THE JOURNAL OF THE AMERICAN DENTAL ASSOCIATION
JADA

The impact of polyol-containing chewing gums on dental caries: A systematic review of original randomized controlled trials and observational studies

Amol Deshpande and Alejandro R. Jadad

J Am Dent Assoc 2008;139;1602-1614

The impact of polyol–containing chewing gums on dental caries

A systematic review of original randomized controlled trials and observational studies

Amol Deshpande, MD, MBA; Alejandro R. Jadad, MD, DPhil, FRCP(C)

ABSTRACT

Background. The authors conducted a systematic review of original studies that was designed to assess the impact of polyol-containing chewing gum on dental caries compared with the effect with no chewing gum.

Review Methods. The authors searched MEDLINE, The Cochrane Library and Google Scholar up to May 2008 to identify peer-reviewed articles that compared polyol-containing chewing gum with no chewing gum. The authors extracted study characteristics, data on incremental dental caries and quality by consensus. Data on prevented fraction (PF) were pooled across studies.

Results. The results of 19 articles with data from 14 study populations showed that the use of xylitol, xylitol-sorbitol blend and sorbitol were associated with mean PF (95 percent confidence interval) of 58.66 percent (35.42-81.90), 52.82 percent (39.64-66.00) and 20.01 percent (12.74-27.27), respectively. For the sorbitol-mannitol blend, it was 10.71 percent (–20.50-41.93), which was not statistically significant. Sensitivity analyses confirmed the robustness of the findings.

Clinical Implications. Although research gaps exist, particularly on optimal dosing and relative polyol efficacy, research evidence supports using polyol-containing chewing gum as part of normal oral hygiene to prevent dental caries.

Key Words. Polyol; xylitol; sorbitol; mannitol; dental caries; chewing gum; systematic review; evidence-based; meta-analysis.
JADA 2008;139(12):1602-1614.

Almost all adults and more than 90 percent of children have experienced caries at some point in their lives.[1] In the United States, dental caries is the most common chronic childhood disease.[2] Recent evidence suggests that specific populations in the United States and Australia could be experiencing an increase in dental caries.[3,4] Standard recommendations for caries prevention from many public health and dental care authorities have been based on the use of fluoride at home and in dental offices, the application of sealants, reduction of sugar intake and regular dental checkups. Although specific preventive programs have been developed to target high-risk groups, a population approach to reduce the overall caries burden could be more beneficial from a public health perspective.[5]

Globally, many strategies have focused on the avoidance, or at least the reduction, of sugar intake to prevent dental caries. Despite these efforts, world consumption of sugar continues to increase, with global demand in 2007 and 2008 increasing to 157 million tons—3.5 million tons more than in 2006 and 2007.[6] Most of this growth is driven by lower prices, as well as rising

Dr. Deshpande is a consultant, Foresight Links, Toronto, and a consultant, Comprehensive Pain Program, University Health Network and University of Toronto.
Dr. Jadad is owner, Foresight Links, Toronto. He also is chief innovator and the founder, Centre for Global eHealth Innovation, Canada research chair in eHealth Innovation, Rose Family chair in Supportive Care, and a professor, Dalla Lana School of Public Health; Department of Health Policy, Management and Evaluation; and Department of Anesthesia, University Health Network, University of Toronto. Address reprint requests to Dr. Jadad at 225 Jarvis St., Suite 302, Toronto, Ontario, Canada M5B 2C1, e-mail "ajadad@gmail.com". Address reprint requests to Dr. Jadad.

demand from Asia owing to expansion of use in the food and beverage industries. The increasing demand for sugar, coupled with its potential detrimental effect on systemic health (obesity, type 2 diabetes mellitus) and oral health (dental caries), has led to increasing interest in sugar substitutes. One such class of substitutes known as "polyols" or "sugar alcohols" is nonfermentable sugars. The most common polyols are sorbitol and xylitol, and they have been used extensively as sugar substitutes in chewing gum. Experts recognize that regular use of polyol-containing chewing gums could play a role in preventing caries by increasing salivary flow through mastication, reversing decreases in plaque pH and enhancing remineralization of subsurface enamel lesions.[7-12] Xylitol also may decrease the amount of dental caries as a result of its unique ability to alter microbial composition by reducing the viability and survival of virulent *Streptococcus mutans*.[13,14]

The most common polyols are sorbitol and xylitol, and they have been used extensively as sugar substitutes in chewing gum.

Authors of reviews have concluded that the use of xylitol and, to a lesser extent, sorbitol in chewing gum is noncariogenic or even anticariogenic.[7-12] Lingstrom and colleagues,[15] however, reported that the existing evidence for the impact of sorbitol or xylitol on dental caries remains inconclusive. In all reviews, investigators completed a qualitative analysis of original studies but did not describe the reasons for avoiding a quantitative assessment of the literature. To date, no rigorous quantitative systematic efforts have been made to synthesize the evidence available from clinical research on the effect of different polyol-containing chewing gums on the development of dental caries. We designed this review to fill this gap.

METHODS

Literature search. We prepared a protocol a priori and followed it throughout our review. In May 2008, we identified eligible studies through an electronic search of MEDLINE (from 1950), The Cochrane Library and Google Scholar (first 200 hits) in May 2008. Our search strategy consisted of "ANDing" three clusters with the terms "polyols," "chewing gum" and "dental caries." The detailed search strategy is available on request from the corresponding author. We appropriately modified the search strategy for each of the electronic databases.

Selection criteria. We selected an article for inclusion if it met the following criteria: it evaluated the effect of one or more chewing gums containing at least one polyol (xylitol, sorbitol, mannitol or maltitol) on caries development, it was published in English in a peer-reviewed journal, and it provided original data generated by means of a comparative design (experimental or observational). We excluded articles if they were available in only abstract form (for which it was not possible to access original data sets), described only the pharmacodynamic or pharmacokinetic properties of polyols or did not include a no-treatment arm in the study (defined as recommended or conventional oral hygiene, including flossing and regular brushing with a fluoride- or nonfluoride-containing toothpaste).

We independently screened potentially eligible citations and categorized them into one of three groups: keep (met inclusion criteria according to information provided in the abstract), investigate further (obtain the full article to determine if it met inclusion criteria) and drop (did not meet inclusion criteria). We then met to discuss the results of our categorizing efforts. We resolved discrepancies by means of discussion, referring to the inclusion and exclusion criteria and, whenever necessary, by getting input from a third reviewer. We categorized unresolved discrepancies as "investigate further" and obtained the full article for a more detailed review. Any disagreement between reviewers was resolved by means of consensus.

We obtained hard copies of articles labeled as "keep" or "investigate further" from electronic databases, print journals or interlibrary loans. When necessary, we contacted authors to request a copy of their article, if available.

Data extraction. Using the complete article or full-text version, we each independently extracted the following information: general characteristics (for example, name of lead author, publication title, source of funding, year of publication and country of primary author), study type (for example, randomized clinical trial, controlled

ABBREVIATION KEY. CCT: Controlled clinical trial. **ΔDMFS:** Incremental dental caries. **PF:** Prevented fraction. **RCT:** Randomized controlled trial.

clinical trial [CCT], cohort study or case-control studies), population studied (for example, children, adults, caries risk status), duration of study, type of polyol (for example, xylitol, sorbitol, mannitol, maltitol) or polyol blend used and dose, comparison groups, and caries outcomes and main findings (for example, decayed, missing and filled surfaces score, incremental caries scores). We recorded only outcome results from the final assessment of the original study for the review (we did not use interim results for data analysis). We decided a priori that caries increment outcome data reported on surface level would be chosen over data reported on tooth level. We chose data for all surfaces combined over specific types. If data were reported separately for clinical and radiological examinations, we chose the results for combined data over clinical outcomes alone and the results for clinical outcomes alone over radiological results.[16]

For original studies with missing (or partially missing) data, we imputed values by using linear regression of logarithmic SDs on logarithmic mean caries increments according to the method used by van Rijkom and colleagues.[17] We combined the results from individual studies with multiple intervention arms and one control group, such as those in which different doses of a specific polyol were evaluated, so we could use all relevant outcome data for meta-analysis.

For the purposes of meta-analysis, we converted incremental dental caries (ΔDMFS) outcomes from individual studies to prevented fraction (PF). PF is the proportional reduction in dental caries between experimental and control groups relative to the control group, expressed as a percentage. The PF could be either negative or positive, implying a relatively greater or smaller number of incremental caries in the experimental group, respectively, compared with the control group. A PF of zero implies equivalence between the experimental and control groups. This term is defined as follows:

$PF = (\overline{X}_C - \overline{X}_E)/\overline{X}_C$

Where,

$\overline{X}_C$ is the mean increment in the control group

$\overline{X}_E$ is the mean increment in the group with the polyol-containing chewing gum

We calculated a 95 percent confidence interval (CI) for the PF for each study by using a formula by Dubey and colleagues.[18]

Prevented fraction is the proportional reduction in dental caries between experimental and control groups relative to the control group.

Quality assessment. We independently completed quality assessments on all studies. We used the Jadad scale to evaluate randomized controlled trials (RCTs). The Jadad scale is a validated instrument designed to assess the quality of RCTs. The scale ranges from 0 to 5, and trials scoring greater than 2 are considered to be of high quality.[19] Trials scoring 2 or less are considered to be of poor quality. We used the U.S. Preventive Services Task Force criteria to grade the internal validity of individual nonrandomized studies.[20] The U.S. Preventive Health Services Task Force is an instrument designed to assess the quality of observational studies. The "score" is qualitative and categorizes studies as "poor," "fair" or "good."

Data analysis. We produced evidence tables to summarize the information we extracted from the articles. We calculated descriptive statistics for various fields of the database. We grouped studies according to type of polyol for pooling of aggregate data. We performed meta-analyses on separate groups by using the PF from individual studies weighted by the inverse variance of the mean. Results of pooling were expressed as PF with a 95 percent CI. We assessed statistical heterogeneity (that is, whether variation between individual study results in the meta-analysis was significant or due to chance alone [homogeneity]) by using I^2. The I^2 result, which varies between 0 and 100 percent, indicates the percentage of total variation across studies due to heterogeneity as opposed to chance alone. Higher values suggest greater levels of heterogeneity.

We pooled aggregate data by using a random-effects model (accounting for within-study sampling error and between-study variation) and a fixed-effects model (accounting for only within-study variability). Using both models, we were able to provide additional assessment of the robustness of the findings. If identical or similar, such findings would be deemed more trustworthy than if they had been significantly different. We used the software program RevMan 5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to analyze the results.

We assessed each study with respect to its pop-

ulation, intervention, methodology and outcome to determine clinical heterogeneity. We further assessed heterogeneity a posteriori by inspecting graphical displays of studies with their mean treatment effects and 95 percent CI. To investigate the effect of various sources of heterogeneity on pooled treatment effects, we performed sensitivity analyses (the impact on meta-analysis outcomes of alterations in inclusion and exclusion of specific studies) on different subgroups.

There is always a risk of overestimating treatment effects when meta-analyses rely on published articles as the sole source of data. The "file drawer problem," as coined by Rosenthal[21] in 1979, refers to the tendency of studies with no significant results to remain unpublished, buried in the file drawers of researchers. To account for this potential bias, also known as "publication bias," we calculated Rosenthal's fail-safe N for each group. This test is used to calculate the number of new studies, with mean null result, that would be necessary to reduce the combined significance level to at least $P = .05$.

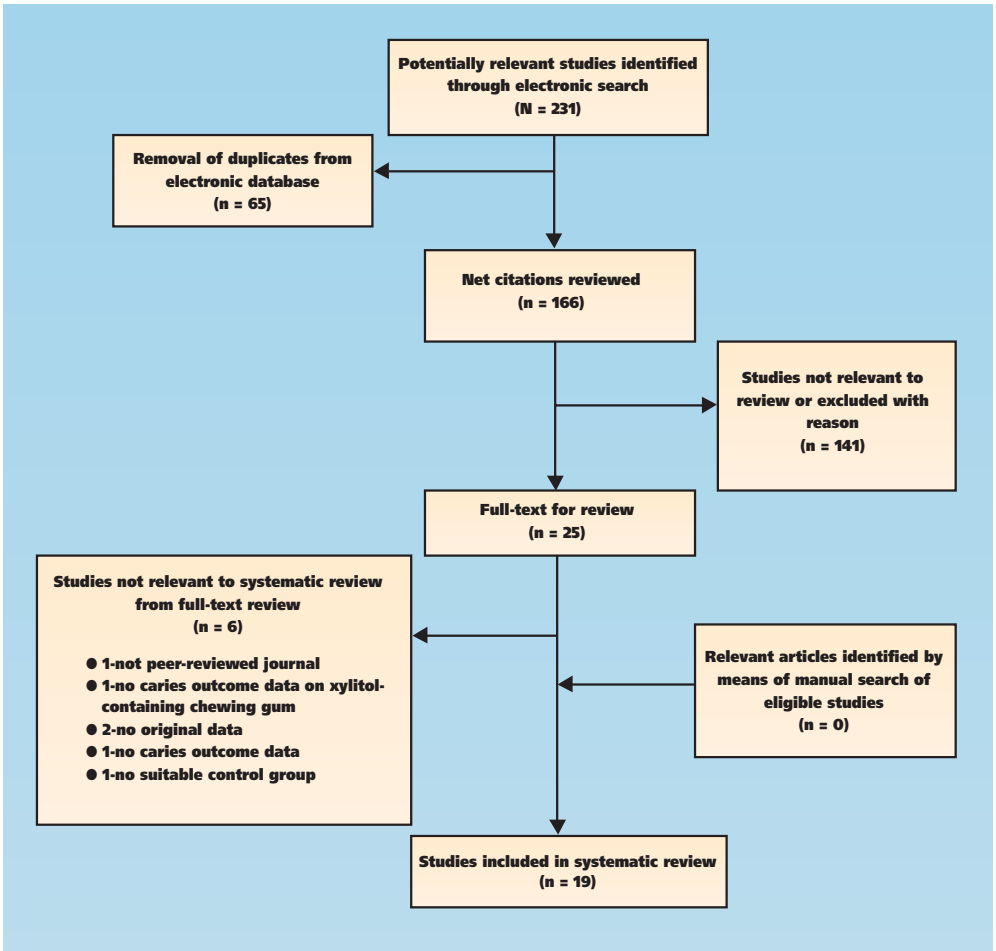

Figure 1. Quality of reporting in meta-analysis flowchart of selected articles.

We did not use polyol exposure as a variable when conducting sensitivity analyses. Since there is no consensus regarding the ideal dose for polyols, it would have been difficult to determine a specific cutoff dose, and any chosen value would have been arbitrary.

To explore the hypothesis that the amount of polyol influences treatment effect, we plotted the polyol load against the PF and its 95 percent CI. We performed a simple linear regression analysis by using polyol load as a covariate to determine the correlation between the two parameters. We characterized polyol load as a participant's total exposure to a specific polyol (in grams) for the duration of the study. The term "polyol load" takes into account the daily dose and the duration of exposure. Mathematically, we defined this as grams of polyol per day multiplied by the study duration (days). We could not analyze the xylitol-sorbitol or the sorbitol-mannitol blends in this way because of the difficulty in determining the relative weighting of each polyol.

RESULTS

Search results. We identified 231 potentially eligible articles in our search. After our initial screening of titles and abstracts, we determined that 65 article citations were duplicates, and 141 were unrelated to our review. We retrieved the full texts of 25 articles (Figure 1). Of these articles, we deemed six to be ineligible for the review.[22-27] Summaries of the final 19 articles we included in our review are presented in Table 1[28-46] (an additional table showing the characteristics of each of the

TABLE 1

Included studies.

AUTHOR	YEAR	JOURNAL	COUNTRY	FUNDING SOURCE	STUDY DESIGN	QUALITY ASSESSMENT*
Isokangas and Colleagues[28]	1988	JADA	Finland	Not reported	CCT†	Fair
Isogangas and Colleagues[29]	1993	Caries Research	Finland	Not reported	Cohort study‡	Fair
Isokangas and Colleagues[30]	1991	Caries Research	Finland	Not reported	Cohort study‡	Fair
Isokangas and Colleagues[31]	1989	Community Dentistry and Oral Epidemiology	Finland	Not reported	Cohort study‡	Fair
Hujoel and Colleagues[32]	1999	Journal of Dental Research	United States	Huhtamaki (Leaf Group), Finnish Cultural Fund	Cohort study	Fair
Makinen and Colleagues[33]	1996	Caries Research	United States	Huhtamaki (Leaf Group), Finnish Cultural Fund, Orion Diagnostica, University of Michigan, University of Turku	CCT	Good
Kandelman and Gagnon[34]	1987	Journal of Dental Research	Canada	Association of Physicians of the Departements de Sante Communautaire of the Montreal General Hospital	CCT	Fair
Makinen and Colleagues[35]	1995	Journal of Dental Research	United States	Huhtamaki (Leaf Group), Huhtamaki Oy Fund	CCT	Good
Glass[36]	1983	Caries Research	United States	Not reported	Cluster RCT§ (unit of randomization: household)	Jadad Scale = 3
Beiswanger and Colleagues[37]	1998	JADA	United States	William Wrigley Jr. Co.	Cluster RCT (unit of randomization: classroom)	Jadad Scale = 1
Finn and Colleagues[38]	1978	JADA	United States	National Institutes of Health	RCT	Jadad Scale = 2
Kovari and Colleagues[39]	2003	Acta Odontologica Scandinavica	Finland	Leaf Co. donated chewing gum for the study	Cluster RCT (unit of randomization: day-care centers)	Jadad Scale = 1
Kandelman and Gagnon[40]	1990	Journal of Dental Research	Canada	Association of Physicians of the Departements de Sante Communautaire of the Montreal General Hospital	CCT	Fair
Moller and Poulsen[41]	1973	Community Dentistry and Oral Epidemiology	Denmark	Not reported	CCT	Fair
Petersen and Razanamihaja[42]	1999	International Dental Journal	Denmark	Not reported	CCT	Poor
Szoke and Colleagues[43]	2001	Journal of Dental Research	Hungary	William Wrigley Jr. Co.	CCT	Good
Machiulskiene and Colleagues[44]	2001	Community Dentistry and Oral Epidemiology	Lithuania	Dandy A/S (Fertin A/S), Aarhus University Foundation, Nordic Council of Ministers	Cluster RCT (unit of randomization: schools)	Jadad Scale = 5
Alanen and Colleagues[45]	2000	Community Dentistry and Oral Epidemiology	Estonia	Leaf Co. and the Finnish Dental Association	RCT	Jadad Scale = 1
Peng and Colleagues[46]	2004	Acta Odontologica Scandinavica	China	Hubei Committee for Oral Health, University of Copenhagen	CCT	Fair

* All studies designed as randomized controlled trials (RCTs) were evaluated by using the Jadad scale. The Jadad scale is a validated instrument designed to assess the quality of RCTs.[19] The scale ranges from 0 to 5 and trials scoring greater than 2 are considered to be high quality. Studies designated as observational were evaluated using the U.S. Preventive Services Task Force criteria. The U.S. Preventive Health Services Task Force is an instrument deigned to assess the quality of observational studies.[20] The "score" is qualitative and categorizes studies as "poor," "fair" or "good."
† CCT: Controlled clinical trial.
‡ Follow-up study of Isokangas and colleagues.[28]
§ RCT: Randomized controlled trial.

included studies can be found in the supplemental data online [found at "http://jada.ada.org"]).

General study characteristics. The 19 articles provided results for 14 study populations. Four studies were based on observations of one population,[28-31] and Hujoel and colleagues[32] reported five-year follow-up results based on a population originally assessed by Makinen and colleagues.[33] One article published results for the first year of a two-year study.[34]

Six articles originated from the United States,[32,33,35-38] and five originated from Finland.[28-31,39] Canada[34,40] and Denmark[41,42] each produced two articles, three articles originated in other European countries,[43-45] and one originated in China.[46] Two articles were published before 1980,[38,41] 12 were published in the 1980s or 1990s, and five were published since 2000.[39,43-46]

Seven articles[32,33,35,37,39,43,45] documented a corporate sponsor as either the sole or partial source of funding. Seven articles[28-31,36,41,42] did not report a funding source.

Study designs included six RCTs[36-39,44,45] with four classified as cluster RCTs[36,37,39,44] and nine as CCTs[28,33-35,40-43,46] (experimental studies in which the participants do not receive the interventions randomly). The four cohort studies[29-32] included in the review reported original outcomes on previously assessed populations. In only one of the four cluster RCTs,[37] was the statistical analysis to account for clustering adjusted.

Four studies included multiple parallel intervention arms assessing different polyols.[33,35,40,44] In seven studies,[28,33,35,39,40,44,45] xylitol-containing chewing gum was assessed; in five studies,[33,35,40,42,46] a xylitol-sorbitol blend in varying ratios was assessed; in five studies,[33,35,36,41,44] sorbitol was evaluated; and in three studies,[27,38,43] a sorbitol-mannitol blend was reviewed (Table 2).

In all studies, the effect of polyol-containing chewing gums was assessed in school-aged children. The 14 original study populations registered more than 11,700 participants, although outcome data were based on 8,600 participants. The largest study enrolled 2,601 participants,[37] and the smallest study had 340.[41] Dropout rates varied significantly across studies. One study[36] appeared to have no dropouts, although the authors did not report the number of participants randomly assigned to the study arms compared with the number who completed. The highest dropout rate was 52.3 percent.[40] None of the studies provided a detailed account of reasons for participant withdrawal.

Study duration of the original trials varied from 24 to 40 months. Seven studies lasted two years,[28,33,36,40,41,43,46] four studies lasted three years,[37,42,44,45] one had a duration of 40 months,[35] and another,[38] described as lasting three years, reported all outcome data "after 30 months." The duration of one study[39] could not be determined. Five articles[39,40,42,45,46] reported dispensing chewing gum only during school days, and the remainder reported daily consumption.

The doses of polyol varied considerably across groups. Xylitol and sorbitol ranged from a low of approximately 2.9 grams per day to a high of 10.67 g per day. The ratio for the xylitol-sorbitol blend (xylitol:sorbitol) varied between 3:40 and 1.27:1. The three studies[37,38,43] in which a combination of sorbitol and mannitol was assessed reported only a percentage range of polyol for its chewing gum, which precluded us from determining a specific amount of polyol exposure.

Nine studies[28,33,35,36,38,40,42,45,46] reported participants' consuming gum at specific times of the day or loosely associated with traditional mealtimes (for example, "around breakfast," "at dinner time"). Five studies specifically reported chewing gum "after meals."[37,39,41,43,44]

All original studies, except two,[39,41] reported ΔDMFS outcomes. Outcomes in all but one study[37] were based solely on per-protocol analysis. Beiswanger and colleagues[37] completed an intention-to-treat analysis, but this calculation appeared incorrect, because it did not include all participants randomly assigned to treatment. Thirteen of 19 studies reported some form of intraexaminer or interexaminer reliability rating with greater than 90 percent agreement and a κ value higher than 0.85. The four cohort studies[29-32] and two RCTs[36,37] did not report reliability scores.

Quality assessment. Two RCTs[36,44] received a Jadad score of 3 or higher, implying a low likelihood of bias. Three CCTs[33,35,43] were deemed to be good according to the U.S. Preventive Services Task Force criteria. Masking was used in all three CCTs that received a good rating. One study[33] provided a detailed explanation of dropouts, and another[35] addressed confounding factors. RCTs[37-39,45] of lower quality did not report mechanisms of randomization, the role of masking to prevent ascertainment bias or a detailed description of dropouts. Similarly, in most CCTs that received a rating of fair or poor and all cohort studies,

TABLE 2

Prevented fraction and 95 percent confidence interval associated with polyol load for studies included in meta-analysis.

POLYOL	STUDY (POLYOL DOSE IN GRAMS)	POLYOL LOAD (GRAMS)	MEAN PREVENTED FRACTION (95 PERCENT CONFIDENCE INTERVAL)
Xylitol Only	Alanen and colleagues[45] (5.0)	3,000.0	0.58 (0.45-0.70)
	Isokangas and colleagues[28] (10.5)*	7,665.0	0.43 (0.35-0.52)
	Kandelman and Gagnon[40] (3.4)*	1,462.0	0.66 (0.60-0.71)
	Machiulskiene and colleagues[44] (2.9)	3,175.5	0.35 (0.21-0.48)
	Makinen and colleagues[35] (4.3)	5,226.4	0.82 (0.80-0.84)
	Makinen and colleagues[35] (5.4)	6,563.0	0.98 (0.96-1.00)
	Makinen and colleagues[35] (8.5)	10,331.0	1.16 (1.14-1.18)
	Makinen and colleagues[35] (9.0)	10,939.0	0.88 (0.86-0.90)
	Makinen and colleagues[33] (10.42)	7,607.0	0.47 (0.31-0.63)
	Makinen and colleagues[33] (10.67)	7,789.0	0.63 (0.47-0.80)
	Makinen and colleagues[35] (xylitol pooled)†	—	0.96 (0.94-0.97)
	Makinen and colleagues[33] (xylitol pooled)†	—	0.52 (0.39-0.65)
Xylitol-Sorbitol‡	Kandelman and Gagnon[40] (0.8 of xylitol per 2.4 of sorbitol)*	—	0.61 (0.55-0.66)
	Makinen and colleagues[35] (2.0 of xylitol per 6.0 of sorbitol)	—	0.88 (0.86-0.90)
	Makinen and colleagues[35] (5.9 of xylitol per 3.8 of sorbitol)	—	0.55 (0.53-0.57)
	Makinen and colleagues[33] (7.11 of xylitol per 2.70 of sorbitol)	—	0.49 (0.34-0.64)
	Makinen and colleagues[33] (9.68 of xylitol per 2.69 of sorbitol)	—	0.55 (0.41-0.69)
	Peng and colleagues[46] (0.12/1.6)	—	0.42 (0.19-0.66)
	Petersen and Razanamihaja[42] (0.09/1.2)*	—	0.30 (0.18-0.42)
	Makinen and colleagues[35] (pooled results)	—	0.71 (0.68-0.74)
	Makinen and colleagues[33] (pooled results)	—	0.52 (0.40-0.64)
Sorbitol Only	Glass[36] (unknown dose)	Unknown	0.01 (–0.17-0.20)
	Machiulskiene and colleagues[44] (2.845)	3,113.6	0.05 (–0.15-0.24)
	Machiulskiene and colleagues[44] (2.945)	3,223.0	0.27 (0.11-0.44)
	Makinen and colleagues[35] (9.0)	10,944.0	0.22 (0.20-0.25)
	Makinen and colleagues[33] (10.42)	7,602.4	0.24 (0.01-0.48)
	Makinen and colleagues[33] (10.67)	7,784.8	0.63 (0.47-0.80)
	Makinen and colleagues[33] (sorbitol pooled)†	—	0.37 (0.21-0.54)
	Machiulskiene and colleagues[44] (sorbitol pooled)†	—	0.18 (0.02-0.33)
Sorbitol-Mannitol‡	Beiswanger and colleagues[37‡]	40-60 percent sorbitol; 4-15 percent mannitol	0.08 (0.01-0.15)
	Finn and colleagues[38‡]	50-70 percent polyols	–0.09 (–0.13- –0.05)
	Szoke and colleagues[43‡]	65 percent polyol	0.33 (0.32-0.34)

* Imputed standard deviation from linear regression of logarithmic standard deviations on logarithmic mean caries increments.
† Pooled results from parallel intervention arms with weighted average polyol load.
‡ Polyol load not calculable.

detailed dropout rates or reasons for withdrawal were not provided, masking was not used or possible confounding factors were not addressed.

Study outcomes. We performed meta-analyses by using data from five RCTs[36-38,44,45] and eight CCTs.[28,33,35,40-43,46] We excluded six studies eli-

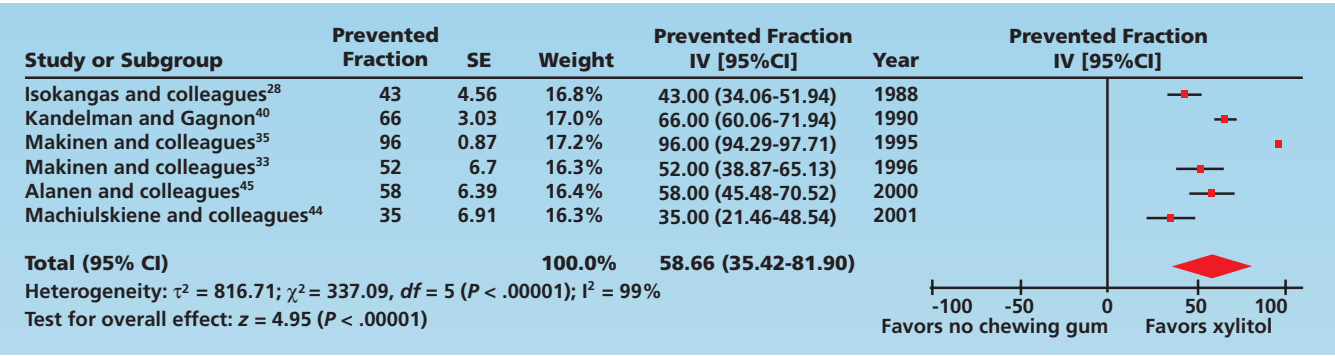

Figure 2. Forest plot for xylitol-containing chewing gum (random-effects model). SE: Standard error. IV: Inverse variance. CI: Confidence interval. *z*: z test.

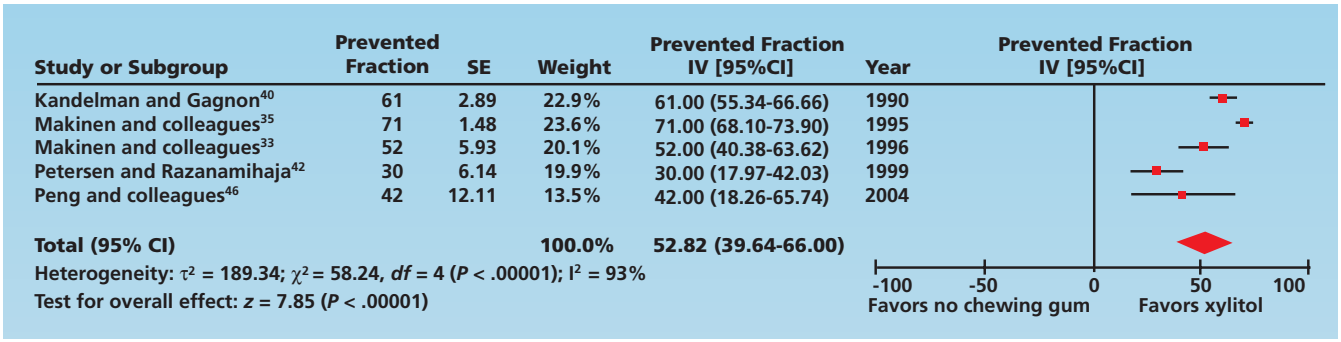

Figure 3. Forest plot for xylitol-sorbitol–containing chewing gum (random-effects model). SE: Standard error. IV: Inverse variance. CI: Confidence interval. z: z test.

gible for the review for various reasons. Four cohort studies[29-32] were follow-up assessments of populations included in previous trials. One article[34] published results for the first year of a two-year trial. Another[39] did not include outcomes for ΔDMFS, and we could not calculate the results from the reported data. Moller and Poulsen[41] did not report ΔDMFS outcomes, but the published data allowed us to calculate this value. Three[38,40,42] of the 13 studies included in the meta-analyses did not report SDs. We contacted the authors of these studies by e-mail to request the SDs. One author responded to our request but could not provide the requested data.[40] We imputed the missing SDs from original data sets by using linear regression of logarithmic SDs on logarithmic mean caries increments.

The linear regression equation we derived (logarithmic [SD of caries increment] = –0.072 + 0.64 × logarithmic [mean caries increment]; R^2 = 67 percent) included all intervention arms with available data. The PF and 95 percent CI for the individual intervention arms are presented in Table 2.

For the purpose of meta-analyses, we categorized the studies into four groups. In group I, we compared xylitol-containing chewing gum with no chewing gum. In group II, we compared xylitol-sorbitol–containing chewing gum with no chewing gum. In group III, we compared sorbitol-containing chewing gum with no chewing gum. In group IV, we compared sorbitol-mannitol–containing chewing gum with no chewing gum.

Group I. Two RCTs and four CCTs met the inclusion criteria for this group.[28,33,35,40,44,45] We pooled the results of two studies[33,35] with multiple intervention arms before we conducted the meta-analysis. Two studies in this group contained imputed SDs.[28,40] Pooled results from the six studies revealed a PF (95 percent CI) of 58.66 (35.42-81.90), with I^2 = 99 percent by using the random-effects model (Figure 2) and 90.18 (88.60-91.75) with the fixed-effects model. Sensitivity analyses for this group involved using the random-effects model to calculate pooled results by assessing study type (RCTs and CCTs), eliminating the study with the highest PF and excluding studies with imputed results (Table 3).

Group II. In five CCTs,[33,35,40,42,46] the effect on dental caries of using a xylitol-sorbitol–containing chewing gum was assessed. Meta-analysis favored the use of xylitol-sorbitol–containing chewing gum with a PF (95 percent CI) of 52.82 (39.64-66.00), with I^2 = 93 percent by using the

TABLE 3

Sensitivity analyses (random-effects model).

SENSITIVITY ANALYSIS	MEAN PREVENTED FRACTION (95% CONFIDENCE INTERVAL)
Xylitol Versus No Chewing Gum	
Randomized controlled trials[44,45]	46.65 (24.11-69.19), I^2 = 83%
Controlled clinical trials[28,33,35,40]	64.56 (37.56-91.57), I^2 = 99%
Excluding study with highest prevented fraction[35]	51.27 (39.16-63.39), I^2 = 86%
Excluding studies with imputed SDs[28,40]	60.61 (27.40-93.82), I^2 = 98%
Xylitol-Sorbitol Blend Versus No Chewing Gum	
Excluding study with highest prevented fraction[35]	47.14 (31.57-62.71), I^2 = 86%
Excluding studies with imputed SDs[40,42]	57.44 (39.81-75.07), I^2 = 87%
Sorbitol Versus No Chewing Gum	
Randomized controlled trials[36,44]	10.46 (–6.09-27.01), I^2 = 47%
Controlled clinical trials[33,35,41]	22.82 (15.64-30.00), I^2 = 52%
Excluding study with highest prevented fraction[33]	18.05 (11.33-24.78), I^2 = 47%
Sorbitol-Mannitol Blend Versus No Chewing Gum	
Randomized controlled trials[37,38]	–0.8 (–17.45, 15.85), I^2 = 94%
Excluding study with lowest prevented fraction[38]	20.77 (–3.72, 45.27), I^2 = 98%

random-effects model (Figure 3) and 66.26 (63.81-68.72) with the fixed-effects model. Sensitivity analysis included two subgroups—the study with the highest PF and studies without imputed SDs (Table 3).

Group III. In five studies,[33,35,36,41,44] including two cluster RCTs and three CCTs, the use of sorbitol-containing chewing gum was compared with no chewing gum. Results favored sorbitol-containing chewing gum, with a mean PF (95 percent CI) of 20.01 (12.74-27.77), with I^2 = 56 percent by using the random-effects model (Figure 4) and 21.70 (19.60-23.79) with the fixed-effects model. Sensitivity analysis included assessing results by study type (RCTs and CCTs) and by excluding the study with the highest PF in the group (Table 3).

Group IV. Three studies[37,38,43] involved a combination of sorbitol and mannitol. Of the two RCTs in this group, one[38] reported that the use of sorbitol-mannitol–containing chewing gum was not associated with a difference in ΔDMFS when compared with no chewing gum, and results from the other study[37] showed a statistically significant result favoring the use of the sorbitol-mannitol–containing chewing gum. Pooled results of all three studies by using the random-effects model revealed a mean PF (95 percent CI) of 10.71 (–20.50-41.93), with I^2 = 100 percent, which was not statistically significant (P = .50) (Figure 5). In contrast, when we used a fixed-effects model, the results favored the use of sorbitol-mannitol–containing chewing gum, with a mean PF (95 percent CI) of 30.95 (30.19-31.71), $P < .0001$. Sensitivity analysis included pooling RCTs and excluding the study with the lowest prevented fraction (Table 3).

Fail-safe N. The fail-safe N for xylitol, xylitol-sorbitol blend and sorbitol was 320, 565 and 89, respectively. Given the number of articles we identified for this review, it is unlikely that there are more than 80 unpublished studies documenting a null effect with the use of sorbitol-containing chewing gum.

Polyol load and PF. With respect to xylitol load and treatment effect, Figure 6 (page 1612) shows a positive trend; that is, greater xylitol loads appeared to be associated with larger treatment effects. For the imperfect matching of xylitol load to PF outcomes (that is, not accounting for confounding factors between studies), simple univariate linear regression between the two parameters revealed a coefficient of determination of R^2 = 49 percent. The same calculation for sorbitol yielded even less correlation, R^2 = 34 percent.

DISCUSSION

The pooled results of the studies consistently favored the use of xylitol and sorbitol over no chewing gum. The random-effects model was associated with a treatment effect in terms of PF varying between a high of 58.66 percent with xylitol to a low of 20.01 percent with sorbitol. Although the point estimate also favored the use of a sorbitol-mannitol blend, the difference was not statistically significant. While we judged only approximately 25 percent of studies to be of high quality, most studies displayed consistent results with respect to direction of treatment effect but showed less consistency with magnitude.

Meta-analyses were considered suitable for data analysis on the basis of comparable populations (that is, school-aged children), assessment of similar outcomes (ΔDMFS) and consistency of findings, with 11 of the 13 studies showing statistically significant positive results. There were, however, important differences in study design (RCT versus

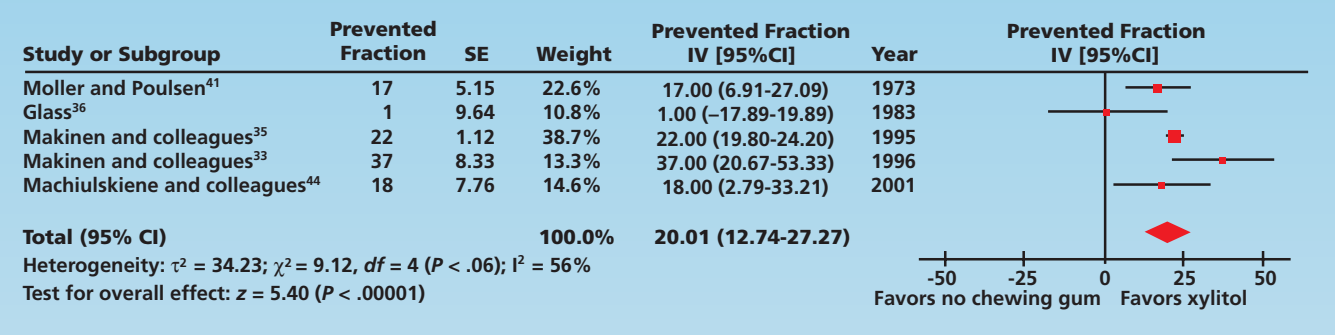

Figure 4. Forest plot for sorbitol-containing chewing gum (random-effects model). SE: Standard error. IV: Inverse variance. CI: Confidence interval. z: z test.

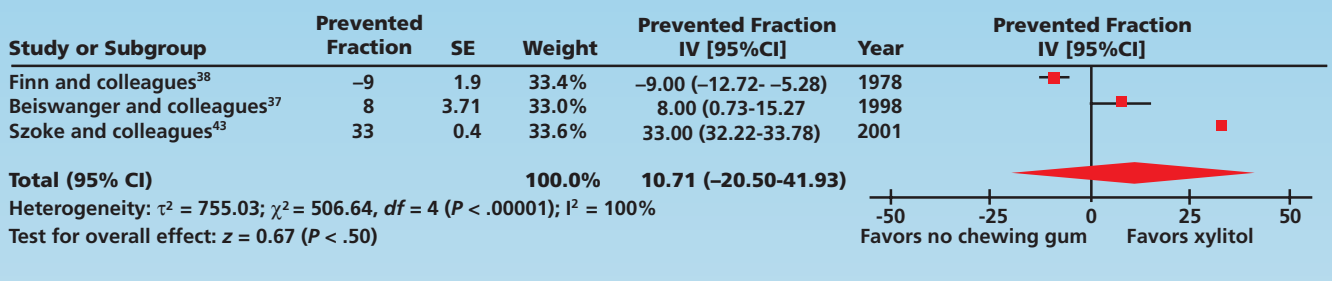

Figure 5. Forest plot for sorbitol-mannitol–containing chewing gum (random-effects model). SE: Standard error. IV: Inverse variance. CI: Confidence interval. z: z test.

CCT), methodological quality and polyol load. The main objective of the extensive sensitivity analyses we performed in this review was to explore the impact of some of these differences on treatment effect.

The difference among the studies in terms of control and intervention groups, the limited information provided on duration of treatment, the lack of variability measurements for outcomes and the discrepancies in reporting data likely contributed to the level of statistical heterogeneity observed.[47] This heterogeneity calls for caution in interpreting the summary effect estimates for individual polyols.

To determine the likelihood of bias associated with study type, we obtained the pooled estimates of RCTs and non-RCTs separately whenever possible. We found that the results of analyses of the non-RCTs were associated with treatment effects that were 38.4 percent and 118.2 percent greater than that of RCTs in the xylitol and sorbitol groups, respectively. The combined results in three of the subgroups were statistically significant, and three subgroups displayed lower heterogeneity compared with their corresponding original groups. Results of RCTs in which sorbitol was assessed favored the use of sorbitol, but the results were not statistically significant. The study by Glass[36] may have contributed to this finding as it had SDs larger than the mean, suggesting nonnormal distribution. Heterogeneity in one subgroup, non-RCTs in which xylitol was assessed, remained unchanged. We could not perform similar calculations for the xylitol-sorbitol blend since there were no RCTs in this group.

Because the methodological quality of a study could affect the magnitude or even direction of treatment effect, we performed sensitivity analyses on studies with low and high quality.[48] On the basis of subgroup analyses for xylitol and the xylitol-sorbitol blend, we found that pooled results of prospective nonrandomized studies that received a rating of fair or poor were associated with an underestimation of treatment effect relative to findings with their higher-quality counterparts by 26.5 percent and 27.9 percent, respectively. Again, the findings in all subgroups were statistically significant. These results are consistent with the findings that study quality may not be associated reliably with exaggeration of treatment effect.[49]

Although a significant beneficial effect of polyol-containing chewing gum was observed across many studies, the most notable exception was illustrated with the sorbitol-mannitol blend. Sensitivity analyses on various subgroups pro-

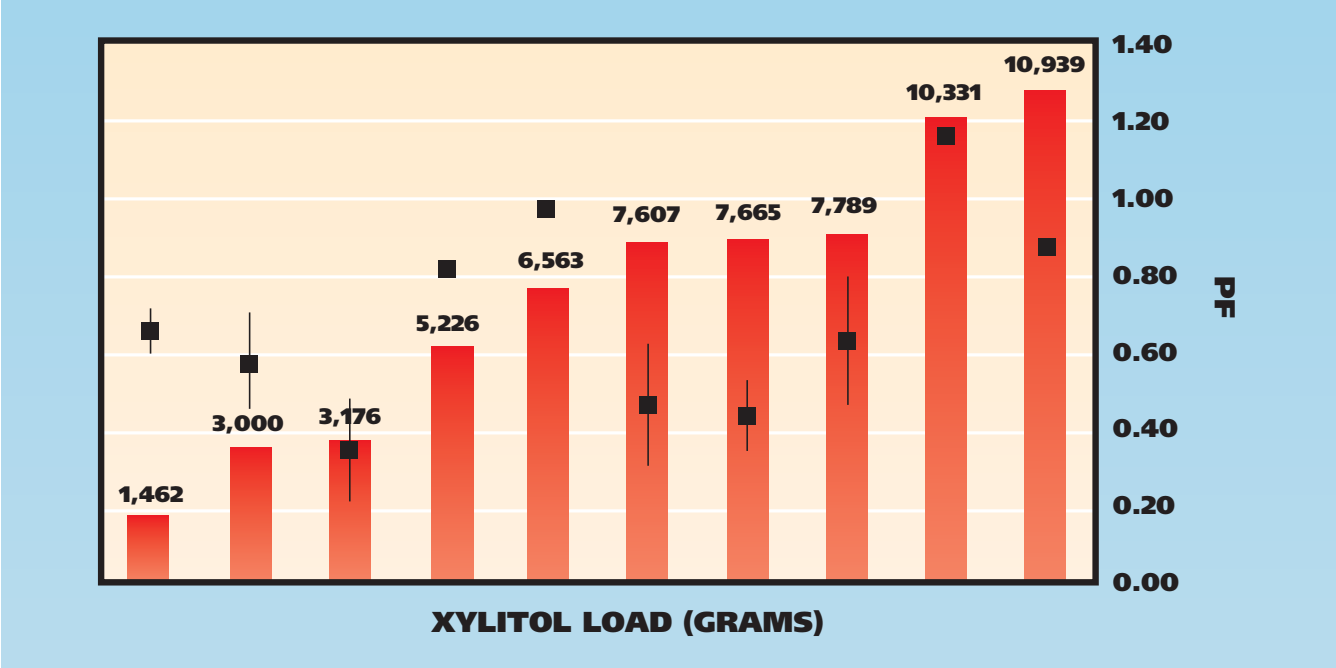

Figure 6. Bar graph of xylitol load versus prevented fraction (PF). Simple univariate linear regression was used to determine dose-response yields a coefficient of determination (R^2 = 49 percent).

duced both favorable and nonfavorable point estimates, but results in all subgroups were not statistically significant. This finding could be explained by a number of factors, including mixed study designs, varying methodological quality and variation in polyol administration.

The findings also suggest that polyols could have a direct effect on caries, complementing the changes in salivary dynamics triggered by the chewing process. It is likely that for polyols to be efficacious, they need to be consumed frequently and on a daily basis to achieve a minimum (as yet undetermined) polyol exposure. In our study, we assessed the impact of total polyol load and did not control for the independent variables that could affect caries such as frequency of chewing, dose of polyol per pellet or slab, and total duration of chewing gum use. Furthermore, the number and designs of the studies, which lacked head-to-head comparisons, were not sufficient for us to draw firm conclusions about the relationship between polyol load and treatment effect or comparisons between polyols. Our review focused on comparisons with no chewing gum as control rather than with other polyols, and this limitation should be considered when comparing the results of the meta-analyses. Nevertheless, the data we reviewed suggest that there might be a correlation between xylitol load and PF that could be greater than that for sorbitol. In fact, the results of a study have shown that xylitol has an effect on dental caries beyond that expected from simple mastication, through a direct effect on *S. mutans*.[50] The potential differences of polyol effect detected through our meta-analyses should be considered a hypothesis to be rejected or supported by future high-quality studies with head-to-head comparisons.

The findings of our review do not agree with those reported by Lingstrom and colleagues[15] that deemed the evidence for the use of sorbitol or xylitol in chewing gum inconclusive. Finding discordant reviews is not rare in the literature.[51] The main differences between these reviews relate to inclusion criteria, quality scales, classification of study design and conclusions based on studies that were considered to be of high quality. We rated two original studies[33,35] classified as low quality by Lingstrom and colleagues[15] as high quality. We performed a sensitivity analysis by eliminating these two studies and still produced statistically significant results across all categories, further confirming the robustness of our findings.

CONCLUSIONS

The results of many original experimental studies have shown that polyol-containing chewing gums reduce dental caries. However, gaps in the litera-

ture continue to exist around dose-response relationships and the relative efficacy of different polyols. In addition to addressing these issues, future research needs to consider more rigorous study designs, head-to-head comparisons of all polyols at optimal doses and higher methodological quality.

We conclude from our quantitative systematic review of the available research that there is consistent evidence to support the use of xylitol- and sorbitol-containing chewing gum as part of normal oral hygiene to prevent dental caries. ■

Disclosures: Foresight Links is a consulting firm owned by Dr. Jadad. Cadbury Adams USA, commissioned Foresight Links to perform an independent review of the impact of polyol-containing chewing gums on dental caries. Cadbury Adams USA owns Trident, which manufacturers xylitol-containing chewing gums. Representatives from Cadbury Adams USA did not participate in the study selection and appraisal, data extraction, analysis or reporting. Dr. Deshpande was a consultant to and received remuneration from Foresight Links for this study.

The authors would like to thank the following people for their support and assistance in the preparation of this article: the external oral care consultants for the sponsor, Drs. Ken Burrell, Mike Barnett and Jack Vincent, who provided guidance and feedback during development of the data extraction form and acted as our experts in the field; Dr. Amid Ismail, an expert in the field of evidence-based dentistry for critically evaluating the manuscript according to the Assessment of Multiple Systematic Reviews guidelines; Dijana Vasic and Jose Vallejo, who assisted in retrieving the articles; Dr. Valeria Marinho, who provided guidance for the statistical analysis and data imputation; Martha Garcia, who acted as project manager; and Svjetlana Kovacevic for her support in retrieving articles.

1. Petersen PE. The World Oral Health Report 2003: Continuous Improvement of Oral Health in the 21st century—The Approach of the WHO Global Oral Health Programme. Geneva: World Health Organization; 2003.
2. Healthy People: 2010. "www.healthypeople.gov/". Accessed Sep. 17, 2008.
3. Armfield JM, Spencer AJ. Quarter of a century of change: caries experience in Australian children, 1977-2002. Aust Dent J 2008;53(2): 151-159.
4. Dye BA, Tan S, Smith V, et al. Trends in oral health status: United States, 1988-1994 and 1999-2004. Vital Health Stat 11 2007;(248):1-92.
5. Batchelor PA, Sheiham A. The distribution of burden of dental caries in schoolchildren: a critique of the high risk caries prevention strategy for populations. BMC Oral Health 2006;6(1):3.
6. Food Outlook: Global Market Analysis. "www.fao.org/docrep/010/ah876e/ah876e07.htm". Accessed Jun. 8, 2008.
7. Burt BA. The use of sorbitol- and xylitol-sweetened chewing gum in caries control (published correction appears in JADA 2006;137[4]:447). JADA 2006;137(2):190-196.
8. Hayes C. The effect of non-cariogenic sweeteners on the prevention of dental caries: a review of the evidence. J Dent Educ 2001;65(10): 1106-1109.
9. Stookey GK. The effect of saliva on dental caries. JADA 2008; 139(suppl 2):11S-17S.
10. Van Loveren C. Sugar alcohols: what is the evidence for caries-preventive and caries-therapeutic effects? Caries Res 2004;38(3): 286-293.
11. Edgar WM. Sugar substitutes, chewing gum and dental caries: a review. Br Dent J 1998;184(1):29-32.
12. Ly KA, Milgrom P, Rothen M. Xylitol, sweeteners, and dental caries. Pediatr Dent 2006;28(2):154-163;discussion 192-198.
13. Trahan L, Bourgeau G, Breton R. Emergence of multiple xylitol-resistant (fructose PTS-) mutants from human isolates of mutans streptococci during growth on dietary sugars in the presence of xylitol. J Dent Res 1996;75(11):1892-1900.
14. Holgerson PL, Sjostrom I, Stecksen-Blicks C, Twetman S. Dental plaque formation and salivary mutans streptococci in schoolchildren after use of xylitol-containing chewing gum. Int J Paediatr Dent 2007;17(2):79-85.
15. Lingstrom P, Holm AK, Mejare I, et al. Dietary factors in the prevention of dental caries: a systematic review. Acta Odontol Scand 2003;61(6):331-340.
16. Marinho VC, Higgins JP, Logan S, Sheiham A. Systematic review of controlled trials on the effectiveness of fluoride gels for the prevention of dental caries in children. J Dent Educ 2003;67(4):448-458.
17. van Rijkom HM, Truin GJ, van 't Hof MA. A meta-analysis of clinical studies on the caries-inhibiting effect of fluoride gel treatment. Caries Res 1998;32(2):83-92.
18. Dubey SD, Lehnhoff RW, Radike AW. A statistical confidence interval for true per cent reduction in caries-incidence studies. J Dent Res 1965;44(5):921-923.
19. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1-12.
20. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20(3 suppl):21-35.
21. Rosenthal R. The "file drawer problem" and tolerance for null results. Psychol Bull 1979;86(3):638-641.
22. Makinen KK, Makinen PL, Pape HR Jr, et al. Stabilisation of rampant caries: polyol gums and arrest of dentine caries in two long-term cohort studies in young subjects. Int Dent J 1995;45(1 suppl 1): 93-107.
23. Makinen KK, Makinen PL, Pape HR, Jr., et al. Conclusion and review of the Michigan Xylitol Programme (1986-1995) for the prevention of dental caries. Int Dent J 1996;46(1):22-34.
24. Chewing gum and the dental health balance. FDI World 1993; 2(5):13-16.
25. Kandelman D, Bar A, Hefti A. Collaborative WHO xylitol field study in French Polynesia. I: baseline prevalence and 32-month caries increment. Caries Res 1988;22(1):55-62.
26. Barmes D, Barnaud J, Khambonanda S, Infirri JS. Field trials of preventive regimens in Thailand and French Polynesia. Int Dent J 1985;35(1):66-72.
27. Rekola M. A planimetric evaluation of approximal caries progression during one year of consuming sucrose and xylitol chewing gums. Proc Finn Dent Soc 1986;82(4):213-218.
28. Isokangas P, Alanen P, Tiekso J, Makinen KK. Xylitol chewing gum in caries prevention: a field study in children. JADA 1988;117(2):315-320.
29. Isogangas P, Makinen KK, Tiekso J, Alanen P. Long-term effect of xylitol chewing gum in the prevention of dental caries: a follow-up 5 years after termination of a prevention program. Caries Res 1993;27(6):495-498.
30. Isokangas P, Tenovuo J, Soderling E, Mannisto H, Makinen KK. Dental caries and mutans streptococci in the proximal areas of molars affected by the habitual use of xylitol chewing gum. Caries Res 1991;25(6):444-448.
31. Isokangas P, Tiekso J, Alanen P, Makinen KK. Long-term effect of xylitol chewing gum on dental caries. Community Dent Oral Epidemiol 1989;17(4):200-203.
32. Hujoel PP, Makinen KK, Bennett CA, et al. The optimum time to initiate habitual xylitol gum-chewing for obtaining long-term caries prevention. J Dent Res 1999;78(3):797-803.
33. Makinen KK, Hujoel PP, Bennett CA, Isotupa KP, Makinen PL, Allen P. Polyol chewing gums and caries rates in primary dentition: a 24-month cohort study. Caries Res 1996;30(6):408-417.
34. Kandelman D, Gagnon G. Clinical results after 12 months from a study of the incidence and progression of dental caries in relation to consumption of chewing-gum containing xylitol in school preventive programs. J Dent Res 1987;66(8):1407-1411.
35. Makinen KK, Bennett CA, Hujoel PP, et al. Xylitol chewing gums and caries rates: a 40-month cohort study. J Dent Res 1995;74(12): 1904-1913.
36. Glass RL. A two-year clinical trial of sorbitol chewing gum. Caries Res 1983;17(4):365-368.
37. Beiswanger BB, Boneta AE, Mau MS, Katz BP, Proskin HM, Stookey GK. The effect of chewing sugar-free gum after meals on clinical caries incidence. JADA 1998;129(11):1623-1626.
38. Finn SB, Frew RA, Leibowitz R, Morse W, Manson-Hing L, Brunelle J. The effect of sodium trimetaphosphate (TMP) as a chewing gum additive on caries increments in children. JADA 1978;96(4):651-655.
39. Kovari H, Pienihakkinen K, Alanen P. Use of xylitol chewing gum in daycare centers: a follow-up study in Savonlinna, Finland. Acta Odontol Scand 2003;61(6):367-370.
40. Kandelman D, Gagnon G. A 24-month clinical study of the incidence and progression of dental caries in relation to consumption of chewing gum containing xylitol in school preventive programs. J Dent

Res 1990;69(11):1771-1775.
41. Moller IJ, Poulsen S. The effect of sorbitol-containing chewing gum on the incidence of dental caries; plaque and gingivitis in Danish schoolchildren. Community Dent Oral Epidemiol 1973;1(2):58-67.
42. Petersen PE, Razanamihaja N. Carbamide-containing polyol chewing gum and prevention of dental caries in schoolchildren in Madagascar. Int Dent J 1999;49(4):226-230.
43. Szoke J, Banoczy J, Proskin HM. Effect of after-meal sucrose-free gum-chewing on clinical caries. J Dent Res 2001;80(8):1725-1729.
44. Machiulskiene V, Nyvad B, Baelum V. Caries preventive effect of sugar-substituted chewing gum. Community Dent Oral Epidemiol 2001;29(4):278-288.
45. Alanen P, Isokangas P, Gutmann K. Xylitol candies in caries prevention: results of a field study in Estonian children. Community Dent Oral Epidemiol 2000;28(3):218-224.
46. Peng B, Petersen PE, Bian Z, Tai B, Jiang H. Can school-based oral health education and a sugar-free chewing gum program improve oral health? Results from a two-year study in PR China. Acta Odontol Scand 2004;62(6):328-332.
47. Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. BMJ 1994;309(6965):1351-1355.
48. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352(9128):609-613.
49. Balk EM, Bonis PA, Moskowitz H, et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. JAMA 2002;287(22):2973-2982.
50. Trahan L. Xylitol: a review of its action on mutans streptococci and dental plaque—its clinical significance. Int Dent J 1995;45(1 suppl 1):77-92.
51. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. CMAJ 1997;156(10):1411-1416.