned the responsibility of coding, packaging, and shipping all dentifrices in this study.. NaF dentifrice was compared to.....and a fluoride free dentifrice." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 24.7% in 2 years (534/2156, all 5 groups combined). Drop out by group: Not reported. Reasons for losses: Not re-

		ported Comment: Numbers lost were not unduly high given length of follow-up; It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants examined after 2 years
Free of selective reporting?	Yes	Outcomes reported: DFS increment - cl+xr, reported at 2 years follow-up. DMFS. DMFT. DFT. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 16.88 (12.81) FD1, 14.03 (10.16) FD2, 14.89 (10.19) FD3, 15.70 (10.96) PL DFT: 8.53 (5.49) FD1, 7.61 (4.80) FD2, 6.04 PL; 7.59 (5.01) FD3, 8.07 (5.02) PL DMFT: 8.84 (5.86) FD1, 7.87 (4.80) FD2, 2.94 PL; 7.91 (5.34) FD3, 8.35 (5. 21) PL DMFS: 18.43 (13.91) FD1, 15.33 (11.08) FD2, 16.48 (12.86) FD3, 17.09 (11.68) PL Dental age: 21.12 (6.59) FD1, 22.28 (6. 47) FD2, 20.49 (6.51) FD3, 21.70 (6.29) PL Comment: Initial caries appears balanced although adjustment for baseline imbalance was made in the analysis**.**
Free of contamination/co-intervention?	Yes	Quotes: "As the study group was assembled, all siblings were noted to permit limitiation of one dentifrice code to a family." "New shipments supplied every 8 to 10 weeks, and new toothbrushes supplied every 6 months." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Buhe 1984

Methods	Stratified random allocation; double-blind; placebo-controlled; 18% drop out after 3 years (study duration = 3 years). No differential group losses
Participants	1286 children analysed at 3 years (available at final examination). Age range at start: 11-13 years (average = 12). Surfaces affected at start: 17.4 DMFS. Background exposure to fluoride: data not obtained for fluoridation status of site. Year study began: 1976. Location: FRG.
Interventions	FT (2 groups) versus PL (SMFP groups = 1000 ppm F and 1500 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.
Outcomes	3yNetDFS increment - cl+xr. Reported at 3 years follow-up. DMFS. DMFS (U). DMFT.
Notes	Participants randomised (n = 1562). Baseline characteristics (age, TAR, DMFS) 'balanced' (DFS baseline data not reported) . Clinical (VT) caries assessment; diagnostic threshold not reported; state of tooth eruption included E/U. Radiographic caries assessment; diagnostic threshold not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "...stratified randomisation..." Comment: Translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment?	Unclear	Translation of report not detailed enough to make a categorical decision regarding allocation concealment
Blinding? All outcomes	Yes	Quotes: "Double blind study." "...as compared to the placebo group.." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 17.7% in 3 years. Drop out by group: FD1 99/520, FD2 82/520, PL 95/522. Reasons for losses not reported

Buhe 1984 (*Continued*)

		Comment: Numbers lost were not unduly high given length of follow-up and showed no differential loss between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Free of selective reporting?	Unclear	Outcomes reported: DFS increment - cl+xr, reported at 3 years follow-up. DMFS. DMFS (U). DMFT. Comment: Trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	Yes	Prognostic factors reported: Mean age 12.3 years (for all groups). DMFS: 17.1 FD1, 17.4 FD2, 17.8 PL. TAR: 15.4 FD1, 15.5 FD2, 15.3 PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Unclear	Translation of report not detailed enough to make a categorical decision regarding any contamination and/or co-intervention

Cahen 1982

Methods	Stratified random allocation; double-blind; placebo-controlled; 20% drop out after 3 years (study duration = 3 years). Natural losses and exclusions based on presence in all follow-up examinations; any differential group losses not assessable
Participants	2008 children analysed at 3 years (present for all examinations). Age range at start: 6-8 years (average = 7). Surfaces affected at start: 1.4 DMFS (control group only). Background exposure to fluoride: data not obtained for fluoridation status of site. Year study began: 1977. Location: France.
Interventions	FT (2 groups) versus PL (SMFP group = 1500 ppm F, AmF group = 1500 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP in the SMFP and placebo toothpaste, Ca carbonate/Na and Al silicates in the AmF toothpaste

Cahen 1982 (*Continued*)

Outcomes	3yDMFS increment - cl+xr. Reported at 3 years follow-up. DMFT. df-rate.
Notes	Participants randomised (n = 2500); numbers by group not reported. Baseline characteristics (age, gender) 'balanced'. Clinical (V) caries assessment by 6 examiners; diagnostic threshold not reported; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold not reported; partial recording. Inter- and intra-examiner reproducibility of clinical and radiographic caries diagnosis assessed in 10% sample ("good reproducibility, no significant difference between or within examiners")

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "...children were stratified by age, sex...were then randomly distributed into 3 groups. Additional modifications were made by placing brothers and sisters in the same groups in order to ensure that only one type of dentifrice entered the household during the trial period." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The dentifrices were packed in neutral white tubes with no other inscription than 'Pate Dentifrice'...allocation code was known only by the manufacturer until the final results were obtained." "The whole study was conducted double-blind. The yellow toothpaste was not fluoridated and ..." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 19.7% in 3 years (492/2500). Drop out by group: Not reported. Reasons for losses: Sickness, change of address, exclusion based on presence at all examinations (not reported by group) "The balance between boys and girls, and between age groups was preserved in each

Cahen 1982 (*Continued*)

		treatment group...allowing unbiased comparisons." Comment: Overall drop out not unduly high for length of follow-up; it is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced, and how balance between groups was maintained. Caries data used in the analysis pertain to participants present at all examinations
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 3 years follow-up. DMFT. df rate. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Unclear	Prognostic factors reported: Age and gender reported as balanced; DMFS: 1.42 (PL) ; DMFT: 0.98 (PL) Comment: Initial caries derived for the control group only.
Free of contamination/co-intervention?	Yes	Quote: "...by placing brothers and sisters in the same groups in order to ensure that only one type of dentifrice entered the household during the trial period." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Chesters 2002

Methods	Stratified random allocation; double-blind. 15.8% drop out (for all study groups combined) after 2 years (study duration = 2 years). Reasons for attrition not reported
Participants	2011 children analysed at 2 years (available at final examination). Age range at start: 11-14 years (average = 13). Surfaces affected at start: not reported. Background exposure to fluoride: none reported. Year study began: 1999. Location: Lithuania.
Interventions	FT (2 groups) 1000 ppm F SMFP versus 2500 ppm F SMFP. Home use twice daily/unsupervised; daily brushing at school. Abrasive system: silica (both groups).

Outcomes	2yNet DMFS Increment cl(DSTM) FOTI at D_3 all radiographic lesions. D_1MFS Increment (DSTM only). D_3MFS Increment (DSTM only). D_1MFS Events (DSTM). D_3MFS Events (DSTM). Reported at 1 and 2 year follow-up.
Notes	Participants randomised (n = 2387). Baseline characteristics (sex, baseline caries) 'well balanced' No significant D_1MFS or D_3MFS or baseline differences (values not stated). Examinations carried out by a single examiner. Intra-examiner reliability: repeat DSTM and FOTI examinations held throughout the baseline, 12 and 24 month examinations on 5% to 10% of subjects. For radiography, baseline and 12 and 24 month radiographs re-assessed for 5% to 10% of subjects. Reproducibility "excellent", Kappa values >0.8

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: " . .randomized to one of two silica-based dentifrices." Quote: "...stratified into 12 strata ...allocated to a product group according to a pre-prepared list of randomized blocks?"
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quote: "... double-blind study." Quote: "Neither the subjects, clinical examiners, nor those distributing the test products were aware of the product identities at any time during the trial. The investigators were supplied with sealed code-break envelopes that could be opened in an emergency. This was not required and the integrity of the product code was confirmed with regular GPC monitoring and independent audit." Quote: "The products were identical except for the fluoride level and different coloured packaging for each product code?"
Incomplete outcome data addressed? All outcomes	Yes	2387 randomised (994/1193 included in final main analysis in low fluoride group; 1017/1194 in high fluoride group) Comment: Not unreasonable drop-out rate; similar in both groups. Reasons unlikely to be due to intervention

		Comment: Numbers absent and withdrawn are given for each group. Well balanced between groups. No further information about drop outs given
Free of selective reporting?	Unclear	Comment: Results reported traditional increment and DSTM increment at different levels of diagnosis. DMFT and proportion developing new caries missing. DSTM, FOTI and radiographic assessments
Baseline characteristics balanced?	Yes	Comment: Balance of gender and baseline DMFS.
Free of contamination/co-intervention?	Unclear	Comment: Unlikely as used different colours for toothpaste tubes/cartons, but possibility of contamination during school brushing sessions

Conti 1988

Methods	Stratified random allocation; double-blind. 39% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for high attrition described: moved, withdrew, absent or not available for examination; no differential group losses
Participants	2415 children analysed at 3 years (available at final examination). Age range at start: 7-11 years (average = 10). Surfaces affected at start: 2.8 DMFS. Background exposure to fluoride: water <0.3 ppm F in community. Year study began: in/before 1984. Location: USA.
Interventions	FT (2 groups) 1000 ppm SMFP, 1500 ppm SMFP. Home use/supervised brushing at school, daily frequency assumed. Abrasive system: silica (both groups).
Outcomes	3yNetDFS increment - cl+xr. Reported at 3 years follow-up. DMFS. DMFT. DFT. DFS Prox. Oral (soft tissue) findings. Compliance.
Notes	Participants randomised (n = 3957). Baseline characteristics (age, gender, sound surfaces, DMFT, DMFS) 'balanced'. Clinical examinations carried out by 1 primary examiner and 2 back-up examiners.10%

Conti 1988 (*Continued*)

	of children randomly selected each year to be re-examined

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: " . .stratified according to age and sex and then randomly assigned to one of two treatment groups by a computer program."
Allocation concealment?	Yes	Quote: "assigned by computer program designed for this purpose."
Blinding? All outcomes	Yes	Quote: "The study was double blind, multiple codes were used for each product, the dentrifices used were identical in appearance and flavour and the packaging were similar for both products."
Incomplete outcome data addressed? All outcomes	Unclear	2415/3957 children received clinical and radiographic assessment (39% attrition rate; similar across both groups). Quote: "Moved, withdrew, absent or not available." Comment: Attrition rate was high after 3 years, 38% and 40% in the groups. Although reasons for drop outs unlikely to be due to intervention, high rates could influence results
Free of selective reporting?	Yes	Comment: Results reported DMFT, DMFS, per cent caries free at 3 years. Clinical and radiography assessments
Baseline characteristics balanced?	Yes	Comment: Comparable age, gender, baseline DMFT DMFS.
Free of contamination/co-intervention?	Yes	Comment: School co-ordinators hired and trained to supervise daily toothbrushing. Contamination possible in school brushing sessions but unlikely under supervision

Davies 2002

Methods	Random allocation; single-blind (clinical assessors). 32% drop out after 5 years (study duration 5 years). Reasons for attrition: refused to participate (9%), change of residence (19%); product related and dental recommended withdrawals in high fluoride group only (0.07%)
Participants	3731 children analysed at 5 years (remained in the study and available at final examination); 5028 children analysed at 5 years (initially allocated to study groups and available at final examination). Age range at start: 12 months. Surfaces affected at start: 0 dmfs. Background exposure to fluoride: none reported. Year study began: 1993 (5 health districts) 1994 (4 health districts). Location: UK.
Interventions	FT (440 ppm NaF, 1450 ppm NaF). Control group receiving no intervention also reported.** Home use/unsupervised, daily frequency assumed. Abrasive system: not reported.
Outcomes	5ydmft increment - cl. Reported at 5 years follow-up. mt. Prevalence of caries experience (dmft >0).
Notes	Participants initially randomised (n = 7422). Baseline characteristics: not reported. Clinical (VT) caries assessments by trained, standardised, calibrated examiners. Clinical data only. Reliability values not reported **Control group (n = 2462) not considered.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "..randomised controlled parallel group clinical trial." Quote: "..centrally allocated to either one of the two test groups or a control group using random number tables."
Allocation concealment?	Yes	Quote: "..centrally allocated to either one of the two test groups or a control group." Comment: Centralised allocation.
Blinding? All outcomes	Unclear	Quote: "Dental examinations were conducted under blind conditions but as "off the shelf" toothpaste was delivered to the participants, subjects and their families were aware of which toothpaste they were

Davies 2002 (*Continued*)

		using." Comment: Clinical assessors blinded, but participants and their families were not. Participants very young children so knowledge of intervention unlikely to influence outcome
Incomplete outcome data addressed? All outcomes	Yes	1677/2472 available for examination in low fluoride group; 1696/2488 available in the high fluoride group. Total drop-out rate of 32% Comment: Drop-out rate mainly due to refusal to participate, change of residence; product related and dental recommended withdrawals in high fluoride group only but this number is very small. Reasons for drop outs primarily unlikely to be due to intervention
Free of selective reporting?	Yes	Comment: Routine caries diagnosis. No radiographs taken; clinical examination only. Caries indices reported: mt, dmft, caries free
Baseline characteristics balanced?	Unclear	Comment: No baseline data presented. Study undertaken in deprived areas of North West of England with comparable caries prevalence in 5 year olds
Free of contamination/co-intervention?	Unclear	Comment: Contamination possible. Toothpaste supplied for use by children participating in the trial only and not to other family members

Di Maggio 1980

Methods	Random allocation; double-blind; placebo-controlled; 16% drop out (for both study groups combined) after 2 years (study duration = 2 years). Main reason for attrition described: left institution; any differential group losses not assessable
Participants	42 children analysed at 2 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 11.7 DMFS. Background exposure to fluoride: data not obtained for fluoridation status of site. Year study began: in/before 1977. Location: Italy.
Interventions	FT versus PL (SMFP-NaF group = 2500 ppm F). Institution use/supervised, 3 times a day.

Di Maggio 1980 (*Continued*)

	Abrasive system: not clearly specified.
Outcomes	2yDMFS increment - cl. Reported at 1 and 2 years follow-ups. DMFT.
Notes	Participants randomised (n = 50). Baseline characteristics (DMFS, DMFT) 'balanced'. Clinical caries assessment by 2 examiners; diagnostic threshold not reported; state of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "... following a randomisation list the children were allocated to 2 groups..." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "...to 2 treatment groups that differed only by the presence or absence of fluoride. ...the dentifrices were indistinguishable by colour or flavour." "...using the most strict double-blind condition." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 16% (8/50) in 2 years. Drop out by group: Not reported. Reasons for losses: Essentially due to leaving the orphanage Comment: Numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examinations
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl, reported at 1 and 2 years follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes were reported and

Di Maggio 1980 (*Continued*)

		were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFT: 5.68 FD, 5.90 PL. DMFS: 11.50 FD, 11.85 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "The institute personnel actively collaborated in controlling the regular dentifrice use, as prescribed." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Fan 2008

Methods	Stratified random allocation; double-blind; placebo-controlled; drop outs not obtainable. Reasons for attrition not reported; differential losses not assessable
Participants	998 children analysed after 2 years (present for the entire trial period). Age range at start: 4 years. Surfaces affected at start: 3.6 dfs. Background exposure to fluoride: public drinking water <0.3 ppm F. Year study began: in or before 2005. Location: China.
Interventions	FT (2 groups) versus PL (both SMFP groups = 1500 ppm F). Home use/unsupervised, twice daily frequency assumed. Abrasive system: not reported.
Outcomes	2ydfs increment - cl. Reported at 2 years follow-up. Compliance. Side effects.
Notes	Participants randomised (numbers not reported). Baseline characteristics (age, gender, dfs) 'well balanced'. Clinical (VT) assessment by 1 examiner. A subsample of 40 children were re-assessed Kappa >0.9 Analysis of covariance adjusted for baseline dfs. Children with orthodontic appliances or participating in any other clinical study during the 3 months prior to baseline examination were excluded

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Subjects were randomly assigned. .."

Fan 2008 (*Continued*)

Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quote: "...employed a double-blind..." "Dentifrices were packaged in white tubes or overwrapped with white tape so as to mask their identity."
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "A total of 1200 qualifying children...entered the study." Quote: "Subjects who did not complete the study dropped out for reasons unrelated to the use of the treatments." Comment: Number randomised/ excluded/withdrawn not reported.
Free of selective reporting?	Yes	Mean dfs increment. Clinical (VT) assessment only.
Baseline characteristics balanced?	Unclear	Comment: Analysis adjusted for baseline dfs. Baseline data reported for participants completing the trial only. However groups analysed are similar with respect to gender and mean dfs score at baseline
Free of contamination/co-intervention?	Unclear	Comment: Insufficient information. Possibility of contamination during brushing sessions

Fanning 1968

Methods	Stratified random allocation; double-blind; placebo-controlled; 22% natural drop out after 2 years (study duration = 2 years); no differential group losses (46% drop out based on analysis performed for randomised block design)
Participants	844 children analysed at 2 years (422 complete replicates of each group available). Age range at start: 12-14 years (average = 13). Surfaces affected at start: 17.7 DMFS (from sample randomised). Background exposure to fluoride: none. Year study began: 1964. Location: Australia.
Interventions	FT** versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.

Fanning 1968 (*Continued*)

Outcomes	2yDMFS increment - (CA)cl+(ER)xr. Reported at 2 years follow-up. Stain score.
Notes	Participants randomised (n = 1576). Baseline characteristics (DMFS, DMFT, SAR) 'balanced'. Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA. Radiographic assessment (5 BW) by 2 examiners; diagnostic threshold = ER. State of tooth eruption included = E/U. Intra- and inter-examiner reproducibility of clinical caries diagnosis (DFS) assessed annually by duplicate examination of 10% random sample ("error relatively small, NS difference between or within examiners") **Na N-lauroyl sarcosinate/SMFP toothpaste group not considered (additional non-F active agent used in this group only)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Within each school students were separated into groups according to sex and examiner; within each group they were listed in order of increasing DMFS, and then allotted at random to the treatments by the method of taking successive groups of three subjects from the ordered lists...in a randomised block design."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "At no time was it possible for the examiners or recorders to identify a subject with a dentifrice group....subjects did not know what dentifrice they were using." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 46.4% in 2 years. Drop out by group: 139/788 FD, 163/788 PL. Reasons for losses: Children leaving school Comment: Numbers lost were unduly high for the length of follow-up. No differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants in complete randomised blocks at final examination

Fanning 1968 (*Continued*)

Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (CA)cl+(ER)xr, reported at 2 years follow-up. Stain score. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 19.84 FD, 19.89 PL; SAR: 112.42 FD, 112.58 PL; DMFT: 10.39 FD, 10.39 PL Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quotes: "At the beginning of each month, enough dentifrice was sent for the entire family." "All siblings were placed in the same treatment group to ensure that only one dentifrice formula was sent to a home." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Fogels 1979

Methods	Random allocation; double-blind; placebo-controlled; 40% drop out after 3 years (study duration = 3 years). Reasons for attrition described: graduations, change of residence/school, parental requests, and ortho treatment; no differential group losses
Participants	1339 children analysed at 3 years (available at final examination). Age range at start: 6-11 years (average = 9). Surfaces affected at start: 4.9 DFS. Background exposure to fluoride: none reported. Year study began: 1972. Location: USA.
Interventions	FT (2 groups) versus PL (both SnF_2 groups = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: silica gel in one SnF_2 and placebo toothpaste, Ca pyrophosphate in the other.
Outcomes	3yNetDFS increment - (CA)cl+(ER)xr. Reported at 3 years follow-up. MD-DFS. DFS (U).

Fogels 1979 (*Continued*)

	DMFT. Oral soft tissues lesions (data not reported). Proportion of children with tooth staining (data not reported)
Notes	Participants randomised (n = 2218). Baseline characteristics (DFS) 'balanced'. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment (postBW) by 2 examiners; diagnostic threshold = ER. State of tooth eruption included E/U. Results shown for each examiner and for the pooled data from both (F-ratios less than unit for examiner by treatment interactions); combined results considered

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Children were stratified according to age and sex, and randomly assigned one of the 3 dentifrices." Comment: Insufficient information.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "Throughout the duration of the study, the double-blind design was maintained; neither the examiners nor the hygienists had access to the identity of the dentifrice codes or to the findings of the previous examination." "Parents were informed that the dentifrices would be assigned randomly and that their children had 1:3 chance to be assigned a non-fluoride dentifrice." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 40% in 3 years. Drop out by group: 280/731 FD1, 296/735 FD2, 303/752 PL. Reasons for losses: Graduations, change of residence/school, parental requests, and ortho treatment Comment: Numbers lost are not unduly high for length of follow-up, with no differential loss between groups. It is unclear if reasons for the missing data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examinations

Fogels 1979 (*Continued*)

Free of selective reporting?	Yes	Outcomes reported: DFS increment - (CA)cl+(ER)xr, reported at 3 years follow-up. MD-DFS. DFS (U). DMFT. Oral soft tissues lesions (data not reported). Proportion of children with tooth staining (data not reported) Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 5.69 FD1, 6.04 FD2, 6.04 PL. FS: 2.69 FD, 2,30 FD2, 2.94 PL. Age (months): 114.0 FD, 114.6 FD2, 115.0 PL. Dental age: 14.93 FD, 15.23 FD2, 15.09 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quotes: "To avoid assigning two different dentifrices to children in the same household, only one child per family, usually the oldest child, was used in the randomisation." "No evidence of switching dentifrices among children was found." "Care was taken to ensure each child got the correct product." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Fogels 1988

Methods	Stratified random allocation; double-blind; 20.7% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: withdrawal from the study or absent from final examination; no differential group losses
Participants	1913 children analysed at 3 years (available at final examination). Age range at start: 6-11 years (average = 9). Surfaces affected at start: 3.7 DMFS. Background exposure to fluoride: drinking water fluoride adjusted to 1 ppm. Year study began: 1981. Location: USA.

Fogels 1988 (*Continued*)

Interventions	FT (2 groups) 1000 ppm F SMFP and 1500 ppm SMFP. Home use/supervised brushing at school, daily frequency assumed. Abrasive system: silica (both groups).
Outcomes	3yNet DMFS increment cl+xr. Reported at 3 years follow-up. DMFT increment. DF Prox. increment. Proportion developing caries. Adverse effects.
Notes	Participants randomised (n = 2411). Baseline characteristics (age, gender, DMFS, DMFT, sound surfaces) 'balanced'. 1 trained and calibrated examiner used. 10% of children randomly re-examined to assess consistency of scoring: decayed surfaces 84.7% to 88.9% consistent, filled surfaces 95.1% to 98.8% consistent 18.8% of children had orthodontic treatment with banded teeth excluded from the analysis and 8.4% were given sealants

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: " . .subjects were stratified according to age and sex and were randomly assigned to one of two fluoride dentifrices."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quote: "...double-blind study."
Incomplete outcome data addressed? All outcomes	Unclear	Comment: Attrition rate was moderate after 3 years, 21% and 21% in 1000, 1500 groups Quote: "The drop-outs either withdrew from the study during the course of the trial or were absent at the third year clinical or radiographic examination." Comment: Not given for each group separately.
Free of selective reporting?	Yes	Comment: Results reported DMFT, DMFS, per cent caries free at 3 years
Baseline characteristics balanced?	Yes	Comment: Balance of gender, age and caries disease at baseline comparable

Fogels 1988 (*Continued*)

Free of contamination/co-intervention?	Unclear	Comment: Possible in school brushing sessions. A proportion of the subjects were fitted with sealants during the course of the study and this proportion was higher (9.6% as opposed to 7.2%) in the higher fluoride group which showed a lower caries increment

Forsman 1974

Methods	Random allocation; double-blind; placebo-controlled; 18% drop out after 2 years (study duration = 2 years). Reasons for attrition described with respective total numbers: change of residence/school, ortho treatment, did not wish to continue; no differential group losses reported (but not assessable)
Participants	559 children analysed at 2 years (available at final examination). Age range at start: 10-11 years. Surfaces affected at start: 5.1 DMFS. Background exposure to fluoride: mouthrinse. Year study began: in/before 1970. Location: Sweden.
Interventions	FT (3 groups) versus PL (250 ppm NaF, 250 ppm SMFP, 1000 ppm SMFP). Home use/unsupervised, daily frequency assumed. Abrasive system: silica in all toothpastes.
Outcomes	2yDMFS increment - (NCA)cl. Reported at 2 years follow-up. BLMD-DFS (clin). MD-DFS (x-ray). Proportion of children with new smooth surface caries.
Notes	Participants randomised (n = 681); numbers by group not reported. Baseline characteristics (dental age, DMFS) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold = NCA. Radiographic assessment (postBW) by 1 examiner; diagnostic threshold = ER. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "From lists for girls resp. boys in all classes each fourth child on the Vaxjo lists and each third child on the Ljungby lists was randomly selected for the respective groups."

Forsman 1974 (*Continued*)

		Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The toothpaste was delivered in tubes with the word 'Toothpaste' printed in different colours. During the period of investigation, only the manufacturer knew the code." "...study was designed as a double-blind experiment." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 17.9% (122/681) in 2 years. Drop out by group: Not reported. Reasons for losses: Orthodontic treatment (6), moved away (39), did not wish to continue (77) (not reported by group) Comment: Numbers lost are not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants continuing the study up to year 2 (children completing tests)
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (NCA)cl, reported at 2 years follow-up. BLMD-DFS (clin). MD-DFS (x-ray). Proportion of children with new smooth surface caries. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 5.57 FD1, 4.87 FD2, 4.53 FD3, 5.16 PL. Dental age: 18.89 FD1, 19.08 FD2, 18.66 FD3, 19.03 PL. Comment: Initial caries appears balanced.

Forsman 1974 (*Continued*)

Free of contamination/co-intervention?	Yes	Quote: "The dentifrice was distributed every second month in amounts calculated to meet the needs of the whole family, to ensure as far as possible that the participants did not have access to other toothpastes." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Forsman 1974a

Methods	Random allocation; double-blind; placebo-controlled; 16% drop out after 2 years (study duration = 2 years). Reasons for attrition described with respective total numbers: change of residence/school, ortho treatment, did not wish to continue; no differential group losses reported (but not assessable)
Participants	394 children analysed at 2 years (available at final examination). Age range at start: 10-12 years. Surfaces affected at start: 12.9 DMFS. Background exposure to fluoride: mouthrinse. Year study began: in/before 1970. Location: Sweden.
Interventions	FT (2 groups) versus PL (one SMFP group = 250 ppm F, another SMFP group = 1000 ppm F) Home use/unsupervised, daily frequency assumed. Abrasive system: Ca carbonate in all toothpastes.
Outcomes	2yDMFS increment - (NCA)cl. Reported at 2 years follow-up. BLMD-DFS (clin). MD-DFS (x-ray). Proportion of children with new smooth surface caries.
Notes	Participants randomised (n = 469); numbers by group not reported. Baseline characteristics (dental age, DMFS) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold = NCA. Radiographic assessment (postBW) by 1 examiner; diagnostic threshold = ER. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "From lists for girls resp. boys in all classes each fourth child on the Vaxjo lists and each third child on the Ljungby lists was randomly selected for the respec-

		tive groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The toothpaste was delivered in tubes with the word Toothpaste printed in different colours. During the period of investigation, only the manufacturer knew the code." "...study was designed as a double-blind experiment." Comment: Blind outcome assessment and use of placebo described.
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 16% (75/469) in 2 years. Drop out by group: Not reported. Reasons for losses: orthodontic treatment (27), moved away (22), did not wish to continue (26, not reported by group) Comment: Numbers lost are not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants continuing the study up to year 2 (children completing tests)
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (NCA) cl, reported at 2 years follow-up. BLMD-DFS (clin). MD-DFS (x-ray). Proportion of children with new smooth surface caries. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 13.08 FD1, 12.90 FD2, 12.74 PL. Dental age: 20.72 FD1, 21.21 FD2, 21.24 PL. Comment: Initial caries appears balanced.

Forsman 1974a (*Continued*)

Free of contamination/co-intervention?	Yes	Quote: "The dentifrice was distributed every second month in amounts calculated to meet the needs of the whole family, to ensure as far as possible that the participants did not have access to other toothpastes." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Gish 1966

Methods	Stratified random allocation; double-blind; placebo-controlled; 34% drop out after 3 years (study duration = 5 years). Reasons for attrition not reported; any differential group losses not assessable
Participants	328 children analysed at 3 years (available at final examination). Age range at start: 6-14 years (average = 9). Surfaces affected at start: 3.9 DMFS. Background exposure to fluoride: water. Year study began: in/before 1963. Location: USA.
Interventions	FT versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate.
Outcomes	3yDMFS increment - cl+xr. Reported at 1, 2, 3, 4 and 5 years follow-ups. DMFT.
Notes	Participants randomised (n = 500); numbers by group not reported. Baseline characteristics (age, DMFS) 'balanced'. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold not reported. Radiographic assessment (5-7 BW); diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "The children were stratified by past caries experience and dental age, and then assigned at random to test or control groups." Comment: Not enough information provided.

Gish 1966 (*Continued*)

Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The dentifrices were packed in plain, white, coded tubes. The code was not known by either the subjects or the examiners." "...those in group 2 received an identical dentifrice minus the stannous fluoride." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 34, 4% (172/500) in 3 years. Drop out by group: Not reported. Reasons for losses: Not reported Comment: Numbers lost were not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data pertain to participants present at final examinations (completing the relevant follow-up exam)
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 1, 2, 3, 4 and 5 years follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFMS: 3.73 FD, 4.17 PL; Age: 9.27 FD, 9.25 PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "All of the children and their families received as much dentifrice as they wished, and no instructions were given to either group as to oral hygiene or frequency of use of either product." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Glass 1978

Methods	Stratified random allocation; double-blind; placebo-controlled; 35% drop out after 3 years (study duration = 3 years). Natural losses, increased during 3rd year because an entire grade graduated; exclusions based on presence in all follow-up examinations; any differential group losses not assessable
Participants	346 children analysed at 3 years (present for all examinations). Age range at start: 6-11 years (average = 9). Surfaces affected at start: 4.1 DFS. Background exposure to fluoride: none reported. Year study began: in/before 1974. Location: USA.
Interventions	FT versus PL (SMFP group = 1000 ppm F). School use/supervised, 1 g applied daily (appropriate toothpastes and toothbrushes also provided for home use). Abrasive system: Ca carbonate.
Outcomes	3yNetDFS increment - (CA)cl+(ER)xr. Reported at 1, 2 and 3 years follow-ups. MD-DFS. O-BL-DFS. DFT. CIR. O-BL-CIR. MD-CIR.
Notes	Participants randomised (n = 533); numbers by group not reported. Baseline characteristics (age, DFS, DFT, SAR, TAR) 'balanced'. Clinical (VT) caries assessment (FOTI used) by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. Reversals were small in both groups (about 6% of DFS increments) and equally common (NS different)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "The initial total of 533 subjects, stratified according to age and sex, were assigned at random to one of 2 groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "One group brushed with dentifrice containing MFP, the other with the same dentifrice without MFP."

		"At no time during the clinical examinations or during the interpretation of the radiographs was the identity of the experimental and control group codes known to the examiner or his recorder." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 35% (187/533) in 3 years. Drop out by group: Not reported. Reasons for losses: Left school, exclusion based on presence at all examinations Comment: Numbers lost were not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data pertain to participants present at all examinations
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (CA)cl+(ER)xr, reported at 1, 2 and 3 years follow-ups. MD-DFS. O-BL-DFS. DFT. CIR. O-BL-CIR. MD-CIR. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 3.87 (4.22) FD, 4.38 (4.36) PL. Age (months): 108.80 (17.21) FD, 110.16 (18.29) PL. DFT: 2.32 (2.14) FD, 2.73 (2.45) PL. SAR: 63.90 (27.63) FD, 61.63 (24.93) PL. TAR: 11.30 (5.10) FD, 10.38 (4.48) PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "Subjects living at the same street address were assigned to the same group to avoid the presence of two dentifrices in the same household." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Glass 1983

Methods	Stratified random allocation; double-blind; placebo-controlled; 16% drop out after 2.5 years (study duration = 2.5 years). Natural losses; no losses due to any adverse effects; any differential group losses not assessable
Participants	853 children analysed at 2.5 years (available at final examination). Age range at start: 7-11 years (average = 9). Surfaces affected at start: 2.1 DFS. Background exposure to fluoride: water. Year study began: 1976. Location: USA.
Interventions	FT (2 groups) versus PL (both SMFP groups = 1000 ppm F). School use/supervised, daily (appropriate toothpastes and toothbrushes also provided for home use). Abrasive system: IMP (main abrasive) in one SMFP and placebo toothpaste, Ca carbonate in the other SMFP toothpaste
Outcomes	2.5yNetDFS increment - (CA)cl+(ER)xr. Reported at 2.5 years follow-up. DFT. CIR. Side effects.
Notes	Participants randomised (n = 1017); numbers by group not reported. Baseline characteristics (age, DFS, DFT, SAR, TAR) 'balanced' (for DFT/DFS). Clinical (VT) caries assessment by 2 examiners (independently); diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 2 examiners (independently); diagnostic threshold = ER. Results of one examiner chosen (findings consistent throughout)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "....within strata, subjects were assigned group codes using computer generated random permutations of the digits 1, 2 and 3."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "One group of children brushed with a control dentifrice (no NaMFP), the other groups brushed with one of the dentifrices containing NaMFP." "The study was conducted in a double-blind basis until the results had been analysed."

		Comment: Use of placebo described, but blind outcome assessment not described but probably done since earlier report from same author clearly describe blind outcome assessment
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 16% (164/1017) in 2.5 years. Drop out by group: Not reported. Reasons for losses: Change of residence or school (no losses due to any adverse effect) Comment: Numbers lost were not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced between groups. Caries data pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (CA)cl+(ER)xr, reported at 2.5 years follow-up DFT. CIR. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 2.20 (2.91) FD1, 2.04 (2.63) FD2, 2.09 (2.53) PL. TAR: 11.40 (4.82) FD1, 11.11 (4.14) FD2, 12.20 (5.11) PL. SAR: 62.65 (25.54) FD1, 60.98 (22.27) FD2, 66.73 (26.63) PL. Age: 8.80 (1.49) FD1, 8.65 (1.41) FD2, 8.89 (1.46) PL. DFT: 1.59 (1.74) FD1, 1.51 (1.61) FD2, 1.61 (1.69) PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "Sufficient dentifrice was provided for home use by the entire family in order to minimize the chance of use of other than the dentifrice provided." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Hanachowicz 1984

Methods	Stratified random allocation; double-blind; placebo-controlled; 28% drop out after 3 years (study duration = 3 years). Natural losses and exclusions based on compliance; no differential group losses
Participants	945 children analysed at 3 years (available at final examination and co-operative). Age range at start: 10-12 years. Surfaces affected at start: 5.4 DMFS. Background exposure to fluoride: none reported. Year study began: 1979. Location: France.
Interventions	FT versus PL (SMFP group = 1500 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Al oxide trihydrate.
Outcomes	3yNetDMFS increment - (E)(CA)cl+xr. Reported at 3 years follow-up. DMFT. DMFS (U). O-DMFS. MD-DMFS. BL-DMFS. premolarDMFT. premolarDMFS. Proportion of children with new caries. Compliance.
Notes	Participants randomised (n = 1318). Baseline characteristics (DMFS) 'balanced'. Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA; radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included = E/U. Consistency of clinical and x-ray diagnosis assessed by duplicate examinations of 6% sample (inter-examiner reproducibility ratios 0.24 for clinical and 0.13 for x-ray; intra-examiner reproducibility 0.27 for clinical and 0.14 for x-ray)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quotes: "After baseline examination, the children were stratified with regard to their examiner, caries experience..... Each child was then randomly allocated to the test or toothpaste group. In order that only one type of toothpaste was used in each household an exception was made where two children from one household were participating ...it was arranged for them to have

		the same toothpaste." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "Neither the subjects nor the examiners knew who was receiving the test or the control toothpaste." "The control toothpaste was without sodium monofluorophosphate." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 19.5% in 3 years. Drop out by group: 186/659 FD, 185/659 FD. Reasons for losses: Family moved away (116), lack of co-operation (42) (by not brushing at least 5 times a week), refusal from final examination (30), refused consent for examination (21), moved to boarding school (18), discontinued (11), family difficulties (6), unacceptable taste of toothpaste (equally divided between groups {5}), illness (2), lost to follow-up (2), unacceptable abrasivity of toothpaste (not reported by group {1}) Comment: Numbers lost were not unduly high for length of follow-up, and showed no differential loss between groups. It is unclear if reasons for missing data are acceptable and balanced between groups. Caries data pertain to participants present and co-operative at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (E)(CA)cl+xr, reported at 3 years follow-up. DMFT. DMFS (U). O-DMFS. MD-DMFS. BL-DMFS. premolarDMFT. premolarDMFS. Proportion of children with new caries. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way

Hanachowicz 1984 (*Continued*)

Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 5.36 FD, 5.43 PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quotes: "In order that only one type of toothpaste was used in household, an exception was made where two children from one household were participating in the trial...it was arranged for them to have the same toothpaste." "The distribution of the toothpastes was the responsibility of three ladies...Their duty was to visit each home every 5 weeks to supply the whole family with sufficient amounts of toothpaste. This was considered important to prevent the use of other commercial toothpastes." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Held 1968

Methods	Stratified random allocation; double-blind; placebo-controlled; 65% drop out after 3 years (study duration = 3 years). Reasons for high drop out due to age range at which many leave the institutions; no differential group losses
Participants	63 children analysed at 3 years (available at final examination). Age range at start: 15-16 years. Surfaces affected at start: 14.3 DMFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: 1962. Location: France.
Interventions	FT versus PL (NaF-SnF_2 group = 1000 ppm F). Institution use/supervised, twice a day. Abrasive system: not clearly specified (silica used).
Outcomes	3yDMFS increment - (E) cl. Reported at 3 years follow-up. DMFT. Annual CAR.
Notes	Participants randomised (n = 178). Baseline characteristics (DMFS, DMFT) not balanced. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold not reported; state

	of tooth eruption included = E. Intra-examiner reproducibility checks done

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "...distributed at random to 2 groups." Comment: Translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "Double blind study." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Yes	Quotes: Overall drop out for length of follow-up: 64.6% in 3 years. Drop out by group: 54/86 FD, 61/92 PL. Reason for losses: Participants leaving school (due to age range at which many leave the institutions) Comment: Numbers lost are unduly high for length of follow-up. Although no differential losses between groups are apparent and the only reason given for the missing data is acceptable and balanced between groups, this balance may have occurred by chance, because sample size is too small. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Unclear	Outcomes reported: DMFS increment - (E) cl, reported at 3 years follow-up. DMFT. Annual CAR. Comment: Trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	No	Prognostic factors reported: DMFS: 16.9 FD, 11.7 PL; DMFT: 7.9 FD, 5.7 PL Comment: Initial caries (DMFS) appears imbalanced.

Held 1968 (*Continued*)

Free of contamination/co-intervention?	Unclear	Translation of report not detailed enough to make a categorical decision regarding any contamination and/or co-intervention

Held 1968a

Methods	Stratified random allocation; double-blind; placebo-controlled; 64% drop out after 3 years (study duration = 3 years). Reasons for high drop out due to age range at which many leave the institutions; no differential group losses
Participants	36 children analysed at 3 years (available at final examination). Age range at start: 15-16 years. Surfaces affected at start: 9.6 DMFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: 1961. Location: France.
Interventions	FT versus PL ($NaF\text{-}SnF_2$ group = 1000 ppm F). Institution use/supervised, twice a day. Abrasive system: not clearly specified (silica used).
Outcomes	3yDMFS increment - (E) cl. Reported at 3 years follow-up. DMFT. Annual CAR.
Notes	Participants randomised (n = 101). Baseline characteristics (DMFS, DMFT) not balanced. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold not reported; state of tooth eruption included = E. Intra-examiner reproducibility checks done

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "...distributed at random to 2 groups." Comment: Translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "Double blind study." Comment: Blind outcome assessment and use of placebo described

Held 1968a (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Quotes: Overall drop out for length of follow-up: 64.4% in 3 years. Drop out by group: 33/52 FD, 32/49 PL. Reasons for losses: Participants leaving school (due to age range at which many leave the institutions) Comment: Numbers lost are unduly high for length of follow-up. Although no differential losses between groups are apparent and the only reason given for the missing data is acceptable and balanced between groups, this balance may have occurred by chance, because sample size is too small. Caries data used in analysis pertain to participants present at final examinations
Free of selective reporting?	Unclear	Outcomes reported: DMFS increment - (E) cl, reported at 3 years follow-up. DMFT. Annual CAR. Comment: Trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	No	Prognostic factors reported: DMFS: 11.0 FD, 8.0 PL; DMFT: 5.6 FD, 4.6 PL Comment: Initial caries (DMFS) appears imbalanced.
Free of contamination/co-intervention?	Unclear	Translation of report not detailed enough to make a categorical decision regarding any contamination and/or co-intervention

Held 1968b

Methods	Stratified random allocation; double-blind; placebo-controlled; 62% drop out after 2 years (study duration = 3 years). Reasons for high drop out due to age range at which many leave the institutions; no differential group losses
Participants	32 children analysed at 2* years (available at final examination). Average age at start: 15 years. Surfaces affected at start: 10.2 DMFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: 1961. Location: France.

Held 1968b (*Continued*)

Interventions	FT versus PL (NaF group = 500 ppm F). Institution use/supervised, twice a day. Abrasive system: not clearly specified (silica used).
Outcomes	2y*DMFS increment - (E) cl. Reported at 2 and 3 years follow-ups. DMFT. Annual CAR.
Notes	Participants randomised (n = 85). Baseline characteristics (DMFS, DMFT) not balanced. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold not reported; state of tooth eruption included = E. Intra-examiner reproducibility checks done. *Results for 3 years follow-up not considered due to very high drop-out rate

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "...distributed at random to 2 groups." Comment: Translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "Double blind study." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	No	Quotes: Overall drop out for length of follow-up: 62.4% in 2 years. Drop out by group: 30/44 FD, 23/41 PL. Reasons for losses: Participants leaving school Comment: Numbers lost are unduly high for length of follow-up, with differential losses between groups (68%, 56%). Reasons for the missing data are not balanced between groups. Caries data used in analysis pertain to participants present at each examination
Free of selective reporting?	Unclear	Outcomes reported: DMFS increment - (E) cl, reported at 2 years follow-up. DMFT. Annual CAR.

Held 1968b (*Continued*)

		Comment: Trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	No	Prognostic factors reported: DMFS: 13.7 FD, 7.0 PL; DMFT: 7.1 FD, 4.3 PL Comment: Initial caries (DMFS) appears imbalanced.
Free of contamination/co-intervention?	Unclear	Translation of report not detailed enough to make a categorical decision regarding any contamination and/or co-intervention

Hodge 1980

Methods	Stratified random allocation; double-blind; placebo-controlled; 18% drop out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers: 158 left school, 14 withdrawn by own choice, 8 lack of co-operation; any differential group losses not assessable
Participants	799 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 7.3 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1976. Location: UK.
Interventions	FT (3 groups) versus PL (SMFP group = 1000 ppm F, both SMFP-NaF groups = 1450 ppm F) School use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use). Abrasive system: alumina (in placebo toothpaste, SMFP and in one SMFP-NaF toothpaste), dicalcium phosphate (in another SMFP-NaF toothpaste)
Outcomes	3yNetDFS increment - (E) (CA)cl+(DR)xr. Reported at 3 years follow-up. DMFT. Compliance.
Notes	Participants randomised (n = 979); numbers by group not reported. Baseline characteristics (DMFS, DMFT, SAR) 'balanced' (DFS baseline data not reported). Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E/U; radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = DR. Reproducibility checks done in 10% sample clinically and radiographically (ICC of incremental data between 0.92 and 0.97)

Hodge 1980 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Following the initial baseline examination, subjects were stratified according to school and sex, and randomly assigned to 1 of 4 groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "The trial was double-blind, neither the subjects nor the examiner knew who was receiving test or control products. The test and control dentifrices were indistinguishable in taste and appearance." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 18.4% (180/979) in 3 years. Drop out by group: Not reported. Reasons for losses: Changing school (184), moving away, withdrawal from study (14), exclusion due to lack of co-operation (7) Comment: Numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E) (CA)cl+(DR)xr, reported at 3 years follow-up. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFT: 4.82 (3.02) FD1, 4.62 (3.12) FD2, 4.40 (2.84) FD3, 4.37 (2.62) PL DMFS: 7.81 (5.76) FD1, 7.63 (6.23) FD2, 6.97 (4.91) FD3, 6.93 (4.59) PL

Hodge 1980 (*Continued*)

		SAR: 90.61 (20.13) FD1, 88.05 (22.00) FD2, 90.00 (22.95) FD3, 87.09 (22.36) PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "Dentifrices were used daily in school, either immediately following morning or afternoon registration, the children being under the care of brushing supervisors." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Homan 1969

Methods	Stratified random allocation; double-blind; placebo-controlled; 19% drop out after 1.7 years (study duration = 1.7 years). Reasons for attrition not described; any differential group losses not assessable
Participants	1874 children analysed at 1.7 years. Age range at start: 7-13 years. Surfaces affected at start: data not available nor obtainable. Background exposure to fluoride: none. Year study began: 1965. Location: Australia.
Interventions	FT (3 groups) versus PL (SnF_2 and APF toothpaste concentrations not reported nor obtainable) Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in one SnF_2 toothpaste, calcium-free abrasive in the other SnF_2 toothpaste and in the APF toothpaste; abrasive in placebo toothpaste not reported
Outcomes	Caries increment data not reported nor obtainable. Percentage DFS reductions by gender and age groups reported at 1.7 years follow-up
Notes	Participants randomised (n = 2317); numbers by group not reported. Baseline characteristics not reported. Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA; state of tooth eruption included = E; radiographic assessment; diagnostic threshold = DR. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**

Homan 1969 (*Continued*)

Adequate sequence generation?	Unclear	Quote: "...children were equally divided by sex into two groups.....and randomly allocated to one of four coded dentifrices." Quote from correspondence: "I do not recall method of randomisation." Comment: Not enough information provided.
Allocation concealment?	Unclear	Quote from correspondence: "Yes. The allocation of subjects to groups and the distribution of dentifrices was completely independent of the clinical examiners." Comment: Not enough information provided.
Blinding? All outcomes	Yes	Quote from correspondence: "Neither investigators nor participants knew the toothpaste used by individual participants. This was achieved by packaging of all dentifrices used in the study in identical plain tubes. .....examiners were not provided with any information of the dentifrice used by any child examined." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 19.1% in 1.7 years (443/2317). Drop out by group: Not reported. Reasons for losses: Not reported Comment: Numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced
Free of selective reporting?	Unclear	Outcomes reported: Caries increment (data not obtainable). Percentage DFS reductions by gender and age group reported at 1.7 years follow-up Comment: Trial protocol or full text report (methods) unavailable. Not enough information provided
Baseline characteristics balanced?	Unclear	No information provided.
Free of contamination/co-intervention?	Unclear	No information provided.

Howat 1978

Methods	Random allocation; double-blind; placebo-controlled; 12% drop out after 3 years (study duration = 3 years). Reasons for attrition described with respective total numbers (56 left school, 7 withdrawn by own choice, 2 lack of co-operation); no differential drop out - 65 failed to complete the trial, 39 in placebo group and 26 in fluoride group
Participants	495 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 7.4 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1974. Location: UK.
Interventions	FT versus PL (SMFP group = 1000 ppm F). School use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use). Abrasive system: silica zerogel.
Outcomes	3yNetDMFS increment - (E) (CA)cl+(DR)xr. Reported at 3 years follow-up. antDMFS. postDMFS. PF-DMFS. MD-DMFS. MD-BL-DMFS. DMFT. Compliance.
Notes	Participants randomised (n = 560); numbers by group not reported. Baseline characteristics (DMFS, DMFT, SAR) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E/U; radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = DR. Reproducibility checks done in 10% sample clinically and radiographically (ICC of incremental data between 0.96 and 0.99)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "The subjects were randomly allocated to test and control groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "The trial was double-blind with neither the subjects nor the examiner being aware who was receiving test or control

		products.....dentifrices were indistinguishable in taste and appearance and their composition varied only in their fluoride content." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 11.6% (in 3 years). Drop out by group: 26/279 FD, 39/281 PL. Reasons for losses: Changing school (56), withdrawal from study by choice (7), exclusion due to lack of co-operation (2) Comment: Numbers lost were not unduly high for the length of follow-up, with no differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (E) (CA)cl+(DR)xr, reported at 3 years follow-up. antDMFS. postDMFS. PF-DMFS. MD-DMFS. MD-BL-DMFS. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 7.42 (5.92) FD, 7.37 (5.59) PL. DMFT: 4.63 (3.32) FD, 4.65 (3.17) PL. SAR: 93.48 (19.74) FD, 92.81 (21.52) PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "Active and control dentifrices were used daily at school ...under the care of brushing supervisors... subjects were also given liberal supplies of the same dentifrice for home use....and independent checks of the dispensed dentifrices were carried out at regular intervals to assess the accuracy of the trial supervisors."

Howat 1978 (*Continued*)

		Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Jackson 1967

Methods	Random allocation; double-blind; placebo-controlled; 12% drop-out rate after 3 years (study duration = 3 years). Natural losses; no differential group losses
Participants	871 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 8.7 DMFS. Background exposure to fluoride: none reported. Year study began: 1962. Location: UK.
Interventions	FT versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: dicalcium pyrophosphate.
Outcomes	3yDMFS increment - (E+U)(CA)cl. Reported at 3 years follow-up. DMFT. Proportion of caries-free teeth/surfaces (by tooth type/ surface type) which developed caries. Proportion of children who complained of tooth staining. Compliance.
Notes	Participants randomised (n = 986). Baseline characteristics (age, DMFS, DMFT, TAR, level of treatment, staining) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E/U. Consistency of clinical diagnosis maintained by re-examination of 10% sample and calibration checks made against reserve examiner

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Method used was stratification according to sex, age and school.....Age was calculated to a standard date...boys were paired according to age so that 2 groups were obtained in which mean age and distribution of age was as identical as possible. A coin toss determined whether the group should be nominated O and N."

Jackson 1967 (*Continued*)

Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "The two groups were called O and N respectively. Whereas it was not known at the time which group was the control and which was the experimental group, it is now known that group O was that which received the stannous fluoride dentifrice." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 12% in 3 years. Drop out by group: 56/494 fluoride, 59/492 placebo. Reasons for losses: Not reported Comment: Numbers lost were not unduly high given length of follow-up with no differential losses between groups. It is unclear if the reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (E+U)(CA)cl, reported at 3 years follow-up. DMFT. Proportion of caries-free teeth/surfaces (by tooth type/surface type) which developed caries. Proportion of children who complained of tooth staining. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 8.42 (5.36) FD, 8.93 (5.87) PL. DMFT: 5.43 FD, 5.14 PL. Age: 11.7 FD, 11.7 PL. Treatment index: 65 % FD, 64% PL. TAR: 17.74 FD, 17.46 PL. Staining: 19.9 FD, 18.7 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "The duties of the home visitors were to provide a continuous supply of

		toothpaste to each home for each member of the family...to encourage co-operation.." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

James 1967

Methods	Random allocation; double-blind; placebo-controlled; 23% drop-out rate after 3 years (study duration = 3 years). Reasons for drop out described with respective total numbers: moved away, unco-operative, not present on examination day, disliked toothpaste, staining of teeth, others; no differential group losses
Participants	803 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 11 DFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: 1962. Location: UK.
Interventions	FT versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: dicalcium pyrophosphate.
Outcomes	3yDFS increment - (E) (CA)cl+(ER)xr. Reported at 3 years follow-up. DMFS. DFT. DMFT. postMD-DFS. Proportion of children with tooth staining. Compliance.
Notes	Participants randomised (n = 1043). Baseline characteristics (age, DFS, DFT, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. Diagnostic errors not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "These children were divided, by sex and by school, into 2 groups, using a random number technique for designation

		into groups. Each school therefore contained approximately equal numbers of test and control children, with similar representation of boys and girls."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "Children in the test group were supplied with stannous fluoride...dentifrice, while the control dentifrice was identical in colour, texture and flavour." "Nobody involved in the study, except the manufacturers, knew the identity of the test dentifrice, and the double-blind technique was maintained throughout the investigation." "All radiographs were read by one of us at the end of the study without knowledge of group allocation." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 23% in 3 years. Drop out by group: 124/530 FD, 116/513 PL. Reasons for losses: Moved away (59 FD, 59 PL), uncooperative (31 FD, 24 PL), not present on examination day (27 both groups), disliked toothpaste (3 FD, 2 PL), staining of teeth (2 FD, 2 PL), others (18 FD, 13 PL) Comment: Numbers lost were not unduly high given the length of follow-up with no differential losses between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced between groups. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E) (CA)cl+(ER)xr, reported at 3 years follow-up. DMFS. DFT. DMFT. postMD-DFS. Proportion of children with tooth staining. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-spec-

James 1967 (*Continued*)

		ified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 10.73 FD, 11.32 PL. Age: 11.35 FD, 11.35 PL. DFS: 10.73 FD, 11.32 PL. DFT: 6.12 FD, 6.48 PL. DMFT: 6.12 FD, 6.48 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "It was decided to supply the whole of the subject's family with the appropriate dentifrice to reduce the risk of other brands being used during the test period." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

James 1977

Methods	Stratified random allocation; double-blind; placebo-controlled; 19% drop out after 3 years (study duration = 3 years). Reasons for attrition not reported; exclusions based on presence in all follow-up examinations; any differential group losses not assessable
Participants	782 children analysed at 3 years (present for all examinations). Age range at start: 11-12 years. Surfaces affected at start: 11.2 DMFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: 1970. Location: UK.
Interventions	FT versus PL (SMFP group = 2400 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Al oxide trihydrate.
Outcomes	3yDMFS increment - (CA)cl+(ER)xr. Reported at 3 years follow-up. postMD-DMFS. O-DMFS. BL-DMFS. O-BL-MDDMFS. antDMFS.
Notes	Participants randomised (n = 964); numbers by group not reported. Baseline characteristics (age, gender, DMFS) 'balanced'. Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA; radiographic assessment (2 postBW); state of tooth eruption included not reported. Inter- and intra-examiner reliability for clinical and radiographic diagnosis revealed by re-examination

	of 10% sample

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "After baseline examination, they were stratified by sex, school and level of caries experience and randomly allocated to one or other of two groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "...one of the groups was supplied with the dentifrice containing fluoride, while the other received the paste without it. The two dentifrices were identical in taste, appearance and texture, and the trial was conducted on a double-blind basis." "After the analysis the code was broken...." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 18.9% (182/964) in 3 years. Drop out by group: Not reported. Reasons for losses: Exclusion due to absence from any examination Comment: Numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants who took part in all examinations
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (E+U)(CA)cl, reported at 3 years follow-up. postMD-DMFS. O-DMFS. BL-DMFS. O-BL-MDDMFS. antDMFS. Proportion of caries-free teeth/surfaces (by tooth type/ surface type) which developed

James 1977 (*Continued*)

		caries Proportion of children who complained of tooth staining. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 11.0 FD, 11.4 PL; Mean age: 11.9 FD, 12.0 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Unclear	Quote: "The appropriate pastes were distributed by home visitors to the children's homes.....they were not instructed to supervise or monitor the usage of the paste." Comment: Not enough information provided.

Kinkel 1972

Methods	Random allocation; double-blind; placebo-controlled; 25% drop-out rate after 3 years (study duration = 7 years). Reasons for drop out not described; any differential group losses not assessable
Participants	699 children analysed at 3 years. Average age at start: 10 years. Surfaces affected at start: 2.2 DMFS. Background exposure to fluoride: data not available. Year study began: in/before 1969. Location: Switzerland.
Interventions	FT versus PL (SMFP group F concentration not reported). Home use/unsupervised, daily frequency assumed. Abrasive system: not reported.
Outcomes	3yDMFS increment - (CA)cl+(DR)xr. Reported at 1, 2, 3, 4, 5 and 7 years follow-ups.
Notes	Participants randomised (n = 927); numbers by group not reported. Baseline characteristics (DMFS) 'balanced'. Clinical (V) caries assessment; diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW); diagnostic threshold = DR and ER

Risk of bias

Item	**Authors' judgement**	**Description**

Kinkel 1972 (*Continued*)

Adequate sequence generation?	Unclear	Quote: "...randomly allocated." Comment: Translation of report not detailed enough to make a categorical decision regarding sequence generation
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "Double blind study." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 24.6% (228/927) in 3 years. Drop out by group: Not reported. Reasons for losses: Not reported. Comment: Numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Unclear	Outcomes reported: DMFS increment - (CA)cl+(DR)xr, reported at 1, 2, 3, 4, 5 and 7 years follow-ups Comment: Trial protocol unavailable. Translation of methods section not detailed enough to make a categorical decision regarding selective outcome reporting
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 2.21 fluoride, 2.29 placebo Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Unclear	Translation of report not detailed enough to make a categorical decision regarding any contamination and/or co-intervention

Kleber 1996

Methods	Stratified random allocation; double-blind; placebo-controlled; 10% drop out after 1 year (study duration = 1 year). Main reasons for attrition: changes in residence, few exclusions for initiation of ortho treatment; no differential group losses
Participants	156 children analysed at 1 year (available at final examination). Age range at start: 10-11 years (average = 10.7). Surfaces affected at start: 4.2 DMFS.

Kleber 1996 (*Continued*)

	Background exposure to fluoride: none reported. Year study began: in/before 1994. Location: USA.
Interventions	FT(+Alrins) versus PL(+Alrins) ** (NaF toothpaste = 1100 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: silica.
Outcomes	1yDMFS increment - (CA)cl+(ER)xr. Reported at 0.6 and 1 year follow-ups. DMFT. Proportion of children remaining caries free. Proportion of children with new DMFS. Oral soft tissues lesions. Compliance.
Notes	Participants randomised (n = 174). Baseline characteristics (age, gender, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (postBW) by 2 examiners (independently); diagnostic threshold = ER. Reversals were small in both groups and equally common. Results of 1 examiner chosen (findings consistent throughout). **Rinsing with 500 ppm Al solutions performed daily at school in both relevant groups compared

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Subjects with evidence of caries activity were stratified according to age, gender...then randomly assigned to one of the balanced groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "A double blind comparison of three parallel groups of children... who used a test or placebo dentifrice for a twelve month period." "Radiographs were scored independently by each examiner at a later date.." Comment: Blind outcome assessment and use of placebo described

Incomplete outcome data addressed? All outcomes	Yes	Quote: Overall drop out for length of follow-up: 10% in 1 year. Drop out by group: 10/87 FD, 8/87 PL. Reasons for losses: Changes in residence, exclusion based on orthodontic treatment. Comment: Numbers lost were not unduly high given the length of follow-up with no differential losses between groups. Reasons for the missing outcome data are acceptable. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (CA)cl+(ER)xr, reported at 0.6 and 1 year follow-ups. DMFT. Proportion of children remaining caries free. Proportion of children with new DMFS. Oral soft tissues lesions. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 5.06 (0.58) FD, 4.78 (0.50) PL. DMFT: 3.31 (0.32) FD, 3.32 (0.27) PL. Age: 10.7 FD, 10.6 PL. Gender: 42 M, 45 F (FD); 42 M, 45 F (PL) . Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "Sufficient quantities of the respective products were provided for the participants and their families to use throughout the study. Participants with the same telephone number or address were assigned to the same group to avoid confusion with different test products in the same household. " Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Koch 1990

Methods	Stratified random allocation; double-blind; 10.9% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: relocation, compliance, others; no differential group losses
Participants	1035 children analysed at 3 years (available at final examination). Age range at start: (11-12 years). Surfaces affected at start: 9.9 DFS. Background exposure to fluoride: water <0.1 ppm F in community. Year study began: 1983. Location: Iceland.
Interventions	FT (5 groups) ** 250 ppm NaF 940 ppm F SMFP (no anti-calculus agent) 980 ppm F NaF (anti-calculus agent AHBP) 970 ppm F NaF (no anti-calculus agent) 940 ppm F NaF (anti-calculus agent AHBP). Home use/unsupervised, daily frequency assumed. Abrasive system: NaF silica; SMFP $CaHPO_4 2H_2O$.
Outcomes	3yNet DFS increment cl+xr Reported at 3 years follow-up. DFS increment by surface. DFT increment. New lesions only and restorations. Gingival health (gingival bleeding index). Compliance. Adverse reactions.
Notes	Participants randomised (n = 1161). Baseline characteristics (age, gender, DFS) 'balanced'. Clinical examinations performed by 2 examiners. Prior to each exam, both dentists examined 20 of their assigned children at random who were re-examined at least 1 day later to gauge consistency. ICC of at least 0.75 for acceptable reliability but exact values not stated. **1000 ppm F groups combined for analysis. Groups with anti-calculus agents excluded from analysis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: " ...randomly assigned to one of five treatment groups."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quotes: "...unsupervised double-blind study."

Koch 1990 (*Continued*)

		"...dentifrices were purchased and refilled in laminated tubes to ensure dentifrices were identical."
Incomplete outcome data addressed? All outcomes	Unclear	Comment: Reasons for attrition stated. Attrition rate was low after 3 years, 11% overall and similar in all toothpaste groups. Query compliance as reason for withdrawal and this negates ITT analysis, although only 23/1146 (2%) withdrew or were withdrawn for this reason
Free of selective reporting?	Yes	Comment: Results reported DFT, DFS, on different surface types
Baseline characteristics balanced?	Yes	Comment: Balance of age, gender, DFS.
Free of contamination/co-intervention?	Unclear	Comment: Insufficient information.

Lima 2008

Methods	Random allocation; single-blind; 25% drop-out rate after 1 year (study duration = 1 year) . Reasons for attrition: moved away from study area, children leaving nursery setting; no differential group losses
Participants	90 children analysed at 1 year (available at final examination). Age range at start: 2-4 years (average = 3). Surfaces affected at start: 5.1 DMFS. Background exposure to fluoride: water <0.3 ppm F in community. Year study began: in/before 2006. Location: Brazil.
Interventions	FT (500 ppm NaF) versus FT (1100 ppm NaF). School use/supervised daily frequency; home use/unsupervised, daily frequency assumed. Abrasive system: none reported.
Outcomes	Number of lesions becoming active/cavities or inactive by initial caries status
Notes	Participants randomised (n = 120). Baseline characteristics (age, gender, caries status) 'balanced'. Clinical caries assessment by single examiner; intra-examiner agreement assessed by second clinical exam in 10% of the sample after 15 days (Kappa 0.95)

Risk of bias

Item	**Authors' judgement**	**Description**

Lima 2008 (*Continued*)

Adequate sequence generation?	Unclear	Quote: "..randomised single-blind clinical trial."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quotes: "..randomised single-blind clinical trial" "The study was blinded only for the examiner..." Comment: Examiner was blinded to the treatment allocation.
Incomplete outcome data addressed? All outcomes	Yes	Comment: Reasons for attrition stated. Attrition rate was moderate after 1 year, 25% overall and similar in both toothpaste groups and unlikely to be related to intervention
Free of selective reporting?	Yes	Comment: All pre-specified outcomes reported (progression and arresting of lesions by toothpaste group and inital caries status)
Baseline characteristics balanced?	No	Comment: More males in 1100 ppm F group than females (26:18 versus 23:23), lower mean activated non-cavitated caries lesions in 500 ppm F group (2.5 (1.5 sd) versus 5.3 (6.5 sd))
Free of contamination/co-intervention?	Unclear	Comment: Possible contamination in school brushing sessions but unlikely under supervision. Possible contamination at home brushing

Lind 1974

Methods	Stratified random allocation; double-blind; placebo-controlled; 17% drop-out rate after 3 years (study duration = 3 years). Main reasons for drop out: moved away, sickness; exclusions based on presence in one interim examination; no differential group losses
Participants	1167 children analysed at 3 years (available at intermediate and final examination). Age range at start: 7-12 years (average = 10). Surfaces affected at start: 5.1 DMFS. Background exposure to fluoride: water. Year study began: 1970. Location: Denmark.
Interventions	FT versus PL (SMFP group = 2400 ppm F). Home use/unsupervised, daily frequency assumed.

Lind 1974 (*Continued*)

	Abrasive system: Al oxide trihydrate.
Outcomes	3yNetDMFS increment - (E+U) (CA)cl+(DR)xr. Reported at 1, 2, and 3 years follow-ups. DMFT. ECSI.
Notes	Participants randomised (n = 1407). Baseline characteristics (age, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 2 examiners; diagnostic threshold = CA/NCA; radiographic assessment (2 postBW) by 2 examiners; diagnostic threshold = ER/DR; state of tooth eruption included = E/U. Inter-examiner diagnostic error reported to have no effect on results; reversal rates small and similar in both groups

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "...children were stratified according to age, sex...The experimental and control groups were formed using random assignment. Children from the same household were allocated to the same treatment group to ensure that only one type of dentifrice entered the household during the trial period." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quote: "The trial was in...a double-blind design...The only persons who, of necessity, knew the allocation code of the dentifrices were the factory personnel who manufactured the dentifrices. The packages containing the dentifrices differed only in the color of the neutral text." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 17% in 3 years. Drop out by group: 127/719 fluoride, 113/688 placebo. Reasons for losses: Sickness, change of address and exclusions from analysis due to presence at the first, fourth and at least one other intermediate examination (not reported by group)

Lind 1974 (*Continued*)

		Comment: Numbers lost were not unduly high given the length of follow-up, and show no differential loss between groups. Reasons for missing data are acceptable, but it is unclear if they are balanced. Caries data used in the analysis pertain to participants present for the first, last and at least one other follow-up exam
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (E+U) (CA)cl+(DR)xr, reported at 1, 2, and 3 years follow-ups. DMFT. ECSI. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 9.32 FD, 9.24 PL. Mean age: 10.04 FD, 9.99 PL. DMFT: 5.51 FD, 5.44 PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "Children from the same household however, were allocated to the same treatment group to ensure that only one type of dentifrice entered the household during the trial period." Comment: There is sufficient indication overall of prevention of contamination/co-intervention.

Lu 1987

Methods	Stratified random allocation: double-blind; 55% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition not reported; any differential group losses not assessable
Participants	2055 children analysed at 3 years (available at final examination). Age range at start: 7-15 years (average = 10). Surfaces affected at start: 4.0 DMFS. Background exposure to fluoride: water <0.3 ppm F in community. Year study began: in/before 1983. Location: USA.

Interventions	FT (3 groups)** 1100 ppm F NaF 2800 ppm F SMFP 2800 ppm F NaF. Home use/unsupervised: daily frequency assumed. Abrasive system: silica.
Outcomes	3yDMFS increment - cl+xr Reported at 3 years follow-up. DMFT increment.
Notes	Participants randomised (n = 4494) Baseline characteristics (age, sex, DMFS, DMFT) 'balanced'. Analysis of covariance undertaken. Clinical examination by 1 examiner ** 2800 ppm F groups combined for analysis.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: " . .assigned at random . .."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quotes: " double-blind clinical study." "Toothbrushes and assigned dentifrices labelled with the subjects name and unique identification number were supplied by the study's sponsor in plain white 2,7 oz tubes every 6 months."
Incomplete outcome data addressed? All outcomes	No	Comment: No reasons for attrition reported and 3-year withdrawals are high 53%, 55%, 55% in the 1100, 2800 SMFP, 2800 NaF groups
Free of selective reporting?	Yes	Comment: DMFT, DMFS increments over 3 years.
Baseline characteristics balanced?	Yes	Comment: Balance of age, gender, DMFS, DMFT at baseline. Adjusted analysis (analysis of covariance)
Free of contamination/co-intervention?	Yes	Comment: Toothpaste given at school in named tube for home use for all the family. Contamination unlikely

Mainwaring 1978

Methods	Stratified random allocation; double-blind; placebo-controlled; 18% drop out (for all study groups combined) after 3 years (study duration = 3 years). Natural losses; any differential group losses not assessable
Participants	1107 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 7.9 DFS. Background exposure to fluoride: none reported. Year study began: in/before 1974. Location: UK.
Interventions	FT (2 groups) versus PL (both SMFP groups = 1000 ppm F). Home use/unsupervised, for 1 min, daily frequency assumed. Abrasive system: Ca carbonate in all toothpastes.
Outcomes	3yNetDFS increment - (E)(CA)cl+(ER)xr. Reported at 3 years follow-up. PF-DFS . postMD-DFS. CIR.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, SAR, DFS) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. Intra-examiner reproducibility checks for DFS in 10% sample (ICC for VT/XR over 0.95); error variance less than 5% of total variance; reversal rate less than 5% of observed DFS increment in all groups

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Participants were stratified according to age, sex and then randomly assigned to one of the treatment groups; children from the same family were assigned to the same group." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The study was of double-blind design, neither examiner nor participants knowing the identity of the treatment group to which the subjects had been allocated."

		"...control group were provided with non-fluoride toothpaste." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 18.4% 386/2104 in 3 years (for all 5 groups). Drop out by group: Not reported. Reasons for losses: Not reported Comment: Numbers lost were not unduly high given length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E)(CA)cl+(ER)xr, reported at 3 years follow-up. PF-DFS. postMD-DFS. Caries incidence rate. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: Mean age: 142.2 months (for each group). SAR: 87.73 (20.95) FG, 89.38 (20.94) PL. DFS: 8.19 (6.01) FG, 7.59 (5.56) PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "Sufficient toothpaste was delivered by specifically appointed home visitors at monthly intervals to the subjects' homes for total family requirements." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Mainwaring 1983

Methods	Stratified random allocation; double-blind; placebo-controlled; 19% drop out (for all study groups combined) after 4 years (study duration = 4 years). Natural losses, no losses due to any adverse effects; any differential group losses not assessable
Participants	682 children analysed at 4 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 6.9 DFS. Background exposure to fluoride: none reported. Year study began: in/before 1978. Location: UK.
Interventions	FT (2 groups)** versus PL (SMFP group = 1000 ppm F, SMFP-NaF group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca carbonate in all toothpastes.
Outcomes	4yNetDFS increment - (CA)cl+(ER)xr. Reported at 4 years follow-up. O-DFS. MD-DFS. postMD-DFS. MD-BL-DFS.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, SAR, DFS, FS) 'balanced'. Clinical (VT) caries assessment (FOTI used) by 1 examiner; diagnostic threshold = CA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. Intra-examiner reproducibility checks for DFS in 10% sample (ICC for VT/XR over 0.95). **Ca glycerophosphate/SMFP toothpaste group not considered (additional non-F active agent in this group only)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "The subjects were stratified according to age and sex, and assigned by means of a table of random numbers to one of four dentifrice groups. Siblings were assigned to the same group."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "At no time during the study was the identity of these groups known to the examiner, the subjects or anyone directly associated with the study." "Control group received dentifrice without

		fluoride." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 19% 210/1133 in 4 years (all 4 groups). Drop out by group: Not reported. Reasons for losses: Moving away from the area (and no losses due to any adverse effects) Comment: Numbers lost were not unduly high for the length of follow-up. Any differential losses between groups are not assessable. Reasons for missing outcome data are acceptable but it is unclear if they are balanced between groups. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (CA)cl+(ER)xr, reported at 4 years follow-up. O-DFS. MD-DFS. postMD-DFS. MD-BL-DFS. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 7.38 (0.37) FD1, 6.85 (0.35) FD2, 6.30 (0.34) PL. FS: 4.87 (0.26) FD1, 4.35 (0.26) FD2, 4.12 (0.27) PL. SAR: 91.60 (1.38) FD1, 93.04 (1.39) FD2, 90.49 (1.46) PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "The dentifrices were delivered to the subjects homes by home visitors calling at monthly intervals. At each visit, sufficient toothpaste was provided to satisfy the needs of the whole family." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Marks 1994

Methods	Stratified random allocation; double-blind; 31.8% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition not reported; no differential group losses
Participants	5474 children analysed at 3 years (available at final examiation). Age range at start: 6-14 (average = 9). Surfaces affected at start: 2.5 DMFS. Background exposure to fluoride: water <0.3 ppm F in community. Year study began: 1983. Location: USA.
Interventions	FT (5 groups) 1000 ppm F, 1500 ppm F, 2000 ppm F, 2500 ppm F all SMFP, 2000 ppm F NaF Home use/supervised toothbrushing at school, daily frequency. Abrasive system: silica.
Outcomes	3yDMFS increment - cl xr. Reported at 3 years follow-up. DMFT increment. DFS interproximal increment. Compliance.
Notes	Participants randomised (n = 8027). Baseline characteristics (age, gender, sound surfaces, DMFS, DMFT, DFS Inter) 'very well balanced'. Clinical caries assessment by 1 examiner. Analysis of covariance adjusting for baseline age, gender and DMFS. This is a re-analysis of a previous study with inclusion of 2000 ppm NaF group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: " . .block randomisation scheme was used to balance study groups for age, gender and baseline experience.. .."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quotes: "double-blind caries trial." "All dentifrices were identical in appearance and flavour." Comment: Although not stated examiners probably blinded to group
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Attrition rates ranged from 29.9 per cent in 1000 ppm group to 34.5 in 2000 ppm NaF group and the overall attrition rate over all groups was 31.8 per cent.

Marks 1994 (*Continued*)

		" Comment: No reasons given for losses.
Free of selective reporting?	Yes	Comment: DMFT, DMFS, DFS on inter-proximal surfaces increments over 3 years reported
Baseline characteristics balanced?	Yes	Comment: Balance of age, gender, baseline caries. Analysis of covariance adjusting for baseline age, gender and DMFS
Free of contamination/co-intervention?	Unclear	Comment: Daily supervised toothbrushing and normal home use so contamination unlikely. Insufficient information

Marthaler 1965

Methods	Random allocation; double-blind; placebo-controlled; 43% drop out (for all study groups combined) after 3 years (study duration = 7 years). Exclusions based on variation in toothpaste provision and presence in follow-up examinations; any differential group losses not assessable
Participants	269 children analysed at 3 years (present for all examinations). Age range at start: 6-9 years (average = 8). Surfaces affected at start: 3.3 DMFS. Background exposure to fluoride: salt (suboptimal). Year study began: 1958. Location: Switzerland.
Interventions	FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.
Outcomes	3yNetDFS increment - (CA)cl+(DR)xr. Reported at 1.5, 3, 5 and 7 years follow-ups. postMD-DFS. antMD-DFS. BL-DFS. O-DFS. DMFT. FT. FS. MT. Compliance.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, DMFS, DMFT) 'balanced' (DFS baseline data not reported)

	. Clinical (V) caries assessment by 1 examiner; diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = DR and ER; partial recording. Diagnostic errors not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Randomisation was carried out with the aid of the alphabetical class lists. The dentifrices were assigned to the children listed in this way, in a fixed order according to the code numbers printed on the tubes. The numbers in turn had been randomly assigned to the dentifrices A, B, C, D, E. In this way a random assignment of the dentifrices throughout the school was obtained." Comment: Not enough information provided.
Allocation concealment?	Yes	Central allocation described.
Blinding? All outcomes	Yes	Quotes: "...the examinations were carried out without knowledge of the dentifrice used by the children." "Tubes and content were only distinguishable with the aid of a small mark printed on the neutral tube." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 43% 256/589 drop out (for all 5 groups) after 3 years. Drop out by group: Not reported. Reasons for losses: Exclusions based on variation in toothpaste provision and presence in follow-up examinations (not reported by group) Comment: Numbers lost were high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present for all examinations

Free of selective reporting?	Yes	Outcomes reported: DFS increment - (CA)cl+(DR)xr, reported at 3 years follow-up. postMD-DFS. antMD-DFS. BL-DFS. O-DFS. DMFT. FT. FS. MT. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: Mean age: 7. 6 FD, 7.6 PL; DMFS: 3.45 FD, 3.19 PL; DMFT: 2.39 FD, 2.27 PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "In order to exclude exchange of tubes at the start of the study, two tubes of dentifrices...were sent to the parents. The parents were told that upon returning the empty tubes, their child could get new dentifrice at the local school dental clinic." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Marthaler 1965a

Methods	Random allocation; double-blind; placebo-controlled; 66% drop out (for all study groups combined) after 3 years (study duration = 3 years). Main reason for high drop out: children leaving public school on completion of last compulsory year; exclusions based on variation in toothpaste provision and presence in all follow-up examinations; any differential group losses not assessable
Participants	74 children analysed at 3 years (present for all examinations). Age range at start: 11-14 years (average = 13). Surfaces affected at start: 18.9 DMFS. Background exposure to fluoride: salt (suboptimal). Year study began: 1958. Location: Switzerland.
Interventions	FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, daily frequency assumed.

Marthaler 1965a (*Continued*)

	Abrasive system: IMP.
Outcomes	3yNetDFS increment - (CA)cl+(DR)xr. Reported at 3 years follow-up. postMD-DFS. antMD-DFS. BL-DFS. O-DFS. DMFT. FT. FS. MT. Compliance.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, DMFS, DMFT) 'balanced' (DFS baseline data not reported) . Clinical (V) caries assessment by 1 examiner; diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = DR and ER; partial recording. Diagnostic errors not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Randomisation was carried out with the aid of the alphabetical class lists. The dentifrices were assigned to the children listed in this way, in a fixed order according to the code numbers printed on the tubes. The numbers in turn had been randomly assigned to the dentifrices A, B, C, D, E. In this way a random assignment of the dentifrices throughout the school was obtained." Comment: Not enough information provided.
Allocation concealment?	Yes	Central allocation described.
Blinding? All outcomes	Yes	Quotes: "...the examinations were carried out without knowledge of the dentifrice used by the children." "Tubes and content were only distinguishable with the aid of a small mark printed on the neutral tube." Comment: Blind outcome assessment and use of placebo described

Incomplete outcome data addressed? All outcomes	No	Quote: Overall drop out for length of follow-up: 66.5% 246/370 (for all 4 groups) in 3 years. Drop out by group: Not reported. Reasons for losses: Children completing school; exclusions based on variation in toothpaste provision and presence in follow-up examinations, including those unsatisfactorily radiographed (not reported by group) Comment: Numbers lost are unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present for all examinations**.**
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (CA)cl+(DR)xr, reported at 1.5, 3, 5 and 7 years follow-ups. postMD-DFS. antMD-DFS. BL-DFS. O-DFS. DMFT. FT. FS. MT. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: Mean age: 12.8 FD, 12.5 PL. DMFS: 18.5 FD, 19.34 PL. DMFT: 9.93 FD, 10.25 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "In order to exclude exchange of tubes at the start of the study, two tubes of dentifrices...were sent to the parents. The parents were told that upon returning the empty tubes, their child could get new dentifrice at the local school dental clinic." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Marthaler 1970

Methods	Random allocation; placebo-controlled; 18% drop out (for all study groups combined) after 3 years (study duration = 3 years). Exclusions based on use of orthodontic bands and presence in all follow-up examinations; any differential group losses not assessable
Participants	100 children analysed at 3 years (present for all examinations). Age range at start: 6-7 years (average = 7). Surfaces affected at start: 1 DMFS. Background exposure to fluoride: salt (suboptimal). Year study began: 1966. Location: Switzerland.
Interventions	FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, twice/three times a day/680 times a year estimated. Abrasive system: IMP.
Outcomes	3yNetDFS increment - (CA)cl+(DR)xr. Reported at 1 and 3 years follow-ups. 1stmPF-DFS. 1stmMD-DFS. Compliance.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, DMFS, 1stmDMFS) 'balanced' (DFS baseline data not reported). Clinical (V) caries assessment by 2 examiners; diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 2 examiners; diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of the two examiners known from earlier work."

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "Children were paired according to their sequence in the class lists. The first and second child of each pair was allocated control and fluoride respectively when, in a table of random digits, an even digit was present. In the case of an odd random digit, the first child was allocated fluoride, and the second one control."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Unclear	Quotes: "... the first child was allocated fluoride, and the second one control." "Control group received exactly the same dentifrice, just without fluoride."

		Comment: Use of placebo described. No direct information on whether the examiners were blinded to treatment allocations, although it is probable that clinical and radiographic exams were done independently
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 18.3% 45/246 in 3 years (for all 4 groups). Drop out by group: Not reported. Reasons for losses: Exclusions based on use of orthodontic bands and presence in all follow-up examinations Comment: Numbers lost not unduly high for length of follow-up; any differential losses between groups not assessable. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at all examinations
Free of selective reporting?	Yes	Outcomes reported: DFS increment (CA)cl+(DR)xr, reported at 1 and 3 years follow-ups. 1stmPF-DFS. 1stmMD-DFS. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 1.14 (FD), 0.84 (PL); 1stmDMFS: 0.07 FD, 0.04 PL. Comment: Initial caries appears (DMFS) balanced.
Free of contamination/co-intervention?	Yes	Quote: "...in this case however siblings were both randomly allocated to either the fluoride or control dentifrice group to prevent the exchange of different types of toothpaste within the families." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Marthaler 1970a

Methods	Random allocation; placebo-controlled; 30% drop out (for all study groups combined) after 4 years (study duration = 4 years). Exclusions based on: use of orthodontic bands, and presence in all follow-up examinations; any differential group losses not assessable
Participants	43 children analysed at 4* years (present for all examinations). Age range at start: 7-9 years (average = 8). Surfaces affected at start: 2.3 DMFS. Background exposure to fluoride: salt (suboptimal). Year study began: 1966. Location: Switzerland.
Interventions	FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, twice/three times a day/800 times a year estimated. Abrasive system: IMP.
Outcomes	2y*NetDFS increment - (CA)cl+(DR)xr. Reported at 2 and 4 years follow-ups. 1stmPF-DFS. 1stmMD-DFS. Compliance.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, DMFS, 1stmDMFS) 'balanced' (DFS baseline data not reported). Clinical (V) caries assessment by 2 examiners; diagnostic threshold = CA and NCA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 2 examiners; diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of examiners known from earlier work." *F solution used by all children after 2 years (final 4 years results not considered)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Children were paired according to their sequence in the class lists. The first and second child of each pair was allocated control and fluoride respectively when, in a table of random digits, an even digit was present. In the case of an odd random digit, the first child was allocated fluoride, and the second one control."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Unclear	Quotes: ".....the first child was allocated fluoride, and the second one control." "Control group received exactly the same

		dentifrice, just without fluoride." Comment: Use of placebo described. No direct information on whether the examiners were blinded to treatment allocations, although it is probable that clinical and radiographic exams were done independently
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 29.7% 38/128 in 3 years (for all 4 groups). Drop out by group: Not reported. Reasons for losses: Exclusions based on use of orthodontic bands and presence at all follow-up examinations Comment: Numbers lost not unduly high for length of follow-up; any differential losses between groups not assessable. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at all examinations
Free of selective reporting?	Yes	Outcomes reported: DFS increment (CA)cl+(DR)xr, reported at 1 and 3 years follow-ups. 1stmPF-DFS. 1stmMD-DFS. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 2.00 (FD), 2.75 (PL); 1stmDMFS: 0.0 FD, 0.1 PL. Comment: Initial caries appears (DMFS) balanced.
Free of contamination/co-intervention?	Yes	Quote: "...in this case however siblings were both randomly allocated to either the fluoride or control dentifrice group to prevent the exchange of different types of toothpaste within the families." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Marthaler 1974

Methods	Random allocation; double-blind (A); placebo-controlled; 32% drop out after 6 years (study duration = 6 years). Exclusions based on presence in all follow-up examinations; differential group losses
Participants	109 children analysed at 6* years (present for all examinations). Age range at start: 6-9 years (average = 7.5). Surfaces affected at start: 2.6 DMFS. Background exposure to fluoride: in solution/salt (suboptimal). Year study began: 1966. Location: Switzerland.
Interventions	FT versus PL (AmF group = 1250 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP.
Outcomes	6y*NetDFS increment - (E) (CA)cl+(DR)xr. Reported at 2 and 6 years follow-ups. PF-DFS. postMD-DFS. antMD-B-DFS. DFT. Proportion of children with new DFS.
Notes	Participants randomised (n = 161). Baseline characteristics (DMFS, DMFT, FS, FT, TAR) 'balanced' (DFS baseline data not reported). Clinical (V) caries assessment by 2 examiners; diagnostic threshold = CA and NCA; state of tooth eruption included = E. Radiographic assessment (2 postBW) by 2 examiners; diagnostic threshold = DR and ER; partial recording. "Sufficient agreement of examiners known from earlier work." *Results at 6 years follow-up chosen (reported for all outcomes)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "The children were randomly assigned to either control or fluoride dentifrice. There were 9 pairs of siblings....each pair received either the control or fluoride dentifrice to avoid the provision of one family with different types of dentifrices." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.

Blinding? All outcomes	Yes	Quotes: "The tubes showed no indication whether they contained fluoride or not." "The type of dentifrice to which the child was assigned remained unknown to the examiner during the whole course of the study." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 32.3% in 6 years. Drop out by groups: 29/81 FD, 21/80 PL. Reasons for losses: Exclusions based on presence at all follow-up examinations Comment: Numbers lost were not unduly high for the length of follow-up, with a differential loss between groups (35.8% FD, 26.3% PL). It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at all examinations. Group losses unlikely to be related to intervention
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E) (CA)cl+(DR)xr reported at 2 and 6 years follow-ups. PF-DFS, postMD-DFS, antMD-B-DFS, DFT. Proportion of children with new DFS. Comment: Trial protocol not available. All pre-specified outcomes were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 2.59 FD, 2.54 PL; DMFT: 1.81 FD, 1.74 PL; FS: 2.07 FD, 1.80 PL; TAR: 10.47 FD, 10.88 PL Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "Two dentifrice tubes were mailed once a month to the children via their parents." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Mergele 1968

Methods	Stratified random allocation; double-blind; placebo-controlled; 22% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: natural losses to follow up; any differential group losses not assessable
Participants	387 children analysed at 3 years (available at final examination). Age range at start: 10-13 years (average = 11). Surfaces affected at start: 6.5 DMFS. Background exposure to fluoride: water. Year study began: in/before 1964. Location: USA.
Interventions	FT** versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in fluoride toothpaste, IMP in control toothpaste
Outcomes	3yNetDMFS increment - cl. Reported at 3 years follow-up. DMFT.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, SAR, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported. **Na N-lauroyl sarcosinate/SMFP toothpaste groups not considered (additional non-F active agent used in this group only)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "...population was stratified according to examiner, sex, age, permanent teeth present, past caries experience, oral hygiene rating and prior fluoride history. This stratified population was divided by means of random numbers into 4 balanced groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "All 4 dentifrices were packed in plain white tubes....the labelling was identical except for the name of the subject." "One group used a control toothpaste...did not contain active agent." "All clinical exams performed without reference to previous records."

Mergele 1968 (*Continued*)

		Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 22% 207/929 in 6 years (for all 4 groups). Drop out by groups: Not reported. Reasons for losses: Moved away Comment: Numbers lost were not unduly high for the length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are balanced, although the reasons are acceptable. Caries data used in the analysis pertain to participants present at final examinations
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl, reported at 3 years follow-up. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 6.42 (6.30) FD, 6.52 (6.25) PL. Age: 10.88 FD, 11.04 PL. DMFT: 3.95 (2.85) FD, 3.99 (3.02) PL. SAR: 86.30 (29.17) FD, 87.17 (28.88) PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "Additional dentifrice was provided for the family of a subject as were brushes. " Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Mitropolous 1984

Methods	Stratified random allocation; double-blind; 11% drop out. Reasons for attrition: lack of co-operation, own volition, left study schools, absent at time of final examination; no differential group losses
Participants	725 children analysed at 32 months (available at final examination). Age range at start 12-13 years (average = not reported). Surfaces affected at start: 7.7 DMFS.

Mitropolous 1984 (*Continued*)

	Background exposure to fluoride: water <0.1 ppm F in community. Year study began: in/before 1982. Location: UK.
Interventions	FT (2 groups) 1000 ppm F SMPF 250 ppm F SMPF. Home use/unsupervised but some children (n = 477) also brushed at school under supervision. Abrasive system: silica.
Outcomes	32m netDFS increment -cl+xr. Reported at 32 months follow-up. DMFT increment. DFS increment teeth erupting during the study. DMFT increment teeth erupting during the study.
Notes	Participants randomised (n = 818). Baseline characteristics (baseline DMFS, baseline DMFT, surfaces at risk) 'balanced'. Clinical caries assessment by 1 examiner.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: " . .stratified . . .before being randomly assigned to one of two study groups. " Comment: As author and statistician on study (HW) the children were randomised using random numbers from random number table
Allocation concealment?	Yes	Comment: Not mentioned in trial report, but as author and statistician (HW) this was done
Blinding? All outcomes	Yes	Quotes: "trial was double-blind neither the subjects not the examiner being aware who was receiving test or control products." "Control and test dentifrices were indistinguishable in taste and appearance."
Incomplete outcome data addressed? All outcomes	Yes	Quote: "..drop-out rate of 11 per cent (32 months)." Quote: "Of the 93 subjects who failed to complete the trial (51 in control and 42 in control), four were removed from the trial through lack of co-operation, three left trial of their own choice, 49 left the study schools and 37 were absent at the time of

Mitropolous 1984 (*Continued*)

		the examination." Comment: Low drop out (10% test, 12% control), and balanced between the groups. Reasons not connected to toothpaste
Free of selective reporting?	Yes	Comment: DMFT, DMFS clinical and combined with radiographs, erupting teeth
Baseline characteristics balanced?	Yes	Comment: Balance for baseline gender and caries comparable.
Free of contamination/co-intervention?	Yes	Comment: Pupils received dentifrice for home use through post. 3 of 5 schools had daily brushing sessions. This was checked at regular intervals to assess accuracy of trial supervisors.

Muhler 1955

Methods	Stratified random allocation; double-blind; placebo-controlled; 22% drop out after 1 year (study duration = 1 year). Reasons for attrition not reported; differential group losses
Participants	444 children analysed at 1 year (available at final examination). Age range at start: 6-16 years. Surfaces affected at start: 9.3 DMFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: in/before 1954. Location: USA.
Interventions	FT** versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: heat-treated Ca orthophosphate.
Outcomes	1yDMFS increment - cl+xr. Reported at 6 months and 1 year follow-ups. DMFT.
Notes	Participants randomised (n = 568). Baseline characteristics (DMFS) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Criteria for caries diagnosis reported to have been carefully standardized, diagnostic errors not reported. **NaF-heat treated Ca orthophosphate toothpaste group not considered (abrasive system known to be incompatible with NaF)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "After the initial exam of a subject, his total previous caries experience in terms of DMFS...was corrected by a factor corresponding to his dental age. This factor is one of a series of ratios....The corrected term was taken as an indication of caries expectancy and the subject assigned to one of nine classes on this basis. Within each class, he was assigned to one of the three treatment groups at random." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The examiner had no information about any child relative to group assignment, previous exam data, and so on." "The control dentifrice had no fluoride content." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 22% in 1 year. Drop out by group: 71/290 FD, 53/278 PL. Reasons for losses: Not reported Comment: Numbers lost were not unduly high for the length of follow-up, with differential losses between groups (24.5% FD, 19.1% PL). It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 6 months and 1 year follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factor reported: DMFS: 9.5 FD, 9.1 PL.

Muhler 1955 (*Continued*)

		Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "The entire family of each child was supplied with the dentifrice assigned to the child. Although this increased the cost of the study considerably, it provided additional assurance that the child would use only the dentifrice assigned." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Muhler 1962

Methods	Stratified random allocation; placebo-controlled; 30% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: not stated; no differential group losses
Participants	343 children analysed at 3 years (available at final examination). Age range at start: 6 to 18 years (average = 11). Surfaces affected at start: 13 DMFS. Background exposure to fluoride: water 0.5 ppm F in community. Year study began: in/before 1958. Location: USA.
Interventions	FT (SnF_2 = 1000 ppm F) versus PL. Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate.
Outcomes	3yDMFS increment - cl. Reported at 3 years follow-up. DMFT increment. DMFS increment. Cumulative caries increment. DMFT increment (children present at every examination). DMFS increment (children present at every examination). Proportion developing caries. Compliance.
Notes	Participants randomised (n = 492). 3% aged 17 ar 18 at start of study. Baseline characteristics (DMFS) comparable. Clinical caries assessment by 1 examiner.

Risk of bias

Item	**Authors' judgement**	**Description**

Muhler 1962 (*Continued*)

Adequate sequence generation?	Unclear	Quote: "..assigned at random to study groups after stratification . ."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	No	Quote: "Elements of blindness were compounded in that subjects from several different tests being conducted simultaneously appeared for examination in mixed order." Comment: Dentifrices were different. Test was described as "standard factory product. "
Incomplete outcome data addressed? All outcomes	Unclear	Comment: Moderate drop out (36 months 32% control 28% test), and balanced between the groups. No reasons for drop outs given
Free of selective reporting?	Yes	DMFS and DMFT increments.
Baseline characteristics balanced?	Yes	Comment: Stratified on dental age, past caries, age and gender. Balance for baseline sex, age and disease comparable
Free of contamination/co-intervention?	Unclear	Comment: Unclear but as dentifrices were very different it is unlikely that errors occurred over their use

Muhler 1970

Methods	Stratified random allocation; double-blind; placebo-controlled; 15% drop out after 1 year (study duration = 1 year). Reasons for attrition not reported; differential group losses
Participants	436 children analysed at 1 year (available at final examination). Age range at start: 5-16 years (average = 10). Surfaces affected at start: 10.3 DMFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: in/before 1967. Location: USA.
Interventions	FT** versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate.

Outcomes	1yDMFS increment - cl+xr. Reported at 6 months and 1 year follow-ups. DMFT.
Notes	Participants randomised (n = 510). Baseline characteristics (age, gender, DMFS) with some imbalance. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5-7 BW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported **Na N-lauroyl sarcosinate/SMFP toothpaste group not considered (additional non-F active agent used in this group only)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "...children were divided into 3 groups by separation of age, sex and DMFS, followed by randomization with restrictions to balance by three's within each cell. " Comment: Block randomisation performed.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The first group of children received placebo dentifrice...." "All dentifrices were furnished in plain white tubes with appropriate codes to identify the products." "At no time during the study did the examiner, the recorder or the clinical staff have any knowledge of the patient being examined or the product being used." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 15% in 1 year. Drop out by group: 45/246 FD, 29/264 PL. Reasons for losses: Not reported Comment: Numbers lost were not unduly high for the length of follow-up, but there is differential loss between groups (18% FD, 11% PL). It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain

Muhler 1970 (*Continued*)

		to participants present at final examination. Group losses unlikely to be related to intervention
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 6 months and 1 year follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 10.71 FD, 9.72 PL. Age: 10.33 FD, 10.16 PL. Gender: (106 M, 140 F) FD, (120 M, 144 F) PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "All the children were given new toothbrushes and sufficient dentifrice for their personal use and for their entire family." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Naylor 1967

Methods	Stratified random allocation; double-blind; placebo-controlled; 17% drop out (for all study groups combined) after 3 years (study duration = 3 years). Natural losses; any differential group losses not assessable
Participants	973 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 9.5 DMFS. Background exposure to fluoride: none reported. Year study began: 1961. Location: UK.
Interventions	FT** versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP (main abrasive) in SnF_2 toothpaste, dicalcium phosphate (dihydrate) in placebo toothpaste

Naylor 1967 (*Continued*)

Outcomes	3ycrudeDFS increment - (E+U) (CA)cl+(ER)xr. Reported at 3 years follow-up. DMFT. DMFS. postMD-DFS. 1stmoMD-DFS. Proportion of children with tooth staining.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, gender, SAR, DMFS, DMFT, postMD-DFS) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. Reversal rate less than 4% of observed DFS increment in all groups. High accuracy of diagnosis revealed by 10% sample checks (clinically and radiographically) **Na N-lauroyl sarcosinate/SMFP toothpaste group not considered (additional non-F active agent used in this group only)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Subjects were stratified according to age, sex, race....The stratified population was then divided into three groups A, B and C by means of random numbers."
Allocation concealment?	Yes	Quote: "A sealed envelope containing the allocation of the toothpastes to groups was placed in the safe of the Dean, Guy's Hospital Medical School before the trial began and not opened until analysis of third year results were complete."
Blinding? All outcomes	Yes	Quote: "Throughout the trial, each group received the corresponding toothpaste, the formular of which was unknown to both the examiner and the user.." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 16.9% (300/1789) in 3 years (for all 3 groups). Drop out by group: Not reported. Reasons for losses: "low drop out due to the fact that exams were completed before school leaving age." Comment: Numbers lost were not unduly high for the length of follow-up. It is un-

Naylor 1967 (*Continued*)

		clear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E+U) (CA)cl+(ER)xr, reported at 3 years follow-up. DMFT. DMFS. postMD-DFS. 1stmoMD-DFS. Proportion of children with tooth staining. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 9.45 (6.22) FD, 9.61 (6.43) PL. Gender: (55.5% F) FD, (56.2% F) PL. DMFT: 5.34 (2.84) FD, 5.51 (2.93) PL. SAR: 107.69 (20.46) FD, 106.91 (20.93) PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "In an attempt to ensure that the subjects did not use other pastes, enough was sent to provide for the needs of the whole family." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Naylor 1979

Methods	Stratified random allocation; double-blind; placebo-controlled; 20% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: not reported; any differential group losses not assessable
Participants	625 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 7.9 DFS. Background exposure to fluoride: none reported. Year study began: 1973. Location: UK.

Naylor 1979 (*Continued*)

Interventions	FT** versus PL (SMFP group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca carbonate.
Outcomes	3yDFS increment - (E) (CA)cl+(ER)xr. Reported at 3 years follow-up. DFT. DFT (U). O-BL-DFS. MD-DFS. CIR.
Notes	Participants randomised (numbers for relevant groups not reported). Baseline characteristics (age, SAR, TAR, DFS, DFT) 'balanced'. Clinical (VT) caries assessment (FOTI used) by 2 examiners (independently); diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 2 examiners (independently); diagnostic threshold = ER. Results of 1 examiner chosen (findings consistent throughout) **Ca glycerophosphate/SMFP toothpaste group not considered (additional non-F active agent used in this group only)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "The subjects were stratified according to age and sex and assigned by means of a table of random numbers to dentifrice groups."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "...at no time during the study was the identity of these groups known to the examiners or anyone directly associated with the study." "..control dentifrice same as for group 1 but without the fluoride." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 20.2% (239/1183) in 3 years (for all 3 groups). Drop out by group: Not reported. Reasons for losses: Not reported Comment: Numbers lost were not unduly high for the length of follow-up. It is un-

Naylor 1979 (*Continued*)

		clear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examinations
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E) (CA)cl+(ER)xr, reported at 3 years follow-up. DFT. DFT (U). O-BL-DFS. MD-DFS. CIR. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 7.36 FD, 7.62 PL Mean age: 11.94 (0.30) FD, 11.94 (0.30) PL. TAR: 17.6 FD, 17.66 PL. DFT: 4.99 FD, 5.08 PL. SAR: 95.84 FD, 96.21 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "Sufficient supplies were also left for all other members of the family." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

O'Mullane 1997

Methods	Stratified random allocation; double-blind; 17% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: only changing area of residence given; "this did not affect the balance between/among the toothpaste groups. "
Participants	3467 children analysed at 3 years (available at final examination). Age range at start: 11 to 12 years (average = not stated). Surfaces affected at start: 4.9 DMFS. Background exposure to fluoride: none reported but children from Anglesey were excluded as drinking water was fluoridated. Year study began: 1989. Location: UK.

Interventions	FT (4 groups) ** 1000 ppm NaF 1500 pppm NaF 1000 ppm NaF + 3% TMP 1500 pppm NaF + 3% TMP. Home use/unsupervised, daily frequency assumed. Abrasive system: silica.
Outcomes	3yDMFS increment cl (VT, FOTI)+xr. Reported at 3 years follow-up. DMFS increment cl. Compliance. Rinsing method.
Notes	Participants randomised (n = 4196). Baseline characteristics (DMFS) 'very good'. 2 clinical examiners re-examined 5% of their allocated and 5% of children allocated to the other clinician. Intra- and inter-reliability >0.93. Children who were caries free, dentally immature, or fitted with a fixed orthodontic appliance were excluded from participating in the study. **Factorial design, SMFP and trimetaphosphate (TMP). TMP groups excluded from analysis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quoted: "...prospective participants allocated sequential identification numbers" "...children randomly allocated to 1 of 4 toothpaste groups based on 4 stratifying factors."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quoted: "...double-blind" "radiographs were read by clinical examiners without reference to the clinical findings."
Incomplete outcome data addressed? All outcomes	Yes	3467/4196 children available for analysis. Attrition mainly due to moving away from area; did not alter balance between groups Comment: Reasonable drop-out rate for duration of study; unlikely to be due to intervention
Free of selective reporting?	Yes	DMFS increment. Clinical and radiographic assessments.

O'Mullane 1997 (*Continued*)

Baseline characteristics balanced?	Yes	Comment: No statistically significant difference in DMFS score at baseline for NaF only paste (8% lower in 1500 ppm group for combined NaF/NaF+TMP groups)
Free of contamination/co-intervention?	Yes	Comment: No apparent cause for concern regarding contamination. Sufficient toothpaste supplied for whole family so contamination unlikely

Peterson 1967

Methods	Stratified random allocation; double-blind; placebo-controlled; 16% drop out after 2 years (study duration = 3 years). Reasons for attrition not described; any differential group losses not assessable
Participants	954 children analysed at 2 years (available at this examination). Age range at start: 9-15 years. Surfaces affected at start: 14.3 DMFS. Background exposure to fluoride: data not available for fluoridation status of site. Year study began: in/before 1964. Location: USA.
Interventions	FT (2 groups) versus 'PL' (SnF_2 group = 1000 ppm F, APF group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in SnF_2 toothpaste, IMP in APF toothpaste, control toothpaste abrasive not reported
Outcomes	2y*DMFS increment - cl+xr. Reported at 1, 2 and 3 years follow-ups. DMFT. O-DMFS. BL-DMFS. MD-DMFS.
Notes	Participants randomised (n = 1136); numbers by group not reported. Baseline characteristics (DMFS, DMFT, dental age) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold not reported; state of tooth eruption included not reported; radiographic assessment (3 BW) by 1 examiner; diagnostic threshold not reported. Diagnostic errors not reported. *Results for 3 years follow-up not considered (not fully reported)

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Yes	Quote: "Age, sex and family records were supplied to a computing centre, where the subjects were grouped according to these factors and randomly assigned to three groups." Comment: Most likely computer generated sequence used.
Allocation concealment?	Yes	Sequence generated centrally.
Blinding? All outcomes	Yes	Quotes: "The double blind procedure was used throughout the study." "The dentifrice was supplied in white painted tubes and cartons with 1 of 3 code letters for each dentifrice group." "Group 3, a non-fluoride dentifrice.." "Radiographs were developed and read later..." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 16% (182/1136) in 2 years. Drop out by group: Not reported. Reasons for missing data: Not reported Comment: Numbers lost are not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination (though it was a 2-year report)
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 1, 2 and 3 years follow-ups. DMFT. O-DMFS. BL-DMFS. MD-DMFS Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 13.91 FD1, 13.65 FD2, 15.20 PL.

Peterson 1967 (*Continued*)

		DMFT: 7.63 FD1, 7.47 FD2, 8.02 PL. Dental age: 22.61 FD1, 22.62 FD2, 22.77 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "The participating children were periodically supplied with toothbrushes and a sufficient amount of dentifrice, the amount varying according to the size of the family." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Peterson 1979

Methods	Stratified random allocation; double-blind; placebo-controlled; 25% drop out after 2.5 years (study duration = 2.5 years). Natural losses; exclusions based on presence in all follow-up examinations; any differential group losses not assessable
Participants	712 children analysed at 2.5 years (present for all examinations). Age range at start: 8-12 years (average = 10). Surfaces affected at start: 2.9 DFS. Background exposure to fluoride: water. Year study began: 1971. Location: USA.
Interventions	FT (2 groups) versus PL (both SMFP groups = 1000 ppm F). School use/supervised, daily, (appropriate toothpastes also provided for home use). Abrasive system: Ca carbonate in one toothpaste and in placebo toothpaste, IMP in the other SMFP toothpaste
Outcomes	2.5yDFS increment - cl+xr. Reported at 2.5 years follow-up. DMFT. MD-DFS.
Notes	Participants randomised (n = 950); numbers by group not reported. Baseline characteristics (DFS, MD-DFS, DFT, SAR, TAR) 'balanced'. Clinical (VT) caries assessment (FOTI used) by 1 examiner; diagnostic threshold = CA; state of tooth eruption included not reported; radiographic assessment (postBW) by 1 examiner; diagnostic threshold = ER. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**

Peterson 1979 (*Continued*)

Adequate sequence generation?	Unclear	Quote: "The children were then stratified by age and sex and assigned at random to 1 of 3 dentifrice groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "Except for the absence of NaMFP, this placebo formulation was identical to that of experimental dentifrice." "The double blind technique was used, neither the examiner nor the subjects knowing to which dentifrice group they had been assigned." Comment: Blinding outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 25.1% 238/950 in 2.5 years (all groups). Drop out by group: Not reported. Reasons for losses: Mainly due to moving from the area, and exclusion based on presence at all examinations Comment: Numbers lost are not unduly high for length of follow-up. It is unclear if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present for all examinations
Free of selective reporting?	Yes	Outcomes reported: DFS increment - cl+xr, reported at 2.5 years follow-up. DMFT. MD-DFS. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 3.04 (3.50) FD1, 2.85 (2.92) FD2, 2.69 (2.66) PL. Age (months): 123.88 (13.01) FD1, 124. (11.94) FD2, 124.64 (12.11) PL TAR: 14.49 (5.10) FD1, 15.16 (5.35) FD2, 14.84 (5.24) PL.

Peterson 1979 (*Continued*)

		DFT: 2.23 (2.16) FD1, 2.06 (1.71) FD2, 2.05 (1.70) PL. SAR: 79.73 (26.22) FD1, 83.78 (27.28) FD2, 81.53 (26.37) PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "All subjects periodically received toothbrushes and dentifrices individually labelled for school and home use." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Piccione 1979

Methods	Random allocation; blinding not stated; placebo-controlled; drop-out rate 30% after 12 months (study duration = 1 year). Reasons for attrition not reported; no differential group losses
Participants	Age range at start: 6-11 years. Background exposure to fluoride: none reported. Year study began: in/before 1977. Location: Italy.
Interventions	FT (1000 ppm SMFP + 1500 ppm NaF) versus PL. Home use/unsupervised, daily frequency assumed. Abrasive system: not reported.
Outcomes	1yDMFS increment. DMFT. Compliance.
Notes	Participants randomised (50). Baseline characteristics (DMFS, DMFT) 'homogeneous'.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "...at random, subjects were assigned to one of two groups.."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Unclear	Comment: Insufficient information.

Piccione 1979 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	35/50 available for analysis. No reasons given; did not alter balance between groups 30% drop-out rate at 1 year.
Free of selective reporting?	Unclear	Caries indices reported. Unclear whether clinical and/or radiographic data reported
Baseline characteristics balanced?	Unclear	Comment: Baseline characteristics (DMFS, DMFT) 'homogeneous'
Free of contamination/co-intervention?	Unclear	Comment: Possible contamination. Sufficient toothpaste supplied for trial participant only

Powell 1981

Methods	Stratified random allocation; double-blind; placebo-controlled; drop-out rate not reported nor obtainable (study duration = 4 years). Reasons for attrition not reported; any differential group losses not assessable
Participants	125 children analysed at 4 years (subjects who developed caries). Age range at start: 12-14 years. Surfaces affected at start: 21.4 DMFS (from sample above). Background exposure to fluoride: none reported. Year study began: 1963. Location: Australia.
Interventions	FT (pp/Plsol) versus PL (pp/Plsol)** (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate.
Outcomes	Caries increment data not reported nor obtainable. Progression rate of initial carious lesions in MD surfaces of permanent posterior teeth at annual intervals (for 4 years)
Notes	Participants randomised (numbers not reported). Baseline characteristics (age, gender, DMFS) 'balanced'. Radiographic (postBW) enamel caries progression assessment by 1 examiner; state of tooth eruption included = E. High reproducibility of radiographic diagnosis (ICC = 0.91). **Prior prophylaxis with lava pumice followed by professional application of placebo solution performed every 6 months for 2 years in both relevant groups compared

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Unclear	Quote: "...subjects were assigned to four groups, using systematic random sampling by age, sex, class, and school." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Unclear	Quotes: "To determine the reproducibility of radiographic diagnoses, duplicate readings of radiographs taken at 48 month exam were made by the same examiner. To ensure that the examiner had no knowledge of the group, an independent observer randomly selected the subjects and nominated, at random, one or two lesions from each." "Participants issued with either test or control dentifrice for the full 4 year period of the study." Comment: Blinding of outcome assessor is mentioned but although it appears that only a small sample was assessed blindly for reproducibility
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: Not reported. Drop out by group: Not reported. Reasons for losses: Not reported Comment: It is unclear if numbers lost were high for length of follow-up, if there were any differential losses, and if reasons for missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants who had developed caries at final examination
Free of selective reporting?	Yes	Outcomes reported: Caries increment (data not obtainable). Progression rate of initial carious lesions in MD surfaces of permanent posterior teeth at annual intervals (for 4 years). Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 21.2 (0.90) FD, 21.5 (1.12) PL. Gender (M): 58 FD, 67 PL.

Powell 1981 (*Continued*)

		Age: 13.4 (0.03) FD, 13.4 (0.04) PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Unclear	No information provided.

Reed 1973

Methods	Stratified random allocation; double-blind; placebo-controlled; 28% drop out after 2 years (study duration = 2 years). Reasons for attrition not described; no differential group losses
Participants	1525 children analysed at 2 years (available at final examination). Age range at start: 6-13 years (average = 9). Surfaces affected at start: 3.3 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1970. Location: USA.
Interventions	FT (3 groups) versus PL (NaF groups = 1000 ppm F, 500 ppm F, 250 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate.
Outcomes	2yDMFS increment - cl+xr. Reported at 1 and 2 years follow-ups. DMFT.
Notes	Participants randomised (n = 2104). Baseline characteristics (age, gender, DMFS, DMFT) 'balanced' . Clinical (VT) caries assessment by 1 examiner; diagnostic threshold not reported; state of tooth eruption included not reported. Radiographic assessment (up to 7 BW) by 1 examiner; diagnostic threshold not reported. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "After initial clinical caries examination, children were placed in strata by age, sex and visual DMFS scores. Children within each strata were assigned by random permutation of four, to one of these dentifrices."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The dentifrices were similar in colour, flavour and other consumer proper-

		ties and were supplied in coded tubes. Participants were not aware of the contents of the assigned dentifrice." "The investigator was unaware of the dentifrice assignment for the participants during the examinations and radiographic interpretations." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 28% in 2 years. Drop out by group: 151/513 FD1, 150/537 FD2, 142/531 FD3, 126/523 PL. Reasons for losses: Not reported Comment: Numbers lost were not unduly high given length of follow-up with some differential losses between 2 groups (29.4% FD1, 27.9% FD2, 26.7% FD3, 24.1% PL). It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 1 and 2 years follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 3.36 (3.64) FD1, 3.39 (3.99) FD2, 3.47 (3.69) FD3, 3.46 (3.77) PL DMFT: 2.32 (2.17) FD1, 2.37 (2.41) FD2, 2.45 (2.22) FD3, 2.40 (2.26) PL Gender: (279 M, 252 F) FD1, (273 M, 264 F) FD2, (262 M, 251 F) FD3, (268 M, 255 F) PL Age: 9.02 FD1, 9.00 FD2, 9.02 FD3, 9.06 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "A family supply of the appropriate toothpaste (in coded tubes) and toothbrushes were distributed every 2 months..."

		Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Reed 1975

Methods	Stratified random allocation; double-blind; placebo-controlled; 39% drop out after 2 years (study duration = 2 years). Reasons for high drop out not described; no differential group losses
Participants	344 children analysed at 2 years (available at final examination). Age range at start: 8-13 years (average = 10). Surfaces affected at start: 5 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1968. Location: USA.
Interventions	FT versus PL (NaF group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate.
Outcomes	2yDMFS increment - cl+xr. Reported at 1 and 2 years follow-ups. DMFT.
Notes	Participants randomised (n = 567). Baseline characteristics (age, gender, DMFS, DMFT) with some imbalance. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold not reported; state of tooth eruption included not reported. Radiographic assessment (up to 7 BW) by 1 examiner; diagnostic threshold not reported. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Following the initial clinical caries examinations, the subjects were stratified by age, sex, visual DMFS and assigned at random to one of the following 2 dentifrices.." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "...to one of the following 2 dentifrices: control dentifrice....or test dentifrice....Both products were similar in

		colour, flavour, and other consumer properties." "A double blind study...." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 39% in 2 years. Drop out by group: 111/279 FD, 112/288 PL. Reasons for losses: Not reported Comment: Numbers lost were high given length of follow-up. No differential losses between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 1 and 2 years follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 4.83 FD, 5.19 PL. DMFT: 3.00 FD, 3.24 PL. Age: 9.73 FD, 9.70 PL. Gender: (143 M, 136 F) FD; (152 M, 136 F) PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "A family supply of the appropriate toothpaste (in coded tubes) and toothbrushes were distributed every 2 months... " Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Ringelberg 1979

Methods	Stratified random allocation; double-blind; placebo-controlled; 37% drop out after 2. 5 years (study duration = 2.5 years). Reasons for attrition not described; no differential group losses
Participants	556 children analysed at 2.5 years (available at final examination). Average age at start: 11 years. Surfaces affected at start: 4.2 DMFS. Background exposure to fluoride: none reported. Year study began: 1973. Location: USA.
Interventions	FT (2 groups) versus PL (2 groups) (AmF group = 1250 ppm F, SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in SnF_2 toothpaste and its placebo, not reported for AmF and its placebo
Outcomes	2.5yNetDMFS increment - (CA)cl + (DR)xr. Reported at 2.5 years follow-up. DMFT. Stain score.
Notes	Participants randomised (n = 888). Baseline characteristics (DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment (5 BW) by 2 examiners; diagnostic threshold = DR. State of tooth eruption included not reported. Reversal rate between 4% and 9% of observed caries increment in the groups

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "The baseline examinations were stratified by race and sex within each school, and ordered by increasing DMFT. Study group assignments were made by random permutations of seven within each stratum."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "A double-blind design was used; neither examiner nor subjects were aware of the type of treatment received." "The placebo preparations were all fully formulated like their active fluoride ingredient, but did not have the specific active fluoride ingredient."

		Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 37% in 2.5 years. Drop out by group: 111/295 FD1, 111/297 FD2, 52/147 PL1, 55/149 PL2. Reasons for losses: Not reported Comment: Numbers lost were not unduly high given length of follow-up with no differential losses between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Free of selective reporting?	Unclear	Outcomes reported: DMFS increment - (CA)cl+(DR)xr, reported at 2.5 years follow-up. DMFT. Stain score. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFT: 2.27 (0.17) FD1, 2.49 (0.20) PL1, 2.15 (0.18) FD2, 2.72 (0.28) PL2 DMFS: 4.21 (0.40) FD1, 4.30 (0.41) PL1, 3.69 (0.34) FD2, 4.95 (0.54) PL2 Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "Family members were supplied with the same dentifrice to encourage the use of the test products only by the study participants during the trial. The dentifrice was mailed to their homes to minimize the possibility of the dentifrice being lost, discarded or exchanged." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Ripa 1988

Methods	Stratified random allocation; double-blind; 34% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: change of residence (54%), withdrew (27.4%), orthodontically banded, absent at final examination; no differential group losses
Participants	2509 children analysed at 3 years (available at final examination). Age range at start: 10-12 years (average = 11). Surfaces affected at start: 3.8 DMFS. Background exposure to fluoride: water <0.1 ppm F in community. Year study began: 1982. Location: USA.
Interventions	FT (3 groups) 500 ppm SMFP + 500 ppm NaF 1000 ppm SMFP 1250 ppm SMFP + 1250 ppm NaF. Home use/unsupervised, daily frequency assumed. Abrasive system: IMP then dicalcium phosphate dihydrate for SMFP alone toothpaste; silica for combined SMFP NaF toothpaste
Outcomes	3yDMFS increment - cl Reported at 3 years follow-up. DMFS increment by surface. Compliance.
Notes	Participants randomised (n = 3785). Baseline characteristics (age, gender, baseline DMFS) 'comparable'. Clinical caries assessment by 2 calibrated examiners, whose results were pooled and analysed together. No values for reliability

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: " . .stratified according to age, gender, and initial caries score and were randomly assigned to one [of] three dentrifice groups." Quote: "randomly assigned to one of three dentifrice groups."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quote: "A double-blind protocol was used. " Quote: "dentrifices were identically packaged in plain white tubes except for subject's name and code number on a plain label."

Ripa 1988 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	2509/3785 available at 3 years. Attrition mainly due to moving away from area; did not alter balance between groups. 34% drop out at 3 years; unlikely to be due to intervention. Comment: Some participants were withdrawn.
Free of selective reporting?	Yes	Clinical assessments only.
Baseline characteristics balanced?	Yes	Comment: Comparable values for age, gender and DMFS at baseline
Free of contamination/co-intervention?	Yes	Comment: No apparent cause for concern regarding contamination. Participant's siblings assigned same toothpaste. Toothpaste clearly labelled with participant's name. Compliance assessed by telephone

Rule 1984

Methods	Stratified random allocation; double-blind; placebo-controlled; 24% drop out after 2 years (study duration = 2 years). Reasons for attrition not described; exclusions based on presence in all follow-up examinations; no differential group losses
Participants	876 children analysed at 2 years (present for all examinations). Age range at start: 9-12 years (average = 11). Surfaces affected at start: 8.6 DMFS. Background exposure to fluoride: none reported. Year study began: 1977. Location: USA.
Interventions	FT versus PL (SMFP group = 1000 ppm F). School use/supervised, daily, for 1 min (appropriate toothpastes also provided for home use). Abrasive system: silica zerogel.
Outcomes	2yDFS increment - (E+U) (CA)cl+(ER)xr. Reported at 1 and 2 years follow-ups. DFT. DMFS. DMFT. O-DFS. MD-DFS. Oral soft tissue lesions.

Rule 1984 (*Continued*)

Notes	Participants randomised (n = 1154). Baseline characteristics (age, gender, TAR, DMFS, DMFT, DS, DT) 'balanced' (DFS baseline data not reported). Clinical (VT) caries assessment (FOTI used) by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. Reproducibility checks done in 10% sample clinically and radiographically

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Subjects were stratified according to school, grade and sex and randomly assigned to one of two groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "One group received the sodium monofluorophosphate dentifrice, and other group the placebo. The study was conducted under double-blind conditions. " Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 24% in 2 years. Drop out by group: 135/595 FD, 143/559 PL. Reasons for losses: Exclusion based on presence at all examinations Comment: Numbers lost were not unduly high given length of follow-up with no differential losses between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present for all examinations
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E+U) (CA)cl+(ER)xr, reported at 1 and 2 years follow-ups DFT. DMFS. DMFT. O-DFS.

Rule 1984 (*Continued*)

		MD-DFS. Oral soft tissue lesions. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: Age: 11.30 FD, 11.24 PL; TAR: 13.84 FD, 13.37 PL; Gender: (320 M, 275 F) FD, (283 M, 276 F) PL; DMFS: 8.28 FD, 8.72 PL; DMFT: 5.21 FD, 5.48 PL; DS: 5.87 FD, 6.16 PL; DT: 3.55 FD, 3.78 PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "Sufficient quantity were provided to ensure adequate supply for both students and families throughout the year, including summer vacation." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Segal 1967

Methods	Stratified random allocation; double-blind; placebo-controlled; 23% drop out after 2 years (study duration = 2 years). Reasons for attrition not reported; slight differential group losses
Participants	648 children analysed at 2 years (available at final examination). Age range at start: 7-12 years. Surfaces affected at start: not reported. Background exposure to fluoride: none reported. Year study began: in/before 1964. Location: USA.
Interventions	FT versus PL (SnF_2 group = 1000 ppm F). School use/supervised, daily, (appropriate toothpastes also provided for home use). Abrasive system: IMP (mainly).
Outcomes	2yDFS increment - (CA)cl+xr. Reported at 1 and 2 years follow-ups. DFS (U).
Notes	Participants randomised (n = 845). Baseline characteristics (SAR) 'balanced'. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA. Radiographic assessment as a supplementary aid; diagnostic threshold not reported. State of tooth

Segal 1967 (*Continued*)

	eruption included E/U. Inter- and intra-examiner reproducibility checks done

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "In order to achieve adequate balance between test and control groups in terms of previous caries experience, all the children were classified in blocks according to school, age, sex.....Within each block the subjects were assigned at random to one of four subgroups..." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "...No reference to the findings of previous examinations was permitted at any time. The study was conducted as a double blind investigation. At the time of the initial exam, preassigned coded dentifrices were distributed to the children." "Control dentifrice contained no stannous fluoride." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 23% in 2 years. Drop out by group: 87/425 FD, 110/420 PL. Reasons for losses: Not reported Comment: Numbers lost were not unduly high given length of follow-up, but with some differential losses between groups (20% FD, 26% PL). It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (CA)cl+xr, reported at 1 and 2 years follow-ups. DFS (U). Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-spec-

Segal 1967 (*Continued*)

		ified way
Baseline characteristics balanced?	Yes	Prognostic factor reported: SAR: 77.34 FD, 76.49. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "Sufficient dentifrice was distributed to the panelists for family use." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Slack 1964

Methods	Random allocation; double-blind; placebo-controlled; 32% drop-out rate after 2 years (study duration = 2 years). Reasons for attrition: natural losses and other reasons; exclusions based on presence in all follow-up examinations; no differential group losses
Participants	719 children analysed at 2 years (present for all examinations). Age range at start: 11-13 years. Surfaces affected at start: not reported. Background exposure to fluoride: none reported. Year study began: 1962. Location: UK.
Interventions	FT versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, 3 times/day instructed but daily frequency assumed. Abrasive system: IMP in fluoride toothpaste, dicalcium phosphate (dihydrate) in placebo toothpaste
Outcomes	Caries increment data not reported nor obtainable. Proportion of carious teeth/surfaces (by tooth type) reported at 1 and 2 years follow-ups. Proportion of caries-free teeth/surfaces (by tooth type) which developed caries after each year. Proportion of children with tooth staining.
Notes	Participants randomised (n =1059). Baseline characteristics 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**

Adequate sequence generation?	Unclear	Quote: "The children, whose parents had accepted the invitation, were then allocated at random to the study and control groups. " Comment: Not enough information provided.
Allocation concealment?	Unclear	Comment: No information provided.
Blinding? All outcomes	Yes	Quotes: "The trial was conducted double-blind; the examiner, scribe and the subjects did not know who was receiving the stannous fluoride dentifrice. Furthermore, the identity of the test group was not disclosed until the analysis of the 2 year results had been completed." "Control dentifrice issued to control group. " Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 32% in 2 years. Drop out by group: 169/534 FD, 171/525 PL. Reasons for losses: Attrition: "three children (boys) who withdrew from the trial. In two cases no reason was given, but in the third case, it was stated that 'the toothpaste was staining the teeth'. This family was receiving the control paste", exclusions based on presence at all examinations Comment: Numbers lost were not unduly high given length of follow-up with no differential losses between groups. It is unclear if reasons for the missing outcome data are acceptable and balanced between groups. Caries data used in the analysis pertain to participants present for all examinations
Free of selective reporting?	Yes	Outcomes reported: Caries increment (data not obtainable). Proportion of carious teeth/surfaces (by tooth type) reported at 1 and 2 years follow-ups. Proportion of caries-free teeth/surfaces (by tooth type) which developed caries after each year. Proportion of children with tooth staining.

Slack 1964 (*Continued*)

		Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Unclear	Prognostic factors reported: Percentage DMFT: incisors: 8.6 FD, 8.8 PL; canines: 0.8 FD, 0.7 PL; premolar: 16.2 FD, 17.8 PL Percentage DMFS: incisors: 3.3 FD, 3.6 PL; canines: 0.2 FD, 0.2 PL; premolar: 4.8 FD, 4.7 PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "The aim was to maintain a constant and adequate supply of dentifrice and brushes for the whole family." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Slack 1967

Methods	Random allocation; double-blind; placebo-controlled; 21% drop-out rate after 3 years (study duration = 3 years). Reasons for drop out described with numbers: left school, moved away, staining of teeth, on parents request; exclusions based on presence in all follow-up examinations; no differential group losses
Participants	696 children analysed at 3 years, all female (present for all examinations). Average age at start: 11 years. Surfaces affected at start: 8.9 DFS. Background exposure to fluoride: none reported. Year study began: 1963. Location: UK.
Interventions	FT versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP (dicalcium phosphate (dihydrate) in placebo toothpaste also)
Outcomes	3yNetDFS increment - (E)(CA)cl. Reported at 3 years follow-up. DFT. DMFS. DMFT. postMD-DFS. Proportion of children with tooth staining.

Notes	Participants randomised (n = 886). Baseline characteristics (age, dental age, DFS, DFT, DMFS, DMFT, TAR) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. Consistency of clinical diagnosis maintained by re-examination of 10% sample and calibration checks made against reserve examiner

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "As permission was received for participation, each child was randomly allocated within his own school, to the control and study groups." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "This 3 year clinical trial.....was conducted double-blind." "The films from all 4 examinations were read at the end of the trial by one examiner, and charted seperate from the clinical examination data. The examiner did not know to which group the films belonged." "The control dentrifice was essentially the insoluble metaphosphate silica paste as used for the study product." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Yes	Quote: Overall drop out for length of follow-up: 21% in 3 years. Drop out by group: 87/443 FD, 103/443 PL. Reasons for losses: Staining: 6 FD, 1 PL; moved away: 29 FD, 39 PL, changed school: 5 FD, 5 PL; parents' request: 5 FD, 6 PL; exclusion based on presence at all examinations: 42 FD, 52 PL Comment: Numbers lost were not unduly high given length of follow-up with no differential losses between groups. Reasons for the missing outcome data are acceptable and balanced, except for staining, which although related to the intervention, would not affect outcome due to very small

Slack 1967 (*Continued*)

		loss (causing no obvious imbalance). Caries data used in the analysis pertain to participants present at all examinations
Free of selective reporting?	Yes	Outcomes repoted: DFS increment - (E)(CA)cl, reported at 1, 2 and 3 years follow-ups. DFT. DMFS. DMFT. postMD-DFS. Proportion of children with tooth staining. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 8.72 FD, 9.13 PL. DFT: 6.21 FD, 6.06 PL; DMFS: 12.36 FD, 12.25 PL. DMFT: 6.82 FD, 6.86 PL; Age: 12 FD, 12 PL. Dental age: 24.80 FD, 24.33 PL; TAR: 18.61 FD, 18.27 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "The dentifrices were supplied by mail to the participants and their families. ...One tube per person per month in each family was supplied..." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Slack 1967a

Methods	Random allocation; double-blind; placebo-controlled; 21% drop-out rate after 3 years (study duration = 3 years). Reasons for drop out described with numbers: left school, moved away, staining of teeth, on parents request; exclusions based on presence in all follow-up examinations; no differential group losses
Participants	757 children analysed at 3 years, all female (present for all examinations). Age range at start: 11-12 years. Surfaces affected at start: 7 DFS. Background exposure to fluoride: none reported. Year study began: 1962. Location: UK.

Slack 1967a (*Continued*)

Interventions	FT versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: dicalcium pyrophosphate.
Outcomes	3yDFS increment - (E) (CA)cl. Reported at 3 years follow-up. DFT. DMFS. DMFT. postMD-DFS. Proportion of children with tooth staining.
Notes	Participants randomised (n = 961). Baseline characteristics (age, dental age, DFS, DFT, DMFS, DMFT, TAR) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included = E/U. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. Consistency of clinical diagnosis maintained by re-examination of 10% sample and calibration checks made against reserve examiner

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "These girls were randomly allocated within the 18 schools to either the control or study group." Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The films from all were read at the end of the trial by one examiner, and charted seperate from the clinical examination data. The examiner did not know to which group the films belonged." "The dentifrices were wrapped in non-proprietary wrapping and package identified by the manufacturer's code." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Yes	Quote: Overall drop out for length of follow-up: 21% in 3 years. Drop out by group: 103/479 FD, 101/482 PL. Reasons for losses: Staining: 2 FD, 0 PL; moved away: 35 FD, 32 PL, changed school: 2 FD, 3

		PL; parents' request: 7 FD, 3 PL; exclusion based on presence at all examinations: 57 FD, 63 PL Comment: Numbers lost were not unduly high given length of follow-up with no differential losses between groups. Reasons for the missing outcome data are acceptable and balanced, except for staining, which although related to the intervention, did not affect outcome (very small loss causing no real imbalance). Caries data used in the analysis pertain to participants present at all examinations
Free of selective reporting?	Yes	Outcomes reported: DFS increment - (E)(CA)cl, reported at 1, 2 and 3 years follow-ups. DFT. DMFS. DMFT. postMD-DFS. Proportion of children with tooth staining. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 7.18 FD, 6.76 PL; DFT: 4.90 FD, 4.75 PL; DMFS: 9.23 FD, 9.23 PL; DMFT: 5.31 FD, 5.24 PL; Age: 12 FD, 12 PL; Dental age: 23.98 FD, 23.62 PL; TAR: 19.06 FD, 18.87 PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "To aid co-operation and the opportunity for personal contact, two home visitors were appointed to deliver the products personally. The toothpastes were delivered to the homes of the subjects in quantities sufficient to provide a constant supply for all members of the household." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Slack 1971

Methods	Random allocation; double-blind; placebo-controlled; 33% drop-out rate after 3 years (study duration = 3 years). Main reasons for drop out: moved away, left school, away on examination day, disliked toothpaste taste, brown staining of teeth; no differential group losses
Participants	1110 children analysed at 3 years (available at final examination). Age range at start: 11-12 years. Surfaces affected at start: 11.6 DMFS. Background exposure to fluoride: none reported. Year study began: 1965. Location: UK.
Interventions	FT (3 groups) versus 'PL' (Both SnF_2 groups = 1000 ppm F, APF group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: IMP in one SnF_2 toothpaste and in APF toothpaste, dicalcium pyrophosphate in another SnF_2 toothpaste; control toothpaste abrasive not reported.
Outcomes	3yCrudeDMFS increment - (CA)cl+(ER)xr. Reported at 3 years follow-up.
Notes	Participants randomised (n = 1665). Baseline characteristics (age, gender, DMFS, previous F toothpaste use) 'balanced'. Clinical (VT) caries assessment by 1 examiner; diagnostic threshold = CA; state of tooth eruption included not reported. Radiographic assessment (2 postBW) by 1 examiner; diagnostic threshold = ER. Consistency of clinical diagnosis revealed by 10% sample checks at each examination

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "The children were randomly allocated to groups, apart from brothers, sisters and others living in the same household who were allocated to the same group. " Comment: Not enough information provided.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "Dentifrices were made up in large white tubes marked only with a double letter codes... 3 fluoride and 1 non-fluoride." "At the time of examination, the examiner had no knowledge of the group to which any child belonged." Comment: Blind outcome assessment and use of placebo described

Incomplete outcome data addressed? All outcomes	Unclear	Quote: Overall drop out for length of follow-up: 33% in 3 years. Drop out by group: 163/423 FD1, 153/422 FD2, 130/412 FD3, 119/408 PL. Reasons for losses: Staining of teeth: 3 FD, 4 PL; unpleasant taste (mainly fluoride groups); moved away, changed school, away on examination day Comment: Numbers lost were not unduly high given length of follow-up with differential losses between groups (FD1 39%, FD2 34%, FD3 32%, PL 29%). It is unclear if reasons for the missing outcome data are acceptable and balanced. Caries data used in the analysis pertain to participants present at final examination. Group losses unlikely to be related to intervention
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (CA)cl+(ER)xr, reported at 3 years follow-up. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 12.20 FD1, 11.59 FD2, 10.87 FD3, 11.81 PL. Mean age: 12 years (all groups). Gender (M/F%): 52.9/47.8 FD1, 52.6/47.4 FD2, 53/47 FD3, 52.6/47.4 PL Fluoride users (%): 10.4 FD1, 11 FD2, 10.8 FD3, 10.1 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "...children joining the trial were randomly allocated to 5 groups, apart from brothers, sisters and others living in the same household who were allocated to the same group." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Sonju Clasen 1995

Methods	Cluster random allocation by kindergarten; single-blind (clinical assessors). 46% drop out after 22 months (study duration 22 months). Reasons for attrition: change in residence or moving to new kindergarten in the area; no differential group losses
Participants	172 children analysed at 22 months (available at final examination). Age range at start: 2-5 years (average = 4). Surfaces affected at start: 2.2 dmfs. Background exposure to fluoride: none reported. Year study began: August 1991. Location: Germany.
Interventions	FT (250 ppm NaF, 1450 ppm NaF). School use/supervised daily brushing. Abrasive system: silica.
Outcomes	2ydmfs increment - cl. Reported at 2 years follow-up. dmft increment. ds. fs. dt. ft. Proportion remaining caries free.
Notes	Participants initially randomised in 10 clusters (n = 319). Baseline characteristics (age, gender, proportion caries free, dmft) comparable. Clinical (VT) caries assessments by 1 examiner. Clinical data only. Intra-examiner reliability on 30 children. Scott's pi for dmfs 0.89 Cluster-randomised trial reported as individual randomised.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: " . .Salzgitter was divided into five geographical areas from which two kindergartens were randomly assigned."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Unclear	Quote: "Neither the kindergarten children nor the kindergarten staff were aware of the purpose of the study, nor were they told that a toothpaste containing different amount of fluoride was given to other kindergartens." Quote: "At the time of the examinations the examiner was not aware if the child belonged to the study group or not."

Sonju Clasen 1995 (*Continued*)

		Comment: Clinical assessors blinded, but unclear whether participants and kindergarten staff blinded. Participants very young children so knowledge of intervention unlikely to influence outcome
Incomplete outcome data addressed? All outcomes	No	83/155 available for examination in low fluoride group; 89/164 available in the high fluoride group. Total drop-out rate of 46% Quote: "The majority of children who failed to complete the study either went to new kindergartens in the area or to a lesser extent change residence." Comment: High drop-out rate, mainly due to change of kindergarten or change of residence. Although reasons for drop outs unlikely to be due to intervention, high rates could influence results
Free of selective reporting?	Yes	Comment: Routine caries diagnosis. No radiographs taken; clinical examination only. All possible caries indices are reported: ds, fs, dmfs, dt ft, dmft, caries free. Data on different surfaces also presented
Baseline characteristics balanced?	Unclear	Comment: Baseline data only available for those assessed at 22 months Comment: As a cluster-randomised trial more information about the individual clusters is required to evaluate this
Free of contamination/co-intervention?	Yes	Comment: Unlikely as cluster randomised. All children used 250 ppm F toothpaste at home but undertook supervised daily brushing with study toothpastes in kindergarten. Children using fluoride supplements were excluded from the study

Stephen 1988

Methods	Stratified random allocation; double-blind; 23% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: excluded for non-compliance, withdrew, absent at final examination; no differential group losses
Participants	2317 children analysed at 3 years (available at final examination). Age range at start: 11-14 years (average = 12). Surfaces affected at start: 10.2 DMFS. Background exposure to fluoride: not stated.

Stephen 1988 (*Continued*)

	Year study began: 1983. Location: UK.
Interventions	FT (6 groups)** 1000 ppm SMFP 1500 ppm SMFP 2500 ppm SMFP 1000 ppm SMFP + 0.5% ZCT 1500 ppm SMFP + 0.5% ZCT 2500 ppm SMFP + 0.5% ZCT. Home use/unsupervised, daily frequency assumed. Abrasive system: alumina trihydrate.
Outcomes	3yNetDMFS increment - cl+xr. Reported at 3 years follow-up. DMFS increment by gender, clinician, tooth type, surface type
Notes	Participants randomised (n = 3044). Baseline characteristics (baseline DMFS) 'well balanced'. Clinical (VT) caries assessment undertaken by 2 calibrated examiners. 5% re-examined annually by allocated examiner and 5% by alternate examiner. Good intra- (0.92 to 0. 99 clinical, 0.98 to 0.99 radiographic) and inter-examiner (0.92 to 0.97 clinical, 0.99 radiographic) reliability **Equivalent fluoride concentration groups combined for analysis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "...prospective participants were allocated sequential numbers ... one clinician saw all odd-numbered ... the other all even-numbered ... [following baseline examination] children were allocated to one of six toothpaste groups by stratified randomisation ... using computer constructed random number tables."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quote: "double blind." Quote: "The dentrifices were supplied in colour coded tubes, the particular composition of the toothpastes being unknown to the clinicians, home visitors or subjects."
Incomplete outcome data addressed? All outcomes	Unclear	2317/3044 available for analysis. Due to leaving the trial, excluded for non-compliance, or absent at examination; did not al-

Stephen 1988 (*Continued*)

		ter balance between groups 23% drop-out rate at 3 years. Comment: Some participants were excluded for non-compliance.
Free of selective reporting?	Yes	DMFS increment. Clinical and radiographic assessments.
Baseline characteristics balanced?	Yes	Comment: Baseline caries scores from combined clinical/radiographic data comparable
Free of contamination/co-intervention?	Yes	Comment: No apparent cause for concern regarding contamination. Sufficient toothpaste supplied for whole family

Stephen 1994

Methods	Stratified random allocation; double-blind; 18% drop out (for all study groups combined) after 3 years (study duration = 3 years). Reasons for attrition: change of residence/withdrew (8.4%), absent at final examination (8.6%), fixed orthodontic applicance (1%) ; no differential group losses
Participants	3517 children analysed at 3 years (available at final examination). Age range at start: 11-12 years (average = 12). Surfaces affected at start: 7.4 DMFS Background exposure to fluoride: not stated. Year study began: 1988. Location: UK.
Interventions	FT (6 groups)** 1000 ppm SMFP 1500 ppm SMFP 1000 ppm NaF 1500 ppm NaF 1000 ppm NaF + 3% TMP 1500 ppm NaF + 3% TMP. Home use/unsupervised, daily frequency assumed. Abrasive system: silica.
Outcomes	3yNetDMFS increment - cl (VT+FOTI). Reported at 3 years follow-up. DMFS increment - xr. Subgingival calculus. Plaque. Oral pathologies (assessed but not reported). Oral hygiene habits (assessed reported in Chestnutt 1998).

Stephen 1994 (*Continued*)

	Compliance.
Notes	Participants randomised (n = 4294). Selected for participation on grounds of caries in the permanent dentition and dental maturity. Baseline characteristics (DMFS) comparable. 42% of children were radiographed at baseline and 86% at final examination (36% at both); being restricted initially for ethical reasons. Clinical (VT and FOTI) caries assessment by 2 examiners. 5% of children re-examined at each annual examination. Intra- and inter-examiner reliabilities of 0.93 to 0.95 (reliability coefficient) and 0.91 to 0.97 by Kappa for DMFS. All radiographs read by 1 examiner. 5% of radiographs re-assessed for reproducibility. Kappa 0.87 DFS. Analysis adjusted for examiner, baseline caries, baseline calculus, active type and fluoride level, plus all 2-way interactions. ** TMP groups excluded from analysis. Groups with equivalent fluoride concentration combined for analysis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: " ...subjects allocated by a stratified randomisation process."
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quote: "...they [toothpastes] could not be differentiated by appearance, flavour, or other in-use characteristics. The dentifrices were supplied to participants in coded tubes, ensuring the double-blind nature of the study." Quote: "double blind" "carried out under strict observance of the double-blind principle." Comment: Dentrifices could not be identified by appearance, flavour or any other characteristic
Incomplete outcome data addressed? All outcomes	Yes	Low attrition rate, mainly due to moving away from area or absent from school on day of examination; did not alter balance between groups 18% drop-out rate at 3 years; unlikely to be due to intervention
Free of selective reporting?	Yes	Clinical and radiographic assessments.

Stephen 1994 (*Continued*)

Baseline characteristics balanced?	Yes	Comment: Baseline caries scores comparable.
Free of contamination/co-intervention?	Yes	Comment: No apparent cause for concern regarding contamination. Sufficient toothpaste supplied for whole family

Stookey 2004

Methods	Stratified random allocation; double-blind; 29% drop out (for all study groups combined) after 2 years (study duration = 2 years). Reasons for attrition (84% of non-completers): change of residence, withdrew, absent at final examination, fixed orthodontic applicance; no differential group losses
Participants	683 children analysed at 2 years (available at final examination). Age range at start: 9-12 years (average = 10). Surfaces affected at start: 8.0 DMFS (Examiner A). Background exposure to fluoride: water <0.1 ppm F in community. Year study began: in/before 2001. Location: Puerto Rico.
Interventions	FT (4 groups)** 500 ppm NaF 2800 ppm NaF 1100 ppm SnF_2-HMP 1100 ppm NaF. School use/supervised, twice daily. Abrasive system: silica.
Outcomes	2yDMFS increment - cl (VT) + xr D_2 through D_4 Reported at 2 years follow-up. Subgroup analysis for children who attended at least 60% of supervised brushing sessions
Notes	Participants randomised (n = 955). Baseline characteristics (age, sex, baseline caries) 'well balanced'. Children undergoing orthodontic therapy or with extensive prosthetic appliances were excluded from the study. Clinical (VT) and radiographic assessments undertaken by 2 calibrated examiners. 50 participants re-examined for clinical repeatability; bitewing films for 20 participants re-examined for radiographic repeatability. Weighted Kappa for clinical assessment was 0.90 - 0.95; x-ray sensitivity 97.7% to 100% and x-ray specificity 92.6% to 95.8%. Covariance analysis adjusted for age, baseline DMFS, baseline dental age, baseline surfaces at risk, dental age ** SnF_2-HMP toothpaste group excluded from analysis.

Risk of bias

Item	Authors' judgement	Description

Stookey 2004 (*Continued*)

Adequate sequence generation?	Unclear	Quote: "...randomised double-blind study. "
Allocation concealment?	Unclear	Comment: Insufficient information.
Blinding? All outcomes	Yes	Quote: "...randomised double-blind study. " Quote: "Subject and examiner blindness to treatment were maintained throughout the study."
Incomplete outcome data addressed? All outcomes	Unclear	Comment: 28.5% attrition in year 2, reasons not stated.
Free of selective reporting?	Yes	
Baseline characteristics balanced?	Yes	Quote "..baseline caries level...similar amongst the four treatment groups." Comment: Balance for baseline gender and caries comparable.
Free of contamination/co-intervention?	Yes	Comment: Siblings assigned the same toothpaste to reduce contamination but possible with home brushing

Thomas 1966

Methods	Stratified random allocation; double-blind; placebo-controlled; 32% drop out after 2 years (study duration = 2 years). Reasons for attrition not reported; no differential group losses
Participants	464 children analysed at 2 years (present for the entire study period). Average age at start: 7-16 years (average = 12). Surfaces affected at start: 10.7 DFS. Background exposure to fluoride: none reported. Year study began: 1961. Location: USA.
Interventions	FT (2 groups) versus PL (Both SnF_2 groups = 1000 ppm F). Institution use/supervised, twice a day. Abrasive system: IMP in one SnF_2 and placebo toothpaste, Ca pyrophosphate in another SnF_2 toothpaste.
Outcomes	2yDFS increment - cl+xr. Reported at 6 months, 1, 1.5 and 2 years follow-ups. DFT.

Notes	Participants randomised (n = 679). Baseline characteristics (DFS, DFT, TAR) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (10 BW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Check of diagnostic errors done

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "The children were stratified according to age, DMF permanent teeth... before dentifrices were assigned randomly within strata. Each formulation of dentifrice was assigned 8 numbers at random. These numbers were arranged into random subsets of three; each subset contained a number for each of the three formulations. This sequence was continued across strata boundaries and repeated until all of the participating children had been allocated." Comment: Still not enough information provided on the actual method of sequence generation
Allocation concealment?	Yes	Quote: "The list of names and dentifrice numbers was forwarded to the grantor, who provided the dentifrices in plain white wax-lined tubes labelled with each child's name, home and cottage number...The code of dentofrice numbers...and the three formulations were placed in a sealed envelope and stored in the school safe.."
Blinding? All outcomes	Yes	Quotes: "The control and experimental dentifrices were identically formulated except for SnF_2 which was omitted in the control toothpaste. Both toothpastes were coloured blue." "The participating subjects, as well as the examiner were unaware of the arrangement of numbers into dentifrice groups and the specific formulas throughout the study." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 32% in 2 years. Drop out by group:

Thomas 1966 (*Continued*)

		73/224 FD1, 68/226 FD2, 74/229 PL. Reasons for losses: Not reported Comment: Numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present for the entire study period.
Free of selective reporting?	Yes	Outcomes reported: DFS increment - cl+xr, reported at 6 months, 1, 1.5 and 2 years follow-ups. DFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DFS: 10.66 FD1, 10.57 FD2, 10.88 PL. DFT: 7.05 FD1, 6.72 FD2, 7.01 PL. Mean age: 11.56 FD1, 11.37 FD2, 11.48 PL. TAR: 12.04 FD1, 11.47 FD2, 11.59 PL. Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Yes	Quote: "The tubes were readily identified by the child's name on the label. Thus it was easy for the housemothers to prevent the children from exchanging toothpaste during brushing." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Torell 1965

Methods	Random allocation; double-blind; placebo-controlled; 13% drop-out rate after 2 years (study duration = 2 years). Reasons for attrition: natural losses mainly; no differential group losses
Participants	668 children analysed at 2 years (available at final examination). Age at start: 10 years. Surfaces affected at start: 14.5 DMFS (from sample randomised). Background exposure to fluoride: none reported. Year study began: 1962. Location: Sweden.

Torell 1965 (*Continued*)

Interventions	FT (2 groups) versus PL (2 groups) (SnF_2 group = 1000 ppm F, NaF group = 1100 ppm F). Home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed. Abrasive system: Ca pyrophosphate in SnF_2 toothpaste and its placebo, Na bicarbonate in NaF toothpaste and its placebo
Outcomes	2yDMFS increment - (CA)cl. Reported at 1 and 2 years follow-ups. MD-DMFS. FS. Proportion of children with new carious lesions (U)xr.
Notes	Participants randomised (n = 766). Baseline characteristics (DMFS, MD-DMFS) 'balanced'. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold = CA; radiographic assessment (BW) by 2 examiners; diagnostic threshold = DR. State of tooth eruption included not reported. Inter- and intra-examiner reproducibility checks done for clinical caries in 4% and 2% sample respectively; duplicate examination of x-rays records done and any discrepancies discussed before final diagnosis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "The groups were randomly constituted and randomly assigned to the test different test methods, according to a system worked out with the assistance of statisticians..."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The control dentifrice had the same composition with the exception of the fluoride." "On the registration charts the different groups were referred to by their code numbers. The examiners did not have access to the code during the course of the investigation." "The study was a blind test as the examination charts did not refer to the treatment or to the code number of the groups." Comment: Blind outcome assessment and use of placebo described

Torell 1965 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 13% in 2 years. Drop out by group: 27/196 FD1, 29/198 PL1, 30/196 FD2, 22/176 PL2. Reasons for losses: Changing school, moving away, appearance of new caries, unpleasant taste (not reported by group) Comment: Numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examinations
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (CA)cl, reported at 1 and 2 years follow-ups. MD-DMFS. FS. Proportion of children with new carious lesions (U) xr. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS (xr): 3.77 FD1, 3.85 PL1, 3.94 FD2, 4.17 PL2; DMFS (cl): 14.2 FD1, 14.5 PL1, 14.7 FD2, 14.6 PL2 Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Unclear	No information provided.

Torell 1965a

Methods	Random allocation; double-blind; placebo-controlled; 20% drop-out rate after 2 years (study duration = 2 years). Natural losses mainly; differential group losses
Participants	285 children analysed at 2 years (available at final examination). Average age at start: 10 years. Surfaces affected at start: 11.7 DMFS (from sample randomised). Background exposure to fluoride: none reported. Year study began: 1962. Location: Sweden.

Interventions	FT versus PL (SMFP group = 1000 ppm F). Home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed. Abrasive system: Ca carbonate.
Outcomes	2yDMFS increment - (CA)cl. Reported at 2 years follow-up. MD-DMFS. FS.
Notes	Participants randomised (n = 357). Baseline characteristics (DMFS, MD-DMFS) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; radiographic assessment (BW) by 2 examiners; diagnostic threshold = DR. State of tooth eruption included not reported. Intra-examiner reproducibility check done for clinical caries in a sample; duplicate examination of x-rays records done and any discrepancies discussed before final diagnosis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "The groups were randomly constituted and randomly assigned to the test different test methods, according to a system worked out with the assistance of statisticians..."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The control dentifrice had the same composition with the exception of the fluoride." "On the registration charts the different groups were referred to by their code numbers. The examiners did not have access to the code during the course of the investigation." "The study was a blind test as the examination charts did not refer to the treatment or to the code number of the groups." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 20% in 2 years. Drop out by group: 29/177 FD, 43/180 PL. Reasons for losses:

Torell 1965a (*Continued*)

		Changing school, moving away, appearance of new caries, unpleasant taste (not reported by group) Comment: Numbers lost were not unduly high for the length of follow-up. Differential losses between groups (16.4% FD, 23.9% PL). It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examinations. Group losses unlikely to be related to intervention
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (CA)cl, reported at 2 years follow-up. MD-DMFS. FS. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS (cl): 11.30 FD, 12.02 PL; DMFS (xr): 2.29 FD, 2.46 PL; Mean age: 10 years (both groups) Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Unclear	No information provided.

Torell 1965b

Methods	Random allocation; double-blind; placebo-controlled; 15% drop-out rate after 2 years (study duration = 2 years). Reasons for attrition natural losses mainly; no differential group losses
Participants	368 children analysed at 2 years (available at final examination). Average age at start: 11 years. Surfaces affected at start: 15 DMFS (from sample randomised). Background exposure to fluoride: none reported. Year study began: 1962. Location: Sweden.
Interventions	FT versus PL (SMFP group = 1000 ppm F). Home use/unsupervised, twice a day instructed but daily frequency assumed, post-brushing water rinse instructed. Abrasive system: Ca carbonate.

Outcomes	2yDMFS increment - (CA)cl. Reported at 2 years follow-up. MD-DMFS. FS.
Notes	Participants randomised (n = 432). Baseline characteristics (DMFS, MD-DMFS) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold = CA; radiographic assessment (BW) by 2 examiners; diagnostic threshold = DR. State of tooth eruption included not reported. Intra-examiner reproducibility check done for clinical caries in a sample; duplicate examination of x-rays records done and any discrepancies discussed before final diagnosis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "The groups were randomly constituted and randomly assigned to the test different test methods, according to a system worked out with the assistance of statisticians..."
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "The control dentifrice had the same composition with the exception of the fluoride." "On the registration charts the different groups were referred to by their code numbers. The examiners did not have access to the code during the course of the investigation." "The study was a blind test as the examination charts did not refer to the treatment or to the code number of the groups." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 15% in 2 years. Drop out by group: 27/215 FD, 37/217 PL. Reasons for losses: Changing school, moving away, appearance of new caries, unpleasant taste (not reported by group) Comment: Numbers lost were not unduly high for the length of follow-up with no

Torell 1965b (*Continued*)

		differential losses between groups (12.6% FD, 17.1% PL). It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examinations
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (CA)cl, reported at 2 years follow-up. MD-DMFS. FS. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS (xr): 3.76 FD, 4.13 PL; DMFS (cl): 14.52 FD, 15.41 PL; Mean age: 11 years (both groups). Comment: Initial caries appears balanced between groups.
Free of contamination/co-intervention?	Unclear	Comment: No information provided.

Weisenstein 1972

Methods	Stratified random allocation; double-blind; placebo-controlled; 42% drop out after 1.8 years (study duration = 1.8 years). Reasons for high drop out described: change of residence, absent on examination day; no differential group losses
Participants	402 children analysed at 1.8 years (available at final examination). Age range at start: 5-15 years (average = 9.5). Surfaces affected at start: 6.8 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1969. Location: USA.
Interventions	FT versus PL (NaF group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate.
Outcomes	1.8yDMFS increment - cl+xr. Reported at 9 months, 1.4 and 1.8 years follow-ups. DMFT.

Weisenstein 1972 (*Continued*)

Notes	Participants randomised (n = 694). Baseline characteristics (age, gender, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 2 examiners, diagnostic threshold not reported. Radiographic assessment (7 BW) by 2 examiners; diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported. Results of 1 examiner chosen

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "...each child was assigned one of two dentifrices randomly within the strata of age, sex and visual-tactile DMFS exam results." Comment: Not enough information presented.
Allocation concealment?	Unclear	No information presented.
Blinding? All outcomes	Yes	Quotes: "The control and test dentifrices were similar in colour, flavour and other properties." "The examiners had no knowledge of the dentifrice assigned to each child, and the children had no knowledge of the identities of the dentifrices assigned to them. All clinical exams and radiographic interpretations were made independent of previous exam records." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 42% in 1.8 years. Drop out by group: 117/348 FD, 113/329 PL. Reasons for losses: Change of residence, absent on examination day Comment: Numbers lost were unduly high for the length of follow-up. No differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 9 months, 1.4 and 1.8 years follow-ups.

Weisenstein 1972 (*Continued*)

		DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 7.01 FD, 6.99 PL; DMFT: 4.02 FD, 4.18 PL; Age: 9.39 FD, 9.49 PL; Gender: (169 M, 177 F) FD, (168 M, 180 F) PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "The possible effect of a non-study dentifrice was minimized because enough dentifrice was given each child to supply the household for the duration of the study. " Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Winter 1989

Methods	Random allocation; double-blind; 28% drop out after 3 years (study duration = 3 years) . Reasons for attrition not reported; no differential group losses
Participants	2177 children analysed at 3 years (available at final clinical examination, only 905 available for final clinical and radiological examination). Age range at start: 2 years (average = 2). Surfaces affected at start: 0 DMFS. Background exposure to fluoride: none reported. Year study began: 1984. Location: UK.
Interventions	FT (1055 ppm SMFP, 550 ppm SMFP NaF). Home use/supervised, daily frequency assumed. Abrasive system: Ca glycerophosphate.
Outcomes	3ydmfs increment - cl+xr. Reported at 3 years follow-up. dmft. dmfs. ds. ms. fs. Proportion developing new caries. Plaque. Compliance.

Notes	Participants randomised (n = 3040). Baseline characteristics not reported. Clinical (VT) caries assessment by 3 calibrated examiners, radiographic assessment by single examiner. Clinical and radiographic reliability assessed by 10% re-examination of sample. Kappa scores inter-rater reliability 0.65 to 0.71. Radiographic assessment by 1 examiner. Kappa scores inter-rater reliability 0.92

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "...randomly allocated."
Allocation concealment?	Unclear	Quote: "...12 assistants to visit the children's homes on a monthly basis for the next 3 years." Comment: Probably done.
Blinding? All outcomes	Yes	Quote: "..double-blind clinical trial." Quote: "...toothpaste was supplied ..... group code."
Incomplete outcome data addressed? All outcomes	Unclear	Comment: 28% drop out after 3 years for clinical examination alone; 70% drop out for clinical and radiographic examination. Reasons for drop out not stated; no differential group losses. High drop out likely to effect study estimates of treatment effect
Free of selective reporting?	Yes	Clinical and radiographic assessments. dmfs and dmft indices reported
Baseline characteristics balanced?	Unclear	Comment: Age of participant at start of trial 2 years, no baseline caries assumed for all participants
Free of contamination/co-intervention?	Yes	Quote: "Sufficient toothpaste was provided for the whole family to avoid mistaken use of another product for the child." Comment: Contamination unlikely.

Zacherl 1970

Methods	Stratified random allocation; double-blind; placebo-controlled; 43% drop out after 2.5 years (study duration = 2.5 years). Reasons for attrition not reported; no differential group losses
Participants	512 children analysed at 2.5 years (available at final examination). Age range at start: 6-9 years. Surfaces affected at start: 4.6 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1963. Location: USA.
Interventions	FT versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate.
Outcomes	2.5yDMFS increment - cl+xr. Reported at 10 months, 1.5 and 2.5 years follow-ups. DMFT.
Notes	Participants randomised (n = 902). Baseline characteristics (dental age, gender, DMFS, DMFT, oral hygiene) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5-10 BW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quotes: "Only grades 1 and 2, and grade 7 were selected. Each of these 2 age groups were divided into 2 similar subgroups according to age, sex and caries history...Adjacent subjects within arrays were assigned by coin toss to one of two groups simply indicated D or H."
Allocation concealment?	Unclear	Insufficient information.
Blinding? All outcomes	Yes	Quotes: " The investigator did not know which was the control and which was the experimental group." "The study was double blind." "The control dentifrice lacked the tin compounds but was otherwise identical." Comment: Blind outcome assessment and use of placebo described

Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 43% in 2.5 years. Drop out by group: 210/461 FD, 180/441 PL. Reasons for losses: Not reported Comment: Numbers lost were somewhat high for the length of follow-up. No differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr,reported at 10 months, 1.5 and 2.5 years follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 5.06 FD, 4.69 PL; DMFT: 2.69 FD, 2.51 PL. Dental age: 6.99 FD, 6.78 PL; Gender: (257 M, 204 F) FD, (228 M, 213 F) PL Oral hygiene: 1.58 FD, 1.63 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "To minimize the possible effect of non-study dentifrice, enough dentifrice was provided monthly to each individual to supply the household for the test period. " Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Zacherl 1970a

Methods	Stratified random allocation; double-blind; placebo-controlled; 35% drop out after 2. 5 years (study duration = 2.5 years). Reasons for attrition not reported; no differential group losses
Participants	528 children analysed at 2.5 years (available at final examination). Age range at start: 13-14 years. Surfaces affected at start: 23.5 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1963.

Zacherl 1970a (*Continued*)

	Location: USA.
Interventions	FT versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate.
Outcomes	2.5yDMFS increment - cl+xr. Reported at 10 months, 1.5 and 2.5 years follow-ups. DMFT.
Notes	Participants randomised (n = 811). Baseline characteristics (dental age, gender, DMFS, DMFT, oral hygiene) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5-10 BW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quotes: "Only grades 1 and 2, and grade 7 were selected. Each of these 2 age groups were divided into 2 similar subgroups according to age, sex and caries history... Adjacent subjects within arrays were assigned by coin toss to one of two groups simply indicated D or H."
Allocation concealment?	Unclear	Insufficient information.
Blinding? All outcomes	Yes	Quotes: " The investigator did not know which was the control and which was the experimental group." "The control dentifrice lacked the tin compounds but was otherwise identical." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 35% in 2.5 years. Drop out by group: 148/408 FD, 135/403 PL. Reasons for losses: Not reported Comment: Numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present

Zacherl 1970a (*Continued*)

		at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 10 months, 1.5 and 2.5 years follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 24.55 FD, 23.97 PL; DMFT: 12.21 FD, 12.03 PL. Dental age: 25.12 FD, 25.17 PL; Gender: (207 M, 201 F) FD, (200 M, 203 F) PL Oral hygiene: 1.61 FD, 1.60 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "To minimize the possible effect of non-study dentifrice, enough dentifrice was provided monthly to each individual to supply the household for the test period. " Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Zacherl 1972

Methods	Stratified random allocation; double-blind; placebo-controlled; 34% drop out after 2 years (study duration = 2 years). Reasons for attrition not reported; no differential group losses
Participants	447 children analysed at 2 years (available at final examination). Age range at start: 6-15 years (average = 10). Surfaces affected at start: 11.7 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1969. Location: Canada.
Interventions	FT versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in SnF_2 toothpaste, placebo toothpaste abrasive not reported.

Outcomes	2yDMFS increment - cl+xr. Reported at 1 and 2 years follow-ups. DMFT.
Notes	Participants randomised (n = 677). Baseline characteristics (age, gender, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5-10 BW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "...subjects were classified by age, sex and DMFS. The subjects were then assigned by random number to one of the two dentifrices, identified only by code letter."
Allocation concealment?	Unclear	Insufficient information provided.
Blinding? All outcomes	Yes	Quotes: "A double blind investigation..." "The control dentifrice was the same as the test dentifrice except that it had no active ingredients..." Comment: Use of placebo described but blind outcome assessment not clearly described, although it was probably done as earlier report by same author clearly described blind outcome assessment
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 34% in 2 years. Drop out by group: 117/348 FD, 113/329 PL. Reasons for losses: Not reported Comment: Numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examinations
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 1 and 2 years follow-ups. DMFT. Comment: Trial protocol not available. All

		pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 12.10 FD, 12.44 PL; DMFT: 6.27 FD, 6.33 PL; Age: 10.22 FD, 10.17 PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Unclear	No information provided.

Zacherl 1972a

Methods	Stratified random allocation; double-blind; placebo-controlled; 36% drop out after 1.7 years (study duration = 1.7 years). Reasons for high drop out not reported; exclusions based on presence in both examinations; no differential group losses
Participants	894 children analysed at 1.7 years (present for both follow-up examinations). Age range at start: 7-14 years (average = 9). Surfaces affected at start: 7.3 DMFS. Background exposure to fluoride: water. Year study began: in/before 1969. Location: Canada.
Interventions	FT (4 groups) versus PL (SnF_2 group, NaF group, SMFP group, APF group = 1000 ppm F each). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in all toothpastes.
Outcomes	1.7yDMFS increment - cl+xr. Reported at 1 and 1.7 years follow-ups. DMFT.
Notes	Participants randomised (n = 1405). Baseline characteristics (age, gender, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5-10 BW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "The subjects were arrayed by sex, age and initial visual-tactile DMFT and then assigned by random number to one of five groups identified only by code letter."

Zacherl 1972a (*Continued*)

Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "A double blind clinical investigation..." "All dentifrices were similar in colour, flavour and other consumer properties." "All examinations and interpretations were independent of previous records." Comment: Use of placebo described but blind outcome assessment not clearly described, although it was probably done as earlier report by same author clearly described blind outcome assessment
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 36% in 1.7 years. Drop out by group: 98/272 FD, 94/304 PL. Reasons for losses: Exclusion based on presence at all examinations Comment: Numbers lost were somewhat high for the length of follow-up. No differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at all examinations
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 1 and 1.7 years follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 7.63 FD1, 7.33 FD2, 6.98 FD3, 7.28 FD4, 7.60 PL. DMFT: 4.34 FD1, 4.19 FD2, 4.00 FD3, 4.17 FD4, 4.13 PL. Age: 9.31 FD1, 9.28 FD2, 9.37 FD3, 9.25 FD4, 9.17 PL. Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Unclear	No information provided.

Zacherl 1973

Methods	Stratified random allocation; double-blind; placebo-controlled; 34% drop out after 2 years (study duration = 2 years). Reasons for attrition not reported; no differential group losses
Participants	444 children analysed at 2 years (available at final examination). Age range at start: 5-12 years (average = 9). Surfaces affected at start: 8.5 DMFS. Background exposure to fluoride: none reported. Year study began: in/before 1970. Location: USA.
Interventions	FT** versus PL (SnF_2 group = 1000 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in SnF_2 toothpaste, placebo toothpaste abrasive not reported.
Outcomes	2yDMFS increment - cl+xr. Reported at 1 and 2 years follow-ups. DMFT.
Notes	Participants randomised (n = 677). Baseline characteristics (age, DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment by 1 examiner, diagnostic threshold not reported. Radiographic assessment (5-10 BW) by 1 examiner; diagnostic threshold not reported. State of tooth eruption included not reported. Diagnostic errors not reported **Na N-lauroyl sarcosinate/SMFP toothpaste group not considered (additional non-F active agent used in this group only)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Sample was stratified by age, sex and DMFS, and assigned by random permutations to the 3 dentifrices identified only by code letter." Comment: Probably done. Earlier reports by the same author clearly describe use of random sequeunces (Zacherl 1972)
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Yes	Quotes: "All examinations were independent of previous examination records." "A third dentifrice containing no known caries inhibiting agents was used as control. " "The study was double blind..."

Zacherl 1973 (*Continued*)

		Comment: Use of placebo described but blind outcome assessment not clearly described, although it was probably done as earlier report by same author clearly described blind outcome assessment
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 34% in 2 years. Drop out by group: 124/344 FD, 109/333 PL. Reasons for losses: Not reported Comment: Numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - cl+xr, reported at 1 and 2 years follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 8.06 FD, 8.02 PL; DMFT: 4.41 FD, 4.37 PL; Age: 8.78 FD, 8.76 PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Yes	Quote: "The assigned dentifrice was supplied to the entire families of the study participants approximately every 2 months during the study." Comment: There is sufficient indication overall of prevention of contamination/co-intervention

Zacherl 1981

Methods	Stratified random allocation; double-blind; placebo-controlled; 43% drop out after 3 years (study duration = 3 years). Reasons for attrition described: change of residence, absent on examination day, poor quality of x-rays; no differential group losses
Participants	1754 children analysed at 3 years (available at final examination). Age range at start: 6-13 years (average = 9). Surfaces affected at start: 5.8 DMFS.

	Background exposure to fluoride: none reported. Year study began: in/before 1977. Location: USA.
Interventions	FT (2 groups) versus PL (SnF_2 group = 1000 ppm F, NaF group = 1100 ppm F). Home use/unsupervised, daily frequency assumed. Abrasive system: Ca pyrophosphate in SnF_2 and placebo toothpastes, silica in NaF toothpaste.
Outcomes	3yDMFS increment - (CA)cl+(ER)xr. Reported at 1, 2 and 3 years follow-ups. DMFT.
Notes	Participants randomised (n = 3093). Baseline characteristics (DMFS, DMFT) 'balanced'. Clinical (VT) caries assessment (FOTI used) by 1 examiner, diagnostic threshold = CA. Radiographic assessment (postBW) by 1 examiner; diagnostic threshold = ER. State of tooth eruption included not reported. Intra-examiner reproducibility checks for incremental clinical and radiographic caries data in 10% sample (ICC score 0.9). Reversal rate very low and similar among groups

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "Following the baseline examinations, the subjects were seperated by sex, age and DMFS. Within these strata, they were assigned to a treatment regimen by random permutations of seven in a 1:3:3 ratio.."
Allocation concealment?	Unclear	Quote: "Following initial assignment of subjects to treatment groups, the investigator was supplied with a file of tamper proof, sealed opaque envelopes which contained the name and identification number of each subject. Within each envelope, the treatment identity for the subject was printed." Comment: Allocation concealment should be dealt with prior to not after assignment
Blinding? All outcomes	Yes	Quotes: "No situations occurred during the study that required any of the envelopes to be opened. At no time during the course of the study did the examiner or the subjects know which dentifrice the subjects were as-

		signed." "The design used for this study is a modification of the classical double-blind placebo controlled clinical trial. In this study, three times as many subjects were assigned to the groups constituting the primary comparison, than were assigned to the placebo group." Comment: Blind outcome assessment and use of placebo described
Incomplete outcome data addressed? All outcomes	Unclear	Quotes: Overall drop out for length of follow-up: 43% in 3 years. Drop out by group: 568/1328 FD, 184/438 PL. Reasons for losses: Changing of residence, poor quality radiographs, exclusion due to absence at final examination Comment: Numbers lost were not unduly high for the length of follow-up with no differential losses between groups. It is unclear if reasons for missing outcome data are acceptable and balanced. Caries data used in analysis pertain to participants present at final examination
Free of selective reporting?	Yes	Outcomes reported: DMFS increment - (CA)cl+(ER)xr, reported at 1, 2 and 3 years follow-ups. DMFT. Comment: Trial protocol not available. All pre-specified outcomes (in Methods) were reported and were reported in the pre-specified way
Baseline characteristics balanced?	Yes	Prognostic factors reported: DMFS: 6.06 (6.15) FD1, 5.65 (5.60) FD2, 5.59 (5.02) PL; DMFT: 3.61 (3.31) FD1, 3.49 (3.07) FD2, 3.44 (2.77) PL Comment: Initial caries appears balanced.
Free of contamination/co-intervention?	Unclear	Quote: "Toothbrushes and dentifrice labelled with the subject's name and unique identification number were supplied by the study's sponsor in plain white tubes...." Comment: Not enough information provided.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andlaw 1983	Equivalent fluoride concentration (SMFP 1000 ppm F (2 groups). Placebo plus 3% TMP)
Baysan 2001	Inadequate follow-up period (6 months).
Beiswanger 1981	Equivalent fluoride concentration (1000 ppm SnF_2, 1100 ppm NaF).
Beiswanger 1989	Equivalent fluoride concentration (1100 ppm NaF, 1100 ppm SMFP)
Bibby 1945	Random allocation not stated or indicated.
Biesbrock 2003	Participants initially randomised to placebo toothpaste switched to either NaF 500 ppm F or NaF 1450 ppm F after 9 months. Inadequate follow-up of 9 months
Bixler 1966	Study participants included children and adults (age range 11 to 23 years)
Blinkhorn 1988	Equivalent fluoride concentration (1400 ppm NaF, 1400 ppm SMFP, 1000 ppm SMFP + 450 ppm NaF)
Curnow 2002	Comparison of children receiving fluoridated toothpaste as part of a supervised toothbrushing programme with children receiving no intervention
Cutress 1992	Post-trial evaluation. Data coding problems in original trial
De Paola 1993	Equivalent fluoride concentration (1000 ppm SMFP, 1000 ppm NaF, 1000 ppm NaF)
Dolles 1980	Additional non-fluoride active agent (chlorhexidine).
Downer 1976	Non-randomised. Additional topical fluoride-based intervention
Edlund 1977	Equivalent fluoride concentration (1000 ppm SMFP, 1000ppm NaF)
Ennever 1980	Random allocation not stated or indicated.
Feng 2007	Inadequate follow-up period (6 months).
Finn 1963	Medically compromised institutionalised children.
Frankl 1968	Additional non-fluoride agent in placebo toothpaste (N-lauroyl sarcosinate). Equivalent fluoride concentration (1000 ppm SnF_2, 1000 ppm SMFP). 31% of participants had been in an earlier trial of fluoridated toothpaste
Gerdin 1972	Systematic allocation.
Gish 1965	Additional topical fluoride-based intervention.
Hargreaves 1973	Systematic allocation.

(*Continued*)

Heidmann 1997	Aluminium-containing test toothpaste.
Hill 1959	Random allocation not stated or indicated.
Horowitz 1966	Systematic allocation.
Horowitz 1966a	Dentifrice versus aqueous solution.
Jordan 1959	Only 2 clusters (schools), each randomised to 1 of the 2 interventions compared
Koch 1967	Systematic allocation.
Koch 1972	Potassium fluoride and manganese chloride test toothpaste.
Koch 1982	Additional topical fluoride-based intervention.
Kunzel 1977	Additional fluoride-based intervention with fluoride toothpaste
Kyes 1961	Adults. Non-randomised.
Lu 1985	Additional non-fluoride agent in test toothpaste only.
Mergele 1968a	Medically compromised institutionalised young adults and children selected
Moller 1968	Additional agent added to fluoride toothpaste.
Muhler 1958	Random allocation not stated.
Muhler 1960	Non-random allocation.
Murray 1980	Random allocation not stated.
Onisi 1970	Random allocation not stated or indicated.
Patz 1970	Significant proportion of participants 17 years or older at commencement of study (average age 16 years 4 months)
Peffley 1960	Random allocation not stated. Inadequate follow-up period (10 months)
Petersson 1991	Additional non-fluoride active agent.
Ran 1991	Placebo gel versus AmF gel or toothpaste (fortnightly application) in addition to usual toothbrushing practice
Riethe 1975	Non-randomised.
Ripa 1990	Equivalent fluoride concentration (1100 ppm NaF, 1000 ppm SMFP)
Saporito 2000	Equivalent fluoride concentration (1100 ppm NaF, 1000 ppm SMFP)

(*Continued*)

Sjorgren 1995	Additional non-fluoride agent added to dentifrice A.
Stookey 1975	Random allocation not stated or indicated.
Tavener 2006	Prevalence and severity of fluorosis. No caries data.
Thomas 1970	Additional agent added to fluoride toothpastes.
Triol 1987	Equivalent fluoride concentration (1000 ppm SMFP, 500 ppm SMFP + 500 ppm NaF)
You 2002	Additional oral health intervention for fluoride group.

DATA AND ANALYSES

Comparison 1. Fluoride toothpaste versus placebo or other fluoride toothpaste

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 D(M)FS increment (prevented fraction) - nearest to 3 years (74 trials)	74		Prevented fraction (Random, 95% CI)	19.79 [16.72, 22.87]
1.1 Placebo versus 250 ppm	3		Prevented fraction (Random, 95% CI)	8.90 [-1.62, 19.42]
1.2 Placebo versus 440/500/550 ppm	2		Prevented fraction (Random, 95% CI)	7.91 [-6.11, 21.94]
1.3 Placebo versus 1000/1055/1100/1250 ppm	54		Prevented fraction (Random, 95% CI)	22.20 [18.68, 25.72]
1.4 Placebo versus 1450/1500 ppm	4		Prevented fraction (Random, 95% CI)	22.07 [15.26, 28.88]
1.5 Placebo versus 2400/2500/2800 ppm	4		Prevented fraction (Random, 95% CI)	36.55 [17.46, 55.64]
1.6 250 ppm versus 1000/1055/1100/1250 ppm	2		Prevented fraction (Random, 95% CI)	16.80 [8.47, 25.12]
1.7 440/500/550 ppm versus 1000/1055/1100/1250 ppm	1		Prevented fraction (Random, 95% CI)	0.48 [-14.98, 15.94]
1.8 440/500/550 ppm versus 2400/2500/2800 ppm	1		Prevented fraction (Random, 95% CI)	12.66 [-1.65, 26.97]
1.9 1000/1055/1100/1250 ppm versus 1450/1500 ppm	6		Prevented fraction (Random, 95% CI)	9.58 [2.52, 16.64]
1.10 1000/1055/1100/1250 ppm versus 1700/2000/2200 ppm	2		Prevented fraction (Random, 95% CI)	9.44 [2.12, 16.76]
1.11 1000/1055/1100/1250 ppm versus 2400/2500/2800 ppm	6		Prevented fraction (Random, 95% CI)	12.15 [5.95, 18.35]
2 D(M)FT increment (prevented fraction) - nearest to 3 years (54 trials)	54		Prevented fraction (Random, 95% CI)	21.16 [16.86, 25.47]
2.1 Placebo versus 250 ppm	1		Prevented fraction (Random, 95% CI)	15.75 [2.78, 28.72]
2.2 Placebo versus 440/500/550 ppm	2		Prevented fraction (Random, 95% CI)	31.66 [-11.63, 74.95]
2.3 Placebo versus 1000/1055/1100/1250 ppm	41		Prevented fraction (Random, 95% CI)	22.39 [16.85, 27.93]
2.4 Placebo versus 1450/1500 ppm	4		Prevented fraction (Random, 95% CI)	22.27 [16.46, 28.09]
2.5 Placebo versus 2400/2500/2800 ppm	3		Prevented fraction (Random, 95% CI)	37.38 [18.96, 55.81]
2.6 250 ppm versus 1000/1055/1100/1250 ppm	2		Prevented fraction (Random, 95% CI)	14.66 [7.70, 21.62]
2.7 1000/1055/1100/1250 ppm versus 1450/1500 ppm	3		Prevented fraction (Random, 95% CI)	11.88 [-2.37, 26.14]

2.8 1000/1055/1100/1250 ppm versus 1700/2000/2200 ppm	2		Prevented fraction (Random, 95% CI)	6.57 [0.26, 12.89]
2.9 1000/1055/1100/1250 ppm versus 2400/2500/2800 ppm	3		Prevented fraction (Random, 95% CI)	12.40 [7.64, 17.16]
3 D(M)FS increment (SMD) - nearest to 3 years (74 trials)	74	73684	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.27, -0.20]
3.1 Placebo versus 250 ppm	3	1460	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.19, 0.02]
3.2 Placebo versus 440/500/550 ppm	2	816	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.21, 0.06]
3.3 Placebo versus 1000/1055/1100/1250 ppm	54	31727	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.32, -0.24]
3.4 Placebo versus 1450/1500 ppm	4	4406	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.51, -0.18]
3.5 Placebo versus 2400/2500/2800 ppm	4	2041	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-1.11, -0.33]
3.6 250 ppm versus 1000/1055/1100/1250 ppm	2	1346	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.31, -0.09]
3.7 440/500/550 ppm versus 1000/1055/1100/1250 ppm	1	342	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.21, 0.22]
3.8 440/500/550 ppm versus 2400/2500/2800 ppm	1	348	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.39, 0.04]
3.9 1000/1055/1100/1250 ppm versus 1450/1500 ppm	6	12200	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.14, -0.03]
3.10 1000/1055/1100/1250 ppm versus 1700/2000/2200 ppm	2	5534	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.13, -0.02]
3.11 1000/1055/1100/1250 ppm versus 2400/2500/2800 ppm	6	13464	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.18, -0.05]
4 D(M)FT increment (SMD) - nearest to 3 years (54 trials)	54	53095	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.28, -0.20]
4.1 Placebo versus 250 ppm	1	776	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.30, -0.02]
4.2 Placebo versus 440/500/550 ppm	2	816	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.72, 0.15]
4.3 Placebo versus 1000/1055/1100/1250 ppm	41	24837	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.31, -0.21]
4.4 Placebo versus 1450/1500 ppm	4	4406	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.50, -0.24]
4.5 Placebo versus 2400/2500/2800 ppm	3	1259	Std. Mean Difference (IV, Random, 95% CI)	-1.05 [-2.14, 0.04]
4.6 250 ppm versus 1000/1055/1100/1250 ppm	2	1346	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.32, -0.08]
4.7 1000/1055/1100/1250 ppm versus 1450/1500 ppm	3	6564	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.17, 0.01]
4.8 1000/1055/1100/1250 ppm versus 1700/2000/2200 ppm	2	5534	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.11, -0.00]

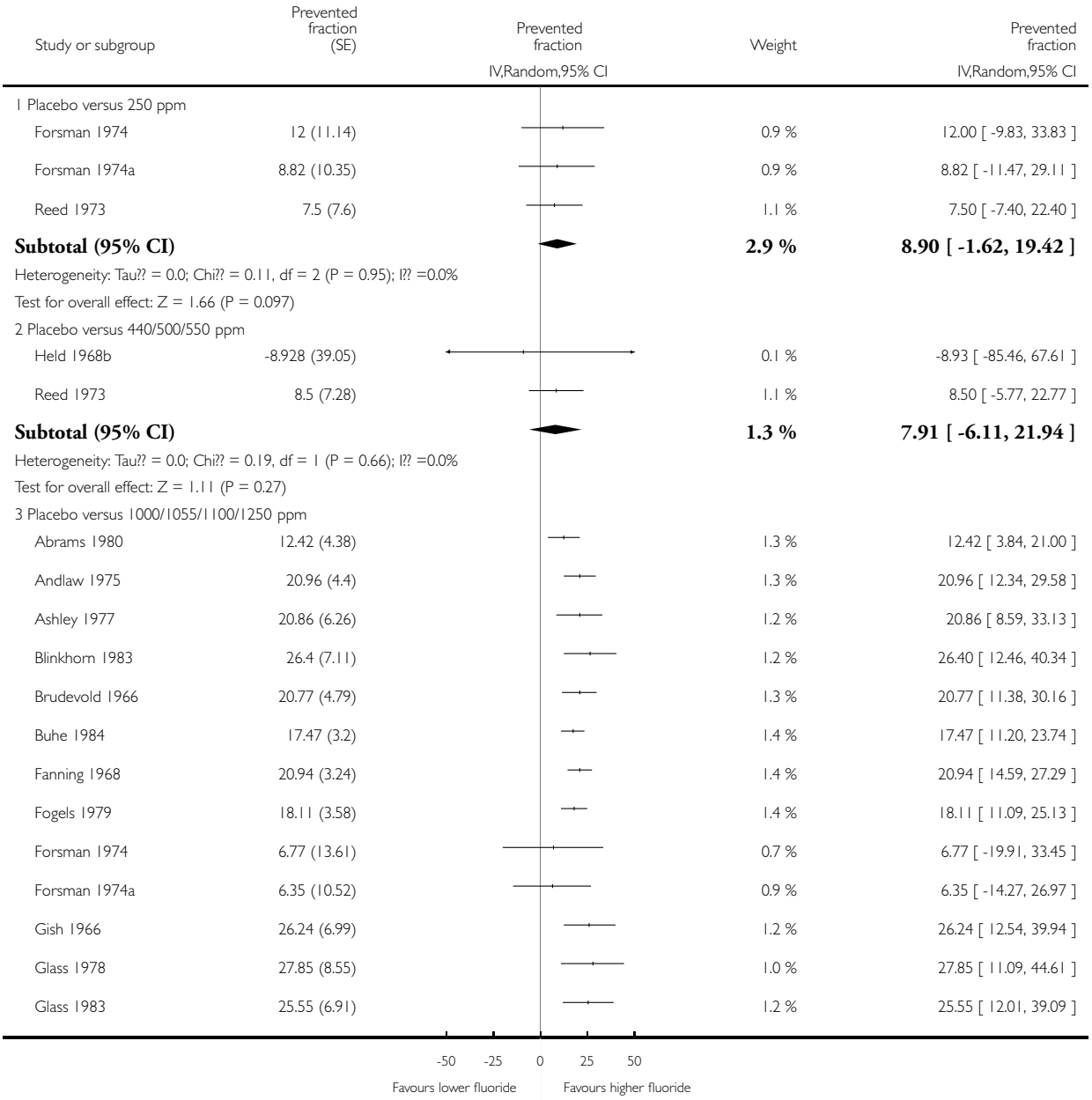
4.9 1000/1055/1100/1250 ppm versus 2400/2500/2800 ppm	3	7557	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.16, -0.07]
5 d(m)fs increment (prevented fraction) - nearest to 3 years (3 trials)	3		Prevented fraction (Fixed, 95% CI)	34.82 [25.68, 43.96]
5.1 Placebo versus 1450/1500 ppm	1		Prevented fraction (Fixed, 95% CI)	39.32 [29.19, 49.45]
5.2 250 ppm versus 1450/1500 ppm	1		Prevented fraction (Fixed, 95% CI)	41.4 [-6.87, 89.67]
5.3 440/500/550 ppm versus 1000/1055/1100/1250 ppm	1		Prevented fraction (Fixed, 95% CI)	9.0 [-14.52, 32.52]
6 d(m)ft increment (prevented fraction) - nearest to 3 years (3 trials)	3		Prevented fraction (Fixed, 95% CI)	12.18 [5.08, 19.29]
6.1 250 ppm versus 1450/1500 ppm	1		Prevented fraction (Fixed, 95% CI)	33.3 [-21.77, 88.37]
6.2 440/500/550 ppm versus 1000/1055/1100/1250 ppm	1		Prevented fraction (Fixed, 95% CI)	16.0 [-1.64, 33.64]
6.3 440/500/550 ppm versus 1450/1500 ppm	1		Prevented fraction (Fixed, 95% CI)	11.0 [3.16, 18.84]
7 Proportion developing new caries (permanent) (8 trials)	8	5348	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.94, 1.02]
7.1 Placebo versus 250 ppm	2	684	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.26]
7.2 Placebo versus 1000/1055/1100/1250 ppm	6	1806	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.82, 0.95]
7.3 Placebo versus 1450/1500 ppm	1	945	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.91, 0.98]
7.4 1000/1055/1100/1250 ppm versus 1450/1500 ppm	1	1913	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [1.00, 1.14]
8 Proportion developing new caries (deciduous) (3 trials)	3		Risk Ratio (Fixed, 95% CI)	0.87 [0.81, 0.93]
8.1 250 ppm versus 1450/1500 ppm	1		Risk Ratio (Fixed, 95% CI)	1.01 [0.63, 1.62]
8.2 440/500/550 ppm versus 1000/1055/1100/1250 ppm	1		Risk Ratio (Fixed, 95% CI)	0.89 [0.80, 0.99]
8.3 440/500/550 ppm versus 1450/1500 ppm	1		Risk Ratio (Fixed, 95% CI)	0.85 [0.78, 0.93]

Analysis 1.1. Comparison 1 Fluoride toothpaste versus placebo or other fluoride toothpaste, Outcome 1 D(M)FS increment (prevented fraction) - nearest to 3 years (74 trials).

Review: Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents

Comparison: 1 Fluoride toothpaste versus placebo or other fluoride toothpaste

Outcome: 1 D(M)FS increment (prevented fraction) - nearest to 3 years (74 trials)



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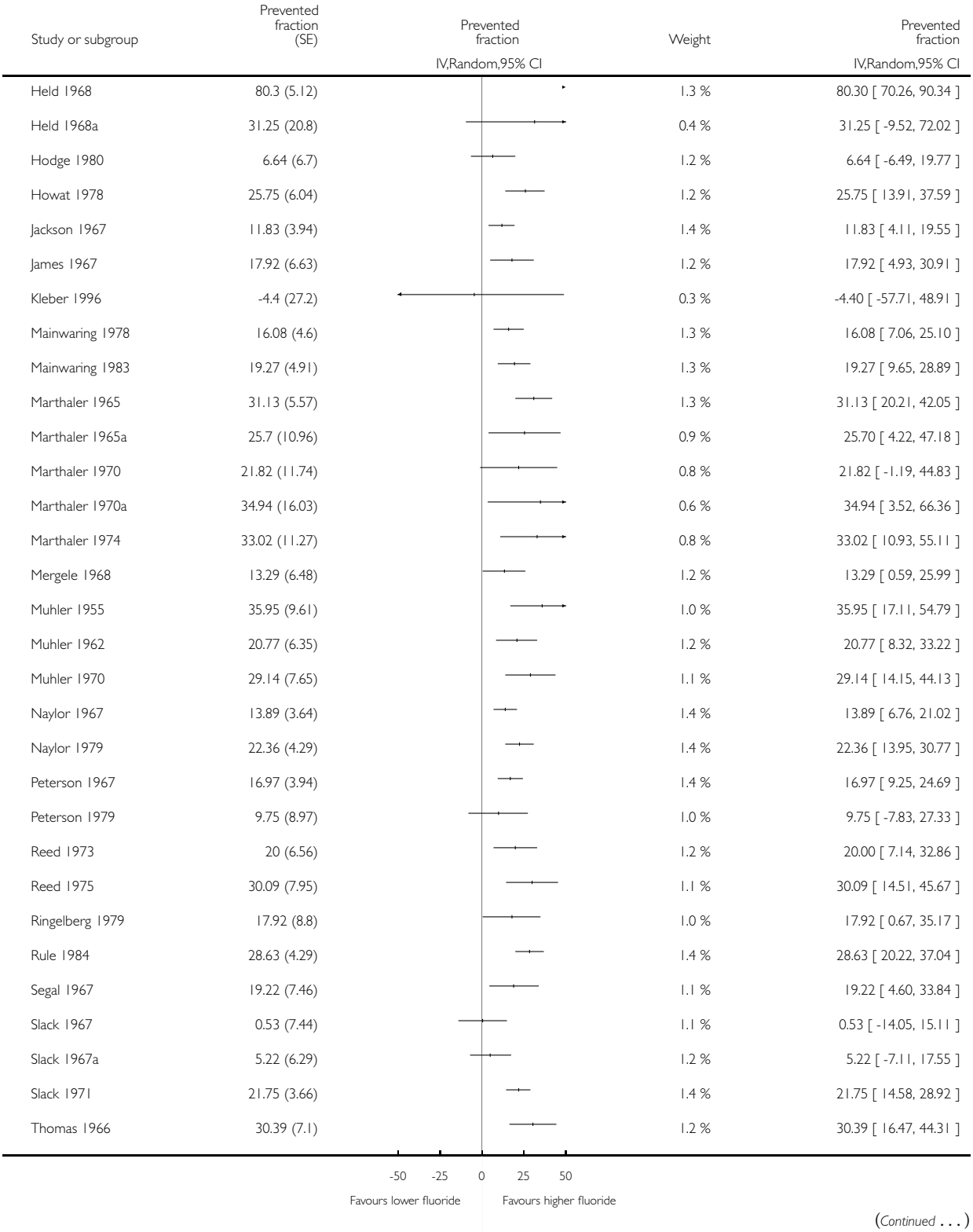

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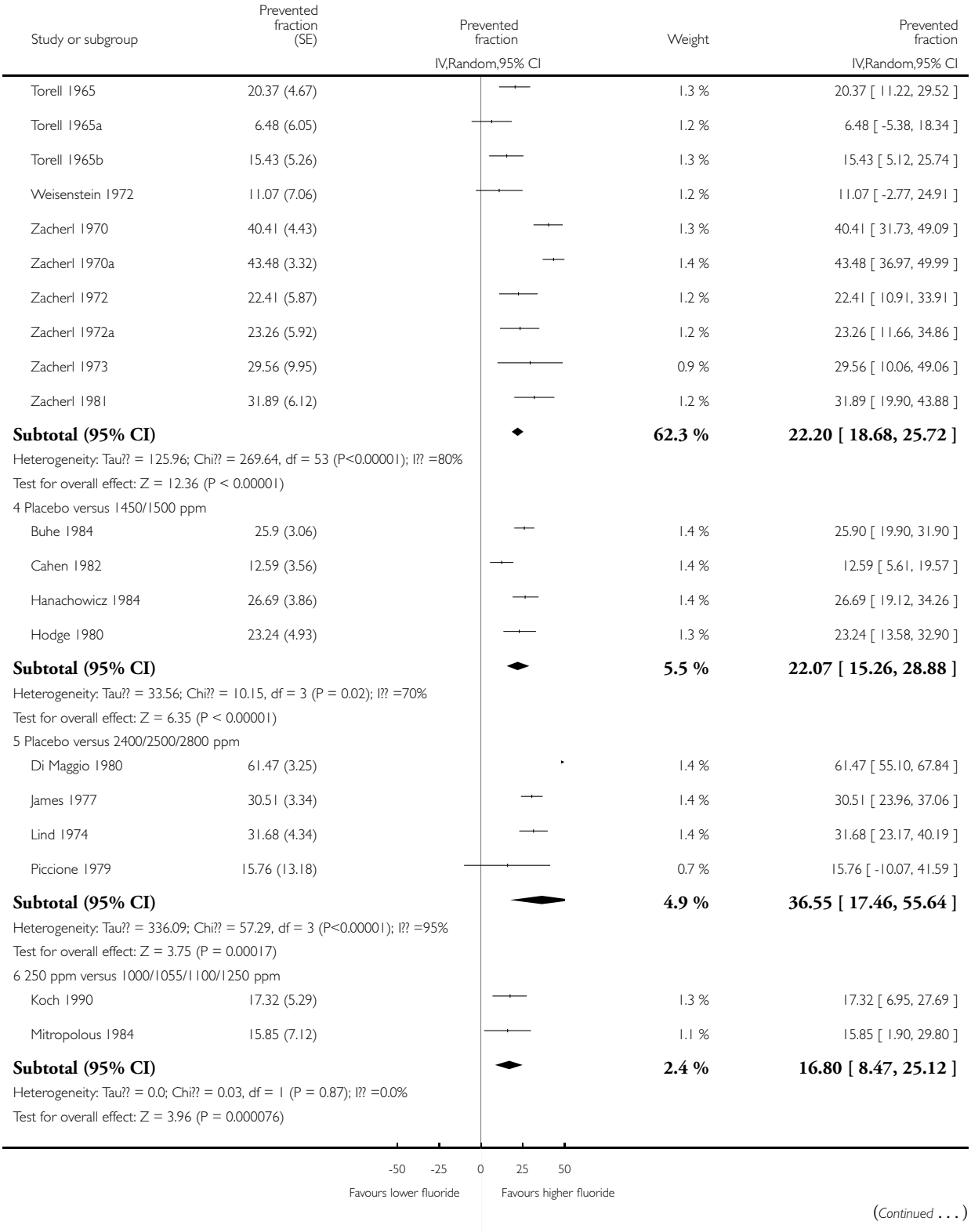

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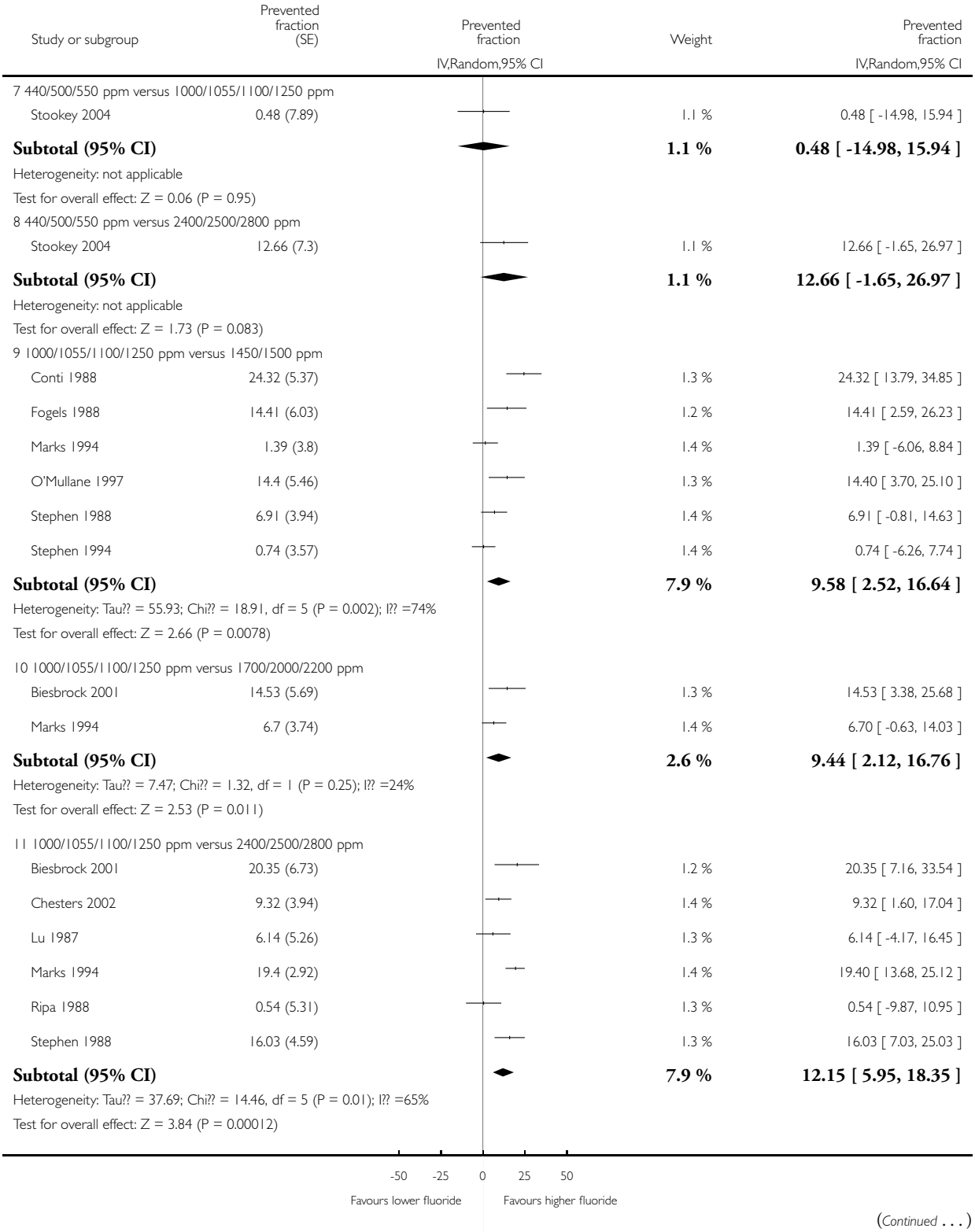

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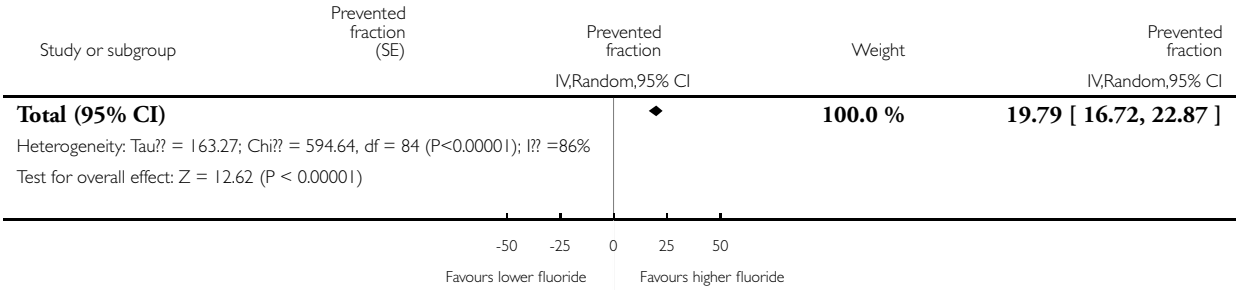
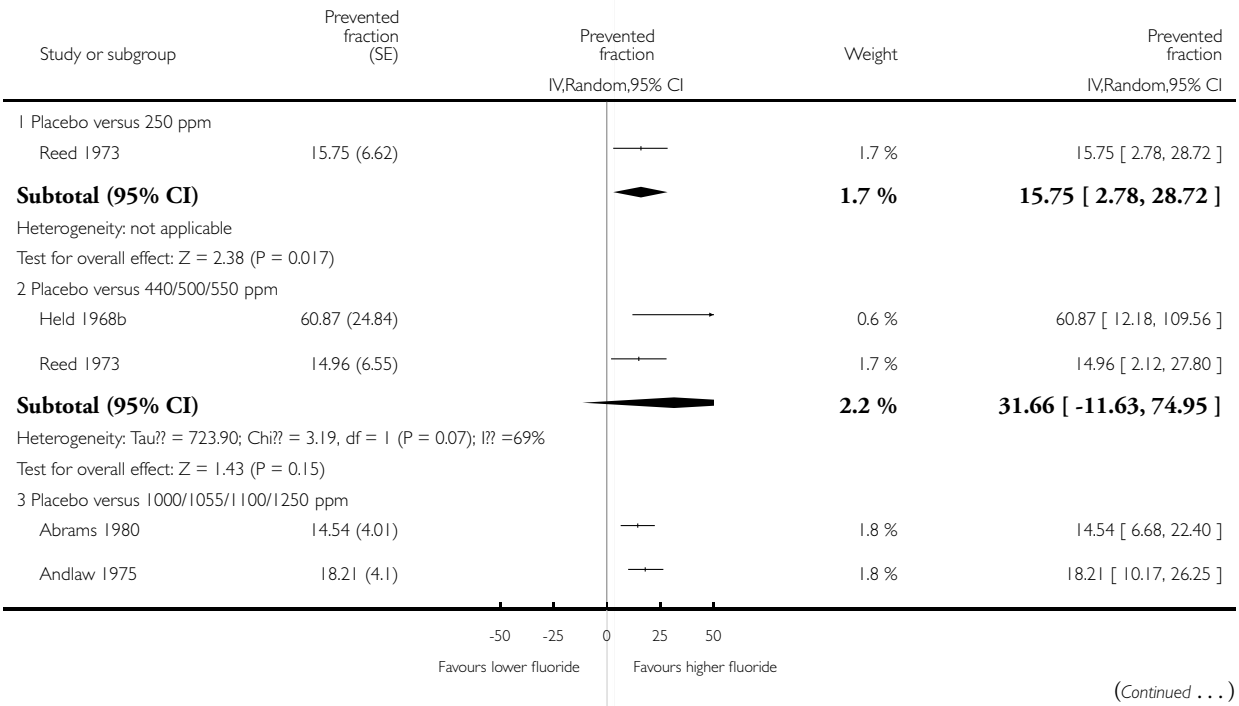


Analysis 1.2. Comparison 1 Fluoride toothpaste versus placebo or other fluoride toothpaste, Outcome 2 D(M)FT increment (prevented fraction) - nearest to 3 years (54 trials).

Review: Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents

Comparison: 1 Fluoride toothpaste versus placebo or other fluoride toothpaste

Outcome: 2 D(M)FT increment (prevented fraction) - nearest to 3 years (54 trials)



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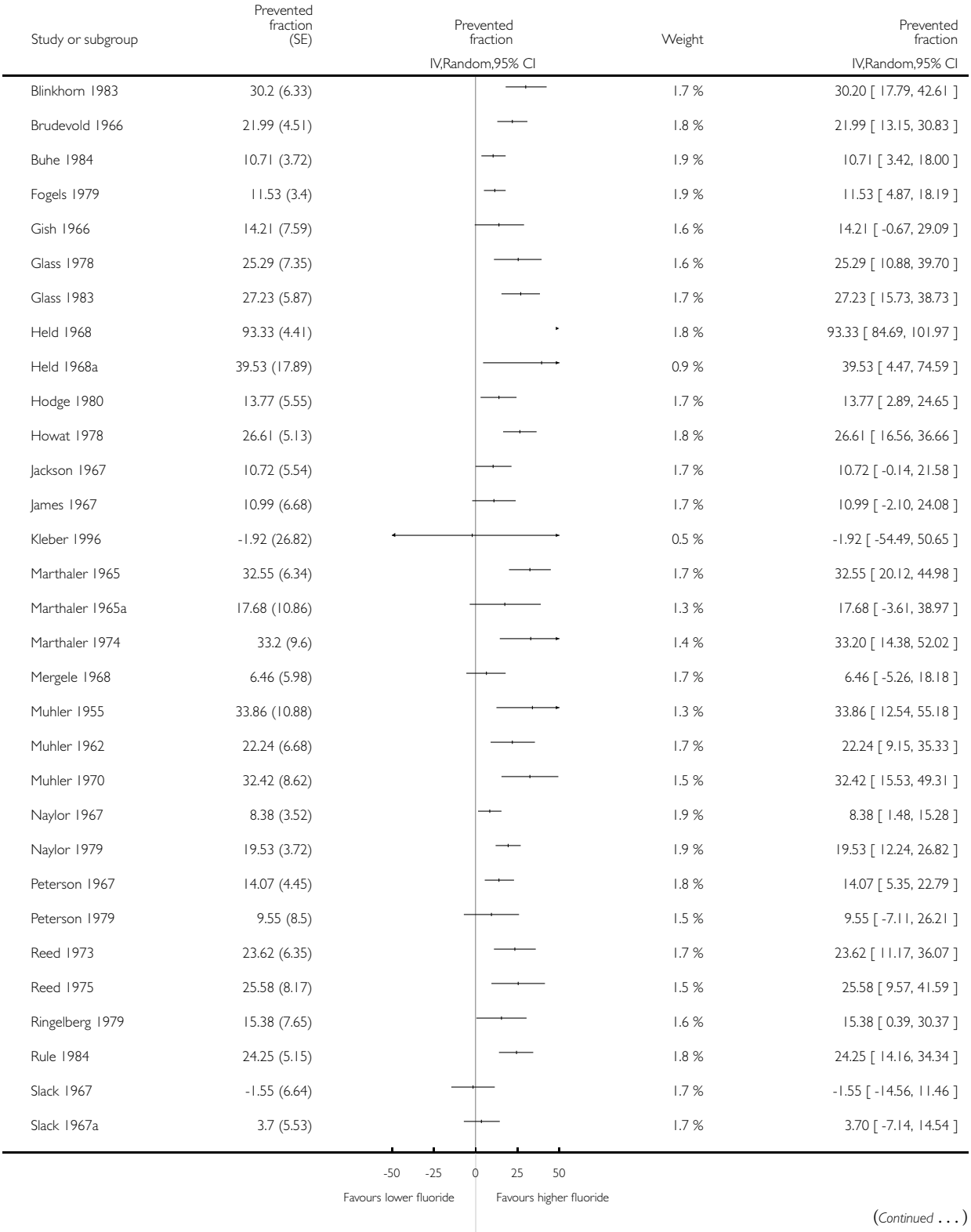

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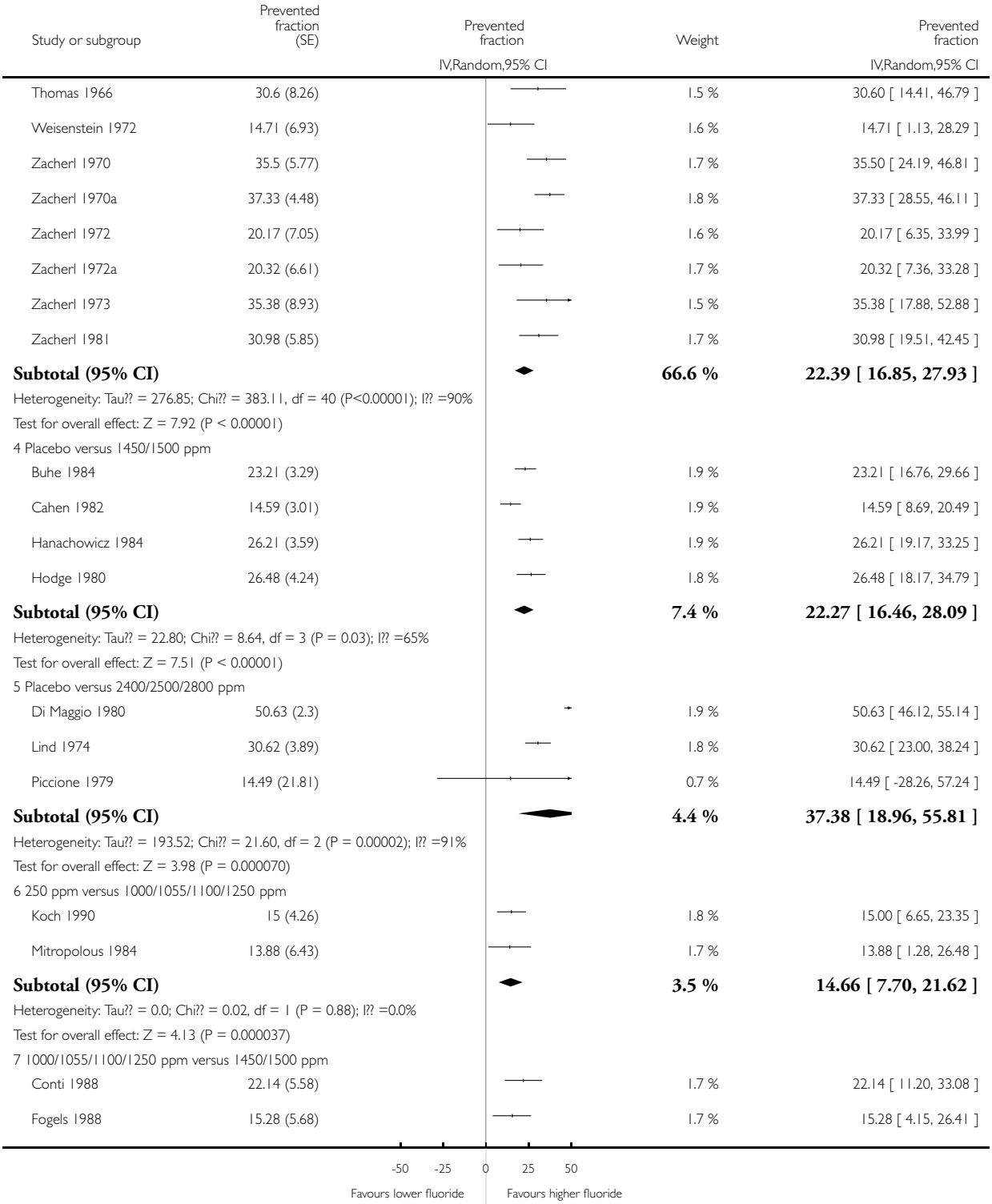

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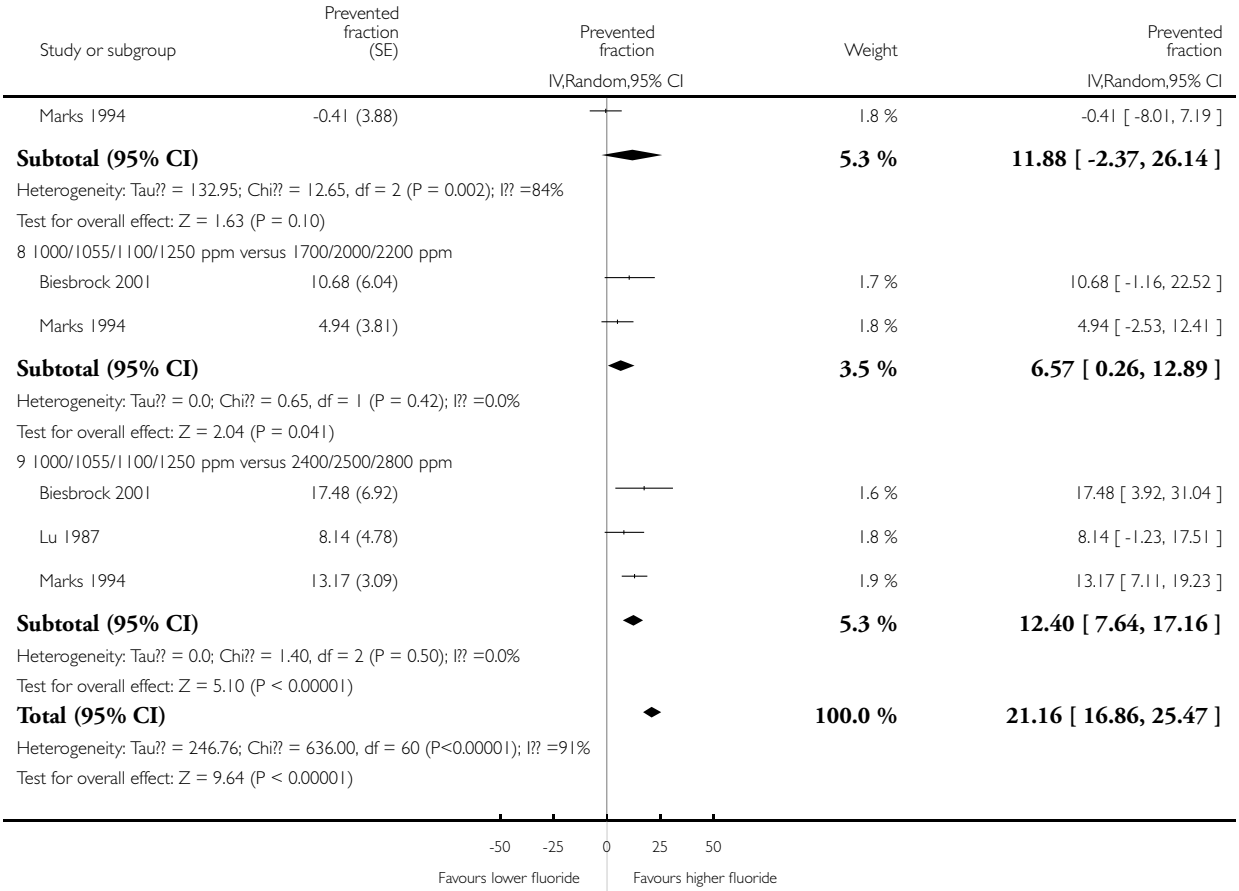

Analysis 1.3. Comparison 1 Fluoride toothpaste versus placebo or other fluoride toothpaste, Outcome 3 D(M)FS increment (SMD) - nearest to 3 years (74 trials).

Review: Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents

Comparison: 1 Fluoride toothpaste versus placebo or other fluoride toothpaste

Outcome: 3 D(M)FS increment (SMD) - nearest to 3 years (74 trials)

Study or subgroup	Higher fluoride N	Mean(SD)	Lower fluoride N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Placebo versus 250 ppm							
Forsman 1974	277	2.86 (3.573)	145	3.25 (3.8)		1.1 %	-0.11 [-0.31, 0.09]
Forsman 1974a	130	5.17 (4.778)	132	5.67 (5)		0.9 %	-0.10 [-0.34, 0.14]
Reed 1973	379	3.7 (4.5)	397	4 (4.18)		1.3 %	-0.07 [-0.21, 0.07]
Subtotal (95% CI)	**786**		**674**			**3.4 %**	**-0.09 [-0.19, 0.02]**
Heterogeneity: Tau?? = 0.0; Chi?? = 0.11, df = 2 (P = 0.95); I?? =0.0%							
Test for overall effect: Z = 1.60 (P = 0.11)							
2 Placebo versus 440/500/550 ppm							
Held 1968b	14	6.1 (5.182)	18	5.6 (4.969)		0.2 %	0.10 [-0.60, 0.80]
Reed 1973	387	3.66 (4.25)	397	4 (4.18)		1.3 %	-0.08 [-0.22, 0.06]
Subtotal (95% CI)	**401**		**415**			**1.6 %**	**-0.07 [-0.21, 0.06]**
Heterogeneity: Tau?? = 0.0; Chi?? = 0.24, df = 1 (P = 0.63); I?? =0.0%							
Test for overall effect: Z = 1.05 (P = 0.29)							
3 Placebo versus 1000/1055/1100/1250 ppm							
Abrams 1980	761	6.42 (5.314)	380	7.33 (5.672)		1.4 %	-0.17 [-0.29, -0.04]
Andlaw 1975	364	6.07 (4.97)	376	7.68 (5.24)		1.3 %	-0.31 [-0.46, -0.17]
Ashley 1977	246	4.44 (4.02)	243	5.61 (4.64)		1.2 %	-0.27 [-0.45, -0.09]
Blinkhorn 1983	184	4.6 (4.33)	184	6.25 (5.55)		1.1 %	-0.33 [-0.54, -0.13]
Brudevold 1966	955	5.57 (6.1)	323	7.03 (6.11)		1.4 %	-0.24 [-0.37, -0.11]
Buhe 1984	438	13.7 (7.95)	427	16.6 (9.23)		1.4 %	-0.34 [-0.47, -0.20]
Fanning 1968	422	9.67 (6.37)	422	12.23 (6.37)		1.3 %	-0.40 [-0.54, -0.27]
Fogels 1979	890	6.83 (5.478)	449	8.34 (6.043)		1.4 %	-0.27 [-0.38, -0.15]
Forsman 1974	137	3.03 (3.676)	145	3.25 (3.804)		1.0 %	-0.06 [-0.29, 0.17]
Forsman 1974a	132	5.31 (4.841)	132	5.67 (5)		1.0 %	-0.07 [-0.31, 0.17]
Gish 1966	165	4.75 (4.24)	163	6.44 (5.18)		1.0 %	-0.36 [-0.57, -0.14]
Glass 1978	178	5.31 (5.95)	168	7.36 (7.68)		1.1 %	-0.30 [-0.51, -0.09]
Glass 1983	567	2.39 (3)	286	3.21 (4.04)		1.3 %	-0.24 [-0.38, -0.10]

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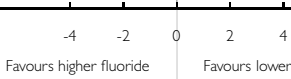
Study or subgroup	Higher fluoride N	Mean(SD)	Lower fluoride N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Held 1968	32	2.6 (3.409)	31	13.2 (7.571)		0.3 %	-1.79 [-2.38, -1.20]
Held 1968a	19	5.5 (4.926)	17	8 (5.92)		0.2 %	-0.45 [-1.11, 0.21]
Hodge 1980	194	7.31 (5.68)	202	7.83 (5.49)		1.1 %	-0.09 [-0.29, 0.10]
Howat 1978	253	5.71 (5.49)	242	7.69 (6.39)		1.2 %	-0.33 [-0.51, -0.15]
Jackson 1967	438	7.23 (4.7)	433	8.2 (5.45)		1.4 %	-0.19 [-0.32, -0.06]
James 1967	406	4.26 (5.2)	397	5.19 (5.42)		1.3 %	-0.17 [-0.31, -0.04]
Kleber 1996	77	1.66 (2.8)	79	1.59 (2.13)		0.7 %	0.03 [-0.29, 0.34]
Mainwaring 1978	791	6.94 (5.96)	316	8.27 (6.62)		1.4 %	-0.22 [-0.35, -0.09]
Mainwaring 1983	458	8.88 (6.4)	224	11 (8.23)		1.3 %	-0.30 [-0.46, -0.14]
Marthaler 1965	145	5.31 (3.75)	124	7.71 (4.7)		0.9 %	-0.57 [-0.81, -0.32]
Marthaler 1965a	42	11.33 (7.59)	32	15.25 (8.55)		0.4 %	-0.48 [-0.95, -0.02]
Marthaler 1970	43	3.44 (2.52)	57	4.4 (3.14)		0.5 %	-0.33 [-0.73, 0.07]
Marthaler 1970a	23	2.57 (2.1)	20	3.95 (2.704)		0.3 %	-0.56 [-1.18, 0.05]
Marthaler 1974	50	5.62 (5.5)	59	8.39 (5.77)		0.6 %	-0.49 [-0.87, -0.10]
Mergele 1968	197	4.83 (3.28)	190	5.57 (4.3)		1.1 %	-0.19 [-0.39, 0.01]
Muhler 1955	219	1.55 (2.645)	225	2.42 (3.291)		1.2 %	-0.29 [-0.48, -0.10]
Muhler 1962	174	8.28 (6.2)	169	10.45 (7.54)		1.1 %	-0.31 [-0.53, -0.10]
Muhler 1970	201	2.87 (3.47)	235	4.05 (3.99)		1.1 %	-0.31 [-0.50, -0.12]
Naylor 1967	494	7.94 (5.09)	479	9.22 (6.2)		1.4 %	-0.23 [-0.35, -0.10]
Naylor 1979	319	8.09 (6.09)	306	10.42 (6.47)		1.3 %	-0.37 [-0.53, -0.21]
Peterson 1967	634	7.63 (5.59)	320	9.19 (6.12)		1.4 %	-0.27 [-0.40, -0.14]
Peterson 1979	467	2.87 (3.66)	245	3.18 (3.86)		1.3 %	-0.08 [-0.24, 0.07]
Reed 1973	362	3.2 (3.79)	397	4 (4.18)		1.3 %	-0.20 [-0.34, -0.06]
Reed 1975	168	3.02 (3.31)	176	4.32 (4.21)		1.1 %	-0.34 [-0.55, -0.13]
Ringelberg 1979	370	5.13 (5.85)	186	6.25 (7.35)		1.2 %	-0.18 [-0.35, 0.00]
Rule 1984	460	4.56 (4.7)	416	6.39 (4.69)		1.4 %	-0.39 [-0.52, -0.26]
Segal 1967	338	2.69 (3.46)	310	3.33 (3.46)		1.3 %	-0.18 [-0.34, -0.03]
Slack 1967	356	5.59 (5.34)	340	5.62 (5.62)		1.3 %	-0.01 [-0.15, 0.14]
Slack 1967a	376	5.64 (4.83)	381	5.95 (5.68)		1.3 %	-0.06 [-0.20, 0.08]
Slack 1971	821	10.04 (7.68)	289	12.83 (8.31)		1.4 %	-0.36 [-0.49, -0.22]
Thomas 1966	309	2.84 (2.92)	155	4.08 (4.11)		1.1 %	-0.37 [-0.56, -0.17]



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Study or subgroup	Higher fluoride N	Mean(SD)	Lower fluoride N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Torell 1965	335	8.09 (6.86)	333	10.16 (6.59)		1.3 %	-0.31 [-0.46, -0.15]
Torell 1965a	148	10.11 (5.11)	137	10.81 (6.2)		1.0 %	-0.12 [-0.36, 0.11]
Torell 1965b	188	10.25 (6.03)	180	12.12 (7.24)		1.1 %	-0.28 [-0.49, -0.08]
Weisenstein 1972	206	4.98 (4)	196	5.6 (4.34)		1.1 %	-0.15 [-0.34, 0.05]
Zacherl 1970	251	3.79 (3.49)	261	6.36 (4.69)		1.2 %	-0.62 [-0.80, -0.44]
Zacherl 1970a	260	8.5 (6.61)	268	15.04 (8.19)		1.2 %	-0.88 [-1.05, -0.70]
Zacherl 1972	231	6.51 (5.21)	216	8.39 (6.58)		1.2 %	-0.32 [-0.50, -0.13]
Zacherl 1972a	684	5.08 (5.21)	210	6.62 (6.25)		1.3 %	-0.28 [-0.44, -0.13]
Zacherl 1973	220	3.55 (5.77)	224	5.04 (6.39)		1.2 %	-0.24 [-0.43, -0.06]
Zacherl 1981	1500	4.1 (5.63)	254	6.02 (7.71)		1.4 %	-0.32 [-0.45, -0.19]
Subtotal (95% CI)	**18698**		**13029**			**60.4 %**	**-0.28 [-0.32, -0.24]**
Heterogeneity: Tau?? = 0.02; Chi?? = 161.89, df = 53 (P<0.00001); I?? =67%							
Test for overall effect: Z = 13.05 (P < 0.00001)							
4 Placebo versus 1450/1500 ppm							
Buhe 1984	421	12.3 (7.88)	427	16.6 (9.23)		1.3 %	-0.50 [-0.64, -0.36]
Cahen 1982	1300	3.54 (3.18)	708	4.05 (3.46)		1.5 %	-0.16 [-0.25, -0.06]
Hanachowicz 1984	473	5.3 (4.45)	472	7.23 (5.59)		1.4 %	-0.38 [-0.51, -0.25]
Hodge 1980	403	6.01 (4.87)	202	7.83 (5.49)		1.2 %	-0.36 [-0.53, -0.19]
Subtotal (95% CI)	**2597**		**1809**			**5.5 %**	**-0.34 [-0.51, -0.18]**
Heterogeneity: Tau?? = 0.02; Chi?? = 19.80, df = 3 (P = 0.00019); I?? =85%							
Test for overall effect: Z = 4.10 (P = 0.000042)							
5 Placebo versus 2400/2500/2800 ppm							
Di Maggio 1980	22	4.45 (0.98)	20	11.55 (3.53)		0.2 %	-2.75 [-3.61, -1.88]
James 1977	403	8.2 (5.993)	379	11.8 (7.165)		1.3 %	-0.55 [-0.69, -0.40]
Lind 1974	592	3.71 (4.38)	575	5.43 (5.28)		1.4 %	-0.35 [-0.47, -0.24]
Piccione 1979	25	13.9 (7.77)	25	16.5 (8.45)		0.3 %	-0.32 [-0.87, 0.24]
Subtotal (95% CI)	**1042**		**999**			**3.2 %**	**-0.72 [-1.11, -0.33]**
Heterogeneity: Tau?? = 0.11; Chi?? = 31.70, df = 3 (P<0.00001); I?? =91%							
Test for overall effect: Z = 3.61 (P = 0.00031)							
6 250 ppm versus 1000/1055/1100/1250 ppm							
Koch 1990	418	10.5 (8)	203	12.7 (9.3)		1.2 %	-0.26 [-0.43, -0.09]
Mitropolous 1984	360	3.61 (3.93)	365	4.29 (4.99)		1.3 %	-0.15 [-0.30, -0.01]
Subtotal (95% CI)	**778**		**568**			**2.5 %**	**-0.20 [-0.31, -0.09]**
Heterogeneity: Tau?? = 0.0; Chi?? = 0.92, df = 1 (P = 0.34); I?? =0.0%							
Test for overall effect: Z = 3.52 (P = 0.00043)							

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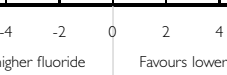
Study or subgroup	Higher fluoride N	Mean(SD)	Lower fluoride N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
7 440/500/550 ppm versus 1000/1055/1100/1250 ppm							
Stookey 2004	174	6.27 (4.5)	168	6.24 (4.5)		1.1 %	0.01 [-0.21, 0.22]
Subtotal (95% CI)	**174**		**168**			**1.1 %**	**0.01 [-0.21, 0.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.06 (P = 0.95)							
8 440/500/550 ppm versus 2400/2500/2800 ppm							
Stookey 2004	180	5.45 (4.49)	168	6.24 (4.5)		1.1 %	-0.18 [-0.39, 0.04]
Subtotal (95% CI)	**180**		**168**			**1.1 %**	**-0.18 [-0.39, 0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.63 (P = 0.10)							
9 1000/1055/1100/1250 ppm versus 1450/1500 ppm							
Conti 1988	1187	1.68 (3.06)	1228	2.22 (3.64)		1.5 %	-0.16 [-0.24, -0.08]
Fogels 1988	963	2.02 (3.21)	950	2.36 (3.47)		1.5 %	-0.10 [-0.19, -0.01]
Marks 1994	1116	4.27 (3.91)	1120	4.33 (3.91)		1.5 %	-0.02 [-0.10, 0.07]
O'Mullane 1997	474	5.17 (5.1)	491	6.04 (5.95)		1.4 %	-0.16 [-0.28, -0.03]
Stephen 1988	930	6.33 (5.72)	921	6.8 (6.22)		1.5 %	-0.08 [-0.17, 0.01]
Stephen 1994	1401	6.75 (6.54)	1419	6.8 (6.36)		1.6 %	-0.01 [-0.08, 0.07]
Subtotal (95% CI)	**6071**		**6129**			**9.1 %**	**-0.08 [-0.14, -0.03]**
Heterogeneity: Tau?? = 0.00; Chi?? = 11.50, df = 5 (P = 0.04); I?? =57%							
Test for overall effect: Z = 2.91 (P = 0.0036)							
10 1000/1055/1100/1250 ppm versus 1700/2000/2200 ppm							
Biesbrock 2001	2211	1.47 (3.125)	1127	1.72 (2.79)		1.6 %	-0.08 [-0.15, -0.01]
Marks 1994	1076	4.04 (3.91)	1120	4.33 (3.91)		1.5 %	-0.07 [-0.16, 0.01]
Subtotal (95% CI)	**3287**		**2247**			**3.1 %**	**-0.08 [-0.13, -0.02]**
Heterogeneity: Tau?? = 0.0; Chi?? = 0.02, df = 1 (P = 0.88); I?? =0.0%							
Test for overall effect: Z = 2.85 (P = 0.0044)							
11 1000/1055/1100/1250 ppm versus 2400/2500/2800 ppm							
Biesbrock 2001	1093	1.37 (3.11)	1127	1.72 (2.79)		1.5 %	-0.12 [-0.20, -0.04]
Chesters 2002	1017	4.96 (5.04)	994	5.47 (5.08)		1.5 %	-0.10 [-0.19, -0.01]
Lu 1987	1352	4.13 (5.12)	703	4.4 (5.17)		1.5 %	-0.05 [-0.14, 0.04]
Marks 1994	2162	3.49 (3.91)	1120	4.33 (3.91)		1.6 %	-0.21 [-0.29, -0.14]
Ripa 1988	858	3.67 (4.59)	1651	3.69 (4.78)		1.5 %	0.00 [-0.09, 0.08]
Stephen 1988	466	5.71 (5.6)	921	6.8 (6.22)		1.4 %	-0.18 [-0.29, -0.07]
Subtotal (95% CI)	**6948**		**6516**			**9.1 %**	**-0.11 [-0.18, -0.05]**
Heterogeneity: Tau?? = 0.00; Chi?? = 17.49, df = 5 (P = 0.004); I?? =71%							
Test for overall effect: Z = 3.30 (P = 0.00097)							



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Study or subgroup	Higher fluoride N	Mean(SD)	Lower fluoride N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Total (95% CI)	**40962**		**32722**			**100.0 %**	**-0.24 [-0.27, -0.20]**
Heterogeneity: Tau?? = 0.02; Chi?? = 421.14, df = 84 (P<0.00001); I?? =80%							
Test for overall effect: Z = 13.04 (P < 0.00001)							

-4 -2 0 2 4

Favours higher fluoride Favours lower fluoride

Analysis 1.4. Comparison 1 Fluoride toothpaste versus placebo or other fluoride toothpaste, Outcome 4 D(M)FT increment (SMD) - nearest to 3 years (54 trials).

Review: Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents

Comparison: 1 Fluoride toothpaste versus placebo or other fluoride toothpaste

Outcome: 4 D(M)FT increment (SMD) - nearest to 3 years (54 trials)

Study or subgroup	HIgher fluoride N	Mean(SD)	Lower fluoride N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Placebo versus 250 ppm							
Reed 1973	379	2.14 (2.55)	397	2.54 (2.45)		1.9 %	-0.16 [-0.30, -0.02]
Subtotal (95% CI)	**379**		**397**			**1.9 %**	**-0.16 [-0.30, -0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.22 (P = 0.026)							
2 Placebo versus 440/500/550 ppm							
Held 1968b	14	0.9 (1.626)	18	2.3 (2.325)		0.3 %	-0.67 [-1.38, 0.05]
Reed 1973	387	2.16 (2.52)	397	2.54 (2.45)		1.9 %	-0.15 [-0.29, -0.01]
Subtotal (95% CI)	**401**		**415**			**2.1 %**	**-0.28 [-0.72, 0.15]**
Heterogeneity: Tau?? = 0.06; Chi?? = 1.88, df = 1 (P = 0.17); I?? =47%							
Test for overall effect: Z = 1.27 (P = 0.20)							
3 Placebo versus 1000/1055/1100/1250 ppm							
Abrams 1980	761	3.41 (2.702)	380	3.99 (2.868)		2.0 %	-0.21 [-0.33, -0.09]
Andlaw 1975	364	3.73 (2.8)	376	4.56 (2.72)		1.8 %	-0.30 [-0.45, -0.16]

-4 -2 0 2 4

Favours higher fluoride Favours lower fluoride

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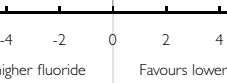
Study or subgroup	HIgher fluoride N	Mean(SD)	Lower fluoride N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Blinkhorn 1983	184	2.45 (2.37)	184	3.51 (2.61)		1.5 %	-0.42 [-0.63, -0.22]
Brudevold 1966	955	2.59 (2.75)	323	3.32 (2.75)		2.0 %	-0.27 [-0.39, -0.14]
Buhe 1984	438	5 (3.21)	427	5.6 (3.25)		1.9 %	-0.19 [-0.32, -0.05]
Fogels 1979	890	4.22 (2.93)	449	4.77 (3.07)		2.0 %	-0.18 [-0.30, -0.07]
Gish 1966	165	3.14 (2.65)	163	3.66 (2.71)		1.4 %	-0.19 [-0.41, 0.02]
Glass 1978	178	3.19 (3.07)	168	4.27 (3.61)		1.4 %	-0.32 [-0.53, -0.11]
Glass 1983	567	1.55 (1.68)	286	2.13 (2.35)		1.9 %	-0.30 [-0.44, -0.16]
Held 1968	32	0.3 (1.07)	31	4.5 (3.003)		0.4 %	-1.85 [-2.45, -1.26]
Held 1968a	19	2.6 (2.436)	17	4.3 (2.951)		0.3 %	-0.62 [-1.29, 0.05]
Hodge 1980	194	4.07 (2.68)	202	4.72 (2.9)		1.5 %	-0.23 [-0.43, -0.03]
Howat 1978	253	3.2 (2.65)	242	4.36 (3.12)		1.6 %	-0.40 [-0.58, -0.22]
Jackson 1967	438	4.58 (4.34)	433	5.13 (4.48)		1.9 %	-0.12 [-0.26, 0.01]
James 1967	406	2.252 (2.55)	397	2.53 (2.47)		1.9 %	-0.11 [-0.25, 0.03]
Kleber 1996	77	1.06 (1.67)	79	1.04 (1.51)		1.0 %	0.01 [-0.30, 0.33]
Marthaler 1965	145	2.57 (2.13)	124	3.81 (2.65)		1.3 %	-0.52 [-0.76, -0.27]
Marthaler 1965a	42	5.12 (3.04)	32	6.22 (3.18)		0.6 %	-0.35 [-0.81, 0.11]
Marthaler 1974	50	3.26 (2.64)	59	4.88 (3.09)		0.8 %	-0.56 [-0.94, -0.17]
Mergele 1968	197	3.62 (2.25)	190	3.87 (2.43)		1.5 %	-0.11 [-0.31, 0.09]
Muhler 1955	219	0.84 (1.584)	225	1.27 (1.854)		1.6 %	-0.25 [-0.44, -0.06]
Muhler 1962	174	4.02 (3.3)	169	5.17 (3.9)		1.4 %	-0.32 [-0.53, -0.10]
Muhler 1970	201	1.48 (2.18)	235	2.19 (2.39)		1.6 %	-0.31 [-0.50, -0.12]
Naylor 1967	494	4.48 (2.74)	479	4.89 (2.86)		2.0 %	-0.15 [-0.27, -0.02]
Naylor 1979	319	4.49 (2.81)	306	5.58 (2.92)		1.8 %	-0.38 [-0.54, -0.22]
Peterson 1967	634	3.42 (2.67)	320	3.98 (2.93)		1.9 %	-0.20 [-0.34, -0.07]
Peterson 1979	467	1.99 (2.35)	245	2.2 (2.56)		1.8 %	-0.09 [-0.24, 0.07]
Reed 1973	362	1.94 (2.47)	397	2.54 (2.45)		1.9 %	-0.24 [-0.39, -0.10]
Reed 1975	168	1.92 (2.06)	176	2.58 (2.39)		1.4 %	-0.29 [-0.51, -0.08]
Ringelberg 1979	370	2.86 (2.92)	186	3.38 (3.29)		1.7 %	-0.17 [-0.35, 0.01]
Rule 1984	460	2.78 (3.22)	416	3.67 (3.06)		1.9 %	-0.28 [-0.42, -0.15]
Slack 1967	356	3.27 (2.83)	340	3.22 (2.73)		1.8 %	0.02 [-0.13, 0.17]
Slack 1967a	376	3.64 (2.75)	381	3.78 (3.08)		1.9 %	-0.05 [-0.19, 0.09]



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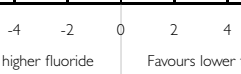
Study or subgroup	HIgher fluoride N	Mean(SD)	Lower fluoride N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Thomas 1966	309	1.61 (2.06)	155	2.32 (2.61)		1.5 %	-0.31 [-0.51, -0.12]
Weisenstein 1972	206	2.9 (2.31)	196	3.4 (2.77)		1.5 %	-0.20 [-0.39, 0.00]
Zacherl 1970	251	1.69 (1.9)	261	2.62 (2.26)		1.7 %	-0.44 [-0.62, -0.27]
Zacherl 1970a	260	3.19 (3.06)	268	5.09 (3.27)		1.7 %	-0.60 [-0.77, -0.42]
Zacherl 1972	231	2.89 (2.72)	216	3.62 (3.28)		1.6 %	-0.24 [-0.43, -0.06]
Zacherl 1972a	684	2.51 (2.68)	210	3.15 (3.22)		1.8 %	-0.23 [-0.38, -0.07]
Zacherl 1973	220	1.68 (2.79)	224	2.6 (3.01)		1.6 %	-0.32 [-0.50, -0.13]
Zacherl 1981	1500	2.25 (3.03)	254	3.26 (3.92)		1.9 %	-0.32 [-0.45, -0.18]
Subtotal (95% CI)	**14616**		**10221**			**64.5 %**	**-0.26 [-0.31, -0.21]**
Heterogeneity: Tau?? = 0.01; Chi?? = 112.04, df = 40 (P<0.00001); I?? =64%							
Test for overall effect: Z = 11.16 (P < 0.00001)							
4 Placebo versus 1450/1500 ppm							
Buhe 1984	421	4.3 (2.84)	427	5.6 (3.25)		1.9 %	-0.43 [-0.56, -0.29]
Cahen 1982	1300	1.58 (1.28)	708	1.85 (1.33)		2.2 %	-0.21 [-0.30, -0.12]
Hanachowicz 1984	473	3.21 (2.56)	472	4.35 (3)		1.9 %	-0.41 [-0.54, -0.28]
Hodge 1980	403	3.47 (2.63)	202	4.72 (2.9)		1.7 %	-0.46 [-0.63, -0.29]
Subtotal (95% CI)	**2597**		**1809**			**7.7 %**	**-0.37 [-0.50, -0.24]**
Heterogeneity: Tau?? = 0.01; Chi?? = 12.27, df = 3 (P = 0.01); I?? =76%							
Test for overall effect: Z = 5.52 (P < 0.00001)							
5 Placebo versus 2400/2500/2800 ppm							
Di Maggio 1980	22	1.95 (0.21)	20	3.95 (0.98)		0.2 %	-2.83 [-3.71, -1.96]
Lind 1974	592	2.47 (2.68)	575	3.56 (2.88)		2.0 %	-0.39 [-0.51, -0.28]
Piccione 1979	25	5.9 (5.1)	25	6.9 (5.51)		0.4 %	-0.19 [-0.74, 0.37]
Subtotal (95% CI)	**639**		**620**			**2.6 %**	**-1.05 [-2.14, 0.04]**
Heterogeneity: Tau?? = 0.84; Chi?? = 29.91, df = 2 (P<0.00001); I?? =93%							
Test for overall effect: Z = 1.89 (P = 0.059)							
6 250 ppm versus 1000/1055/1100/1250 ppm							
Koch 1990	418	5.1 (3.3)	203	6 (3.3)		1.7 %	-0.27 [-0.44, -0.10]
Mitropolous 1984	360	2.11 (2.14)	365	2.45 (2.4)		1.8 %	-0.15 [-0.30, 0.00]
Subtotal (95% CI)	**778**		**568**			**3.5 %**	**-0.20 [-0.32, -0.08]**
Heterogeneity: Tau?? = 0.00; Chi?? = 1.17, df = 1 (P = 0.28); I?? =15%							
Test for overall effect: Z = 3.33 (P = 0.00087)							
7 1000/1055/1100/1250 ppm versus 1450/1500 ppm							
Conti 1988	1187	1.02 (1.89)	1228	1.31 (2.14)		2.2 %	-0.14 [-0.22, -0.06]
Fogels 1988	963	1.22 (1.86)	950	1.44 (2)		2.2 %	-0.11 [-0.20, -0.02]



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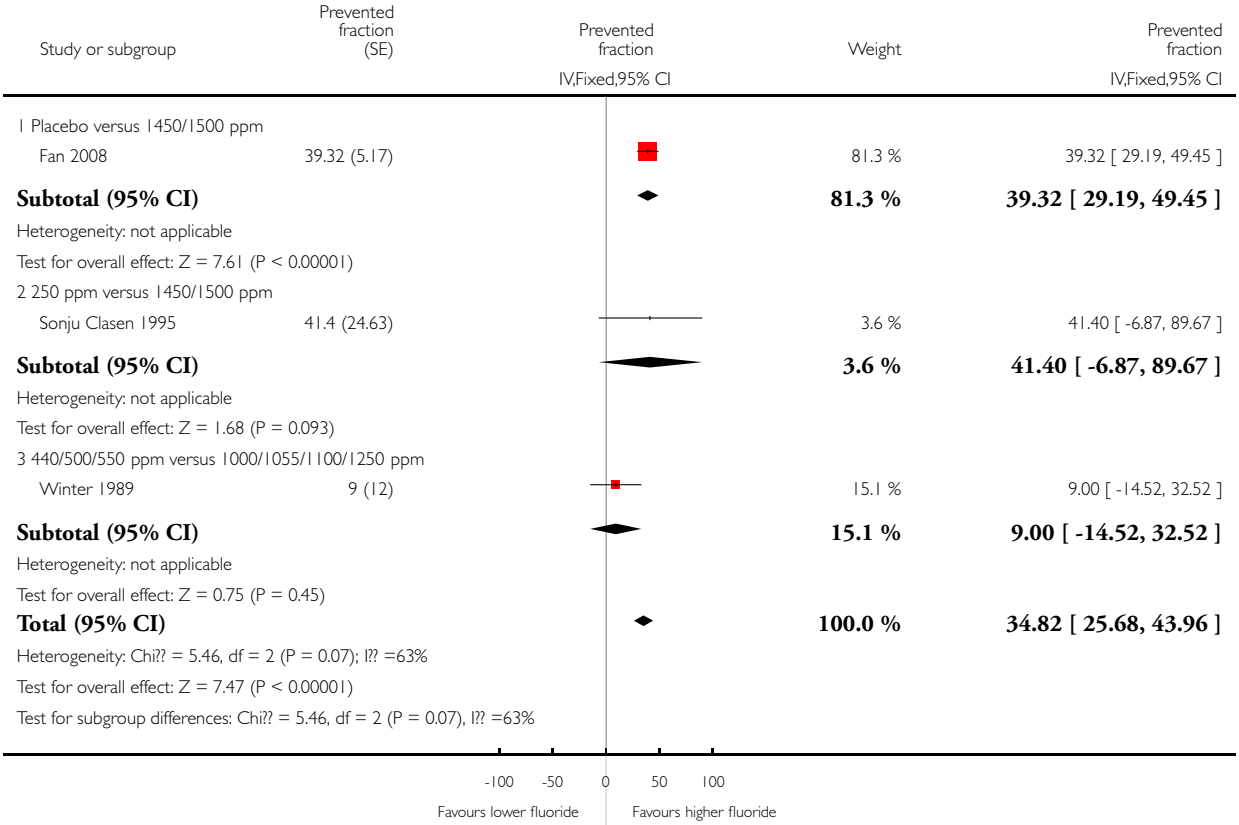
Study or subgroup	Hlgher fluoride N	Mean(SD)	Lower fluoride N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Marks 1994	1116	2.44 (2.22)	1120	2.43 (2.22)		2.2 %	0.00 [-0.08, 0.09]
Subtotal (95% CI)	**3266**		**3298**			**6.6 %**	**-0.08 [-0.17, 0.01]**
Heterogeneity: Tau?? = 0.00; Chi?? = 6.93, df = 2 (P = 0.03); I?? =71%							
Test for overall effect: Z = 1.83 (P = 0.068)							
8 1000/1055/1100/1250 ppm versus 1700/2000/2200 ppm							
Biesbrock 2001	2211	0.92 (1.81)	1127	1.03 (1.81)		2.2 %	-0.06 [-0.13, 0.01]
Marks 1994	1076	2.31 (2.22)	1120	2.43 (2.22)		2.2 %	-0.05 [-0.14, 0.03]
Subtotal (95% CI)	**3287**		**2247**			**4.4 %**	**-0.06 [-0.11, 0.00]**
Heterogeneity: Tau?? = 0.0; Chi?? = 0.01, df = 1 (P = 0.90); I?? =0.0%							
Test for overall effect: Z = 2.08 (P = 0.037)							
9 1000/1055/1100/1250 ppm versus 2400/2500/2800 ppm							
Biesbrock 2001	1093	0.85 (1.82)	1127	1.03 (1.81)		2.2 %	-0.10 [-0.18, -0.02]
Lu 1987	1352	2.37 (2.66)	703	2.58 (2.86)		2.2 %	-0.08 [-0.17, 0.01]
Marks 1994	2162	2.11 (2.22)	1120	2.43 (2.22)		2.2 %	-0.14 [-0.22, -0.07]
Subtotal (95% CI)	**4607**		**2950**			**6.6 %**	**-0.11 [-0.16, -0.07]**
Heterogeneity: Tau?? = 0.0; Chi?? = 1.42, df = 2 (P = 0.49); I?? =0.0%							
Test for overall effect: Z = 4.70 (P < 0.00001)							
Total (95% CI)	**30570**		**22525**			**100.0 %**	**-0.24 [-0.28, -0.20]**
Heterogeneity: Tau?? = 0.02; Chi?? = 268.88, df = 60 (P<0.00001); I?? =78%							
Test for overall effect: Z = 11.80 (P < 0.00001)							

Analysis 1.5. Comparison 1 Fluoride toothpaste versus placebo or other fluoride toothpaste, Outcome 5 d(m)fs increment (prevented fraction) - nearest to 3 years (3 trials).

Review: Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents

Comparison: 1 Fluoride toothpaste versus placebo or other fluoride toothpaste

Outcome: 5 d(m)fs increment (prevented fraction) - nearest to 3 years (3 trials)

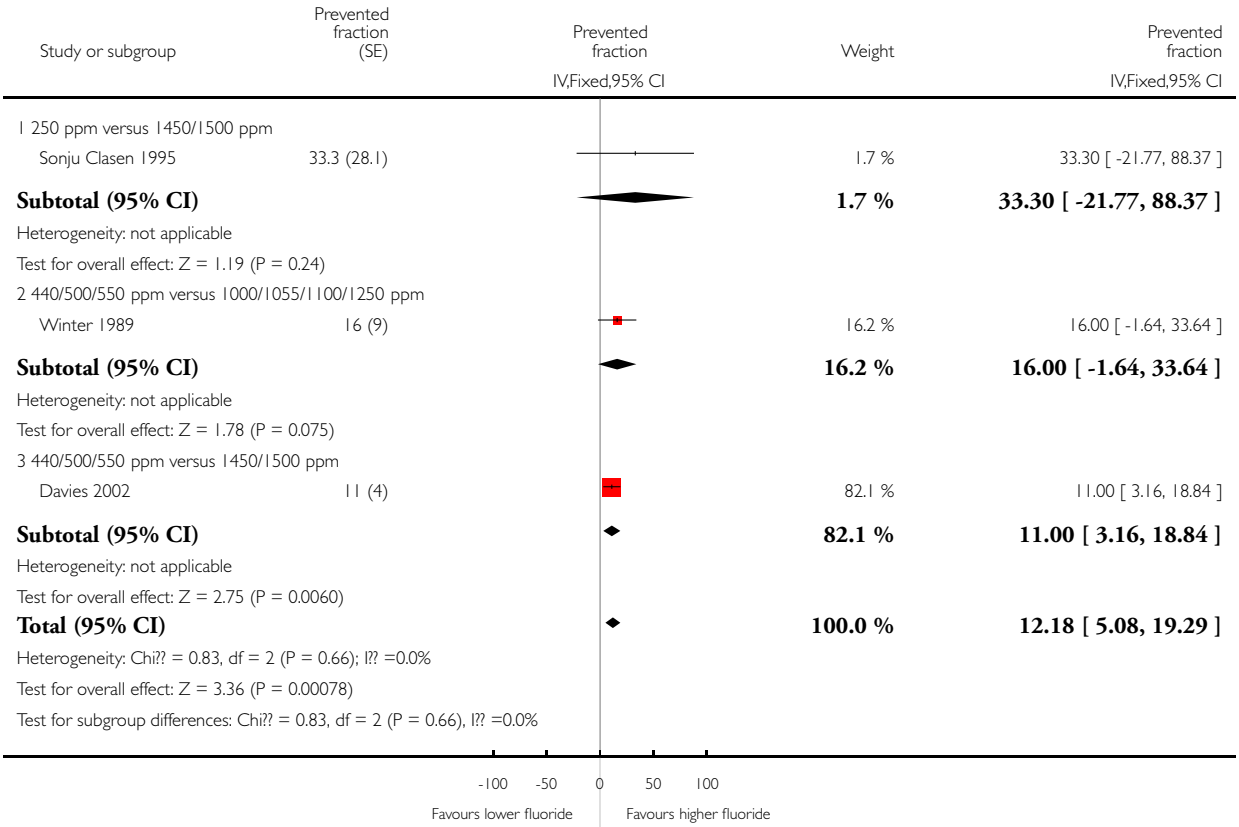


Analysis 1.6. Comparison 1 Fluoride toothpaste versus placebo or other fluoride toothpaste, Outcome 6 d(m)ft increment (prevented fraction) - nearest to 3 years (3 trials).

Review: Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents

Comparison: 1 Fluoride toothpaste versus placebo or other fluoride toothpaste

Outcome: 6 d(m)ft increment (prevented fraction) - nearest to 3 years (3 trials)

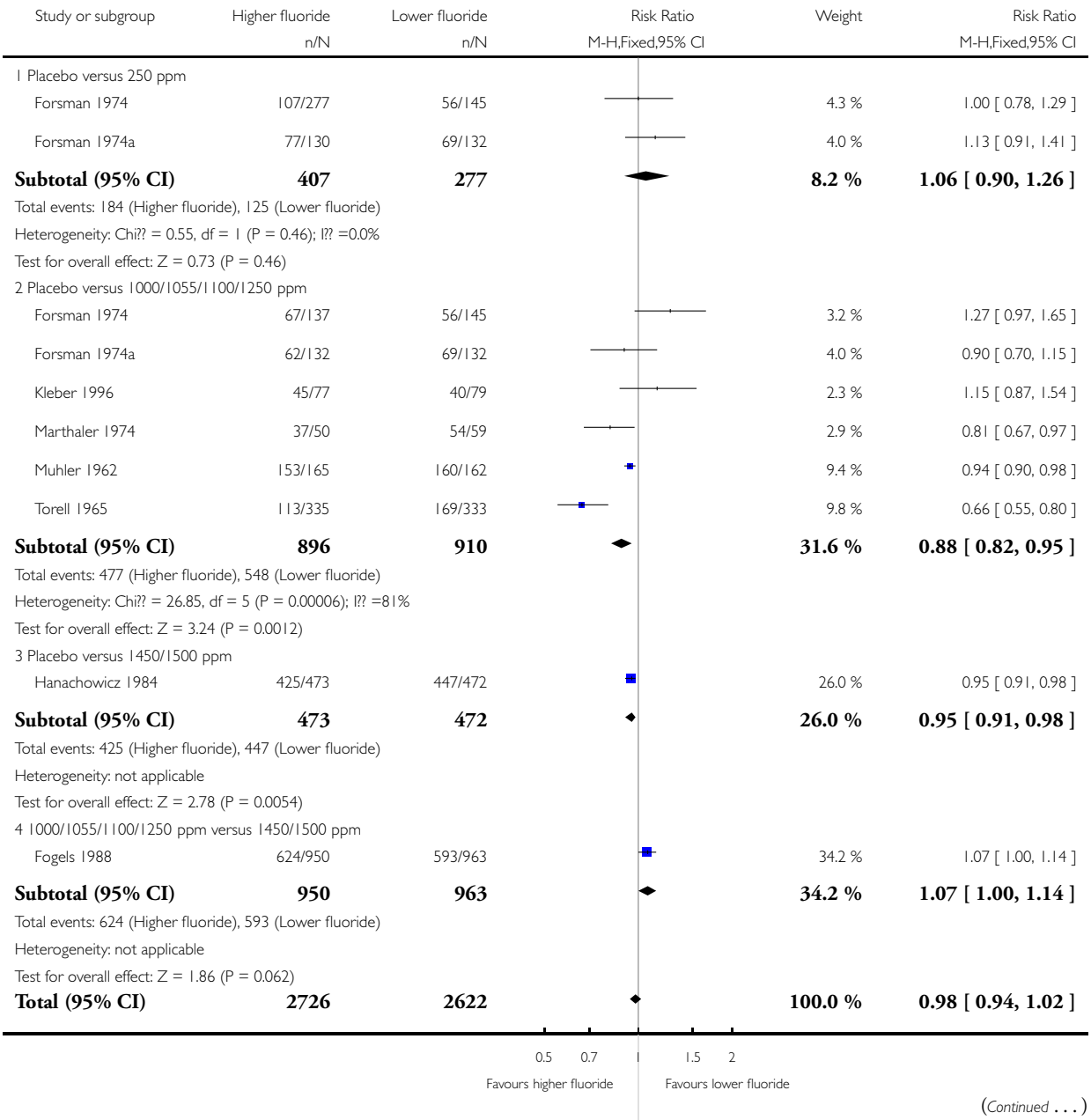


Analysis 1.7. Comparison 1 Fluoride toothpaste versus placebo or other fluoride toothpaste, Outcome 7 Proportion developing new caries (permanent) (8 trials).

Review: Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents

Comparison: 1 Fluoride toothpaste versus placebo or other fluoride toothpaste

Outcome: 7 Proportion developing new caries (permanent) (8 trials)



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Study or subgroup	Higher fluoride n/N	Lower fluoride n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 1710 (Higher fluoride), 1713 (Lower fluoride)					
Heterogeneity: Chi?? = 40.33, df = 9 (P<0.00001); I?? =78%					
Test for overall effect: Z = 1.15 (P = 0.25)					

Analysis 1.8. Comparison 1 Fluoride toothpaste versus placebo or other fluoride toothpaste, Outcome 8 Proportion developing new caries (deciduous) (3 trials).

Review: Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents

Comparison: 1 Fluoride toothpaste versus placebo or other fluoride toothpaste

Outcome: 8 Proportion developing new caries (deciduous) (3 trials)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 250 ppm versus 1450/1500 ppm				
Sonju Clasen 1995	0.00995 (0.2403)		2.0 %	1.01 [0.63, 1.62]
Subtotal (95% CI)			**2.0 %**	**1.01 [0.63, 1.62]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.04 (P = 0.97)				
2 440/500/550 ppm versus 1000/1055/1100/1250 ppm				
Winter 1989	-0.11653 (0.054361)		39.7 %	0.89 [0.80, 0.99]
Subtotal (95% CI)			**39.7 %**	**0.89 [0.80, 0.99]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.14 (P = 0.032)				
3 440/500/550 ppm versus 1450/1500 ppm				
Davies 2002	-0.16252 (0.04487)		58.3 %	0.85 [0.78, 0.93]
Subtotal (95% CI)			**58.3 %**	**0.85 [0.78, 0.93]**
Heterogeneity: not applicable				
Test for overall effect: Z = 3.62 (P = 0.00029)				
Total (95% CI)			**100.0 %**	**0.87 [0.81, 0.93]**
Heterogeneity: Chi?? = 0.83, df = 2 (P = 0.66); I?? =0.0%				
Test for overall effect: Z = 4.11 (P = 0.000040)				
Test for subgroup differences: Chi?? = 0.83, df = 2 (P = 0.66), I?? =0.0%				

ADDITIONAL TABLES

Table 1. Table (D(M)FS increment PF)

Fluoride concentration	Direct comparison	Network meta-analysis
pairwise[1,2]	8.90 [-1.62, 19.42]	9.14 [-3.62, 21.96]
pairwise[1,3]	7.91 [-6.11, 21.94]	15.35 [-1.89, 32.53]
pairwise[1,4]	22.20 [18.68, 25.72]	22.99 [19.34, 26.58]
pairwise[1,5]	22.07 [15.26, 28.88]	29.29 [21.24, 37.46]
pairwise[1,6]		33.7 [16.52, 50.77]
pairwise[1,7]	36.55 [17.46, 55.64]	35.52 [27.23, 43.62]
pairwise[2,3]		6.22 [-13.96, 26.33]
pairwise[2,4]	16.80 [8.47, 25.12]	13.83 [1.09, 26.45]
pairwise[2,5]		20.14 [5.29, 34.96]
pairwise[2,6]		24.59 [3.13, 45.53]
pairwise[2,7]		26.35 [11.47, 41.2]
pairwise[3,4]	0.48 [-14.98, 15.94]	7.63 [-9.50, 24.78]
pairwise[3,5]		13.97 [-4.73, 32.72]
pairwise[3,6]		18.31 [-5.49, 41.85]
pairwise[3,7]	12.66 [-1.65, 26.97]	20.14 [2.31, 38.00]
pairwise[4,5]	9.58 [2.52, 16.64]	6.31 [-1.52, 14.25]
pairwise[4,6]	9.44 [2.12, 16.76]	10.68 [-6.11, 27.6]
pairwise[4,7]	12.15 [5.95, 18.35]	12.53 [4.49, 20.47]
pairwise[5,6]		4.35 [-13.2, 21.89]

Table 1. Table (D(M)FS increment PF) (*Continued*)

pairwise[5,7]		6.22 [-4.58, 16.82]
pairwise[6,7]		1.81 [-16.18, 19.74]

1. Placebo 0 ppm F; 2. 250 ppm F; 3. 440/500/550 ppm F; 4. 1000/1055/1100/1250 ppm F; 5. 1450/1500 ppm F; 6. 1700/2000/2200 ppm F; 7. 2400/2500/2800 ppm F.

Table 2. Table (D(M)FT increment PF)

Fluoride concentration	Direct comparison	Network meta-analysis
pairwise[1,2]	15.75 [2.78, 28.72]	13.47 [-5.2, 32.26]
pairwise[1,3]	31.66 [-11.63, 74.95]	23.79 [-3.36, 51.68]
pairwise[1,4]	22.39 [16.85, 27.93]	24.53 [19.46, 29.61]
pairwise[1,5]	22.27 [16.46, 28.09]	30.08 [17.28, 42.86]
pairwise[1,6]		34.41 [13.65, 55.16]
pairwise[1,7]	37.38 [18.96, 55.81]	44.71 [30.69, 58.32]
pairwise[2,3]		10.38 [-18.76, 39.97]
pairwise[2,4]	14.66 [7.70, 21.62]	11.11 [-7.64, 29.58]
pairwise[2,5]		16.65 [-5.68, 38.83]
pairwise[2,6]		20.99 [-6.81, 48.36]
pairwise[2,7]		31.23 [8.09, 54.08]
pairwise[3,4]		0.75 [-27.40, 28.08]
pairwise[3,5]		6.29 [-23.97, 35.97]
pairwise[3,6]		10.64 [-24.14, 44.67]
pairwise[3,7]		20.99 [-10.40, 51.06]
pairwise[4,5]	11.88 [-2.37, 26.14]	5.56 [-7.10, 18.22]
pairwise[4,6]	6.57 [0.26, 12.89]	9.90 [-10.55, 30.22]

Table 2. Table (D(M)FT increment PF) (*Continued*)

pairwise[4,7]	12.40 [7.64, 17.16]	20.18 [6.38, 33.68]
pairwise[5,6]		4.32 [-18.19, 26.50]
pairwise[5,7]		14.63 [-3.85, 32.62]
pairwise[6,7]		10.27 [-12.80, 33.20]

Table 3. Table (D(M)FS increment SMD)

Fluoride concentration	Direct comparison	Network meta-analysis
pairwise[1,2]	-0.09 [-0.19, 0.02]	-0.11 [-0.23, 0.01]
pairwise[1,3]	-0.07 [-0.21, 0.06]	-0.17 [-0.33, 0]
pairwise[1,4]	-0.28 [-0.32, -0.24]	-0.28 [-0.32, -0.25]
pairwise[1,5]	-0.34 [-0.51, -0.18]	-0.35 [-0.43, -0.28]
pairwise[1,6]		-0.38 [-0.53, -0.23]
pairwise[1,7]	-0.72 [-1.11, -0.33]	-0.42 [-0.5, -0.34]
pairwise[2,3]		-0.06 [-0.25, 0.14]
pairwise[2,4]	-0.20 [-0.31, -0.09]	-0.17 [-0.3, -0.05]
pairwise[2,5]		-0.25 [-0.39, -0.1]
pairwise[2,6]		-0.27 [-0.46, -0.07]
pairwise[2,7]		-0.31 [-0.46, -0.17]
pairwise[3,4]	0.01 [-0.21, 0.22]	-0.11 [-0.28, 0.05]
pairwise[3,5]		-0.19 [-0.37, 0]
pairwise[3,6]		-0.21 [-0.43, 0.01]
pairwise[3,7]	-0.18 [-0.39, 0.04]	-0.25 [-0.43, -0.08]
pairwise[4,5]	-0.08 [-0.14, -0.03]	-0.07 [-0.15, 0]
pairwise[4,6]	-0.08 [-0.13, -0.02]	-0.09 [-0.24, 0.05]

Table 3. Table (D(M)FS increment SMD) (*Continued*)

pairwise[4,7]	-0.11 [-0.18, -0.05]	-0.14 [-0.22, -0.06]
pairwise[5,6]		-0.02 [-0.18, 0.13]
pairwise[5,7]		-0.07 [-0.17, 0.04]
pairwise[6,7]		-0.04 [-0.2, 0.11]

Table 4. Table (D(M)FT increment SMD)

Fluoride concentration	Direct comparison	Network meta-analysis
pairwise[1,2]	-0.16 [-0.30, -0.02]	-0.10 [-0.25, 0.04]
pairwise[1,3]	-0.28 [-0.72, 0.15]	-0.18 [-0.41, 0.04]
pairwise[1,4]	-0.26 [-0.31, -0.21]	-0.26 [-0.31, -0.23]
pairwise[1,5]	-0.37 [-0.50, -0.24]	-0.35 [-0.45, -0.25]
pairwise[1,6]		-0.35 [-0.5, -0.21]
pairwise[1,7]	-1.05 [-2.14, 0.04]	-0.4 [-0.52, -0.3]
pairwise[2,3]		-0.08 [-0.33, 0.16]
pairwise[2,4]	-0.20 [-0.32, -0.08]	-0.17 [-0.31, -0.02]
pairwise[2,5]		-0.25 [-0.42, -0.08]
pairwise[2,6]		-0.25 [-0.45, -0.05]
pairwise[2,7]		-0.31 [-0.49, -0.13]
pairwise[3,4]		-0.09 [-0.31, 0.14]
pairwise[3,5]		-0.17 [-0.41, 0.08]
pairwise[3,6]		-0.17 [-0.43, 0.1]
pairwise[3,7]		-0.23 [-0.47, 0.02]
pairwise[4,5]	-0.08 [-0.17, 0.01]	-0.08 [-0.18, 0.01]
pairwise[4,6]	-0.06 [-0.11, -0.00]	-0.08 [-0.23, 0.06]

Table 4. Table (D(M)FT increment SMD) (*Continued*)

pairwise[4,7]	-0.11 [-0.16, -0.07]	-0.14 [-0.25, -0.04]
pairwise[5,6]		0 [-0.16, 0.15]
pairwise[5,7]		-0.06 [-0.2, 0.08]
pairwise[6,7]		-0.06 [-0.22, 0.1]

APPENDICES

Appendix 1. MEDLINE (OVID) search strategy

1. Dental Caries.mp. or exp Dental Caries/
2. Dental Caries Activity Tests/
3. Dental Caries Susceptibility/
4. carie$.mp.
5. DMF$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. exp Fluorides/
7. exp Fluorides, Topical/
8. FLUOR$.mp.
9. AMF.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10. AMINE F.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11. SNF2.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12. STANNOUS F.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
13. NAF.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14. SODIUM F.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. APF.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16. SMFP.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
17. MFP.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
18. monofluor$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
19. exp Cariostatic Agents/
20. exp Dentifrices/
21. toothpaste$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
22. paste$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
23. dentrifice$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
24. 4 or 1 or 3 or 2 or 5
25. 6 or 11 or 7 or 9 or 17 or 12 or 15 or 14 or 8 or 18 or 19 or 16 or 10 or 13
26. 22 or 21 or 23 or 20
27. 25 and 24 and 26

WHAT'S NEW

Last assessed as up-to-date: 25 August 2009.

Date	Event	Description
20 January 2010	Amended	Minor edits (contact details and acknowledgements).

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

Draft the protocol	Anne-Marie Glenny (AMG), Tanya Walsh (TW), Helen Worthington (HW), Valeria Marinho (VM)
Develop a search strategy	AMG, VM
Search for trials	AMG, Priscilla Appelbe (PA)
Obtain copies of trials	PA
Select which trials to include	TW, HW, VM
Extract data from trials	TW, HW, VM, PA
Enter data into RevMan	PA
Carry out the analysis	AMG, TW, HW, VM, Xin Shi (XS)
Interpret the analysis	AMG, TW, HW, VM, XS
Draft the final review	AMG, TW, HW, VM
Update the review	AMG, TW, HW, VM

DECLARATIONS OF INTEREST

Helen Worthington has an office located in the University of Manchester's Dental Health Unit which is jointly supported by the University of Manchester and Colgate Palmolive. Helen Worthington does not receive any funding from Colgate Palmolive and does not view this as a conflict of interest. Helen Worthington was involved in the design and analysis of three included trials. She did not undertake the risk of bias assessment or the data extraction for these trials. There are no other known potential conflicts of interest.

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INDEX TERMS

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Cariostatic Agents [administration & dosage; *therapeutic use]; Dental Caries [*prevention & control]; Fluorides [administration & dosage; *therapeutic use]; Randomized Controlled Trials as Topic; Toothpastes [chemistry; *therapeutic use]

MeSH check words

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