Supplemental fluoride use for moderate and high caries risk adults: a systematic review

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Abstract

Objectives: Multiple systematic reviews have evaluated fluorides for caries prevention in children, but a need to review the literature regarding supplemental fluoride use in adults still remains. The purpose of this systematic review is to evaluate the research regarding professional and/or supplemental self-applied fluoride for preventing and remineralizing caries in moderate and high caries risk adults.
Methods: Utilizing multiple databases, a comprehensive search was undertaken in both foreign and English languages. Studies included were randomized control trials (RCT) or clinical trials conducted in moderate or high caries risk adult populations, evaluating self- or professionally applied fluoride with the outcomes of caries reduction/remineralization. Studies were excluded if they were *in situ*, *in vitro*, split mouth design, or with unclear outcomes specific to fluorides. A quality evaluation of the studies used a checklist of critical domains and elements for an RCT.
Results: Seventeen studies were included in the systematic review. Findings were categorized into the following groups: sodium fluoride (NaF) and amine/potassium fluoride mouthrinses of varying strengths, NaF gels and pastes, NaF varnish, and stannous fluoride. Quality evaluation scores varied from 50.2 percent to 88.9 percent.
Conclusions: The strongest studies demonstrated the following modalities as moderately effective in higher caries risk adults: low strength NaF rinses [relative risk reduction (RRR) for carious lesions: 50-148 percent]; 1.1 percent NaF pastes/gels (RRR for root lesion remineralization: 35-122 percent); fluoride varnishes [RRR for RC remineralization: 63 percent; RRR for decrease in decayed, missing, and filled surfaces: 50 percent]. Evidence regarding 1.1 percent NaF and 5 percent NaF varnishes related primarily to root caries and older adults.

Introduction

Dental caries is as much of a problem in adults as in children. US data from 1999-2004 demonstrate that the prevalence of decayed and filled tooth surfaces (DFS) in adults younger than 64 years of age was 19 surfaces; in persons over 65, this number rises to nearly 30 surfaces (1). Griffin *et al.* estimated the incidence of new carious lesions in adults to be one new coronal lesion per year (2). Given a mean of 19 retained teeth in seniors (1), along with issues of exposed root surfaces and reduced ability to perform oral self-care that accompanies many diseases, caries remains an important issue in oral health care for adults.

One of dentistry's important and well-studied tools for reducing caries is fluoride. Although the positive effects are well documented in children, there is recent, less extensive evidence suggesting that fluoride reduces carious lesions in adults (3). In erupted teeth, fluoride is known to reduce caries in three ways: inhibiting bacterial metabolism of fermentable carbohydrates; enhancing remineralization by the incorporation of

available fluoride into the tooth structure during acid attacks; and reducing the tooth's solubility during subsequent acid attacks (4,5).

Previous systematic reviews have partially addressed the question of appropriate use of fluoride for adults who are at moderate or high risk for caries. In 2001, Bader *et al*. reviewed caries prevention methods that included fluoride (6). However, only one reference addressed adult use of fluoride alone (except for the review in patients receiving radiotherapy). In 2006, the American Dental Association (ADA) published evidence-based clinical recommendations regarding professionally applied fluoride, but did not encompass the use of prescription or home fluorides in this population (7). In 2007, Griffin *et al*. provided a systematic review and meta-analysis that defined the positive benefits of fluoride in the general adult population (3). Despite these advances in our knowledge, none of the previous studies specifically addressed the question of the most appropriate use of supplemental fluoride beyond water fluoridation and over-the-counter fluoride-containing toothpastes when treating adults with moderate or high risk for caries. With these gaps in mind, a systematic review of the literature was conducted to address the following question: What research supports the use of professional and/or supplemental self-applied fluoride for preventing and remineralizing caries in moderate and high risk adult patients? Specifically, we sought to review studies that identified adult populations with at least moderate risk for caries and identified outcomes regarding carious lesions with a dental professional-initiated fluoride intervention.

Methods

One author (MJ) conducted an electronic search under the guidance of an information services and education librarian at Boston University Alumni Medical Library. The databases searched include Ovid MEDLINE (1950 to April Week 1, 2008), PubMed, Cochrane Reviews, Evidence Based Medicine Reviews by the American College of Physicians (ACP) Journal Club, The ADA's Evidence-Based Dentistry Web site and Google Scholar. Search terms utilized in Ovid MEDLINE were fluorides, topical/ or sodium fl/, dental caries/ prevention and control, limited to adults (all groups), and initially limited to the English language. A second search was conducted and not limited to English for relevant studies in other languages. The search terms utilized in PubMed were professionally applied fluoride, fluoride varnish, adult, and caries. Search terms utilized for the Cochrane Reviews, ACP Journal Club and Google Scholar were the same as our Ovid MEDLINE search strategy. In addition, an Ovid AutoAlert and PubMed Alert were established by the librarian to identify newly indexed studies since the time of the initial electronic search. The PubMed alert is still currently active. Finally, a hand search was performed of all references from the full text articles. Figure 1 depicts the flow of article review and selection.

Four authors reviewed the initial list of titles and abstracts (where available) and reached a consensus as to which full text papers were to be retrieved. These full text papers were evaluated independently by two reviewers (MJ, GG) utilizing a screening form slightly modified from the one developed by Griffin and colleagues (3). This enabled us to make a determination whether a particular article was a source of background information or a clinical trial necessitating further review. Inclusion criteria were: randomized control trial (RCT) or clinical trial conducted in adult humans, evaluating a self- or professionally applied fluoride intervention in moderate to high caries risk individuals or populations, and having defined outcomes of either reduction in carious lesions or higher levels of caries remineralization when compared with controls. Study participants were considered at moderate or high risk for caries if they met criteria published in the ADA's recommendations for professional fluoride use (7) or the population demonstrated a high caries history or higher than usual degree of risk. Exclusion criteria were *in situ*, *in vitro*, or of split-mouth design, conducted solely or predominantly in children or adolescents, if the fluoride intervention could not be ascertained, or outcomes were not clear. A table of excluded studies was maintained, indicating the reason for their exclusion (available on request from the first author). The 17 studies that met our inclusion criteria were evaluated by the four authors of this paper and their quality was appraised utilizing the 10 quality domains and their associated elements that are recognized as important for an RCT, as reported by the Agency for Healthcare Research and Quality, and shown in Table 1 (8). Essential elements in each domain are bolded and were given a maximum score of 1.0; nonessential elements were given a maximum score of 0.25. Four reviewers independently evaluated and scored each paper from 0 to 13, and subsequently met as a group to discuss these critical appraisals. An overall quality score was computed by adding the scores from each reviewer, dividing by 52 (the greatest possible score for four reviewers) and multiplying by 100 to convert to a percent. In addition, data abstraction for the evidence table was completed independently by two reviewers, and used for development of Table 2. Specifically, reviewers identified population description, risk assessment, statistical findings, and outcomes related to caries prevention or lesion remineralization pertaining to the fluoride intervention.

Results

The Ovid MEDLINE search produced 146 English language entries with 43 identified for full text review and 50 foreign language entries with 19 identified for further review (see

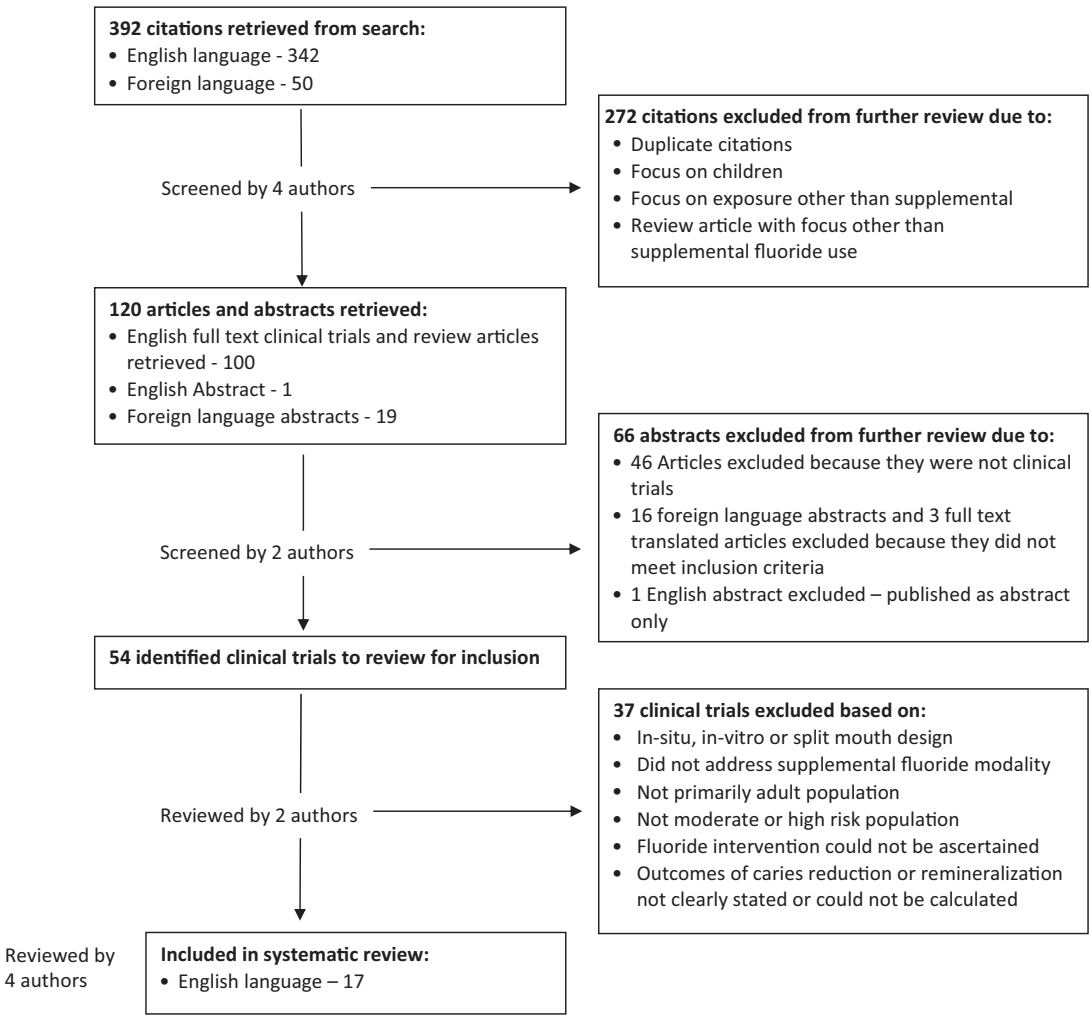

Figure 1 Flow chart of systematic review process.

Figure 1). The PubMed search resulted in 159 entries; many duplicated the Ovid MEDLINE results and 21 were suitable for full text review. Google Scholar retrieved one entry and an additional 34 were located by the hand search of references. This produced a total of 98 full text English language articles and one abstract. Of these 98 articles, 52 were clinical trials of which 15 met the inclusion criteria. Of the 50 foreign language titles, 19 warranted further evaluation. All 19 titles included English language abstracts. Three were found appropriate for full text review and were translated (Italian, Polish, and Swedish), but none were appropriate for inclusion in the final evaluation of articles. Two additional English language RCTs were identified at a later date through PubMed alerts (November 2008 and June 2009), totaling 17 articles for inclusion in the review.

A synopsis of the 17 studies included in the final systematic review of professionally or self-applied topical fluoride is presented in Table 2. Six studies had populations over 60 years of age and four were in populations that were post head and neck radiation treatment. Results are categorized by type of fluoride used: sodium fluoride (NaF) mouthrinses of varying strengths [5 studies (9-13)], 5,000 ppm NaF gel/paste [7 studies (14-20)], NaF varnish [2 studies (20,21)], amine/potassium fluoride mouthrinse [1 study (22)] and stannous fluoride [3 studies (23-26)].

Table 3 presents the overall quality score for each clinical trial with quality scores ≥75 percent bolded, as well as an assessment of the internal and external validity of the 17 studies. Ten of the 17 studies had quality scores ≥75 percent, with representation in all categories of supplemental delivery modes except stannous fluoride where no studies reached the threshold score. Internal validity includes the domain elements of randomization, blinding, clearly detailed interventions, and appropriate statistical analysis, all of which

Table 1 Domains and Elements Used for Quality Evaluation of Included Studies (8)

Domain	Elements
Study question	• **Clearly focused and appropriate question**
Study population	• Description of study population • **Specific inclusion and exclusion criteria** • Sample size justification
Randomization	• Adequate approach to sequence generation • **Adequate concealment method used** • Similarity of groups at baseline
Blinding	• **Double-blinding to treatment allocation**
Interventions	• **Interventions clearly detailed for all study groups** • Compliance with intervention • Equal treatment of groups except for intervention
Outcomes	• **Primary and secondary outcome measures specified** • Assessment method standard, valid, and reliable
Statistical analysis	• **Appropriate analytic techniques that address study withdrawals, loss to follow-up, missing data, and intention to treat** • Power calculation • Assessment of confounding • Methods of handling withdrawals, loss to F/U & missing data • Assessment of heterogeneity, if applicable
Results	• **Measure of effect for outcomes and appropriate measure of precision** • Proportion of eligible subjects recruited into study and followed up at each assessment
Discussion	• **Conclusions supported by results with possible biases and limitations taken into consideration**
Funding or sponsorship	• **Type and sources of support for study**

Note: Elements appearing in bold are considered essential elements. Scoring: Bolded items = 1 point, nonbolded = 0.25 points; maximum total = 13 pts.

strengthen the validity of the findings. None of the studies scored well regarding description of the randomization process; however, six of the ten studies scoring ≥75 percent were rated good in the remaining three categories for internal validity (blinding, interventions, and statistical analysis) with two in each of the modes of NaF mouthrinse, 1.1 percent NaF gel/paste and 5 percent NaF varnish.

External validity or generalizability reflects how applicable these findings may be to a larger population than the study group. Subject characteristics, treatment regimen, and delivery of treatment were taken into consideration by the four reviewers when determining how generalizable these findings might be for a typical dental practice. Three of the six studies with high quality scores and overall good internal validity also had good generalizability. These were one fluoride varnish study [Shaeken *et al.* (21)] and two studies evaluating 1.1 percent NaF fluoride gel/paste [Baysan *et al.* (14) and DePaola (16)].

The category of NaF paste/gels presents the strongest evidence in Table 2. Baysan *et al.* and DePaola evaluated adults with known root caries and interventions with a self-applied highly fluoridated toothpaste or gel (5,000 ppm F); it should be noted, however, that water fluoridation was not reported for either study (14,16). DePaola utilized a professional NaF gel four times per year and a prescription NaF gel daily for the experimental group; therefore, it is unclear how much of the caries reduction was due to the professional NaF application (12,000 ppm F) and how much was attributed to the self-applied NaF (5,000 ppm F) (16). Ekstrand *et al.* also demonstrated the effectiveness of 5,000 ppm F paste at remineralizing root carious lesions (20). This study was conducted in homebound elderly that resided in a fluoride-deficient area. The study by Spak *et al.* involved subjects post head and neck radiation therapy, which is a high risk population, but not very generalizable to a larger adult population (15). The value of this study is that it demonstrates that 5,000 ppm NaF gel was sufficient to inhibit caries almost completely in compliant xerostomic patients that have an unstimulated salivary flow of <0.1 mL min^{-1}.

The NaF rinse category had four studies with scores ≥75 percent. Wyatt *et al.* also had good internal validity scores, but the study evaluated subjects in long term care settings and utilized nursing staff to administer the rinse daily (9). Though very relevant to the growing senior population, this may not necessarily be generalizable to a greater adult population. Ripa *et al.* also had a good overall quality score and good internal validity. They found that the low strength NaF rinse was not significantly beneficial to the overall adult population, but did significantly reduce root caries in a subpopulation of older adults (13). However, this subpopulation was small and not as well described in the study and, therefore, less generalizable. Fure *et al.* and Wallace *et al.* both received quality scores above 75 percent, but only scored adequately on two of the four domains of internal validity (10,11). They noted that using the low level fluoride rinse (226 ppm) would statistically reduce root caries. These findings have good generalizability because they were conducted in participants with a moderate to high individual caries risk (Fure *et al.* (10)), or in a population with a high root caries prevalence that resided in an optimally fluoridated area [Wallace *et al.* (11)].

The two studies evaluating the use of NaF varnish scored well overall and obtained higher scores in three of the four internal validity domains. However, the fluoride varnish

Table 2 Studies Included in Systematic Review

Study (yr) (ref)	Caries risk status	Experimental group (n)	Comparative group (n)	Duration	Outcome (exp versus control)
NaF Mouthrinses					
Wyatt *et al*. (2004) (9)	Population risk: elders in LTC facility; mean # of 6.9 carious surfaces (4.6 root and 2.3 coronal) Water F: not reported	0.2% NaF rinse (905 ppm) daily (38)	Placebo rinse (37)	2 years	–24% versus +6% change in root and coronal carious surfaces/group ($P < 0.001$, X^2)
Fure *et al*. (1998) (10)	Individual risk: at least two of five risk factors: ≥1 active carious lesion, ↑ strep mutans, ↑ *lactobacilli*, low salivary buffer capacity, high plaque index Water F: 0.1-0.2 ppm	0.05% NaF rinse 2×/day × 1 minute and OTC NaF paste (1,500 ppm) (55)	Brush as usual with OTC NaF paste (1,500 ppm) (32)	2 years	RC DFS increments/subject 0.8SD1.4 versus 2.3SD2.1 ($P < 0.002$, ANOVA, test of Scheffe)
Wallace *et al*. (1993) (11)	Population risk: seniors with pop RC prevalence = 69.7% Water F: optimal	0.05% NaF rinse 1×/day (148)	Placebo rinse 1×/day (171)	4 years	RC remineralization/group 1.53SD2.03 versus 1.11SD1.74 ($P < 0.05$, ANCOVA) New RC 1.72SD2.42 versus 1.99SD2.65 NS
Geiger *et al*. (1992) (12)	Individual risk: orthodontic tx Water F: not reported	0.05% NaF rinse 1×/day (113)	Noncompliers w/rinse, used ≤10 mL every other day (93)	9-49 months	White spot lesions/group 21% versus 49% ($P < 0.0001$, X^2)
Ripa *et al*. (1987) (13)	Individual risk: DMFS > 4 Subpop of higher risk because of age Water F: <0.3 ppm	0.05% NaF rinse 1×/day × 1 minute and OTC fluoride paste (381)	Placebo rinse and OTC fluoride paste (350)	3 years	DMFS coronal increments/group 2.38SD2.82 versus 2.43SD2.99 NS DFS RC increments/group 0.36SD1.10 versus 0.43SD1.38 NS 45-65y/o interprox RC increments/group 0.17SD0.56 versus 0.34SD0.89 ($P < 0.05$, *t*-test)
1.1% NaF Paste or Gel					
Baysan *et al*. (2001) (14)	Individual risk: ≥1 RC lesion Water F: not reported	1.1% NaF paste (5,000 ppm) 1×/day (107)	OTC NaF paste (1,100 ppm) at least 1×/day (94)	6 months	RC remineralization/group 56.9% versus 28.6% ($P = 0.002$, logistic regression with # of teeth and baseline plaque scores as covariates, and X^2)
Spak *et al*. (1984) (15)	Individual risk: Post H&N XRT Water F: <0.2 ppm	1.1% NaF gel (5,000 ppm) in trays 1×/day ×5 minutes (18)	1.1% NaF gel thru XRT; then 1.23% APF 1×/day × 4 weeks; then return to 1.1% NaF gel in trays (19)	1 year	Caries increment/group 4.3SD8.6 versus 5.3SD8.8 NS
DePaola (1983) (16)	Individual risk: older adults with ≥1 buccal RC Water F: not reported	2% NaF gel (12,000 ppm) 4×/year and 1.1%NaF gel (5,000 ppm) 1×/day and OTC fluoride paste 2×/day (35)	Placebo gels and OTC fluoride paste 2×/day (36)	1 year	RC remineralization/group 88.6% versus 27.8% ($P < 0.025$, X^2)
Horiot *et al*. (1983) (17)	Individual risk: post H&N XRT Water F: not reported	450 ppm F gel in trays 1×/day × 5 minutes (99)	1,350 ppm F paste 2×/day × 3 minutes (91)	1-3 years	Caries rates/subject 3% versus 11% NS
Toolson *et al*. (1978) (18)	Individual risk: overdenture pts with new caries within 12 months Water F: not reported	1.1% NaF gel (5,000 ppm) 1×/day in denture (53)	Placebo gel 1×/day in denture (43)	1 year	RC rates/group 9.4% versus 32.5% ($P < 0.005$, X^2)

Table 2 *Continued*

Study (yr) (ref)	Caries risk status	Experimental group (n)	Comparative group (n)	Duration	Outcome (exp versus control)
Dreizen *et al*. (1977) (19)	Individual risk: post H&N XRT Water F: not reported	1.1% NaF gel (5,000 ppm) in trays 1x/day x 5 minutes (24)	Placebo gel in tray 1x/day x 5 minutes (14)	3 years	DMFS (mean rate/mo)/group 0.13 versus 2.51 ($P < 0.001$, *t*-test)
Ekstrand *et al*. (2008) (20)	Population risk: nursing referral of frail elderly; mean # root caries lesions = 2.09 Water F: 0.5 ppm	1.1% NaF paste (5,000 ppm) 2×/day (64)	OTC NaF toothpaste (1,450 ppm) 2×/day (54)	8 months	RC remineralization/subject 54% versus 40% ($P = 0.02$, ANOVA)
Fluoride varnish					
Ekstrand *et al*. (2008) (20)	Population risk: nursing referral of frail elderly; mean # of RC lesions = 2.09 Water F: 0.5 ppm	5% NaF varnish (22,600 ppm) 1×/mo, applied to active carious lesions by hygienist after brushing with NaF toothpaste (1,450 ppm) 1×/mo (71)	OTC NaF toothpaste (1,450 ppm) 2×/day (54)	8 months	RC remineralization/subject 65% versus 40% ($P < 0.001$, ANOVA)
Schaeken *et al*. (1991) (21)	Individual risk: ≥ 2 DF RC lesions + history of periosurgery Water F: not reported	5% NaF varnish (22,600 ppm)/ 3 months + 3-month period maintenance (15)	3-month period maintenance (13)	1 year	DF surfaces of RC/group 0.67 versus 1.53 ($P < 0.01$, X^2)
Amine/potassium F mouthrinse					
Petersson *et al*. (2007) (22)	Individual risk: ≥2 RC lesions Water F: not reported	Amine/K F rinse 1 minute, 2×/day and Amine F paste (1,400 ppm) (50)	Placebo rinse with amine F paste (1,400 ppm) (50)	1 year	RC remineralization/group 67% versus 7% ($P < 0.001$, Mann Whitney and signed rank test)
Stannous fluorides					
Al-Jabouri *et al*. (1991) (23)	Individual risk: post H&N XRT Water F: not reported	0.4% SnF_2 gel used as paste (56)	1.1% NaF gel in tray 1×/day × 5 minute for 3 mo, then remin. rinse 2×/day	1 year	DMFT rates/group 0.6 versus 0.6 NS RC increment 1.6 versus 5.1 ($P < 0.05$, ANOVA and test of Scheffe)
Klock *et al*. (1985) (24)	Individual risk: unrestored caries and high SM levels Water F: yes (level not reported)	SnF_2 rinse (200 ppm) 2×/day × 1 minute (12)	NaF rinse (200 ppm) 2×/day × 1 minute (7)	2 years	New lesions year 1/group 2.5SD1.7 versus 4.4SD2.4 ($P < 0.05$, Wilcoxon ranking test) New lesions year 2 3.5SD2.4 versus 5.9SD4.3 NS
Scola *et al*. (1966, 1968) (25,26)	Individual risk: ≥1 active lesion Water F: not reported	Various combinations of SnF_2 prophy paste, professional strength rinse and home dentrifice (528)	Placebo of prophy paste, professional rinse and home dentifrice (118)	2 years	Groups that received the three-agent SnF_2 treatment had the greatest reduction in caries. Data showed that each SnF_2 agent contributed to total observed effect. ($P < 0.05$, *t*-test)

Amine/K, amine/potassium fluoride; ANCOVA, analysis of covariance; ANOVA, analysis of variance; APF, acidulated phosphate fluoride; DF, decayed and filled; DFS, decayed & filled surfaces; DMFS, decayed, missing & filled surfaces; F, fluoride; H&N XRT, head and neck radiation therapy; LTC, long term care; mo, month; NaF, sodium fluoride; NS, not significant; OTC, over the counter; prophy, dental prophylaxis; RC, root caries; SD, standard deviation. SM, Streptococcus mutans; SnF, stannous fluoride; y/o, years old.

Table 3 Quality Evaluation of Included Studies

Fluoride type	Study	Overall quality score	Quality domains affecting internal validity			Generalizability (external validity)
NaF Mouthrinse	Wyatt *et al*. (2004) (9)	**88.9%**	Randomization	25%	Poor	Fair
			Blinding	**100**	**Good**	Participants were elders in long-term care facility
			Interventions	**100**	**Good**	
			Stat. analysis	**88**	**Good**	
NaF Mouthrinse	Fure *et al*. (1998) (10)	**77.9%**	Randomization	17%	Poor	**Good**
			Blinding	0	Poor	Community dwelling older adults with moderate to high risk for dental caries
			Interventions	**96**	**Good**	
			Stat. analysis	**86**	**Good**	
NaF Mouthrinse	Wallace *et al*. (1993) (11)	**81.3%**	Randomization	17%	Poor	**Good**
			Blinding	**100**	**Good**	Participants resided in optimally fluoridated area; high root caries prevalence (69.7%)
			Interventions	**100**	**Good**	
			Stat. analysis	66	Fair	
NaF Mouthrinse	Geiger *et al*. (1992) (12)	67.1%	Randomization	6%	Poor	Fair
			Blinding	0	Poor	Participants undergoing active orthodontic treatment
			Interventions	**98**	**Good**	
			Stat. analysis	**72**	**Good**	
NaF Mouthrinse	Ripa *et al*. (1987) (13)	**88.5%**	Randomization	25%	Poor	Fair
			Blinding	**100**	**Good**	Resided in fluoride deficient communities; participants had DMFS > 4 and assessment of exposed roots
			Interventions	**98**	**Good**	
			Stat. analysis	**86**	**Good**	
NaF Paste	Baysan *et al*. (2001) (14)	**80.4%**	Randomization	33%	Poor	**Good**
			Blinding	**88**	**Good**	Adults with one or more primary root carious lesions
			Interventions	**83**	**Good**	
			Stat. analysis	**80**	**Good**	
NaF Gel	Spak *et al*. (1994) (15)	**79.8%**	Randomization	17%	Poor	Fair
			Blinding	63%	Fair	Participants had radiation therapy to head and neck
			Interventions	**92%**	**Good**	
			Stat. analysis	**84**	**Good**	
NaF Gel	DePaola, (1993) (16)	**84.1%**	Randomization	17%	Poor	**Good**
			Blinding	**100**	**Good**	Adults with at least one buccal root surface lesion
			Interventions	**94**	**Good**	
			Stat. analysis	**84**	**Good**	
NaF Gel	Horiot *et al*. (1983) (17)	50.2%	Randomization	0%	Poor	Fair
			Blinding	0	Poor	Participants had radiation therapy to head and neck
			Interventions	**81**	**Good**	
			Stat. analysis	41	Poor	
NaF Gel	Toolson *et al*. (1978) (18)	63.0%	Randomization	6%	Poor	Fair
			Blinding	**75**	**Good**	Participants wore overdentures and had exposed root surfaces
			Interventions	**73**	**Good**	
			Stat. analysis	61	Fair	
NaF Gel	Dreizen *et al*. (1977) (19)	70.9%	Randomization	21%	Poor	Fair
			Blinding	13	Poor	Participants had radiation therapy to head and neck
			Interventions	**79**	**Good**	
			Stat. analysis	67	Fair	
NaF Varnish NaF Toothpaste	Ekstrand *et al*. (2008) (20)	**79.1%**	Randomization	31%	Poor	Fair
			Blinding	**88**	**Good**	Participants were homebound elderly; varnish group was visited 1×/month by hygienist
			Interventions	**83**	**Good**	
			Stat. analysis	**78**	**Good**	
NaF Varnish	Schaeken *et al*. (1991) (21)	**74.5%**	Randomization	17%	Poor	**Good**
			Blinding	**88**	**Good**	Participants had at least two surfaces of root caries and previous periodontal surgery
			Interventions	**100**	**Good**	
			Stat. analysis	**75**	**Good**	

Table 3 *Continued*

Fluoride type	Study	Overall quality score	Quality domains affecting internal validity			Generalizability (external validity)
Amine/potassium Fluoride Mouthrinse	Petersson *et al*. (2007) (22)	**76.7%**	Randomization **Blinding** **Interventions** Stat. Analysis	6% **75** **100** 61	Poor **Good** **Good** Fair	**Good** Adults with at least two primary root carious lesions
SnF2 Gel NaF Gel	Al-Joburi *et al*. (1991) (23)	72.4%	Randomization Blinding **Interventions** Stat. Analysis	19% 63 **100** 67	Poor Fair **Good** Fair	Fair Participants had radiation therapy to head and neck
SnF2 Rinse NaF Rinse	Klock *et al*. (1985) (24)	64.7%	Randomization Blinding **Interventions** **Stat. Analysis**	15% 25 **83** **72**	Poor Poor **Good** **Good**	Fair Participants had unrestored carious lesions and high S. Mutans levels
SnF2 Topical Application (10%)	Scola *et al*. (1966 and 1968) (25,26)	65.7% and 53.2%	Randomization Blinding **Interventions** **Stat. Analysis**	8/11% 38/0 **77/77** **70/68**	Poor Poor **Good** **Good/Fair**	**Good** Participants had at least one active carious lesion

The internal validity was determined by an objective assessment of the quality domains and their associated elements that evaluate randomization, blinding, interventions, and statistical analysis. An average percentage score (based on four reviewers) was computed for each of the four domains. The criteria for grading were as follows: good = ≥75%; fair = 50-74%; and poor = <50%.
The quality assessment for external validity was determined by participants enrolled in the study, the treatment regimens, and the setting of treatment delivery. The following are denoted in bold: Overall quality score > or equal to 75; Internal validity rated as good; External validity rated as good.

intervention evaluated by Ekstrand *et al*., required hygienists to provide the varnish application to active carious lesions in the patients' home on a monthly basis, which may not be a widely feasible method of treatment (20). The study by Shaeken *et al*. is more generalizable because the subjects were appointed four times per year for the varnish application (21). Unfortunately, the numbers of participants involved in Schaeken's study were small.

One study regarding amine/potassium fluoride mouthrinse was assessed in this review. Petersson *et al*. evaluated the efficacy of low-strength amine/potassium fluoride (250 ppm F) rinse in the reversal of root caries (22). The study received a good overall quality score and evaluated a population that could be generalizable to a larger group, but did not score well regarding the randomization process. While this product is currently not available in the United States, it is utilized in Europe.

Table 4 details the strength of evidence for the four modes of supplemental fluoride delivery with the highest quality of evidence, which are low dose daily NaF rinse, 1.1 percent NaF paste/gel, 5 percent NaF fluoride varnish, and amine/potassium fluoride rinse. To describe the strength of the evidence for each category the review focused on three domains: quality, quantity, and consistency (8). Quality of the evidence was quantified by the number of studies that received quality scores of at least 75 percent within that category. Focusing on only those studies, we then examined the quantity and consistency of the evidence for these four delivery modes of supplemental fluoride. Quantity of the evidence refers to the magnitude to which the treatment can be related to the outcome of interest, in this case, prevention or remineralization of carious lesions. Magnitude is quantified here by reporting the absolute risk reduction (ARR, the difference in the rates of an event in the control group versus the experimental group) and the relative risk reduction (RRR, the reduction in the rate of a negative outcome in the treatment group relative to that in the control group) for the outcome of each study. When possible, we also calculated the effect size using Cohen's delta. This is computed by taking the difference between two means (treatment minus control) and dividing by the pooled standard deviation. Cohen's effect size is specifically used to compare the magnitude of the effect of experimental treatments across different studies (27). Finally we evaluated the consistency of evidence or the extent to which similar findings are reported from various studies looking at the same treatment. It should be also realized that the literature at this point does not allow us to separate strategies for moderate or high caries risk based only upon these findings. Further, it should be emphasized that decisions regarding individual patients require a dental professionals' clinical expertise and judgment regarding each specific patient.

Over-the-counter mouthrinses that contain as little as 226 ppm fluoride were well represented in this systematic

Table 4 Quality, Quantity, and Consistency of Evidence for Various Fluoride Modes

Fluoride category	Quality of evidence*	Quantity of evidence†		Consistency of evidence§
		Magnitude‡	Effect size (Cohen's δ)¶	
NaF Mouthrinse (0.2% for Wyatt study, and 0.05% for others)	4/5 studies with scores ≥75%	Wyatt *et al*. (2004) (9); *n* = 75 ARR: 3.4 fewer carious surfaces versus control RRR: 148% decrease in carious surfaces relative to control	0.65 medium effect	A total of 1,212 participants in four studies. All studies highlighted a reduction in caries with fluoride rinse in older and caries at-risk subjects.
		Fure *et al*. (1998) (10); *n* = 87 ARR: 1.5 fewer carious surfaces versus control RRR: 65% reduction in carious surfaces relative to control	0.83 large effect	
		Wallace *et al*. (1993) (11); *n* = 319 ARR: 0.65 fewer DMFS versus control RRR: 71% fewer DMFS relative to control	0.23 small effect	
		Ripa *et al*. (1987) (13); *n* = 731 (only for 45- to 65-year-old subjects) ARR:0.7 fewer interproximal root caries surfaces versus control RRR: 50% fewer interproximal root caries surfaces relative to control	0.23 small effect	
1.1% NaF Paste and Gel	4/7 studies with scores ≥75%	Baysan *et al*. (2001) (paste) (14); *n* = 242 ARR: 28.3% more subjects in treatment group had at least one root carious lesion remineralize versus controls RRR: 99% improvement in remineralization in the treatment group relative to control group	No standard deviations reported, therefore not possible to calculate.	A total of 468 participants in four studies. All studies highlighted show the efficacy of 1.1% NaF gel or paste in the prevention of root caries [and to a lesser degree coronal caries (15)].
		Spak *et al*. (1994) (gel) (15); *n* = 37 No significant difference in caries incidence between the use of 0.42% NaF gel used daily in trays versus 0.42% NaF gel daily in trays and a 4-week daily application of 1.23% F gel		
		DePaola (1993) (12,000 ppm NaF gel and 5,000 ppm Na F paste) (16); *n* = 71 ARR: 51% more noncavitated lesions arrested versus control group and 49% more cavitated lesions arrested versus control group RRR:122% more noncavitated lesions arrested in treatment group relative to control group and 600% more cavitated lesions arrested in treatment group relative to control group Note: For treatment arm, unclear how much of the caries reduction is due to 12,000 ppm NaF professional application and how much is due to 5,000 ppm NaF		
		Ekstrand *et al*. (2008) (paste) (20); *n* = 118 ARR: absolute difference in remineralization of 14% compared with control RRR: 35% more lesions remineralized in treatment group relative to control		

Table 4 *Continued*

Fluoride category	Quality of evidence*	Quantity of evidence†		
		Magnitude‡	Effect size (Cohen's δ)¶	Consistency of evidence§
NaF Varnish	2/2 studies with scores ≥75%	Ekstrand *et al*. (2008) (20); *n* = 125 ARR: absolute difference in remineralization of 25% compared with control RRR:63% more lesions remineralized in treatment group relative to control Schaeken *et al*. (1991) (21); *n* = 28 ARR: 10 fewer mean DMFS versus control RRR: 50% fewer DMFS in treatment group relative to control	As above – not possible to calculate	A total of 153 participants in two studies. Studies consistent in support for NaF varnish, but only for root caries.
Amine K+ Rinse	1/1 study with score ≥ 75%	Petersson *et al*. (2007) (22); *n* = 100 ARR: 60% more lesions remineralized versus control RRR: amine K + rinse 850 times more likely to result in remineralization relative to control	As above – not possible to calculate	Only one study-unable to assess

Definitions of the three domains:

* Quality: The extent to which a study's design, conduct, and analyses minimized selection, measurement, and confounding bias. Defined as the number of studies for each fluoride category with quality scores ≥ 75%.

† Quantity: The extent to which a relationship has been shown between the intervention and the outcome. Defined as:

‡ Magnitude of a treatment effect:

Absolute Risk Reduction (ARR): the absolute difference in the rates of an event in a control group versus the experimental group.

Relative Risk Reduction (RRR): the reduction in the rate of an outcome in the treatment group relative to that in the control group.

¶ Effect size: The magnitude or size of the experimental effect. Calculated using Cohen's δ, assuming the benchmarks of 0.20 as small, 0.50 as medium and 0.80 as large (27).

§ Consistency: For any given topic, the extent to which similar findings are reported from work using similar and different studies.

review. Four studies received quality scores ≥75 percent (9-11,13) with the magnitude of the evidence demonstrating an RRR of 50-148 percent and varying Cohen's effect size measures from small to large. Generally, there was good consistency that this type of fluoride decreases caries and remineralizes lesions.

Seven of the studies evaluated in this review addressed the use of 5,000 ppm NaF products (14-20). Four of these studies had quality scores greater than 75 percent (14-16,20). Three of the studies, Baysan *et al.* (14), DePaola (16), and Ekstrand *et al.* (20) demonstrated an RRR of 35-122 percent regarding remineralization of root lesions, and there was an overall consistency of these studies to show improvement, primarily in adults with root caries.

The studies included in this systematic review regarding professionally applied fluoride follow closely with the recommendations presented in the ADA's evidence based clinical recommendations (7). Two studies, Ekstrand *et al.* (20) and Schaeken *et al.* (21), addressed the use of NaF varnish in older adults. Both of the studies showed moderate effect magnitude, with RRRs of 50 percent regarding new root caries surfaces [Schaeken (21)] and 63 percent regarding root lesion remineralization [Ekstrand (20)], and consistently show improvement in caries rates.

Discussion

This systematic review of clinical trials presents modest evidence for the effectiveness of supplemental fluoride use for adult patients at moderate and high risk for caries. As identified in Table 4, for several modes of fluoride, there were studies that supported their use that were well executed and reported.

Four studies evaluating NaF rinses were rated ≥75 percent overall, and all found this mode of fluoride effective, with the caveat of Ripa *et al.* only seeing this effect in an older subpopulation. While they did not find a significant difference when using this rinse in the general adult population, for higher risk older patients, they did note a significant improvement between the fluoride rinse and placebo group on interproximal root surfaces (13). This finding coincides with the ADA statement noting adult patients not at moderate or high risk for caries will most likely not receive any benefit from fluoride above what they would receive from daily home brushing and water fluoridation (7). Leverett, who performed a review of the literature regarding fluoride mouthrinses, concluded they were not efficient, given the oral care noted in current US populations, except in cases of higher risk populations (28), which is the focus of this systematic review.

A comparison does not exist between 1.1 percent NaF gel and paste, so choice of delivery should, at least for now, be based on patient compliance. Using the paste instead of the gel has the advantage of a one step procedure, brushing alone, rather than brushing with an OTC toothpaste and then following with an application of the fluoride gel, or using fluoride tray carriers. Nordstrum and Birkhed noted that using a 5,000 ppm toothpaste and spitting without rinsing greatly increased the oral levels of fluoride versus use of an over-the-counter toothpaste, or using the 1.1 percent paste and rinsing afterwards (29).

Published studies suggest that higher levels of fluoride can have a greater impact on the remineralization of teeth on both enamel and root surfaces. ten Cate *et al.* noted that *in vitro*, 5,000 ppm fluoride demonstrated a significantly higher level of remineralization and inhibited demineralization, compared with 1,500 ppm (30). Biesbrock *et al.* demonstrated *in vivo* that as the levels of fluoride in toothpaste rose from 1,100 ppm to 2,800 ppm, the caries reduction levels also rose statistically in a group of children, demonstrating a positive dose-response effect (31). This may be an important consideration for root caries, which involves primarily dentin and cementum, where a higher level of fluoride may be required for remineralization (32,33).

Two studies identified in this review evaluated NaF varnish (20,21). An important limitation is that both studies addressed only root lesions and not coronal lesions. However, this also demonstrates the advantage of this type of fluoride to target root surface lesions. Much like the proof of principle study reported by Nyvad and Fejerskov in 1986, they demonstrate that direct placement of high strength fluoride varnish on the root lesions combined with daily oral care with an over-the-counter strength fluoridated toothpaste (~1,000 ppm F) would arrest active root caries lesions on buccal surfaces (34). NaF varnish may be advantageous over professional strength mouthrinse or gels in trays for special care patients such as medically compromised or frail elderly who have problems with rinsing or swallowing during the application period.

Studies evaluating stannous fluoride interventions showed a generalized finding that this modality demonstrated a decrease in carious lesions compared with placebo, but as a group this category had the lowest quality scores. Two of the three studies were published prior to 1986, possibly accounting for lower levels of reporting key study elements; this may also explain why some of the products evaluated are no longer available on the market. Two studies attempted comparison of stannous and NaF regimens with mixed results. Al-Joburi *et al.* noted that 0.4 percent stannous fluoride was superior to 1.1 percent NaF gel, but the stannous fluoride was used for a year, whereas the 1.1 percent NaF gel was used in trays for only the first 3 months of treatment and then stopped to use a remineralizing mouthrinse, the contents of which were not well described (23). Klock *et al.* compared low strength stannous and NaF rinses, and noted that during year 1, there were fewer new carious lesions with the stannous rinse but found no

statistically significant difference in the caries rates in year two (24).

Evidence for the efficacy of a fluoride modality is only one issue to be evaluated when treating moderate to high caries risk adults. Just as important is choosing the correct mode(s) of fluoride delivery, based on the individual patient. The dental professional must decide how much control the patient is willing to take for the process of fluoride delivery. Kiyak noted that patients who had higher self-efficacy, or confidence in their ability to perform oral self-care, did better in controlling periodontal disease, regardless of what chemotherapeutic intervention was used (35). Similarly, patients who can not commit to daily home fluoride application may be better served by more frequent recall visits and professionally applied fluorides. Those who may sporadically use home fluoride treatments or are at very high risk for caries may benefit from a combination of both home and regularly scheduled professionally applied modalities.

As stated in previous reviews and consensus statements (3,6,36), there is a paucity of evidence regarding fluoride use in adults compared with the available studies conducted in children. Weaknesses of this systematic review included the use of a nonestablished cutoff of 75 percent regarding the overall quality scores. This allowed us to highlight the best quality evidence on this subject without being overly constrictive, given the few studies available. We also used a definition of moderate and high caries risk that included population characteristics as well as studies where individuals *per se* were assessed prior to enrollment. Again, because of the paucity of information, we chose to be more inclusive regarding this criteria. Additionally, an agreed-upon definition of higher caries risk patients is not available. In this regard, studies included in this review were diverse, which can be viewed as a limitation. In light of this limitation, we included the caries risk status for each of the 17 studies in Table 2 for clarification. Also, studies were varied regarding the researchers' targeted outcome (root versus coronal caries, caries reduction versus lesion remineralization). The intent of this systematic review was to present the available research to clinicians and public health professionals to help formulate an opinion on the use of supplemental fluoride for adult patients, given the most up-to-date data. Most patients have multiple risks as well as multiple types of caries to be addressed. The tables provided will hopefully allow readers to address the use of these products in varying situations for at-risk adults.

An important limitation is that many of these studies report on surfaces of caries reduced or remineralized. In so doing, such outcomes ignore the clustering of tooth and surface-level results by person. Thus, future studies should be sure to examine person-level as well as tooth- and surface-level outcomes. An important example of this is the data presented by DePaola, who reports on the percent of the study group who benefitted by remineralization (16).

Finally, many of the studies we found were over 20 years old. Given the longer period of time that is required for such studies, the large numbers of subjects required and the need to target high caries risk patients, these are not studies easily undertaken. Future clinical trials are needed to evaluate whether the modality of fluoride administration in moderate versus high caries risk adults makes a difference in the reduction or remineralization of caries, and whether multiple modalities of fluoride versus use of a single modality are more effective for these patients.

Conclusion

Although the reviewed clinical trials varied greatly in design, conduct, and quality scores, all demonstrated that the use of supplemental and professionally applied fluoride in moderate and high caries risk adults is effective in preventing and/or remineralizing dental caries. Table 4 lists those modalities with the highest ranked evidence regarding the reduction in caries and remineralization of lesions because of a supplemental fluoride intervention. Low dose daily NaF rinses had the most generalizable results for adults at risk for caries. This was followed by evidence for 1.1 percent NaF paste/gel, although these studies are more targeted to root caries lesions. Finally, while small in numbers of participants, 5 percent NaF varnish had two studies with high quality ratings, and showing moderate magnitude in controlling root caries. Ongoing research is needed to confirm (or refute) the findings presented here.

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References

1. Dye BA, Tan S, Smith V, Lewis BG, Barker LK, Thornton-Evans G *et al.* Trends in oral health status: United States, 1988-94 and 1999-2004. National Center for Health Statistics. *Vital Health Stat*. 2007;**11**(248).
2. Griffin SO, Griffin PM, Swann JL, Zlobin N. New coronal caries in older adults: implications for prevention. *J Dent Res.* 2005;**84**(8):715-20.
3. Griffin SO, Regnier E, Griffin PM, Huntley V. Effectiveness of fluoride in preventing caries in adults. *J Dent Res.* 2007;**86**(5): 410-5.
4. Featherstone JDB. The science and practice of caries prevention. *J Am Dent Assoc.* 2000;**131**:887-99.

5. Burt BA, Eklund SA. *Fluoride: human health and caries prevention.* In: Burt BA, Eklund SA, editor(s). *Dentistry, dental practice and the community*. 5th ed. Philadelphia, PA: WB Saunders; 1999.p. 279-96.
6. Bader JD, Shugars DA, Bonito AJ. A systematic review of selected caries prevention and management methods. *Community Dent Oral Epidemiol.* 2001;**29**:399-411.
7. American Dental Association Council on Scientific Affairs. Professionally applied topical fluoride. Evidence-based clinical recommendations. *J Am Dent Assoc.* 2006;**137**: 1151-9.
8. West S, King V, Cary TS, Lohr KN, McKoy N, Sutton SF, Lux L. Systems to rate the strength of scientific evidence. Evidence Report/Technology Assessment No. 47 (Prepared by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center under contract No 290-97-0011). AHRQ Publication No 02-EO16. Rockville, MD: Agency for Healthcare Research and Quality. April 2002.
9. Wyatt CCL, MacEntee MI. Caries management for institutionalized elders using fluoride and chlorhexidine mouthrinses. *Community Dent Oral Epidemiol.* 2004;**32**:322-8.
10. Fure S, Gahnberg L, Birkhed D. A comparison of four home-care fluoride programs on the caries incidence in the elderly. *Gerodontology.* 1998;**15**(2):51-60.
11. Wallace MC, Retief DH, Bradley EL. The 48-month increment of root caries in an urban population of older adults participating in a preventive dental program. *J Public Health Dent.* 1993;**53**(3):133-7.
12. Geiger AM, Gorelick L, Gwinnet AJ, Benson BJ. Reducing white spot lesions in orthodontic populations with fluoride rinsing. *Am J Orthod Dentofacial Orthop.* 1992;**101**(5): 403-7.
13. Ripa LW, Leske GS, Forte F, Varma A. Effect of a 0.05% neutral NaF mouthrinse on coronal and root caries in adults. *Gerodontology.* 1987;**6**(4):131-5.
14. Baysan A, Lynch E, Ellwood R, Davies R, Petersson L, Boorsboom P. Reversal of primary root caries using dentifrices containing 5,000 and 1,100 ppm fluoride. *Caries Res.* 2001;**35**:41-6.
15. Spak CJ, Johnson G, Ekstrand J. Caries incidence, salivary flow rate and efficacy of fluoride gel treatment in irradiated patients. *Caries Res.* 1994;**28**:388-93.
16. DePaola P. Caries in our aging population: what are we learning. In: Bowen WH, Tabak LA, editors. *Cariology for the nineties*. Rochester, NY: University of Rochester Press; 1993. p. 25-35.
17. Horiot JC, Schraub S, Bone MC, Bain Y, Ramadier J, Chaplain G, Nabid N, Thevenot B, Bransfield D. Dental preservation in patients irradiated for head and neck tumors: a 10-year experience with topical fluoride and a randomized trial between two fluoridation methods. *Radiother Oncol.* 1983;**1**:77-82.
18. Toolson LB, Smith DE. A 2-year longitudinal study of overdenture patients. Part I: incidence and control of caries on overdenture abutments. *J Prosthet Dent.* 1978;**40**(5):486-91.
19. Driezen S, Brown LR, Daley TE, Drane JB. Prevention of xerostomia-related dental caries in irradiated cancer patients. *J Dent Res.* 1977;**56**(2):99-104.
20. Ekstrand K, Martignon S, Holm-Pedersen P. Development and evaluation of two root caries controlling programmes for home-based frail people older than 75 years. *Gerodontology.* 2008;**25**:67-75.
21. Schaeken MJM, Keltjens HMAM, Van Der Hoeven JS. Effects of fluoride and chlorhexidine on the microflora of dental root surfaces and progression of root-surface caries. *J Dent Res.* 1991;**70**(2):150-3.
22. Petersson LG, Hakestam U, Baigi A, Lynch E. Remineralization of primary root caries lesions using an amine fluoride rinse and dentifrice twice a day. *Am J Dent.* 2007;**20**(2):93-6.
23. Al-Joburi W, Clark DC, Fisher R. A comparison of the effectiveness of two systems for the prevention of radiation caries. *Clin Prev Dent.* 1991;**13**(5):15-9.
24. Klock B, Serling J, Kinder S, Manwell MA, Tinanoff N. Comparison of effect of SnF2 and NaF mouthrinses on caries incidence, salivary S. mutans and gingivitis in high caries prevalent adults. *Scand J Dent Res.* 1985;**93**(3): 213-7.
25. Scola FP, Ostrom CA. Clinical evaluation of stannous fluoride when used as a constituent of a compatible prophylactic paste, as a topical solution, and in a dentifrice in naval personnel. I. Report of findings after first year. *J Am Dent Assoc.* 1966;**73**(6):1306-11.
26. Scola FP, Ostrom CA. Clinical evaluation of stannous fluoride when used as a constituent of a compatible prophylactic paste, as a topical solution, and in a dentifrice in naval personnel. II. Report of findings after two years. *J Am Dent Assoc.* 1968;**77**(3):594-7.
27. Thalheimer W, Cook S. How to calculate effect sizes from published research articles: a simplified methodology. Retrieved November 17, 2009 from http://work-learning.com/effect_sizes.htm.
28. Leverett DH. Effectiveness of mouth rinsing with fluoride solutions in preventing coronal and root caries. *J Public Health Dent.* 1989;**49**(5):310-6.
29. Nordström A, Birkhed D. Fluoride retention in proximal plaque and saliva using two NaF dentifrices containing 5,000 and 1,450 ppm F with and without water rinsing. *Caries Res.* 2009;**43**:64-9.
30. ten Cate JM, Buijs MJ, Miller CC, Extedate RA. Elevated fluoride products enhance remineralization of advanced enamel lesions. *J Dent Res.* 2008;**87**(10):943-7.
31. Biesbrock AR, Gerlach RW, Bollmer BW, Faller RV, Jacobs SA, Bartizek RD. Relative anti-caries efficacy of 1100, 1700, 2200 and 2800 ppm fluoride ion in a sodium fluoride dentifrice over 1 year. *Community Dent Oral Epidemiol.* 2001;**29**:382-90.
32. Lynch E, Baysan A. Reversal of primary root caries using a dentifrice with a high fluoride content. *Caries Res.* 2001;**35**(Suppl 1):60-4.

33. Herkströter FM, Witjes M, Arenda J. Demineralization of human dentine compared with enamel in pH-cycling apparatus with a constant composition during de and remineralization periods. *Caries Res.* 1991;**25**:317-22.
34. Nyvad B, Fejerskov O. Active root surface caries converted into inactive caries as a response to oral hygiene. *Scand J Dent Res.* 1986;**94**:281-4.
35. Kiyak AH. Measuring psychosocial variables that predict older persons' oral health behavior. *Gerodontology.* 1996;**13**(2):69-75.
36. NIH Consensus Development Conference Statement. Diagnosis and management of dental caries throughout life. *J Dent Educ.* 2001;**65**(10):1162-8.