SYSTEMATIC REVIEW AND META-ANALYSIS

Effectiveness of Xylitol in Reducing Dental Caries in Children

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Abstract: ***Purpose:*** *The purpose of this study was to evaluate the effectiveness of xylitol in reducing dental caries in children compared to no treatment, a placebo, or preventive strategies.* ***Methods:*** *MEDLINE via PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 1, 1995 through Sept. 26, 2016 for randomized and controlled trials on children consuming xylitol for at least 12 months. The primary endpoint was caries reduction measured by mean decayed, missing, and filled primary and permanent surfaces/teeth (dmfs/t, DMFS/T, respectively). The I^2 and chi-square test for heterogeneity were used to detect trial heterogeneity. Meta-analyses were performed and quality was evaluated using GRADE profiler software.* ***Results:*** *Analysis of five randomized controlled trials (RCTs) showed that xylitol had a small effect on reducing dental caries (standardized mean difference [SMD] equals -0.24; 95 percent confidence interval [CI] equals -0.48 to 0.01; P=0.06) with a very low quality of evidence and considerable heterogeneity. Studies with higher xylitol doses (greater than four grams per day) demonstrated a medium caries reduction (SMD equals -0.54; 95 percent CI equals -1.14 to 0.05; P=0.07), with these studies also having considerable heterogeneity and very low quality of evidence.* ***Conclusions:*** *The present systematic review examining the effectiveness of xylitol on caries incidence in children showed a small effect size in randomized controlled trials and a very low quality of evidence that makes preventive action of xylitol uncertain.* *(Pediatr Dent 2017;39(2):103-10) Received January 25, 2016 | Last Revision February 17, 2017 | Accepted February 18, 2017*

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Because of the high worldwide prevalence of dental caries and its immense health burden, there have been many interventions aimed at its prevention. The use of fluoridated toothpaste, topically applied fluorides, fluoridated municipal water, and pit and fissure sealants, along with dietary improvement, remain the mainstay of caries management.[1] The role of fermentable sugars in the etiology of dental caries has been well established. It has been suggested that the replacement of sugar in chewing gum or candies with sugar substitutes, such as sugar alcohols, may contribute to caries prevention. The effect of sugars substitutes, especially xylitol, in reducing dental caries has been studied in vitro and in vivo since the early 1970s.[2]

Xylitol is a five-carbon sugar alcohol derived primarily from birch trees. In contrast to six carbon sugars, xylitol is not readily metabolized by oral bacteria. Research suggests xylitol is more effective as an anticaries agent than other sugar alcohols. Xylitol has been used for years as a sugar substitute, and was approved as a food additive by the FDA in 1963.[3] Sugar alcohols are poorly absorbed in the large intestine and may produce a laxative effect.

The biological mechanism of action of xylitol in preventing dental caries is similar to other sugar alcohols in that these compounds are not readily metabolized by cariogenic microorganisms. Thus, the plaque pH decrease is not at a level necessary to demineralize enamel.[4] The less acidic environment may also decrease mutans streptococci levels in dental plaque, because low pH conditions favor mutans streptococci in a mixed plaque environment.[5] Additionally, sugar alcohols are consumed as gums or lozenges that will stimulate salivary flow, possibly increasing mechanical cleansing, delivering salivary minerals to demineralized enamel, and acting as a buffer to plaque acids.[6] It is speculated that xylitol may have greater anticaries effects than other sugar alcohols. This is because, in habitual xylitol users, resistant strains of mutans streptococci may be less cariogenic due to reduction of insoluble extracellular polysaccharides, thus altering adherence to tooth surfaces or producing less sturdy plaque.[7]

Since the early 1970s, xylitol was examined as an anticariogenic agent, delivered primarily through chewing gum delivery systems. Most trials used xylitol in large doses (two to 14 grams per day) and high frequency (four to five times per day) for extended time periods (several years). Dental caries reduction produced by xylitol chewing gums may be confounded by increased salivation due to the chewing effect.[4] Some studies attempted to control for such confounding bias by selecting chewing gums with other sugar alcohols as controls.[8]

Over the years, several studies have supported the claim that xylitol can prevent dental caries, greater than the mechanical effect of chewing. In addition, several literature reviews[1,6,9] have reported the effectiveness of xylitol in reducing the incidence of dental caries in humans. However, it wasn't until recently that the effectiveness of xylitol was subjected to rigorous systematic reviews, in which inclusion and exclusion criteria were established a priori, and potential risks of biases in studies were carefully evaluated.[1,6,9] Those reviews implied that xylitol reduced dental caries, but these finding were not supported by a high level of evidence due to inconsistent results and/or design of trials. The most recent report by Cochrane[6] did not include nonrandomized trials and did not combine all trials that used xylitol into one meta-estimate.

The purpose of this systematic review was to evaluate whether xylitol reduces dental caries in children between zero to 18 years old by evaluating both randomized and nonrandomized trials. Meta-analyses were performed on trials that met our inclusion criteria to estimate the effect size of caries reduction

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Table 1. INCLUSION (USING PICOS FORMAT) AND EXCLUSION CRITERIA FOR ARTICLES SELECTED TO EXAMINE XYLITOL EFFECTIVENESS IN REDUCING DENTAL CARIES*

Inclusion	Exclusion
P: Healthy pediatric patients age 0-18 years.	• Medically compromised or children with special health care needs.
I: Consumption of xylitol >12 months (all forms, dosages, and frequencies).	• Xylitol consumption <12 months.
C: No treatment, placebo, or routine preventive care.	• Xylitol combined with another sugar alcohol/polyol.
O: Caries increment (dmfs/t; DMFS/T) or mean dmfs/t; DMFS/T.	• Control containing or combined with another sugar polyol.
S: Randomized controlled trials or controlled clinical trials.	• Insufficient data; mean and/or variance not reported.
	• Observational studies.

* dmfs/t=decayed, missing, and filled primary surfaces/teeth; DMFS/T=decayed, missing, and filled permanent surfaces/teeth.

from xylitol consumption for at least one year in a child population. Additionally, the included trials were evaluated for heterogeneity (variation between studies), and risk of bias. In addition, we examined the potential effect of xylitol dose on caries reduction.

Methods

Using the population, intervention, comparison, outcome, and study design (PICOS) format, the following research question was formulated: "In children, does xylitol use for at least 12 months compared to a control group reduce dental caries in controlled clinical trials?"

Our primary outcome measure was caries increment using decayed, missing, and filled primary and permanent surfaces/teeth (**dmfs/t** and **DMFS/T**, respectively) between follow-up and baseline exams. When studies did not report or we could not calculate the incremental caries score, we used the mean dmfs/t or DMFS/T at the last examination. Outcomes recorded in the primary and permanent dentitions were from clinical and/or radiographic observations. Table 1 summarizes the inclusion and exclusion criteria.

We conducted a comprehensive literature search to identify relevant trials in three databases: (1) MEDLINE through PubMed; (2) Thomson Reuters Web of Science; and (3) Cochrane Central Register of Controlled Trials. The search strategy combined the medical subject headings (**MeSH**) or free text words xylitol and dental caries. Age limits were restricted from zero to 18 years. When age limits could not be set, we used the following keywords: infant or child or adolescent, which were joined with the word "and" to the original search. We searched databases for all review articles and clinical trials on human subjects published from Jan.1, 1995 to Sept. 26, 2016 that were restricted to the English language. Additionally, we conducted hand searches using reference lists of previously published articles.

After removing the duplicate studies, two authors independently screened the titles and abstracts identified by the aforementioned protocol. Full texts of all potentially relevant trials were obtained and read independently by the same two authors. Citation lists from review articles and relevant trials were also reviewed for further trial identification. Disagreements or uncertainties about inclusions and exclusions criteria were discussed with a third author. If a trial was excluded, the reasons for exclusion were described. Details of the trial selection process and elimination of studies are illustrated in Figure 1.

Data extraction from the selected trials included: citation; study design; sample source; description of intervention and control groups; number of subjects at baseline/completion of study; study duration; outcome; and risk of bias assessment. Outcomes were recorded from the final examination upon termination of the xylitol intervention, and all interim results were excluded. For clinical trials consisting of more than one treatment group, the group exposed to xylitol as the only polyol was selected. If multiple xylitol groups were present, the group exposed to the highest daily dose and/or frequency of xylitol or that consumed xylitol for the longest duration was considered for the quantitative analysis.

Clinical caries definition was that identified by the authors of the studies; depending on the study, clinical caries could have included white spot lesions, shadowing or opacity under the enamel, loss of enamel structure, dentinal caries, and all cavitated lesions. Radiographic caries, depending on the study, could have included enamel and dentin lesions. When both clinical and radiographic results were reported, only the clinical caries was used for the quantitative analysis. If both DMFS/T and dmfs/t were reported in the same trial, DMFS/T was selected over dmfs/t for analysis. Additionally, we selected the number of surfaces over the number of teeth when both were reported.

Using The Cochrane Collaboration's risk-of-bias assessment tool, the following domains were assessed by two authors: random sequence generation, allocation concealment, blinding of participants and personnel as well as blinding of outcome assessment, incomplete outcome data, selective reporting, and

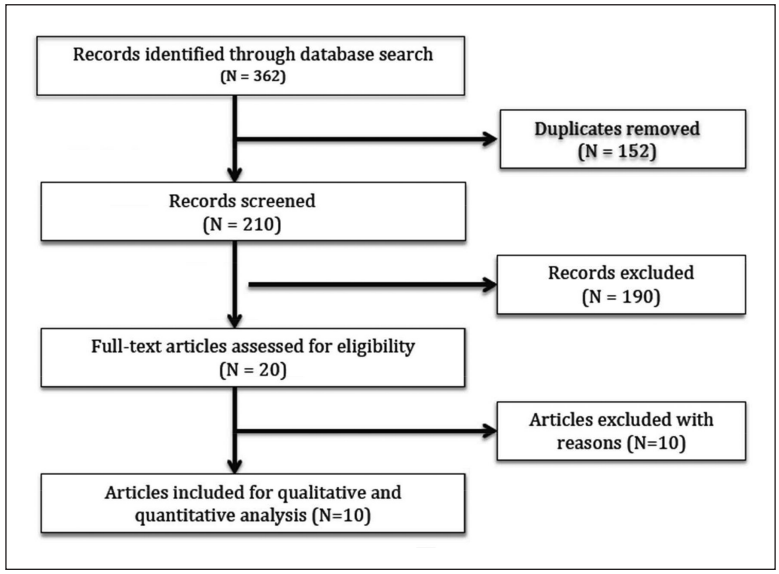

Figure 1. Flowchart of the trial selection process and elimination of studies.

other biases.[10] A summary assessment for risk of bias was provided for each trial. Each trial was characterized as: low risk of bias if all domains were determined to have low risk of bias; unclear risk of bias if at least one domain was determined to have unclear risk of bias; and high risk of bias if at least one domain was determined to have high risk of bias. Two other authors resolved any discrepancies through discussion.

We used mean difference and the 95 percent confidence interval (**CI**) as the effect size measure between xylitol and control groups. We used weighted mean difference (**WMD**) if caries measure was reported on the same scale or standardized mean difference (**SMD**) if different scales were reported. SMD is the mean difference in the caries index score between the xylitol and the control groups divided by the pooled standard deviation. By convention, effect sizes of 0.2, 0.4, and 0.8 are considered small, medium and large, respectively.[11] When pre-intervention measures were reported, adjustments were made in the baseline differences. When necessary, standard errors or CI were converted to standard deviations.[12]

We used random-effect models due to expected heterogeneity because of variation in treatment protocols and subject populations. I^2 and chi-square test for heterogeneity were used to detect trial heterogeneity. Rev-man 5.2 software (The Nordic Cochrane Center, Copenhagen, Denmark) was used to perform statistical analyses.[13] Subgroup analysis included only randomized trials and was carried out using various xylitol doses. The quality of the evidence was evaluated using GRADE profiler 3.6.1 software. The GRADE system allows rating of the evidence in four categories, ranging from very low quality to high quality.[14]

Results

Among 210 citations screened by title and abstract, only 10 trials met our predetermined inclusion and exclusion criteria and were included in this systematic review. Figure 1 presents a flow chart illustrating the study selection process. After full text review, we excluded trials with inadequate intervention[15-18] or control groups.[18-20] Other reasons for exclusion included insufficient data reporting,[21] follow-up studies reporting data from original trials already included in this review,[22,23] or less than a year of xylitol consumption.[24]

As shown in Table 2, five out of the 10 included trials were nonrandomized, and eight were community-based clinical trials. Only one study was conducted in the United States.[25] The vehicle for xylitol delivery included gum,[8,26-30] dentifrice,[31,32] lozenges,[33] and wipes.[25] The frequency of xylitol consumption ranged from three to five times a day, except for the trials examining dentifrices containing xylitol, which was used two times a day. Two trials[31,32] did not report the daily dose of xylitol. However, in the remaining eight trials the daily dose of xylitol ranged from 2.5 g to 10.67 g.[8,25-30,33] Control groups consisted of no gum,[8,26,30] a placebo,[1,25,29,32] or preventative strategies such as sealants,[27] toothbrushing with fluoride dentifrice,[28] or fluoride varnish.[33] No trials were included that had other sugar alcohols as a control group. There were two trials with a minimum one-year follow-up,[25,28] three with a minimum of two years,[30,32,33] and five with a minimum of three years.[8,26,27,29,31] There was one trial with six- to 35-month-olds,[25] two trials with three- to six-year-olds,[28,30] and seven trials with seven- to 14-year-olds.[8,26,27,29,31-33]

Table 3 presents the results for the risk of bias for each trial. We determined that all 10 trials had a high risk of bias. High risk of bias was more frequently found in the domains for random sequence generation,[8,26,30,31,33] blinding of participants and personnel,[8,26-30,33] and funding.[8,25,29-31]

As shown in Figure 2, a total of 2,733 subjects in the xylitol group and 3,232 subjects in the control group completed at least one year of active treatment. From these 10 trials, we found a large caries reduction effect (SMD equals -0.97; 95 percent CI equals -1.39 to -0.55; P=<.001), with a GRADE quality of evidence rated as very low quality. This effect size was associated with an extremely high degree of heterogeneity between the trials (I^2 equals 98 percent). By visual inspection of the forest plot, the study by Makinen et al.[8] was remarkably different and considered a putative outlier. Also, the effect size in this Makinen et al. study showed dental caries incidence reduction by almost 11 times more than any other included study. A sensitivity a nalysis that included a lower frequency and lower dose xylitol group (three times instead of five; and 4.3 g instead of 8.5 g of xylitol per day), from the same Makinen et al. study, showed a pooled effect attenuated by only seven percent, but with the same extremely high degree of heterogeneity (results not shown). After excluding the Makinen et al. study, as shown in Figure 3, the effect size was reduced from large to small (SMD equals -0.28; 95 percent CI equals -0.46 to -0.10; P=0.002); heterogeneity was reduced but still considerably high (I^2 equals 86 percent); and quality of evidence was still very low.

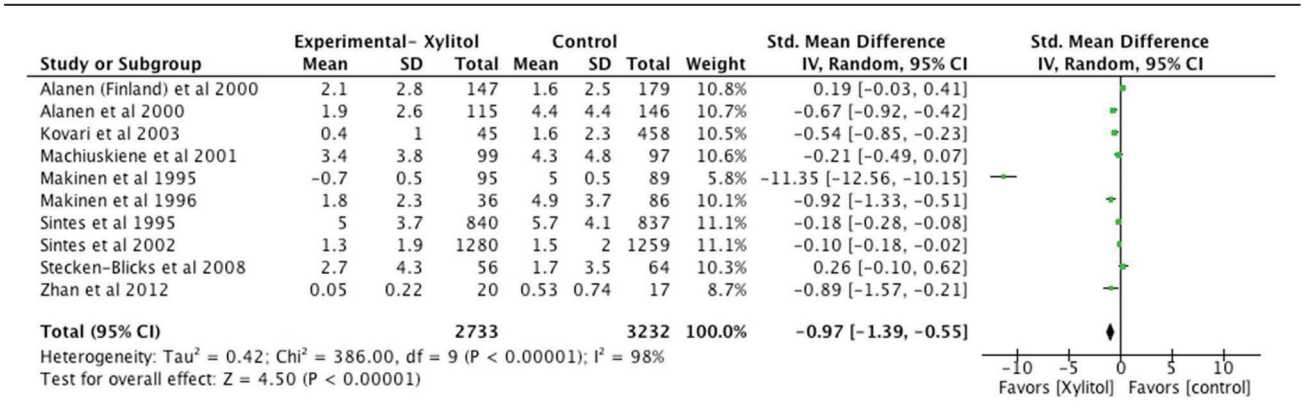

Figure 2. Forest plot showing the estimated effect of xylitol on caries incidence in all 10 included trials.*

* CI=confidence interval; IV=inverse-variance; SD=standard deviation.

Table 2. DEMOGRAPHIC, DESIGN, ANALYTIC, AND RISK OF BIAS ASSESSMENT SUMMARY OF THE 10

Paper and country	Study design/sample from	Intervention group	Control group
Alanen et al., 2000[26] Estonia	Nonrandomized controlled trial/community based	Xylitol gum (65% w/w) School supervised chewing; 2 pieces 3x/day for 10 minutes; average 200 school days for 3 years; total dosage=5 g/day	Routine preventive measures
Alanen et al., 2000[2] Finland	Cluster randomized controlled trial/community based	Xylitol gum (65% w/w) School supervised chewing; 2 pieces 3x/day for approximately 10 minutes; average=190 school days for 3 yrs; total dosage=5 g/day.	Sealant (resin or glass ionomer)
Kavori et al., 2003[28] Finland	Cluster randomized controlled trial/community based	65% (w/w) xylitol gum School supervised chewing; 1 piece chewed 3x/day; first chewing period=8 months; second chewing period=11 mos; third period chewing=11 months; total dose=2.5g/day.	Toothbrushing during lunch with 0.05% NaF toothpaste; school supervised brushing at lunchtime
Machiuskiene et al., 2001[29] Lithuania	Cluster randomized controlled trial/community based	Xylitol gum. School and home supervised chewing; 5x/day for 10 mins. for 3 years; total dosage=2.9 g/day (contained trace amounts of hydrogenated glucose syrup).	Nonacidogenic gum; same supervision and frequency as xylitol group
Makinen et al., 1995[8] Belize	Nonrandomized controlled trial/community based	65% (w/w) xylitol pellet gum. School supervised chewing; group using xylitol 5x/day=2 pieces 5x/day for 5 mins.; group using xylitol 3x/day=2 pieces for the first 2 chewing episodes and 1 piece for the third chewing episode for 5 mins.; average 200 school days/year; total dose=group using xylitol 5x/day=8.5 g/day; group using xylitol 3x/day=4.3 g/day.	No treatment group
Makinen et al., 1996[30] Belize	Nonrandomized controlled trial/community based	65% (w/w) xylitol pellet gum. School supervised chewing; 2 pieces chewed 5x/day for 5 minutes; average 200 school days/year; total dose=10.67 g/day	No treatment group
Sintes et al., 1995[32] Costa Rica	Randomized stratified (age and sex) controlled trial/community based	Dentifrice containing 0.243% NaF/silica with 10% xylitol. School and home supervised brushing; 2x/day for 1 min.; total dose=unclear	Same as intervention but without xylitol
Sintes et al., 2002[31] Costa Rica	Nonrandomized stratified (age and sex) controlled trial/community based	Dentifrice containing 0.836% MFP (1,100 ppm F) in dicalcium phosphate dihydrate base with 10% xylitol. School and home supervised brushing; 2x/day for 1 min.; total dose=unclear	Same as intervention but without xylitol
Stecken-Blicks et al., 2008[33] Sweden	Nonrandomized controlled trial/clinic based	Xylitol lozenges Compliance supervised by study coordinator; 2 tablets chewed 3x/day; total dose = 2.5 g/day.	Topical fluoride varnish 2x/year or 3 applications within 10 days
Zhan et al., 2012[25] USA	Randomized controlled trial/clinic based	Xylitol wipes. 2 wipes 3x/day in addition to toothbrushing; total dose=4.2 g/day	Placebo wipes 2 wipes 3x/day and brushing

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The subgroup analysis of five randomized trials (Figure 4) showed a very low quality of evidence that xylitol had a small effect on reducing dental caries (SMD equals -0.24; 95 percent CI equals -0.48 to 0.01; *P*=0.06), and again with considerable heterogeneity (I^2 equals 80 percent). As shown in Figure 5, three trials that used a lower xylitol dose (less than three grams per day)[28,29,33] had a small effect on dental caries (SMD equals -0.17; 95 percent CI equals -0.60 to 0.25; *P*=0.42), considerable heterogeneity (I^2 equals 82 percent), and very low quality of evidence. Interestingly, one of those trials[33] produced a nonsignificant increase in dental caries incidence for the xylitol group relative to the control group. Four trials, excluding the outlier, that used a greater (greater than four grams per day) xylitol dose,[25-27,30] showed very low quality of evidence with xylitol, had a medium caries reduction effect (SMD equals -0.54; 95 percent CI equals -1.14 to 0.05; *P*=0.07), and exhibited considerable heterogeneity (I^2 equals 92 percent).

Table 4 presents the percent of dental caries reduction derived from the effect size, SMD, and quality of evidence based on GRADE.[14] When all the included trials were analyzed, the percent caries reduction with xylitol intervention was as high as 97 percent; however, when excluding the outlier study (Makinen et al.)[8], the percent caries reduction dropped to 28 percent. When only the randomized trials were assessed, the percent caries reduction dropped further down to 24 percent. For trials that included a xylitol dose of greater than four grams per day, the percent caries reduction was 54 percent; however, when trials that used a xylitol dose of less than three grams per day were analyzed, the percent caries reduction dropped to 17 percent. It is critical to note that the GRADE quality of evidence for all these categories was determined to be very low (⊕⊖⊖⊖) due to the high risk of bias and inconsistency (heterogeneity) seen in the studies. Hence, there is uncertainty about these estimates of effect.

INCLUDED TRIALS SELECTED TO EXAMINE XYLITOL EFFECTIVENESS IN REDUCING DENTAL CARIES			
No. of subjects at baseline/ completed the study	**Study duration**	**Outcome Mean±(SD)/95% confidence interval (intervention vs. control)***	**Risk of bias assessment**
Xylitol gum group=148/115 Control group=180/146	3 years from when the students were 10-13 years old	Significant reduction in DMFS 1.87±2.55 vs. 4.42±4.36	High risk
Xylitol gum group, 3 year use=159/147 Sealant group=194/179	5 years from when the students were in the 5th grade; final results recorded 2 years after termination of xylitol gum	No significant difference in clinical DMFS 2.1±2.8 vs. 1.6±2.5 and in radiographic approximal DFS 0.99±1.86 vs. 1.23±2.33	High risk
Xylitol gum group 3=not reported/45 Toothbrushing group=529/458	Exposure times varied from 1-3 years from the time the children were 3-6 years old; all children completed the last exam at 9 years old	No significant difference in dmft 1.0±1.8 vs. 1.6±2.3 and in DMFT 0.4±1.0 vs. 0.4±0.9	High risk
Xylitol gum group=126/99 Control gum group=120/97	3 years from when the students were age 9-14 years old	No significant difference in clinical DMFS 3.4±2.7-4.2 vs. 4.3±3.3-5.2 and in radiographic DMFS 3.2±2.6-3.8 vs. 2.7±2.0-3.4	High risk
Baseline not reported/xylitol pellet group chewed 5x/day (xylitol 5 pellet) =95; xylitol pellet group chewed 3x/day (xylitol 3 pellet)=97. No gum group=89	40 months from when children were 9-10 years old	Significant difference in DMFS between group using xylitol 5x/day and group using xylitol 3x/day vs. control -0.7±0.5 and 0.8±0.5 vs. 5±0.5	High risk
Baseline not reported/xylitol pellet group=36 No gum group=86	2 years from when children were 6 yrs old	Significant reduction in DMFS 1.8±2.3 vs. 4.9±3.7	High risk
Xylitol dentifrice=840/840 Control dentifrice=837/837	3 years from when the children were 7-12 years old	Significant reduction in DFS 5.0±3.7 vs. 5.7±4.1	High risk
Xylitol dentifrice=1280/1280 Control dentifrice=1259/1259	30 months from when the children were 7-12 years old	Significant reduction in DFS 1.30±1.89 vs. 1.51±2.00 and in DFT 0.69±1.10 vs. 0.81±1.21	High risk
Xylitol lozenge group=80/56 Control group=70/64	2 years from when the children were 10-12 years old	No significant difference in radiographic approximal DMFS 2.7±4.3 vs. 1.7±3.5	High risk
Xylitol wipe group=22/20 Placebo wipe group=22/17	1 year from when the children were 6-35 months old	Significant reduction in ds 0.05±0.22 vs. 0.53±0.74	High risk

* DMFS=decayed, missing, and filled permanent surfaces; DFS= decayed and filled permanent surfaces; DFT= decayed and filled permanent teeth.

Table 3. RISK OF BIAS ASSESSMENT OF THE 10 INCLUDED TRIALS SELECTED TO EXAMINE XYLITOL EFFECTIVENESS IN REDUCING DENTAL CARIES

Author, Year	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other bias/ funding**
Alanen et al., 2000[26] Estonia	High risk	Unclear risk	High risk	Low risk	Low risk	Low risk	High risk
Alanen et al., 2000[27] Finland	Low risk	Unclear risk	High risk	High risk	Unclear risk	Low risk	Low risk
Kavori et al., 2003[28] Finland	Low risk	Unclear risk	High risk	High risk	High risk	Unclear risk	Low risk
Machiuskiene et al., 2001[29] Lithuania	Low risk	Unclear risk	High risk	Unclear risk	High risk	Low risk	Low risk
Makinen et al., 1995[8] Belize	High risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk	High risk
Makinen et al., 1996[30] Belize	High risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk	High risk
Sintes et al.,1995[32] Costa Rica	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	High risk
Sintes et al., 2002[31] Costa Rica	High risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	High risk
Stecken-Blicks et al., 2008[33] Sweden	High risk	High risk	High risk	Low risk	High risk	Low risk	Low risk
Zhan et al., 2012[25] USA	Low risk	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk

Discussion

This review of the putative effect of xylitol on caries reduction in children is important, as there are conflicting results from clinical trials and even from reviews of the literature. Although such conflicts and questions remain regarding the efficacy/effectiveness of xylitol in reducing caries incidence, published clinical guidelines often include recommendations for the use of xylitol for individuals for caries prevention.[34]

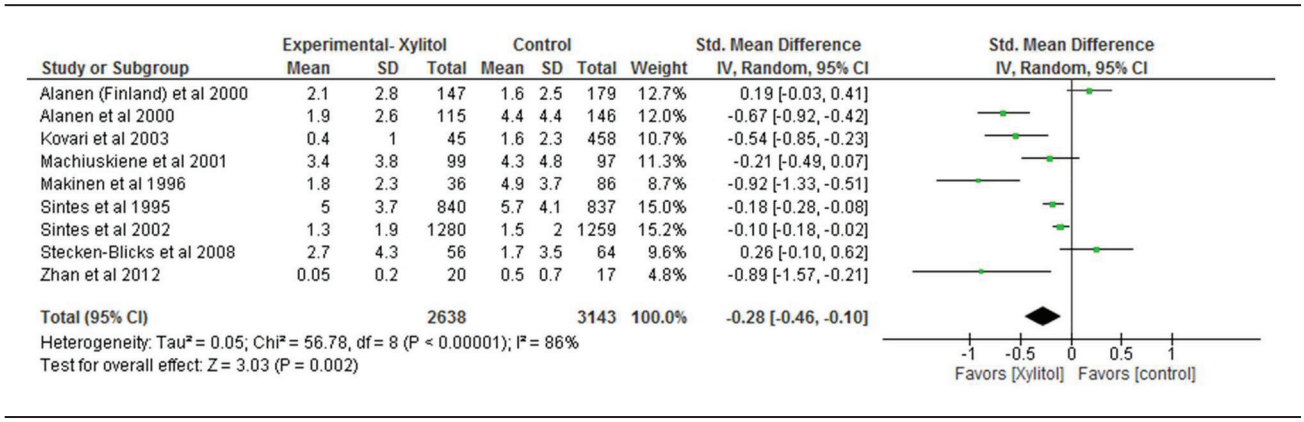

Figure 3. Forest plot showing the estimated effect of xylitol on caries incidence after excluding the putative outlier trial (Makinen et al., 1995[8]).*
* CI=confidence interval; IV=inverse-variance; SD=standard deviation.

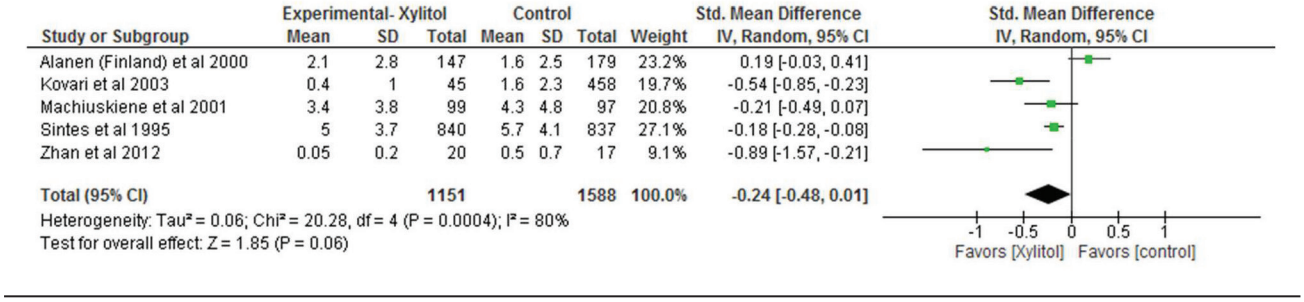

Figure 4. Forest plot showing the estimated effect of xylitol on caries incidence in only randomized controlled trials.*
*CI=confidence interval; IV=inverse-variance; SD=standard deviation.

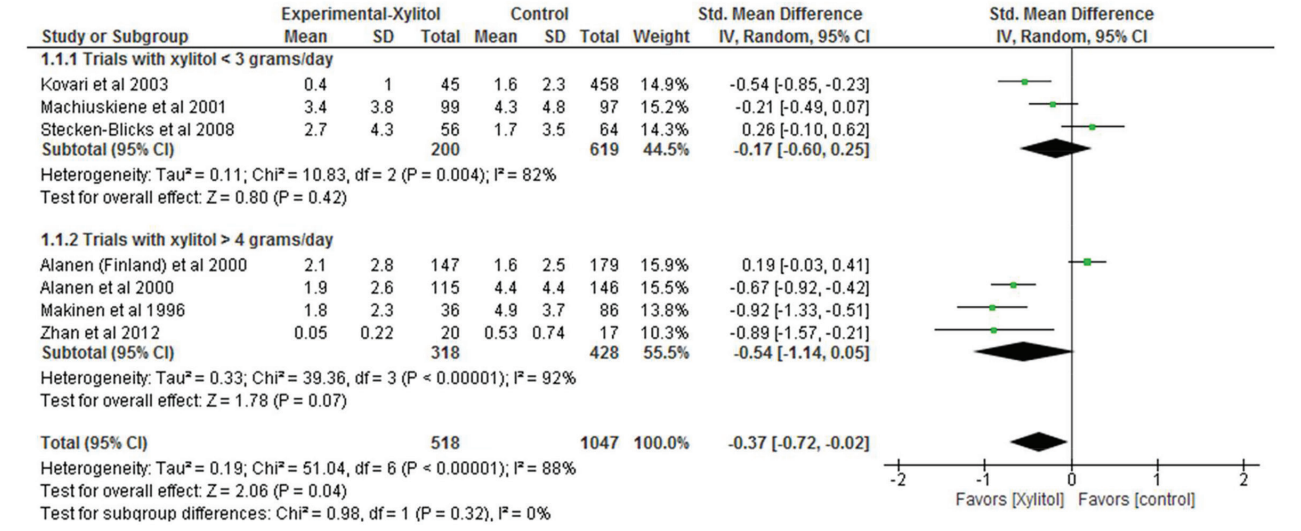

Figure 5. Forest plots showing the estimated effect of xylitol on caries incidence in trials with different dosages.*
* CI=confidence interval; IV=inverse-variance; SD=standard deviation.

Table 4. SUMMARY OF FINDINGS TO EVALUATE EFFECTIVENESS AND QUALITY OF EVIDENCE FOR XYLITOL USE TO REDUCE DENTAL CARIES USING GRADE[14]

Outcomes (caries reduction)	Standardized mean difference (95% confidence interval) xylitol vs. other group	% reduction	No. of participants (studies)	Quality of the evidence (GRADE)*
All trials	-0.97 (-1.39, -0.55)	97	5,965 (10 studies)	⊕⊖⊖⊖ Very low †,§
Excluding one outlier trial (Makinen et al., 1995)	-0.28 (-0.46, -0.10)	28	5,781 (9 studies)	⊕⊖⊖⊖ †,§ Very low
Only randomized controlled trials	-0.24 (-0.48, 0.01)	24	2,739 (5 studies)	⊕⊖⊖⊖ Very low†,§
Only trials with xylitol dose <3 g/day	-0.17 (-0.60, 0.25)	17	819 (3 studies)	⊕⊖⊖⊖ †,§ Very low
Only trials with xylitol dose >4 g/day	-0.54 (-1.14, 0.05)	54	746 (4 studies)	⊕⊖⊖⊖ †,§ Very low

* GRADE levels of confidence: high quality=further research is unlikely to change confidence in the estimate of effect; moderate quality=further research is likely to have an impact on confidence in the estimate of effect and may change the estimate; low quality=further research is very likely to have an impact on confidence in the estimate of effect and is likely to change the estimate; very low quality=uncertain about the estimate.

† All studies were assessed as having high risk of bias (Table 2), with varying risk in different categories (Table 3).

§ High levels of heterogeneity documented (I^2 >75%).

In general, the 10 trials that met our inclusion criteria were rather heterogeneous, in that the experimental groups had various daily doses and various forms of xylitol delivery. Furthermore, the length of the studies, follow-up periods, comparison groups, population age, baseline caries risk of the children, and clinical dental caries definition varied considerably among the studies. We attempted to reduce the observed high heterogeneity, with the exclusion of an outlier, by subgroup analyses based on randomization status and xylitol dose. Even after these procedures, the high heterogeneity of these studies mandates interpretation of the pooled SMD with great caution. It also downgrades the quality of evidence. In addition, these studies also have a high risk of bias, such as lack of random sequence generation, blinding of subjects or examiners, and some being industry sponsored. Furthermore, these studies have large standard deviations, relative to the mean, due either to the true wide variation in the xylitol effect or research variability.

Some specific findings from the included studies showed the potential importance of dose; the three trials utilizing less than three grams of daily xylitol showed a small reduction in dental caries, while an increased xylitol dose of more than four grams daily in four trials showed a greater reduction and increased the effect size from 17 percent to 54 percent. This potential effect of dosage is observational, as dose was not randomized in the included trials.

Since 2008, other systematic reviews have addressed the efficacy of sugar alcohols, specifically xylitol, on dental caries prevention.[1,6,35,36] These systematic reviews generally conclude that there is insufficient evidence to determine whether xylitol products can reduce dental caries incidence. Deshpande et al. concluded that evidence was consistent to support the use of xylitol and sorbitol containing chewing gums as part of a program to prevent dental caries.[35] By contrast, the Antonio et al. systematic review from 2011 concluded that xylitol-based candies and lozenges could favor a reduction in caries increment, but this conclusion was not supported by strong evidence.[36] The 2011 ADA systematic review of nonfluoride caries preventive agents concluded that there is a low level of certainty that xylitol-containing candy and lozenges reduces the incidence of coronal caries.[1] Additionally, the 2014 U.S. Preventive Services Task Force concluded that there is not enough evidence to recommend xylitol regimens for children younger than five years old.[9]

Of note, a 2015 Cochrane Collaboration systematic review also concluded that fluoride toothpaste containing xylitol might be more effective than fluoride-only toothpaste for preventing caries in the permanent teeth of children.[6] By contrast, the studies in our review also included nonrandomized trials that may add to the direction and magnitude of anticipated findings. The current review, however, excluded several trials that were included with The Cochrane Collaboration review, wherein the xylitol groups were confounded with other putative antimicrobials. In addition, in contrast to the Cochrane review, we found a high level of heterogeneity (I^2 equals 80 to 98 percent) in the xylitol trials and evaluated one outlier study that had the potential of skewing the interpretation of other reviews. Lastly, this current review showed the possible effect of large and frequent doses of xylitol on caries incidence.

This current systematic review adds to our understanding of the effect of xylitol on caries incidence in children in that it evaluates and reports effect size, heterogeneity, risk of bias, putative outlier trials, and statistical as well as clinical significance. Limitations of this systematic review include publication bias that might overestimate the effect size and the fact that non-English reports were not evaluated. Also, some trials[31,32] did not report the used xylitol dose.

Conclusions

Based on this study's results, the following conclusions can be made:

1. The present systematic review examining the effectiveness of xylitol on caries incidence in children, showed a small effect size in randomized controlled trials and a very low quality of evidence that makes preventive action of xylitol uncertain.
2. The effect size of xylitol was greater with higher xylitol doses (greater than four grams per day).

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