Long-term effect of erythritol on dental caries development during childhood: a post-treatment survival analysis

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Disclosure statement

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Abstract

Objective: Assess the effect of daily consumption of erythritol, xylitol, and sorbitol candies on caries development in mixed dentition during a three-year intervention and three years after the intervention. **Methods:** 485 Estonian first and second grade primary school children participated. Children were randomly allocated to an erythritol, xylitol, or sorbitol (control) group. Polyol-containing candies were administered on school days with a daily polyol consumption of 3x2.5 g. Yearly, caries development was assessed by calibrated dentists using the ICDAS criteria. Six years after initiation of the study and three years after cessation of daily polyol consumption, 420 participants were re-examined to identify potential long-term effects of polyol consumption. Survival curves were generated at the end of the intervention period and three years post intervention. The model included age of the subjects, schools, tooth surface ages and years of surface exposure to intervention. ICDAS scoring system based events included enamel/dentine caries development, dentine caries development, increase in caries score, and dentist intervention. **Results:** At the end of the intervention, time to enamel/dentine caries development, dentine caries development, increase in caries score, and dentist intervention was significantly longer in the erythritol group as compared to the sorbitol group. Except for increase in caries score, all effects persisted three years after cessation of daily polyol consumption. **Conclusions:** A caries preventive effect of three-year erythritol consumption as compared to sorbitol was established in children with mixed dentition. The effect persisted up to three years after the end of the intervention. Trial registration: ClinicalTrials.gov Identifier NCT01062633.

Introduction

The caries-preventive effect of xylitol-containing chewing gum in comparison with no gum or sugar-based gum has been demonstrated and confirmed throughout multiple clinical trials [Deshpande and Jadad, 2008]. Among the benefits of chewing xylitol-sweetened gums are the stimulation of salivary flow leading to enhanced clearing of cariogenic substrates and increased buffering capacity and remineralization, the reduction of acid production due to the hypo-acidogenic nature of the sugar alcohol, and the xylitol-associated inhibition of *Streptococcus mutans* growth [Van Loveren, 2004; Mäkinen, 2010, 2011]. However, chewing gum has some undesirable properties such as waste problems, is socially unaccepted in some societies, and presents difficulties for individuals with poor dentition [Alanen et al., 2000]. To overcome these hurdles, there is a growing interest in exploring effectiveness of alternative polyol delivery vehicles, including candies and lozenges.

To disentangle pure xylitol-associated caries preventive effects from those inherent to the chewing process itself (including mechanistic plaque removal and increased saliva production and buffering capacity), several field studies using chewing-independent polyol delivery modes have been set-up [Alanen et al., 2000; Honkala et al., 2006; Stecksén-Blicks et al., 2008]. A systematic review assessing the caries preventive effect of consuming xylitol-based candies and lozenges concluded that a reduction in caries increment could be observed in two out of three intervention groups [Gonçalves Antonio et al., 2011]. However, some recent intervention trials did not confirm a significant effect on caries development associated to xylitol lozenge/candy consumption in children [Lenkkeri et al., 2012; Lee et al., 2015] or adults [Fontana and Gonzalez-Cabezas, 2013]. In recent years, erythritol, a polyol of the tetritol type, has been shown to have similar effect on caries risk factors as previously reported for xylitol [Kawanabe et al., 1992; Mäkinen et al., 2005].

We evaluated efficacy of long-term, daily intake of polyol-containing candies on the development of enamel and dentine caries lesions in a cohort of 485 Estonian primary school children through a double blind, randomized, controlled prospective intervention trial [Honkala et al., 2014]. During three years, participating children consumed each four erythritol, xylitol, or sorbitol (control) candies three times per school day, resulting in a total daily polyol intake of 7.5 g. Dental health and caries development were clinically assessed using the International Caries Detection and Assessment System (ICDAS, [Ismail et al., 2007]) at baseline and months 12, 24, and 36 of the intervention. At month 36, erythritol consumption resulted in lower numbers of dentine caries surfaces as compared to xylitol and sorbitol consumption. Moreover, time to enamel/dentine caries development, dentine caries

development, or increase in ICDAS caries score were estimated significantly longer in erythritol-consuming children than in those receiving sorbitol or xylitol candies. An ancillary study [Runnel et al., 2013], aiming to provide a mechanistic insight in the potential caries-preventive effect observed, revealed that daily consumption of erythritol-containing candies resulted in a significant reduction of dental plaque weight, while no such changes could be detected in the xylitol or sorbitol groups. Moreover, at the end of the three-year intervention period, plaque concentrations of acetate and propionate were shown to be lower in erythritol-consuming children as compared to the xylitol and control groups, associated with a significantly reduced abundance of both salivary and plaque *S. mutans*.

Given the changes in oral microbiota and biofilm growth observed, we hypothesized that the effects of long-term erythritol consumption on dental health would stretch beyond the intervention period, as previously reported for xylitol chewing gum [Isokangas et al., 1989, 1993; Hujoel et al., 1999]. Here, three years after completion of the intervention trial and cessation of treatment, we assess the prolonged effects of three-year daily consumption of polyol-containing candies on caries development in a cohort of Estonian school children.

Materials and Methods

Study design and clinical procedures

For an extensive overview of study design and procedures, we refer to an earlier publication [Honkala et al., 2014]. Briefly, the study was set up in 2008 as a double blind, randomized, controlled prospective intervention trial. Baseline study population consisted of 485 first and second grade primary school children enrolled from ten schools in the region around Tartu, southeastern Estonia. At enrollment, participating school classes were randomly divided into an erythritol, xylitol, and sorbitol (control) intervention groups. Randomization was done using computer-generated numbers on the list of classes from participating schools. To reduce a potential school bias, first-grade pupils were allocated in different intervention groups than second-graders of the same school. Children joining participating schools in 2009 and 2010 were invited to take part in the study (Table 1). None of the participants switched intervention group during the three-year trial. CONSORT flow diagram shows the allocation of participants to the intervention groups (fig. 1)

Throughout the intervention trial (2008-2011), pupils consumed erythritol-, xylitol-, and control-containing candies during school days (approximately 200 days per year). Each participant consumed four candies three times per school day. Total daily intake of polyol was about 7.5 g. Candies were distributed by teachers before the start of the classes (8 a.m.), after

school lunch (10:30 a.m.), and at the end of the school day (1:30 or 2:15 p.m.). Consumption of candies was supervised by school teachers who had received training before the start of the intervention trial. Double blind clinical examinations of all participating children were completed four times (baseline and after 12, 24, and 36 months of intervention) by four trained and calibrated investigators using the ICDAS II scoring methodology [Ismail et al., 2007].

The study was conducted according to the ethical principles of the Declaration of Helsinki. The Research Ethics Committee of the University of Tartu approved the study (166/T-7). Approval of the School Management Authority and school principals was received. Only pupils whose parents/caretakers returned a signed consent form were included in the trial. The study was registered to the register of clinical trials (www.clinicaltrials.gov; Identifier NCT01062633).

Follow-up clinical examination

In 2014, six years after the start of the study and three years after the end of the intervention, participants were re-contacted by the research team. Of the 420 children that participated in the 2011 examination, 364 (87%) consented to participating to a follow-up clinical evaluation performed by the calibrated examiners involved in the clinical intervention following the procedures described above (Table 1). Data were analyzed using SPSS (version 19.0) and SAS (9.2 or higher).

Decayed, missing, and filled teeth and surfaces

Permanent dentition was analyzed as described previously [Honkala et al., 2014]. ICDAS caries scores 1-3 were combined to enamel caries teeth ($D_{1-3}T$) and surfaces ($D_{1-3}S$). Scores 4-6 were combined to dentin caries teeth ($D_{4-6}T$) and surfaces ($D_{4-6}S$). Caries experience indices ($D_{4-6}MFT$ and $D_{4-6}MFS$) were calculated. Analyses were limited to pupils that joined the study in 2008 and remained until 2014. Numbers of enamel and dentin caries teeth and surfaces, teeth and surfaces with fillings, and caries experienced teeth and surfaces were compared between the intervention groups using negative binomial regression. Models were adjusted for gender, age (categorized), and school. The natural log of the number of teeth or surfaces present was included as an offset when analyzing the number of enamel/dentin caries and filled teeth or surfaces. Pearson χ^2 goodness-of-fit statistics were used to assess the fit of the models.

Survival analysis

For the purpose of survival analyses, the following events were defined:

(1) enamel/dentine caries development: observed transition of ICDAS caries score 0 to 1-6,

(2) dentine caries development: observed transition of ICDAS caries score 0-3 to 4-6,

(3) increase in caries score: observed transition of ICDAS caries score x to (x+1)-6,

(4) dentist intervention: observed of ICDAS restoration score 0 to 3-8.

Surfaces with partial or full sealants (ICDAS restoration scores 1-2) and surfaces subject to dentist intervention (restoration/extraction) in between study clinical examinations and prior to observed transition of ICDAS score were excluded from survival analysis. As clinical assessment of caries development took place every twelve months, the exact time-points on which the events defined took place occurred could not be determined. Hence, time of events was characterized by lower and upper bounds. The lower bound for time to caries development or dentist intervention (months) was calculated as twelve times the number of examinations where the surface was sound. The upper bound was defined as the lower bound plus twelve.

Besides intervention groups, age of the subjects, and schools, also surface ages (time of eruption) and years of intervention were identified as variables potentially affecting caries development and taken into account in survival modelling efforts. For time of eruption, surfaces were categorized as surface of primary tooth present at start of study, permanent present at start of study, and erupted during a determined period between clinical examinations (2008-2009, 2009-2010, 2010-2011, and 2011-2014). Years of intervention reflects the time a surface was effectively exposed to the intervention. It was estimated taking into account both the moment the subject started participation to the study and time of eruption of the tooth under study. For surfaces erupting in between two clinical examinations, six months of exposure were added to years of intervention. For surfaces that appeared after the 2011 clinical examination, years of intervention was set at zero.

The expected duration of time until occurrence of one of the events defined was statistically analyzed. Accelerated failure time modeling of the interval-censored data was performed using SAS Proc LIFEREG. The distribution of the data was specified as log-logistic, as this allowed the rate of decay to increase or decrease over time [Hannigan et al., 2001]. The model was fitted using the maximum likelihood method and included terms for intervention group, age of the subject, school, time of eruption, and years of intervention. Given the restrictions on distribution of intervention groups over schools imposed during the randomization process, school class was not included as an independent confounder in the

survival model. Survival curves were generated for each intervention group. It was not possible to estimate the median time, as the proportions of events were small.

Results

Decayed, missing, and filled teeth and surfaces

For participants that joined the study in 2008, caries indices in the permanent dentition were calculated for each intervention group at baseline, during the intervention period, and three years after cessation of intervention (Table 2). At the baseline, the number of dentin caries surfaces ($D_{4-6}S$) in the permanent dentition was significantly higher in the sorbitol group than in the erythritol group (relative risk [RR] = 3.10, 95% confidence interval [CI] 1.23-7.80). There were no significant differences between the groups at the 12 months follow-up. At the 24 months examination, the xylitol group had higher number of dentin caries teeth ($D_{4-6}T$; RR = 2.88, 95% CI 1.11-7.43) and surfaces ($D_{4-6}S$; RR = 3.61, 95% CI 1.22-10.75) than the erythritol group. At 36 months, the xylitol group had higher number of dentin caries teeth ($D_{4-6}T$; RR = 2.3, 95% CI 1.19-4.46) and surfaces ($D_{4-6}T$; RR = 2.60, 95% CI 1.31-5.18) than the sorbitol group. Three years after cessation of daily consumption of polyol candies, no significant differences in decayed, missing, and filled teeth and surfaces could be observed between intervention groups.

ICDAS-based definition of caries event transitions

Implementation of the ICDAS score in dental research allows examiners to classify the carious status of each tooth surface using a seven-point ordinal scale ranging from sound to extensive cavitation [Ismail et al., 2007]. As this scale allows discrete stratification of the extensiveness of tooth decay, it enables defining singular transitions or events that allow efficacy analysis in caries-preventive intervention trials. Here, we apply ICDAS-based survival analyses to assess the long-term impact of erythritol, xylitol, and sorbitol candy consumption on enamel and dentine lesion developments, progression of decay, and necessity of dentist intervention. For each event defined, the percentage of transitions observed during the initial intervention trial as well as throughout intervention and follow-up period are listed in Table 3. During the intervention period, percentages of surfaces experiencing a transition was significantly lower for all events defined in children receiving erythritol-containing candies as compared to the participants consuming xylitol or soribitol candies. Three years after cessation of intervention, percentages of surfaces developing enamel/dental caries, dental caries, or subject to dentist intervention was still reduced in erythritol group, while the

latter event was also significantly less frequently observed in the xylitol cohort group using the control group as reference.

Survival analysis

Survival curves, graphic representations of the probabilities of surfaces of not experiencing transition events over time, were generated for each intervention group. The log-logistic model applied included terms for intervention group, age of the subject, school, time of eruption, and years of intervention. Parameter estimate, standard error, p-value, and acceleration factor for intervention groups are presented in Table 4. Both enamel/dentine caries development and increase in caries score were significantly slowed down in the erythritol study group during the trial (acceleration factor>1). Remarkably, time to enamel/dentine caries development and increase in caries score was shorter in the xylitol intervention group when compared to children consuming sorbitol candies. Three years after completion of the polyol intervention, increase in caries score was still significantly faster in pupils that received xylitol-containing candies.

Survival curves were generated for each intervention group using a model taking into account age of the subjects, schools, time of eruptions, and years of surface exposure to intervention (fig. 2). For all events identified, time to transition was significantly prolonged in children consuming erythritol-containing candies as compared to the control group at the end of the intervention period. Three years after completion of the trial, enamel/dentine caries development, dentine caries development, and dentist interventions were still significantly delayed in the erythritol intervention group. No significant benefits were observed for the xylitol cohort. No adverse effects were observed in any of the intervention groups.

Discussion

Dealing with exfoliating and erupting teeth is probably one of the major challenges when analyzing results of caries intervention studies in children with mixed dentition. Using a classic analytical design, robust analyses should probably be limited to those teeth and surfaces present during the entire study period [Larmas, 2015]. However, this limitation weights significantly on the statistical power of the analyses, especially in studies like ours that aim to study caries development over a longer period of time. Here, we use the ICDAS scoring system to define a set of events that allows application of survival analysis on caries development. One of the advantages of applying this analytical technique on mixed dentition is the fact that also data on teeth that exfoliated or erupted during the study can be included in modeling efforts. Moreover, introduction of a term describing age of teeth in the survival

models allows integration of all available information on both primary and permanent dentition, a critical issue in caries intervention studies in mixed dentition [Riley et al., 2015].

Only a few clinical trials have assessed caries-preventive effect of polyol consumption beyond the duration of intervention. A long-term effect of daily consumption of xylitol chewing gum was first reported by Isokangas *et al.* [Isogangas et al., 1989; 1993] in several follow-up studies of the Ylivieska (Finland) trial [Isokangas et al., 1988]. During a two-year intervention, 172 11- to 12-year-old children were asked to chew xylitol gums three times each day, resulting in a daily xylitol consumption of 10.5 g. No gums were provided to the control group (n=152). Based on total caries experience recorded at the beginning of the trial, 66 children (30 xylitol versus 36 control subjects) were classified as high-risk subjects and enrolled in a third year of intervention. Both over the two- and three-year intervention periods, daily chewing of xylitol gums significantly reduced increment in DMFS scores [Isokangas et al., 1988]. Respectively five [Isokangas et al., 1989] and seven [Isogangas et al., 1993] years after the start of the study – two/three and five years after discontinuation of daily xylitol chewing – 269 and 258 (the latter excluding high-risk individuals) subjects that participated in the Ylivieska trial were re-examined to investigate a potential induction of a long-term effect. The caries-preventive effect associated with xylitol gum-chewing was reported to persist and even increase over time.

A second follow-up study with similar results was carried out five years after termination of the Dangriga (Belize) clinical trial [Mäkinen et al., 1996; Hujoel et al., 1999]. During the initial two-year intervention, 510 children averaging six years of age where requested to chew xylitol (10.4 or 10.7 g/day), sorbitol (10.4 or 10.7 g/day) or mixed (xylitol+sorbitol, 7.1+2.7 or 9.7+2.7 g/day) gums five times per day [Mäkinen et al., 1996]. Compared to the no-gum group, all interventions resulted in a decreased caries onset risk for primary surfaces. The largest reduction of caries development risk was observed in the 10.7 g/day xylitol group. Five years after the end of the two-year intervention, 288 children were re-examined to assess a potential long-term effect of habitual polyol gum-chewing [Hujoel et al., 1999]. While no long-term caries preventive effect could be observed in the sorbitol group, both xylitol and mixed gum-chewing reduced caries onset risks significantly.

A third study assessed the impact on caries development of daily consumption of 4.7/4.6 g xylitol/maltitol or 4.5/4.2 g erythritol/maltitol lozenges on caries development over a four-year period (1/2 years of intervention for each treatment) in 496 children from the region of Kotka (Finland), an area with low caries prevalence [Lenkkeri et al., 2012]. Compared to a

passive (no intervention) control group, no additional caries-preventive effect in terms of reduction of DMFS increment associated to lozenge consumption could be observed.

In the present study, using survival analyses, a significant though moderate long-term effect of daily consumption of 7.5 g erythritol under the form of candies was observed. In terms of DMFS score evolution, no differences could be observed between the erythritol intervention and control groups three years after discontinuation of polyol candy consumption. However, analysis of survival curves per intervention group revealed that subjects that had been consuming erythritol candies where characterized by delayed enamel/dentine caries development, delayed dentine caries development, and delayed dentist interventions. These observations confirm the previously reported results of the actual intervention study. The survival models applied include terms addressing variation in age of participants, clustering effects due to school/class-based randomization, and effects of tooth exfoliation and duration of treatment that could affect differences in caries development between intervention groups.

Differences in long-term impact of polyol intervention between the present study and the Ylivieska and Dangriga long-term analyses – reporting up to 64% reduction in caries increment [Isokangas et al., 1989] – are inherent to the set-up of the intervention trial. Not only did we opt for an alternative delivery mode (candies versus gums, reducing the effect of mechanical plaque removal and minimizing the impact of salivary flow stimulation by chewing a gum), we also provided dental health education, toothbrushes, and fluoride toothpaste to participants and included an active control group (administration of sorbitol candies rather than a passive, no intervention group) in the study design. Moreover, compared to the Dangriga trial [Mäkinen et al., 1996], baseline caries risk in the Tartu population was only moderate. Concerning the effect on DMFS increment, results of the present study do align with the findings of the Kotka intervention [Lenkkeri et al., 2012]. They also reveal the need for the implementation of statistically more powerful efficacy analyses when studying caries prevention in low prevalence populations.

The long-term caries-preventive effect of polyol consumption has been explained by Loesche's hypothesis stating that the characteristics of the dental microbiota established at time of eruption determine the life-long caries risk [Loesche, 1985]. Polyol intervention during eruption of permanent teeth – as in the present study - would not only create optimal physicochemical circumstances for optimal tooth maturation, bacterial colonization of teeth by a commensal microbiota would also result in the development of a stable tooth-associated microbial ecosystem hampering posterior infection with *S. mutans* [Isokangas et al., 1989;

Hujoel et al., 1999]. Indeed, it has been demonstrated that erythritol consumption does not only affect plaque weight and acid concentrations, but also reduces salivary and plaque *S. mutans* abundances [Runnel et al., 2013]. The latter has been linked with the inhibiting effect of erythritol on *S. mutans* adherence and its suppression of glucosyl- and fructosyltransferases [Park et al., 2014].

Remarkably, no effect of xylitol intervention in comparison to the sorbitol control could be noted on the events defined when including terms for age of the subject, school, time of eruption, and years of intervention in the survival model. This observation probably reflects the complications inherently associated to the assessment of additional caries-preventive effects in populations with access to adequate dental healthcare. However, it might also indicate potential microbiota adaptation to regular xylitol consumption [Badet et al., 2004; Van Loveren, 2004].

In conclusion, the present study demonstrates that the differences observed in terms of decreased increment of decayed, missing, and filled teeth and surfaces in children with mixed dentition after three-year regular consumption of erythritol-containing candies compared with xylitol and control candies could no longer be observed three years after ending the consumption. However, three years after completion of the intervention trial, survival analysis allowed to detect delayed development of both enamel/dentine and dentine caries and dentist interventions in the erythritol group when compared to control intervention.

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Author Contributions

E.H., K.M., and M.S. designed the study; R.N. and M.S. organized the practicalities of the study; S.H., R.R., J.O., and E.H. performed the clinical examinations; P.L.M. and K.M. performed the biometric measurements; S.R. implemented the oral health education sessions; E.H., K.M., M.S., R.R., S.H., and P.L.M. conducted the school visits; T.V., G.F., E.H. and S.H. analyzed the data; G.F. and S.H. wrote the paper.

References

Alanen P, Isokangas PJ, Gutmann K: Xylitol candies in caries prevention: results of a field study in Estonian children. Community Dent Oral Epidemiol 2000;28:218–224.

Badet C, Richard B, Castaing-Debat M, de Flaujac P., Dorignac G: Adaptation of salivary Lactobacillus strains to xylitol. Arch Oral Biol 2004;49:161–164.

Deshpande A, Jadad AR: The impact of polyol-containing chewing gums on dental caries: a systematic review of original randomized controlled trials and observational studies. J Am Dent Assoc 2008;139:1602–1614.

Fontana M, Gonzalez-Cabezas C: Xylitol lozenges were not effective in overall dental caries prevention in adults. J Evid Based Dent Pract 2013;13:97–99.

Gonçalves Antonio A, Santos Da Silva Pierro V, Cople Maia L: Caries preventive effects of xylitol-based candies and lozenges: a systematic review. J Public Health Dent 2011 Mar 25;71:117–124.

Hannigan A, O'Mullane DM, Barry D, Schäfer F, Roberts AJ: A re-analysis of a caries clinical trial by survival analysis. J Dent Res 2001;80:427–431.

Honkala E, Honkala S, Shyama M, Al-Mutawa SA: Field trial on caries prevention with xylitol candies among disabled school students. Caries Res 2006;40:508–513.

Honkala S, Runnel R, Saag M, Olak J, Nõmmela R, Russak S, Mäkinen P-L, Vahlberg T, Falony G, Mäkinen K, Honkala E: Effect of erythritol and xylitol on dental caries prevention in children. Caries Res 2014;48:482–490.

Hujoel PP, Mäkinen KK, Bennett CA, Isotupa KP, Isokangas PJ, Allen P, Mäkinen PL: The optimum time to initiate habitual xylitol gum-chewing for obtaining long-term caries prevention. J Dent Res 1999;78:797–803.

Ismail AI, Sohn W, Tellez M, Amaya A, Sen A, Hasson H, Pitts NB: The International Caries Detection and Assessment System (ICDAS): an integrated system for measuring dental caries. Community Dent Oral Epidemiol 2007;35:170–178.

Isokangas PJ, Alanen P, Tiekso J, Mäkinen K: Xylitol chewing gum in caries prevention: a field study in children. J Am Dent Assoc 1988;117:315–320.

Isokangas PJ, Tiekso J, Alanen P, Mäkinen KK: Long-term effect of xylitol chewing gum on dental caries. Community Dent Oral Epidemiol 1989;17:200–203.

Isogangas PJ, Mäkinen 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;27:495–498.

Kawanabe J, Hirasawa M, Takeuchi T, Oda T, Ikeda T: Noncariogenicity of erythritol as a substrate. Caries Res 1992;26:358–362.

Larmas M: Comment on the paper entitled “Effect of erythritol and xylitol on dental caries prevention in children.” Caries Res 2015;49:488.

Lee W, Spiekerman C, Heima M, Eggertsson H, Ferretti G, Milgrom P, Nelson S: The effectiveness of xylitol in a school-based cluster-randomized clinical trial. Caries Res 2015;49:41–49.

Lenkkeri A-MH, Pienihäkkinen K, Hurme S, Alanen P: The caries-preventive effect of xylitol/maltitol and erythritol/maltitol lozenges: results of a double-blinded, cluster-randomized clinical trial in an area of natural fluoridation. Int J Paediatr Dent 2012;22:180–190.

Loesche WJ: Nutrition and dental decay in infants. Am J Clin Nutr 1985;41:423–435.

Mäkinen K, Hujoel P, Bennett C, Isotupa K, Mäkinen P-L, Allen P: Polyol chewing gums and caries rates in primary dentition: a 24-month cohort study. Caries Res 1996;30:408–417.

Mäkinen KK, Saag M, Isotupa KP, Olak J, Nõmmela R, Söderling E, Mäkinen PL: Similarity of the effects of erythritol and xylitol on some risk factors of dental caries. Caries Res 2005;39:207–215.

Mäkinen K: Sugar alcohols, caries incidence, and remineralization of caries lesions: a literature review. Int J Dent 2010;2010:981072.

Mäkinen KK: Sugar alcohol sweeteners as alternatives to sugar with special consideration of xylitol. Med Princ Pract 2011;20:303–320.

Park Y-N, Jeong S-S, Zeng J, Kim S-H, Hong S-J, Ohk S-H, Choong-Ho C: Anti-cariogenic effects of erythritol on growth and adhesion of Streptococcus mutans. Food Sci Biotechnol 2014;23:1587–1591.

Riley P, Moore D, Ahmed F, Sharif MO, Worthington H V: Xylitol-containing products for preventing dental caries in children and adults. Cochrane Database Syst Rev 2015;3:CD010743.

Runnel R, Mäkinen K, Honkala S, Olak J, Mäkinen P-L, Nõmmela R, Valhberg T, Honkala E, Saag M: Effect of three-year consumption of erythritol, xylitol and sorbitol candies on various plaque and salivary caries-related variables. J Dent 2013;41:1236–1244.

Stecksén-Blicks C, Holgerson PL, Twetman S: Effect of xylitol and xylitol-fluoride lozenges on approximal caries development in high-caries-risk children. Int J Paediatr Dent 2008;18:170–177.

Van Loveren C: Sugar alcohols: what is the evidence for caries-preventive and caries-therapeutic effects? Caries Res 2004;38:286–293.

Legends for the figures

Fig. 1. CONSORT flow diagram of the Tartu caries study (166/T-7), Clinical Trials.gov Identifier NCT0106233.

Fig. 2. Survival curves for erythritol (E), xylitol (X), and sorbitol (S; control) intervention groups. **(A) Time to enamel/dentine caries development** (2008-2011 log-rank test p-value≤0.0001, pairwise to control: xylitol p-value=0.6464, erythritol p-value=0.0004; 2008-2014 log-rank test p-value=0.0084, pairwise to control: xylitol p-value=0.5489, erythritol p-value=0.0197) **(B) Time to dentine caries development** (2008-2011 log-rank test p-value≤0.0001, pairwise to control: xylitol p-value=0.4753, erythritol p-value=0.0002; 2008-2014 log-rank test p-value≤0.0001, pairwise to control: xylitol p-value=0.4893, erythritol p-value=0.0003); **(C) Time to increase in caries score** (2008-2011 log-rank test p-value≤0.0001, pairwise to control: xylitol p-value=0.1394, erythritol p-value=0.0032; 2008-2014 log-rank test p-value=0.0012, pairwise to control: xylitol p-value=0.0749, erythritol p-value=0.0591); **(D) Time to dentist intervention** (2008-2011 log-rank test p-value=<0.0001, pairwise to control: xylitol p-value=0.0788, erythritol p-value=<0.0001; 2008-2014 log-rank test p-value=0.0006, pairwise to control: xylitol=p-value 0.0541, erythritol p-value=0.0001).

445 **Table 1.** Evolution of intervention groups' sizes throughout intervention and follow-up period

	Erythritol				**Xylitol**				**Sorbitol**			
	Joined				**Joined**				**Joined**			
	2008	**2009**	**2010**	**Total**	**2008**	**2009**	**2010**	**Total**	**2008**	**2009**	**2010**	**Total**
2008	165			**165**	156			**156**	164			**164**
2009	142	14		**156**	145	21		**162**	149	14		**163**
2010	132	13	3	**148**	132	16	5	**153**	137	14	5	**156**
2011	122	10	2	**134**	126	13	5	**144**	126	13	3	**142**
2014	117	10	2	**129**	100	11	1	**112**	111	11	1	**123**

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Table 2. Total number of teeth and surfaces, number (%) of decayed and filled teeth and surfaces, and mean (SEM) of decayed, missing, and filled teeth and surface indices in the permanent dentition at baseline (2008), year one (2009), two (2010), and three (2011) of intervention, and three years post intervention (2014)

	Erythritol					**Xylitol**					**Sorbitol**				
	2008	**2009**	**2010**	**2011**	**2014**	**2008**	**2009**	**2010**	**2011**	**2014**	**2008**	**2009**	**2010**	**2011**	**2014**
n	165	142	132	122	**117**	156	**145**	**132**	**126**	**100**	164	149	137	126	**111**
T	2119	2280	2599	2787	**3247**	1864	2143	2327	2717	**2767**	1895	2200	2368	2623	**3053**
S	9298	10161	11632	12568	**14832**	8197	9510	10350	12229	**12639**	8319	9748	10523	11761	**13934**
$D_{1-3}T$	306	254	312	354	**645**	293	273	327	360	**486**	304	281	316	302	**496**
	(14.4)	(11.1)	(12.0)	(12.7)	**(19.9)**	(15.7)	(12.7)	(14.1)	(13.2)	**(17.6)**	(16.0)	(12.8)	(13.3)	(11.5)	**(16.2)**
$D_{1-3}S$	427	351	406	449	**749**	419	375	438	463	**572**	420	375	418	386	**597**
	(4.6)	(3.5)	(3.5)	(3.6)	**(5.0)**	(5.1)	(3.9)	(4.2)	(3.8)	**(4.5)**	(5.0)	(3.8)	(4.0)	(3.3)	**(4.3)**
$D_{4-6}T$	21	27	14	23	**50**	34	30	36	38	**42**	40	33	29	19	**36**
	(1.0)	(1.2)	(0.5)[1]	(0.8)	**(1.5)**	(1.8)	(1.4)	(1.5)[1]	(1.4)[2]	**(1.5)**	(2.1)	(1.5)	(1.2)	(0.7)[2]	**(1.2)**
$D_{4-6}S$	24	31	15	25	**54**	47	40	47	47	**54**	65	44	41	20	**41**
	(0.3)[3]	(0.3)	(0.1)[4]	(0.2)	**(0.4)**	(0.6)	(0.4)	(0.5)[4]	(0.4)[5]	**(0.4)**	(0.8)[3]	(0.5)	(0.4)	(0.2)[5]	**(0.3)**
FT	151	151	188	230	**397**	97	123	156	200	**309**	90	147	189	202	**320**
	(7.1)	(6.6)	(7.2)	(8.3)	**(12.2)**	(5.2)	(5.7)	(6.7)	(7.4)	**(11.2)**	(4.7)	(6.7)	(8.0)	(7.7)	**(10.5)**
FS	186	195	252	323	**538**	123	160	204	259	**384**	126	200	265	297	**429**
	(2.0)	(1.9)	(2.2)	(2.6)	**(3.6)**	(1.5)	(1.7)	(2.0)	(2.1)	**(3.0)**	(1.5)	(2.1)	(2.5)	(2.5)	**(3.1)**
D_{4-6} MFT	1.10	1.23	1.50	2.01	**3.67**	0.88	1.07	1.44	1.86	**3.41**	0.92	1.18	1.56	1.74	**3.11**
	(0.13)	(0.13)	(0.15)	(0.20)	**(0.29)**	(0.12)	(0.13)	(0.15)	(0.15)	**(0.29)**	(0.12)	(0.12)	(0.16)	(0.18)	**(0.28)**
D_{4-6} MFS	1.62	1.68	2.01	2.87	**5.09**	1.42	1.44	1.97	2.52	**4.29**	1.82	1.66	2.29	2.69	**4.24**
	(0.24)	(0.20)	(0.22)	(0.31)	**(0.51)**	(0.25)	(0.19)	(0.24)	(0.24)	**(0.43)**	(0.37)	(0.21)	(0.27)	(0.34)	**(0.46)**

T, number of teeth; S, number of surfaces; $D_{1-3}T/S$, number of teeth/surfaces with enamel caries; $D_{4-6}T/S$, number of teeth/surfaces with dentin caries; FT/S, number of teeth/surfaces with fillings; $D_{4-6}MFT/S$, sum of decayed (enamel caries), missing, and filled teeth/surfaces.

[1]xylitol vs erythritol, p=0.029 for difference between groups, negative binomial regression adjusted for gender, age and school; [2]sorbitol vs xylitol, p=0.013; [3]sorbitol vs erythritol, p=0.016; [4]xylitol vs erythritol, p=0.021; [5]sorbitol vs xylitol, p=0.006

Table 3. Percentages of transition events observed for each intervention group during the intervention and follow-up period

Transition event	Erythritol (%)	Xylitol (%)	Sorbitol (%)	Erythritol vs Sorbitol*	Xylitol vs Sorbitol*
Three-year intervention period					
Enamel/dentine caries development	4.6	5.6	5.5	0.0001	0.7299
Dentine caries development	1.3	1.9	1.8	<0.0001	0.5627
Increase in caries score	5.4	6.5	6.2	0.0012	0.1837
Dentist intervention	1.6	2.2	2.4	<0.0001	0.0910
Three year post-intervention/follow-up					
Enamel/dentine caries development	6.6	7.2	7.2	0.0365	0.8380
Dentine caries development	1.5	2.0	2.0	0.0003	0.6847
Increase in caries score	7.5	8.2	8.0	0.0853	0.3959
Dentist intervention	2.8	3.0	3.5	0.0001	0.0178

* Fisher's exact (two-tail) p-value

460 **Table 4.** Interval-censored survival analysis using the control group as a reference.

Transition event	Treatment	Estimate	Standard error	p-value	Acceleration factor
Three-year intervention period					
Enamel/dentine caries development	Erythritol	0.1110	0.0431	0.0100	1.1174
	Xylitol	-0.1009	0.0394	0.0105	0.9040
Dentine caries development	Erythritol	0.1784	0.0948	0.0599	1.1953
	Xylitol	-0.1099	0.0722	0.1278	0.8959
Increase in caries score	Erythritol	0.0900	0.0415	0.0300	1.0942
	Xylitol	-0.1143	0.0382	0.0028	0.8920
Dentist intervention	Erythritol	0.1121	0.0859	0.1922	1.1186
	Xylitol	-0.0111	0.0749	0.8819	0.9889
Three year post-intervention/follow-up					
Enamel/dentine caries development	Erythritol	0.0333	0.061	0.5867	1.0339
	Xylitol	-0.1006	0.0574	0.0797	0.9043
Dentine caries development	Erythritol	-0.0264	0.1343	0.8444	0.9740
	Xylitol	-0.2017	0.1085	0.0630	0.8173
Increase in caries score	Erythritol	0.0038	0.0334	0.9103	1.0038
	Xylitol	-0.0784	0.0313	0.0121	0.9246
Dentist intervention	Erythritol	0.0938	0.0645	0.1460	1.0984
	Xylitol	0.0940	0.0649	0.1475	1.0986

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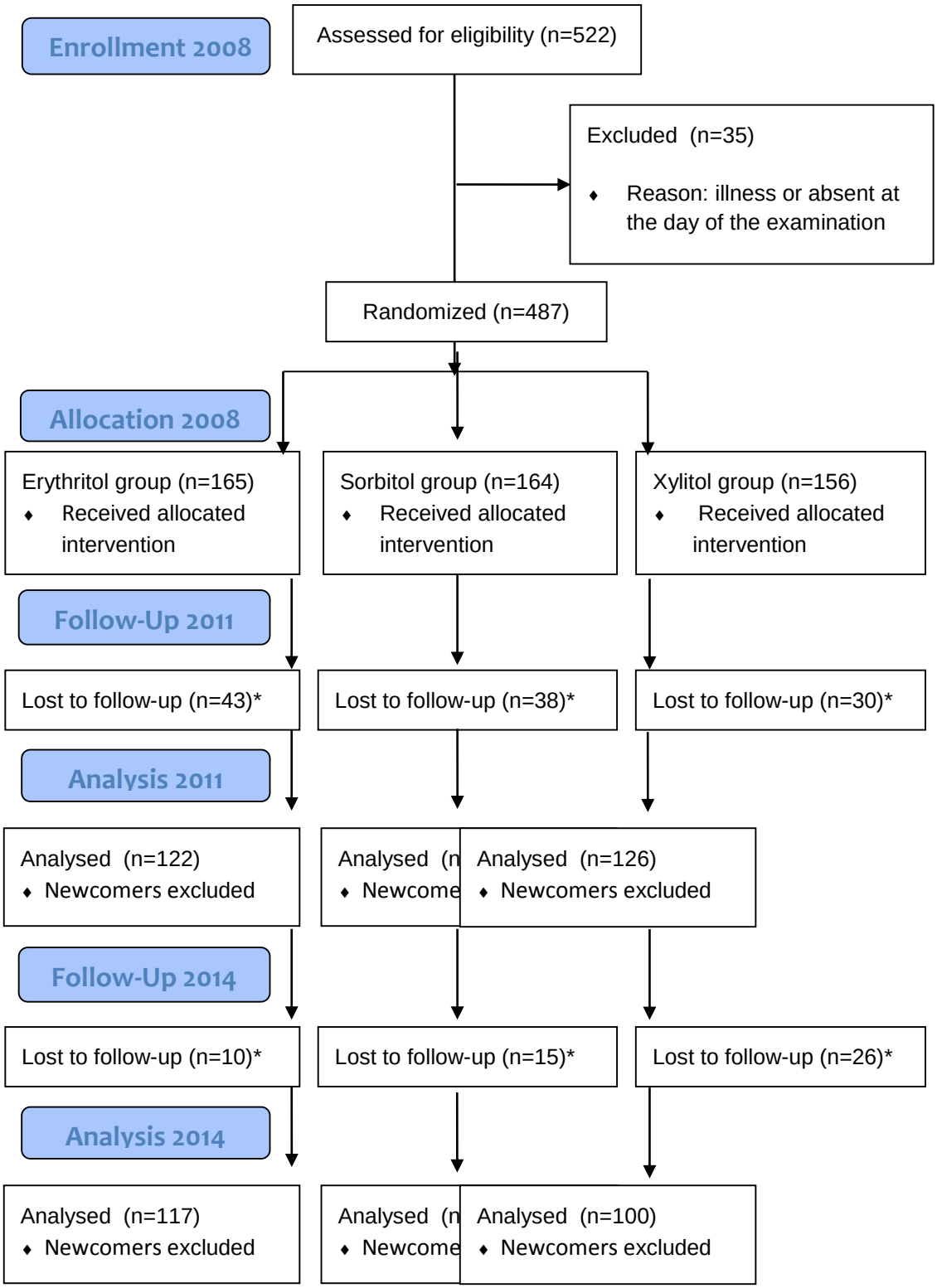
CONSORT Flow chart



462 * Discontinued intervention: were not at school on the day of the examination or had changed the school

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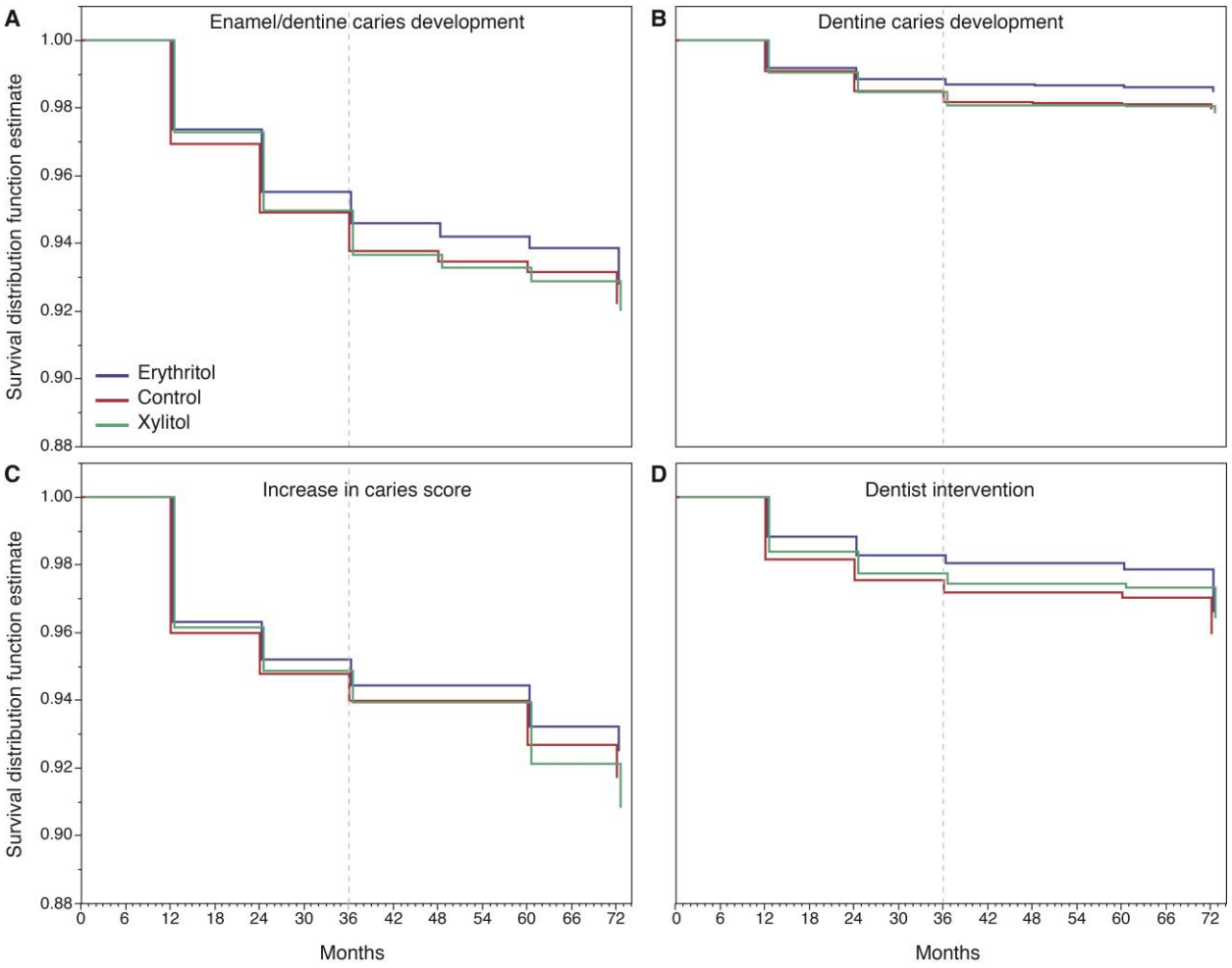
A
Enamel/dentine caries development
B
Dentine caries development
C
Increase in caries score
D
Dentist intervention
Survival distribution function estimate
1.00
0.98
0.96
0.94
0.92
0.90
0.88
Erythritol
Control
Xylitol
0
6
12
18
24
30
36
42
48
54
60
66
72
Months

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