Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Erythritol and Xylitol

Evidence Summary

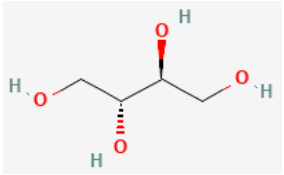
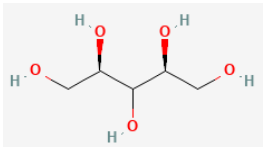
Sugar alcohols are used as low glycemic sweeteners. Low level consumption is generally safe and not associated with adverse metabolic effects to date. High doses have gastrointestinal side effects.

Brain health risk: Altered brain sugar alcohol levels can be a sign of metabolic dysfunction, but there is no clear evidence that sugar alcohol consumption negatively impacts the brain.

Aging and related health concerns: High blood sugar alcohol levels can be a sign of cardiometabolic dysfunction. Evidence to date does not indicate that sugar alcohol consumption contributes to disease. Xylitol helps prevent dental cavities.

Safety: Sugar alcohols, approved as food additive sweeteners, are generally safe and well-tolerated. High doses (>30-50 g/day) have potent laxative effects. Low level consumption is safe, but a safety assessment of long-term high-level consumption is needed.

Availability: OTC; in foods, drinks, gums, and confections	**Dose**: For the prevention of dental caries, the recommended dose of xylitol-containing gum or oral	**Erythritol** **Chemical formula:** $C_4H_{10}O_4$

	health products is 5-10 g/day, chewed/consumed 3x/day.	**MW**: 122.12 g/mol  Source: PubChem **Xylitol** **Chemical formula**: $C_5H_{12}O_5$ **MW**: 152.15 g/mol  Source: PubChem
Half-life: Erythritol ~3 hours Xylitol ~13 minutes	**BBB**: Due to low absorption, it is unclear if consumed sugar alcohols can reach the brain in detectable quantities.	
Clinical trials: Dozens of clinical trials have been carried out testing sugar alcohols, primarily xylitol for the prevention of dental caries and oral health-related outcomes. There have been at least 10 small trials testing the impacts of erythritol or xylitol on cardiometabolic parameters.	**Observational studies**: Elevations in circulating levels of sugar alcohols, including xylitol and erythritol, have been associated with cardiovascular disease metabolic disease, and dementia.	

What is it?

Sugar alcohols, also called polyols, are saccharide (sugar) derivatives that contain a hydroxyl group (-OH) [1]. They are naturally occurring at low levels in some fruits and vegetables. Our bodies also produce very low levels of them in the context of minor pathways of glucose metabolism. Sugar alcohols have a lower glycemic index relative to table sugar (sucrose), and have become widely used as natural sweeteners and bulking agents in processed foods, such as candies and pastries [2]. They are also used in oral health care products such as gums, toothpastes, and mouth rinses to help prevent plaque and cavities. Erythritol and xylitol are two of the most common sugar alcohols used as food additives and for dental health, respectively. Erythritol is about 70% as sweet as sucrose, and with a caloric value of 0.2 kcal/g and a glycemic index of zero, is considered a non-nutritive sweetener [2]. Xylitol has comparable sweetness to sucrose, a caloric value of 2.4 kcal/g, which is approximately half of that for sucrose (4 kcal/g), and a glycemic index of 7-13, in comparison to sucrose with a glycemic index of 60-70 [2].

Brain health risk: Altered brain sugar alcohol levels can be a sign of metabolic dysfunction, but there is no clear evidence that sugar alcohol consumption negatively impacts the brain.

Types of evidence:

- 0 clinical trials assessing the impacts of sugar alcohol consumption on brain health
- 4 biomarker studies showing elevated levels of sugar alcohols in CSF/brain in the context of dementia/neuropathology.
- A few laboratory studies

Human research to suggest harm or prevention of dementia, prevention of decline, or improved cognitive function:

Some observational studies have found an association between regular consumption of artificially sweetened beverages with increased risk for dementia and stroke [3], however, these associations have been inconsistent across studies, and there is no clear evidence specifically linking sugar alcohol consumption, including erythritol and xylitol, with dementia risk. Furthermore, the consumption of sugary drinks has also been associated with increased dementia risk [4], suggesting that these associations are driven by poor dietary patterns. Consumption of sweet beverages allows for a large bolus of sugar or sweetener to enter the bloodstream quite rapidly, particularly if they are devoid of other nutrients that may slow absorption. This may stress the system, and overtime, result in metabolic adaptations.

There is evidence from fluid biomarker studies that changes in brain metabolism resulting in higher levels of sugar alcohols is deleterious for brain health.
The pentose phosphate pathway, also called the hexose monophosphate shunt, is a metabolic pathway involved in glucose metabolism [5]. In contrast to energy generating pathways like glycolysis and oxidative phosphorylation, it is a minor pathway that is used for the generation of ribulose-5-phosphate, a precursor for nucleotide biosynthesis, and NADPH, a cofactor involved in redox homeostasis. This pathway is highly active during brain development, but plays a lesser role in the mature adult brain [6]. In the mature brain, the primary role appears to be for the replenishment of NADPH, a reducing agent that gets used up in the reactions of endogenous antioxidants, such as glutathione [6]. When NADPH levels are too low, the brain is at higher risk from oxidative stress damage. G6PDH is the rate limiting enzyme of this pathway, and its activity is regulated by the availability of glucose and NADPH [6]. The sugar alcohols erythritol and xylitol are intermediates of the pentose phosphate pathway, such that elevations in levels of these sugar alcohols is an indication of increased flux through the pentose phosphate pathway.

Another alternative glucose metabolizing pathway that produces sugar alcohols as an intermediate is the polyol pathway [7]. This pathway converts glucose to fructose with the sugar alcohol, sorbitol, as an intermediate, and it uses up NADPH in the process. It is the hyperactivation of the polyol pathway, resulting in elevated levels of sorbitol and fructose, that appears to be damaging to the brain. Hyperactivation of this pathway is associated with oxidative stress, such as the formation of advanced glycation end products (AGEs), and decreased energy production in the brain. As the increased flux through the polyol pathway depletes levels of NADPH, it stimulates the activation of the pentose phosphate pathway to regenerate NADPH [7]. Therefore, in the context of cerebral metabolic dysfunction, it is common to see elevations in both pathways.

Cerebral hypometabolism, or impaired glucose utilization, is a common feature of many neurological and neurodegenerative diseases [8]. The decrease in the flux of glucose through energy producing pathways may drive the increased flux through alternative pathways, such as the polyol and pentose phosphate pathways. Upregulation of the pentose phosphate pathway has been associated with greater risk for transitioning from mild cognitive impairment (MCI) to Alzheimer's disease (AD) in a prospective cohort serum metabolomics study [9]. Metabolic disturbances, including impaired glycolysis, in combination with enhanced flux through the polyol and pentose phosphate pathways have also been identified in postmortem brain tissue from AD patients. AD brains had higher levels of free glucose, fructose, sorbitol, and erythronic acid [10]. A study assessing CSF metabolites from 161 participants from the Wisconsin Registry for Alzheimer's Prevention identified intermediates of the pentose phosphate pathway, including xylitol and erthryonate, as metabolites associated with AD pathology [8]. A fluid biomarker study including a cohort of 30 individuals from the Anaesthetic Biobank of Cerebrospinal Fluid study found that CSF levels of sorbitol and fructose increased with age, suggesting that the polyol pathway becomes more active during aging [11]. This may be related to a tendency toward impaired glucose tolerance with age, as CSF levels of glucose, sorbitol, and fructose were found to be highest in those with a history of diabetes. A study examining postmortem brain tissue (n=53) found that the brains of individuals with schizophrenia or bipolar disorder showed an altered metabolic profile that was similar to what is observed in the context of diabetes, including increases in the levels of sorbitol, xylitol, and erythritol [12].
Increases in enzymes involved in these pathways such as aldose reductase and G6PDH have also been observed in the context of neurodegenerative disease [13; 14].

Some studies suggest that high levels of sugar alcohols themselves, particularly sorbitol, may be harmful to the brain [11]. But it is unclear how much, if any, of dietary sugar alcohols reach the brain. There is

currently no evidence to indicate whether consumption of sugar alcohols has any meaningful impact on brain metabolism.

Human research to suggest benefit or harm to patients with dementia:

There is no evidence to suggest that the consumption of sugar alcohol-containing products offers outsized benefit or harm to dementia patients relative to the general population.

Mechanisms of action for neuroprotection or harm identified from laboratory and clinical research:

There are limited studies assessing the potential role of sugar alcohol consumption on brain health. One study in APP/PS1 transgenic AD mice found that consuming a 5% xylitol diet for two months had a positive effect on glucose utilization and reduced anxiety-like behavior, but had no effect on the Morris water maze performance, a measure of spatial learning and memory [15]. In contrast, a study in aged (18 month old) wildtype (C57Bl/6N) mice found that consumption of a 5% sorbitol diet for three months led to a reduction in levels of BDNF, neuronal numbers, and motor coordination [16]. Differences in these studies may be related to mouse strains, ages, and/or the type of sugar alcohol.

APOE4 interactions: Not established

Aging and related health risk: High blood sugar alcohol levels can be a sign of cardiometabolic dysfunction. Evidence to date does not indicate that sugar alcohol consumption contributes to disease. Xylitol helps prevent dental cavities.

Types of evidence:

- 4 meta-analyses of trials of xylitol/sugar alcohol use for dental caries prevention
- 7 clinical trials testing erythritol or xylitol for metabolic outcomes
- 7 observational studies of circulating erythritol/xylitol levels and cardiovascular disease
- 4 observational studies of circulating erythritol/xylitol levels and metabolic disease
- 1 biomarker study of xylitol levels and cancer progression
- Numerous laboratory studies

Metabolic disease/Type 2 diabetes: POTENTIAL BENEFIT ON SATIETY HORMONES; ELEVATED CIRCULATING LEVELS ASSOCIATED WITH METABOLIC DYSFUNCTION

Excessive sugar consumption, resulting in hyperglycemia, results in the activation of alternative glucose metabolizing pathways. These include the pentose phosphate pathway and the polyol pathway, both of which produce sugar alcohols as intermediates [7]. The pentose phosphate pathway includes xylitol and erythritol as intermediates, and generates NADPH, which is used in reducing biosynthetic reactions and for redox homeostasis. The polyol pathway converts glucose to fructose, with sorbitol as an intermediate. The polyol pathway uses up NADPH, thus increased cycling of excessive glucose through the polyol pathway may trigger the pentose phosphate pathway as a way to replenish levels of NADPH. The pentose phosphate pathway can also be activated in response to increased levels of oxidative stress, as prominent antioxidant enzymes, such as glutathione, require NADPH as a cofactor.

Observational studies have found that higher circulating levels of several of these sugar alcohol intermediates, such as xylitol, erythritol, and sorbitol, are associated with increased risk for obesity and type 2 diabetes [17]. This increase is considered to be a reflection of heightened activation of the polyol and pentose phosphate pathways due to excessive glucose consumption and/or elevated oxidative stress.

Elevated serum levels of erythronate, a metabolite of erythritol, was found to be a predictor of diabetes risk in a cohort of 2,939 African Americans without diabetes at baseline from the Atherosclerosis Risk in Communities (ARIC) study followed for a median of 20 years (Hazard Ratio [HR]: 1.53, 95% Confidence Interval [CI] 1.23 to 1.91) [18]. Higher serum levels of erythritol were associated with an increased risk of incident diabetes in a cohort of 2,711 US Hispanics/Latinos followed for an average of six years (Risk Ratio [RR]: 1.3, 95% CI 1.08 to 1.69) [19]. Higher erythritol was also associated with sedentary behavior in this study. A cohort of 264 students followed through the nine months of their freshman year at university revealed an association between erythritol and weight gain [20]. Though levels were all in the normal range (4-6%), the students with the highest HbA1c levels at baseline (> 5.05%) had higher blood erythritol levels, and were more likely to experience a gain in central adiposity, suggesting that the increase in erythritol was an indicator of excess sugar consumption/hyperglycemia. The increase in these sugar alcohol intermediates may reflect an alteration to metabolism that makes one more prone to weight/fat gain. A study including 91 obese individuals following a one-year weight loss program found that individuals with lower baseline levels of xylitol were more likely to achieve a ⩾10% weight loss (odds ratio [OR]: 0.2, 95%CI 0.07 to 0.7) [21]. Participants with xylitol levels in the lowest quartiles had a 5.5-fold greater chance of losing ⩾10% weight, while those in the highest quartile had a 14-fold higher risk of achieving a <10% weight change.

While observational studies suggest that elevated levels of sugar alcohols are an indicator of increased risk for metabolic disease, clinical trials indicate that consumed sugar alcohols have an advantageous glycemic profile by inducing satiety hormones without spiking blood sugar. Xylitol has less calories relative to sucrose (2.4 kcal/g vs 4 kcal/g), and a lower glycemic index (7-13 vs 60-70), but can still impact blood sugar levels [2]. Erythritol, on the other hand, is considered a non-nutritive sweetener because of its negligible caloric value (0.2 kcal/g) and lack of effect on blood sugar with a glycemic index of zero.

The consumption of 50 g of xylitol or 75 g of erythritol in 300 mL of water induced the secretion of the satiety hormones, cholecystokinin (CCK), and glucagon-like peptide-1 (GLP-1) to the same degree as glucose (75 g) consumption in a study of 10 lean and 10 obese participants [22]. Consistent with the difference in glycemic index, erythritol consumption had no effect on plasma glucose or insulin, while xylitol led to statistically significant increases in plasma glucose (5.0 ± 0.1 to 5.9 ± 0.2 mmol/l) and insulin (15.3 ± 2.7 to 40.8 ± 7.4 µU/ml), but the increases were modest relative to those seen following the consumption of 75 g of glucose (5.0 ± 0.1 to 8.2 ± 0.5 mmol/l and 15.0 ± 3.6 to 129.2 ± 25.8 µU/ml, for glucose and insulin, respectively). The effect on satiety hormones has been replicated in other studies. A study in 20 healthy volunteers found that consumption of 50 g of erythritol led to an increase in levels of CCK and reduced consumption (calorie intake) during a subsequent test meal [23]. A study by the same group including 18 healthy volunteers found that consumption of 50 g of erythritol induced secretion of CCK, GLP-1, and peptide YY (PYY) without impacting levels of glucose, insulin, or blood lipids (cholesterol and triglycerides) [24]. A study in 12 lean volunteers found that intragastric administration of xylitol containing (7, 17 or 35 g) solutions led to dose-dependent increases in CCK, GLP-1, PYY, insulin, and glucose, while slowing gastric emptying [25]. No effects were observed on motilin, glucagon, glucose-dependent insulinotropic peptide (GIP)-release, or blood lipids. These studies looking at acute consumption of large quantities of sugar alcohols on an empty stomach are not reflective of real-world consumption patterns. Based on the observed dose dependency, the increases in these satiety signals are likely to be quite modest with standard servings. There have been a few studies looking at longer term intake with a more realistic consumption pattern. One study assessed the impact of xylitol or erythritol consumed three times daily at a dose of 8 g and 12 g, respectively for five to seven weeks on glucose absorption in 46 obese participants [26]. The study found that chronic intake had no impact on intestinal glucose absorption. Similarly, another study by this group using the same paradigm (n=42) found that regular intake of sugar alcohols for five weeks had no significant effects on abdominal fat, glucose tolerance, uric acid, hepatic enzymes, or creatinine levels [27].

Overall, these studies do not offer much clarity into the impact of sugar alcohols on long term metabolic health. It remains to be determined whether regular consumption of sugar alcohols results in metabolic adaptations or altered responses to glucose over time.

Preclinical studies also show a lack of effect on body weight or glucose tolerance with chronic erythritol consumption in mice. Notably, plasma erythritol levels were found to be elevated in mice fed a high fat diet or a high sucrose diet, as well as in older animals, relative to young mice, which is consistent with the observational data from human studies [28; 29]. Unlike erythritol, xylitol enters the colon where it is fermented by bacteria in the gut microbiome. Rodent studies indicate that xylitol consumption may modify the microbiome by inducing the production of short chain fatty acids, such as propionate and butyrate, which are associated with health benefits [30]. Some studies also suggest they may have antioxidant properties. Erythritol was found to have radical scavenging capacity *in vitro*, and diabetic rats treated with erythritol showed enhanced antioxidant capacity [31].

Cardiovascular disease: POTENTIAL HARM TO PLATELET REACTIVITY; ELEVATED CIRCULATING LEVELS ASSOCIATED WITH VASCULAR DYSFUNCTION

Observational studies have linked high circulating levels of sugar alcohols with increased risk for adverse cardiovascular events [32; 33]. While these trends are generally a reflection of alterations to endogenous levels, there has been controversy over whether the consumption of exogenous sugar alcohols contributes to the increase in cardiovascular risk [34; 35]. Well-designed clinical studies are needed to clarify this point, but the totality of evidence to date suggests that low to moderate consumption of sugar alcohols as a sugar substitute is unlikely to have a negative impact on cardiovascular function.

There have been two prominent studies linking plasma levels of erythritol and xylitol, respectively, with increased risk for major adverse cardiovascular events (MACE) and an increased propensity for platelet activation and thrombosis [32; 33]. The association between plasma erythritol levels and MACE was assessed in a discovery cohort of 1,157 participants, and validated in a US cohort of 2,149 participants, and a European cohort of 833 participants [32]. After adjustment for cardiovascular risk factors, those with the highest levels of circulating erythritol had a higher incidence of adverse cardiovascular events relative to those with the lowest levels (4th vs. 1st quartile) (adjusted HR: 1.80, 95% CI 1.18 to 2.77 and HR: 2.21, 95% CI 1.20 to 4.07, for the US and European cohorts, respectively), such that for every 1 µM increase in plasma erythritol levels, there were 21% and 16% increases in the adjusted HR for MACE in the US and European cohorts, respectively. The erythritol levels were <3.75 µM for tertile one, 3.75-4.64

µM for tertile two, 4.65-5.96 µM for tertile three, and 5.97-46.1 µM for tertile four. The association between plasma xylitol levels and MACE was assessed in the same discovery cohort (n=1,157) and validated in the US cohort (n=2,149), and was generally similar to what was observed with erythritol in that higher levels of xylitol were associated with worse survival and increased risk for three-year MACE [33]. The xylitol levels were <0.49 µM for tertile one, 0.49-0.69 µM for tertile two, and 0.70-34.2 µM for tertile three. After adjustment for cardiovascular risk factors and systemic inflammation, based on hsCRP, those with the highest levels (3rd tertile) had an increased risk for MACE relative to those with the lowest levels (1st tertile) (adjusted HR: 1.57, 95% CI 1.12 to 2.21), as well as for increased risk for thrombotic events (adjusted HR: 1.80, 95% CI 1.05 to 3.08). The thrombotic risk was attributed to the increased platelet activation observed from erythritol or xylitol-treated platelets in *ex vivo* studies [32; 33].

These findings are largely consistent with other metabolomics profiling studies showing an association between cardiovascular disease and an altered profile of metabolites associated with altered glucose metabolism, including those in the pentose phosphate pathway. The Coronary Atherosclerosis in Outlier Subjects: Protective and Novel Individual Risk Factors Evaluation (CAPIRE) study assessing plasma metabolites in 112 individuals at high cardiovascular risk found that the group of metabolites elevated in those with coronary artery disease included sugars (sucrose, glucose), as well pentose phosphate pathway metabolites (erythritol, lactic acid) [36]. Similarly, a plasma metabolomics study comparing patients with stable angina pectoris (n=80) and acute myocardial infarction (n=30) with healthy controls (n=30) identified pentose phosphate pathway metabolites (erythritol) and a polyol pathway metabolite (fructose) as core differential metabolites, suggesting that hyperglycemia may be a driver of worse cardiovascular outcomes [37]. Elevations in erythritol, which is predominantly (~90%) excreted by the kidneys [38], can also be a reflection of impaired kidney function, itself an established risk factor for cardiovascular disease. Erythritol was identified as one of the top serum metabolites associated with heart failure (HR: 1.16, 95% CI 1.09 to 1.23) in a cohort of 1,744 African Americans from the Atherosclerosis Risk in Communities (ARIC) study, but the association was weakened when adjusted for kidney function [39].

Evidence from genetic studies suggests that these disease associations are driven by alterations to the metabolic pathways that produce sugar alcohols rather than from elevations of the sugar alcohols themselves. A Mendelian randomization study including four different cohorts and a total of 38,689 participants of European descent assessed the relationship between variants near genes expected to regulate endogenous erythritol levels (TKT and AKR1A1) and cardiometabolic outcomes [40]. The study

did not find significant associations with coronary artery disease or glycemic traits. Rare genetic disorders due to deficiencies of transketolase (TKT) or transaldolase (TALDO1) result in chronically high plasma levels of erythritol and other sugar alcohols, but not cardiometabolic disease [17]. Mild cardiac abnormalities stem from birth defects, and these patients show higher tendencies toward bleeding than clotting [17].

The discrepancy between the findings in patients with these mutations and the studies in healthy volunteers showing elevated platelet reactivity in response to erythritol or xylitol could reflect compensatory responses in the patients and/or reflect experimental conditions that differ from real-world application. In the clinical studies, participants rapidly consumed erythritol or xylitol at a level (30 g) near the upper level of total daily consumption on an empty stomach. This is inconsistent with how sugar alcohols are typically consumed, in amounts of 1-5 g at a time, combined with other nutrients, which could slow or modify the absorption. Since sugar alcohols are known to be osmotic, their rapid absorption may induce osmotic stress, a known trigger for platelet activation [17]. Similarly, rodent studies showing an increased risk for thrombosis administered erythritol and xylitol via intravenous injection, a method more likely to induce osmotic stress relative to oral administration. Thrombotic effects triggered by osmotic stress have been observed in prior studies involving the i.v. administration of other sugar alcohols into animal models [17]. While sugar alcohols appear to affect platelet reactivity in experimental conditions, it remains to be established whether this is relevant in real-world conditions.

Short term clinical trials to date have not found an adverse effect of sugar alcohol consumption on vascular function. A pilot open-label trial tested the impact of 12 g packets of erythritol dissolved in 8 oz of water, consumed three times per day for four weeks on vascular function in 24 patients with type 2 diabetes [41]. The study found improvements in endothelial function, as measured by fingertip peripheral arterial tonometry (0.52 ± 0.48 to 0.87 ± 0.29 au), decreased central pulse pressure (47 ± 13 to 41 ± 9 mmHg), and a trend toward decreased carotid-femoral pulse wave velocity relative to baseline. (P = 0.06). A subsequent study in 42 participants with obesity consuming 12 g erythritol or 8 g xylitol dissolved in water three times per day for five weeks found no significant effects on vascular function/arterial stiffness relative to controls [27].

Dental caries: BENEFIT

The interaction of bacteria in the oral microbiome, particularly *Mutans Streptococci*, with dietary sugars is the main contributor to the formation of dental caries. Therefore, interventions that inhibit the growth of the pathogenic bacteria species or restrict the availability of fermentable sugars in the mouth

are likely to be effective. Sugar alcohols have shown promise for preventing the formation of dental caries in adults and children through both of these mechanisms.

Several meta-analyses of clinical studies have found that sugar alcohols, predominantly xylitol, are associated with a reduction in *Mutans Streptococci* bacteria and dental caries in children and adults. A meta-analysis of 32 trials including 4,232 adult or children participants testing the effect of low-intensity sweeteners on cariogenic bacteria found that nearly all studies (30/32) demonstrated a reduction in cariogenic bacteria. Sugar alcohols, particularly xylitol (31 studies), were the predominant sugar substitutes tested in these studies [42]. *Mutans Streptococci* was significantly reduced in dental plaque when comparing xylitol to no treatment (Standardized mean difference [SMD]: −0.73; 5% CI −1.09 to −0.37; 5 studies, n=308), and in saliva (SMD: −1.47, 95% CI −1.94 to −0.99; 3 studies, n=136). A meta-analysis of eight studies (n=1,105) found a reduction in dental plaque with the use of sugar free gum, particularly for xylitol-containing gum (effect size: -0.743, 95% CI -1.148 to -0.338) [43]. A meta-analysis of 15 studies including 6,325 children and adolescents, 11 of which tested xylitol, seven testing sorbitol, and two testing erythritol found that xylitol (SMD: -0.50, 95% CI -0.85 to -0.16, n=1,663) and sorbitol (SMD: -0.10, 95% CI: -0.19 to -0.01, n=3,929) had significant effects in the prevention of dental caries in permanent teeth [44]. The decayed, missed, filled teeth (DMFS/DMFT) index is a measure of dental caries and oral hygiene, with higher scores indicating worse dental health. Consumption of xylitol-containing products was associated with lower DMFS increment. In this analysis, the effects of erythritol were mixed. A meta-analysis of 30 studies found that xylitol containing products prevented dental caries to a significantly greater degree relative to control/non-xylitol containing products (SMD: −0.089, 95% CI −2.04 to 0.026) [45]. The consumption/chewing of xylitol three to five times daily, or after meals, for a total of 5-10 g per day was found to be the most effective for the prevention of dental caries.

There is also some evidence that xylitol may help, to a limited degree, with tooth remineralization. An *in vitro* study using bovine teeth found that the combination of 20% xylitol with fluoride increased the surface remineralization of shallow lesions, but had no effect on deep lesions [46]. The remineralization enhancing effect was not observed with lower doses of xylitol, and there was no effect of xylitol in the absence of fluoride.

Cancer: POTENTIAL BENEFIT AS AN ADJUNCT TO CHEMOTHERAPY (Preclinical)

To date there is no clear evidence to suggest that the consumption of sugar alcohols influences cancer risk in either direction. There are some preclinical studies to suggest that xylitol triggers the death of cancer cells in culture [47]. Xylitol was found to trigger apoptotic cell death in cancer cells through the induction of oxidative stress by inducing the glutathione-degrading enzyme, CHAC1 [47]. In a xenograft mouse model using a human melanoma cell line (MeWo cells), intravenous injection of xylitol (2 g/kg)

suppressed tumor growth, though oral administration had no effect. Xylitol also sensitized cancer cells to chemotherapeutic agents [47]. One study found that xylitol was among the differential metabolites associated with disease progression in multiple myeloma [48]. Those with higher serum levels of xylitol were less likely to experience disease progression (HR: 0.2789, 95% CI 0.07571 to 1.028). It has not been established whether the elevation in xylitol itself is beneficial for limiting progression, or if it is simply a surrogate marker of a metabolic profile that is less favorable for cancer progression.

Safety: Sugar alcohols approved as food additive sweeteners are generally safe and well-tolerated. High doses (>30-50 g/day) have potent laxative effects. Low level consumption is safe, but a safety assessment of long-term high-level consumption is needed.

Types of evidence:

- 3 meta-analyses of trials for xylitol use for dental caries prevention
- 1 EFSA report on safety of erythritol
- 5 clinical trials testing erythritol/xylitol for metabolic outcomes
- 1 clinical study assessing the impact of xylitol on platelet reactivity
- 1 clinical trial assessing pharmacokinetics of erythritol and xylitol
- Numerous laboratory studies

Xylitol and erythritol have been granted generally recognized as safe (GRAS) status for use as food additives by the FDA [49; 50]. They are generally well-tolerated and have not been associated with toxicity in safety studies [51]. Although toxicity is observed in some species, such as dogs, this stems from species-specific metabolism not relevant to humans. The most prominent risk associated with sugar alcohols is their laxative effect at high doses, due to their osmotic effect, triggering watery stools [38; 51]. Indeed, the laxative effect of prunes/plums comes from having moderate levels of the sugar alcohol sorbitol. Doses in excess of 50 g can induce bloating and diarrhea [5].
In a human dosing study, it was found that erythritol is rapidly absorbed in a saturable, dose-dependent manner [38]. It can be metabolized into erythronate, as occurs in the pentose phosphate pathway, which may account for some preclinical studies showing an enhancement of endogenous antioxidant capacity following erythritol intake. However, this occurs at a very low level, >1% gets metabolized, while the rest is excreted intact by the kidneys. Xylitol was found to be very poorly absorbed, and there was no detectable metabolism of xylitol to erythronate [38]. The poor absorption of xylitol allows it to end up in the large intestine where it is fermented by gut microbes, contributing to the gastrointestinal

side effects associated with xylitol. The lack of erythritol accumulation in the colon at standard doses contributes to the better gastrointestinal tolerance of erythritol relative to other sugar alcohols.
Due to the difference in absorption and clearance, blood erythritol levels remain elevated for a much longer time following erythritol consumption relative to what is observed for xylitol. In human studies, xylitol levels have been shown to peak around 30 minutes after intake and have a half-life around 13 minutes such that levels are back to baseline within four to six hours after intake [33]. Erythritol has a half-life around three hours, such that circulating erythritol levels remain elevated for over two days [32]. If elevated levels of these sugar alcohols impact platelet reactivity, then regular consumption, especially for erythritol, could result in chronically elevated blood levels that may impact short or long-term vascular function.
Erythritol is characterized as a non-nutritive sweetener, but several other sugar alcohols, including xylitol, are low-nutritive sweeteners, such that they will trigger elevations in blood glucose and insulin levels [2]. While the glycemic index is much lower than for sucrose, these nutritive sugar alcohols can trigger similar physiological responses, such that excessive consumption may result in some of the same metabolic disturbances as excessive consumption of sugar/sucrose. Additionally, it remains to be seen whether high consumption of these non and low nutritive sugar alcohol sweeteners will lead to metabolic adaptations that negatively impact the physiological/glycemic responses to sugar or other carbohydrates, as has been observed with some artificial sweeteners [52]. The potential risks likely come from a poor diet by which high refined sugar intake is partially replaced by high intake of sugar alcohols contained in processed foods.
The pattern of consumption may also play a role in the risk-benefit profile of sugar alcohols. The physiological effects of sugar alcohols on metabolic hormones or vascular parameters appear to be dose dependent. Many of the studies assessing these effects have used a dose near the recommended maximum daily level. Just as consumption of a large amount of sugar at one time can be metabolically harmful, consumption of large quantities of sugar alcohols at one time may also confer some degree of health risk, though the details of those potential risks remain to be clarified and validated.
The consumption of sugar alcohols naturally contained in fruits and vegetables, as part of a balanced diet, as well as their use in oral health care products is likely to be beneficial and does not pose any significant health risks.

Drug interactions: There are currently no known interactions with erythritol or xylitol.

Sources and dosing:

Erythritol and xylitol are naturally found in some fruits and vegetables, such as strawberries, plums, apples, grapes, pears, mushrooms, and onions. They are also approved as food additives and found in a variety of gums, candies, pastries, and other processed foods. Acceptable daily intake levels for sugar alcohols have not been set by the World Health Organization/Joint FAO/WHO Expert Committee on Food Additives (WHO/JECFA). The European Food Safety Authority (EFSA) has set the acceptable daily intake (ADI) level for erythritol at 0.5 g/kg body weight, which translates to 35 g/day for a 70 kg (155 lb) adult [51]. The EFSA declined to raise this level during a review following a request to increase the intake limit. The threshold was set to prevent laxative side effects. The upper limit of tolerability for erythritol is 0.66 to 0.8 g/kg [17]. Average consumption levels of erythritol have been estimated to range from 13 to 30 g/day. Xylitol is generally considered to be safe and tolerated at levels up to 50 g/day. The recommended dose of xylitol for the prevention of dental caries is a total of 5 to 10 g/day, typically in the form of chewing gum, used 3x/day, following meals.

Research underway:

According to Clinicaltrials.gov, there are currently 17 active clinical trials evaluating erythritol, 16 trials evaluating xylitol, and one involving both. The vast majority of the studies are evaluating erythritol air powder polishing for periodontitis, while the majority of trials evaluating xylitol are for modifying the microbiome or oral health. The possible connection between erythritol and/or xylitol with cardiometabolic risk is also being assessed in several studies, including:
The Effects of Dietary Erythritol on Platelet Reactivity and Vascular Inflammation (EASI) (NCT05967741).
Effect of Daily Erythritol Versus Sucrose Intake Over 5 Weeks on Glucose Tolerance in Adolescents (EryAdo) (NCT04966299).
Consumption of Oral Artificial Sweeteners on Platelet Aggregation and Polyol Excretion (COSETTE) (NCT04731363).
Effects of Oral Xylitol on Subsequent Energy Intake (NCT05671965).

Search terms:
Pubmed, Google: Sugar alcohols, erythritol, xylitol

- Alzheimer's, dementia, cardiovascular, diabetes, metabolic disease, cancer, safety, clinical trials, meta-analysis

Websites visited for Erythritol and Xylitol:

- Clinicaltrials.gov (Erythritol, Xylitol, sugar alcohol)
- Examine.com (Xylitol)
- DrugAge (Xylitol)
- Drugs.com (Xylitol)
- WebMD.com (Erythritol, Xylitol)
- PubChem (Erythritol, Xylitol)
- DrugBank.ca (Erythritol, Xylitol)
- ConsumerLab.com (Sugar substitutes)

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