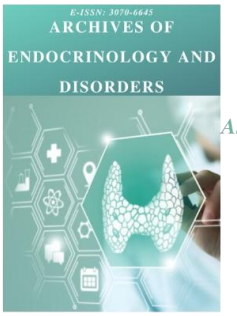

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Review Article

Association Between Non-Nutritive and Nutritive Sweetener Intake and Gastrointestinal Cancer: A Systematic Review and Meta-Analysis

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Abstract

Low-calorie sugar alternatives, including Non-Nutritive Sweeteners (NNS) and Nutritive Sweeteners (NS), demonstrate carcinogenic properties *in-vivo* and *in-vitro*. Therefore, we systematically reviewed the literature to assess whether intake of the most common NNS and NS; including acesulfame potassium, advantame, aspartame, neotame, saccharin, sucralose, erythritol, isomalt, lactitol, maltitol, sorbitol, xylitol, steviol glycosides and monkfruit; is associated with the five most-common types of gastrointestinal cancer: esophageal, pancreatic, liver, stomach and colorectal. Inclusion criteria were adults between 18 and 65 years and a BMI less than 30 kg/m^2. Exclusion criteria included individuals with metabolic syndrome or *H. pylori* infection or taking PPIs. Databases searched included PubMed, Embase, Google Scholar, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and WHO Global Index Medicus through March 15th, 2026. Nine studies were included in the meta-analysis. Risk of bias was assessed using RoB 2 and ROBINS-I. Heterogeneity was moderate between studies (Q=16, df=8, I2 ≈ 50%). Stratified by sweetener, no sweetener had a significant association between a reduction or increase in odds of developing gastrointestinal cancer: aspartame (OR ≈ 0.81, 95% CI 0.68-0.97), sucralose (OR = 1.13, 95% CI 1.02-1.25), isomalt (pooled OR ≈ 2.90, 95% CI wide and crossing unity), lactitol (pooled OR ≈ 0.18, 95% CI wide and crossing unity), steviol glycosides (OR = 1.58, 95% CI 1.10-2.26). When pooled across sweetener types and gastrointestinal cancer outcomes, independent exposure to the sweeteners aspartame, sucralose, isomalt, lactitol and steviol glycosides was not significantly associated with GI cancer risk (random-effects OR ≈ 1.07, 95% CI 0.84-1.36). Limitations of evidence included in the review are a relatively small number of independent datasets and reliance on non-independent evidence from meta-analyses and pooled cohort studies.

Keywords: Nutritive Sweeteners; Sugar Alternatives; Non-Nutritive Sweeteners

Introduction

Non-Nutritive and Nutritive Sweeteners

Driven by an increased incidence of metabolic syndrome, demand for low-calorie or no-calorie sweeteners is on the rise. The FDA separates current food sweeteners into two primary categories, specifically 1) non-nutritive sweeteners which consist of artificial sweeteners and sugar alcohols and 2) nutritive sweeteners which consist of natural sweeteners and refined sugars. Non-nutritive sweeteners are sugar alternatives that contain zero or very low amounts of carbohydrates or energy. Artificial Sweeteners are synthetically created, have minimal calories and are 200-700 times sweeter than table sugar [1]. A potential benefit of artificial sweetener use is a lower caloric density than natural sweeteners, sugar alcohols and refined sugars [1]. Potential risks include increased risk for diabetes, metabolic disease, heart disease, stroke or death; weight gain; a negative impact on digestion or digestive tract physiology; potential to act as a carcinogen suppression of neurotransmitter production; including dopamine, norepinephrine and serotonin; endocrine disruption and specifically a decrease in thyroid hormone production4 and reduced immune function including a reduced hemoglobin level, Hct % and WBC count [2-4]. Examples of FDA-approved artificial sweeteners include acesulfame potassium, Advantame, Aspartame, Neotame, Saccharin and Sucralose [1]. Sugar Alcohols are synthetically-produced sweeteners commonly found in processed foods which are not as sweet as natural or artificial sweeteners [1].The primary benefit of sugar alcohols is that they have fewer calories than natural sweeteners, although more than artificial sweeteners. Risks of sugar alcohol use include gastrointestinal irritation, bloating, blood clotting, heart disease risk and dopaminergic suppression in GI tract [5-7]. Examples of sugar alcohols include erythritol, Isomalt, Lactitol, Maltitol, Sorbitol and Xylitol [1].

Nutritive Sweeteners are caloric sweeteners or sugars that provide energy in the form of carbohydrates [1]. Natural Sweeteners are minimally processed sweeteners from natural sources such as fruits and plants and are calorically more dense than artificial sweeteners [1]. Benefits of natural sweeteners include lower glycemic index than refined sugars; containment of vitamins, fiber, minerals antioxidants and potentially prebiotic oligosaccharides which could promote healthy gut bacteria and improved blood sugar regulation when compared to blood sugar regulation when using refined sugars. Known risks of natural sweeteners include weight gain; increased risk of diabetes, heart disease, peripheral neuropathy and endocrine disruption including increased progesterone, estrogen and cortisol and decreased testosterone [1,8]. Examples of natural sweeteners include stevia, agave and monk fruit [1]. Refined Sugars are sugars processed from a natural source so as to be easily added to foods and drinks, which have limited or very low vitamin and mineral content due to processing [1]. Benefits of refined sugars are the nutritive content, which may be beneficial for athletes looking to increase energy intake and avoid GI discomfort. Risks of refined sugars include weight gain; an increased risk of diabetes, heart disease and peripheral neuropathy and other chronic health conditions including cancer [1]. Examples of refined sugars include white sugar (table sugar), brown sugar and corn syrup [1].

Artificial Sweeteners

Acesulfame Potassium

Acesulfame Potassium (ACE K or Acesulfame K) is an artificial non-nutritive sweetener commercialized mainly under the brands Sunnett and Sweet One. In its physical form, ACE K is an odorless powder 200 times sweeter than sugar, with stability at high temperatures, high solubility in water and stability across a wide range of pH levels [9]. ACE K is typically used in combination with other sweeteners, such as sucralose, aspartame and cyclamate, in diet beverages, confectionery products, baked goods and dairy products [10]. While data are unavailable regarding the consumption of ACE K specifically among US adults and children, a study of 102,825 French participants found that 34% reported consuming ACE K [11-13]. Furthermore, a Canadian study of 3000+ pregnant women found that 29.5% reported consuming artificially sweetened beverages, with 5.1% reporting daily consumption [14]. This is significant, as acesulfame potassium is a primary sweetener in these beverages along with aspartame. Data from the United States Food and Drug Administration (FDA) reports that 44% of women consume artificially-sweetened beverages, with 15.3% reporting daily consumption [15]. As Acesulfame K is not metabolized, its concentrations in plasma and breast milk and its widespread consumption among childbearing women raise concerns about perinatal and infant exposure to these sweeteners. The prevalence of gastrointestinal cancer after ACE-K ingestion in humans is not well established. However, an analysis of the 102,000 participant NutriNet-Santé cohort found that, among 17,601 low consumers of ACE K, 457 (2.6%) developed obesity-related cancers and out of 17,602 high consumers of ACE K, 291 (1.65%) developed obesity-related cancers. Interestingly, out of 67,662 non-consumers, 1,275 (1.89%) developed obesity-related cancers [13]. Obesity-related cancers were classified according to WHO as: "colorectal, stomach, liver, mouth, pharynx, larynx, oesophageal, breast (with opposite associations pre-and postmenopause), ovarian, endometrial and prostate cancers [13]. The researchers do not report data on

specific cancer subtypes. Links between ACE-K and pancreatic cancer have been found in some animal studies, but these results have not been extensively confirmed [16]. While some data exists on the potential carcinogenicity of Acesulfame Potassium, large-cohort studies on its role in the pathogenesis of gastrointestinal cancer are necessary [9].

Advantame

Advantame is a high-intensity, non-nutritive artificial sweetener approved for use in foods and beverages and has a sweetness potency of approximately 20,000 times that of sucrose. Advantame has high heat stability and a wide range of suitable pH conditions, making it suitable for use in baked foods and processed foods [17]. Advantame is most commonly used in diet beverages, baked goods, chewing gum, syrups, flavored dairy products, protein drinks and certain pharmaceutical formulations [17]. Rather than being sold directly to consumers, it is incorporated into reduced-sugar products by major food and beverage manufacturers, with its principal global suppliers being Ajinomoto, Cargill, Tate and Lyle and Ingredion [18]. Dietary exposure assessments conducted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) indicate that estimated intakes of advantame are substantially below the established acceptable daily intake (ADI), with mean exposure across populations estimated at 0.0025 mg/kg body weight/day (0.05% of the ADI), 97.5th percentile exposure at 0.0004 mg/kg body weight/day (0.001% of the ADI) and maximum exposure at the 99th percentile remaining at 0.0009 mg/kg body weight/day (0.002% of the ADI) [19]. Dietary exposure was found to be the highest among children. Ingestion levels still remained low with those aged 2-3 years (0.012 mg/kg BW/day) and 4-9 years (0.011 mg/kg BW/day), intake levels at the 99th percentile across pediatric age groups remain well below the ADI, corresponding to no more than 6.33% of the allowable limit [19]. Toxicological evaluations and long-term carcinogenicity studies have not identified tumor-promoting effects associated with advantame consumption. There is no convincing evidence linking advantame exposure to increased prevalence of liver, stomach, pancreatic or esophageal cancers in humans [16,17,20]. Regulatory agencies and expert reviews, including the American Cancer Society, conclude that advantame is safe when consumed within approved use levels, although continued research is recommended to monitor potential long-term health effects as consumption patterns evolve [21,22].

Aspartame

Aspartame has been marketed as an artificial sweetener under other brand names such as NutraSweet, Equal and Sugar Twin [23]. Aspartame can be found in diet soft drinks such as Diet Coke and Diet Pepsi, sugar-free gum and sweets like Trident and Extra, flavored drinks, reduced calorie yogurt and table-top sweeteners [23]. One study using U.S. surveys revealed that 41% of adults and 25% of children consume at least one low-caloric sweetened food or beverage daily, with an increase in consumption in children since the early 2000s [15,23]. Approximately 60% of Americans consume within the Acceptable Daily Intake [23]. The consumption rate in Canada among more than 3,000 pregnant women was approximately 29.5% for artificially sweetened beverages (mainly aspartame) and 5.1% consume it daily [2,15]. In the U.S., women reported consumption at 44% and 15.3% consume it daily, which is alarming during pregnancy because aspartame converts to phenylalanine [15].

Internationally, the aspartame market size was estimated at $300-400 million in 2024 and projected to reach $350-615 million between 2029-2035, as aspartame continues to be a dominant sweetening agent in developed countries, especially in Asia-Pacific (China, India and Japan) [24].

In current peer-reviewed literature, little evidence exists to support association of aspartame with gastrointestinal cancers or cancers of the gastrointestinal tract in humans. The association was discovered by means of a 2024 network toxicology analysis between aspartame and 373 common targets, which relate to the pathway of gastrointestinal cancer (SRC, EGFR, CCND1, MMP9, CASP3) [22]. As for humans, there are few pieces of evidence. For example, certain studies in Spain indicated an increased risk of stomach cancer (2.0) with vast uncertainty. The association with liver cancer was shown to be week; the IARC classified aspartame in Group 2B, "possibly carcinogenic" to humans [2]. As for cancers of the pancreas or esophagus, there are no proven connections. Future studies should be carried out on large populations, controlling for the influence of aspartame on other sweetening agents.

Neotame

Neotame is a high-intensity, non-nutritive artificial sweetener approved for use in foods and beverages, with a sweetness potency approximately 7,000 to 13,000 times greater than sucrose [25]. Neotame is chemically derived from aspartame but does not process into phenylalanine in significant amounts, making it safe for individuals with Phenylketonuria (PKU) [25]. Neotame is

odorless, highly suitable for all temperatures and remains stable across a wide range of pH conditions, most commonly used in baked goods and processed foods [23]. Due to its extreme sweetness, neotame is used in minimal quantities, neotame can be found in diet beverages, sugar-free goods, powdered drink mixes, canned fruits, toothpaste and pediatric medications [25]. Neotame is not sold directly to consumers; instead, it is incorporated into reduced-sugar products by major food and beverage manufacturers [25]. Neotame is commonly sold to businesses under the brand name Newtame [25]. Population-level dietary surveys, including NHANES, indicate that approximately 41-48% of U.S. adults consume low-calorie sweeteners over a two-day period, though intake data are not disaggregated by individual sweeteners such as neotame [26]. Globally, neotame consumption is highest in the United States, with rapidly increasing use in the Asia-Pacific region as food manufacturers adopt high-potency sweeteners to meet sugar-reduction targets [27]. Children exhibit the highest relative intake due to lower body weight, with estimated exposure at 0.17 mg/kg body weight/day, which remains well below the Acceptable Daily Intake (ADI) of 10 mg/kg body weight/day established by the European Food Safety Authority [28]. Toxicological evaluations and long-term animal studies have demonstrated no adverse effects on the liver, stomach, pancreas or esophagus, even at doses up to 1,000 mg/kg body weight and transient liver enzyme changes observed in earlier studies were determined to be adaptive rather than indicative of organ damage [28]. While a recent *in-vitro* study using human intestinal epithelial (Caco-2) cells reported that neotame exposure may weaken the gut barrier, trigger programmed cell death and promote pathogenic behavior of gut bacteria through activation of the T1R3 sweet-taste receptor, this study did not establish a direct association between neotame and colorectal or other gastrointestinal cancers [29]. Overall, current human and animal evidence does not support a carcinogenic role for neotame when consumed within approved use levels, although emerging mechanistic data suggest further research on gut health effects is warranted.

Saccharin

Saccharin is a widely used non-caloric artificial sweetener found in tabletop sweeteners, diet beverages, low-calorie juices, candies, jams, jellies, baked goods, chewing gum and some medicines, with major brands including Sweet 'N Low [30]. In epidemiologic research, overall saccharin consumption has not been significantly associated with increased cancer risk in the general population, although among individuals with diabetes, higher saccharin intake has been linked to elevated but not statistically significant odds of certain cancers, including colorectal cancer and chronic lymphocytic leukemia, suggesting that diabetes status may modify potential risk and warrants further investigation [31]. For site-specific cancers, current evidence does not conclusively link saccharin exposure to increased prevalence of liver, gastrointestinal, pancreatic or esophageal cancers, indicating that any carcinogenic association at these sites remains unproven [21,32,33]. In terms of exposure, although saccharin-specific intake data are limited, an estimated 41% of US adults and 25% of US children consume non-caloric artificial sweeteners daily and about 30% of pregnant women report intentional use of non-nutritive sweeteners, implying that a substantial proportion of these groups is likely exposed to saccharin [11,34]. Globally, precise prevalence figures are unavailable because intake patterns vary by country, but saccharin has been reapproved and is now permitted as a food additive in more than 100 countries, reflecting broad international availability and widespread potential exposure despite remaining uncertainties about exact consumption levels [35].

Sucralose

Sucralose is found at a high prevalence in international diets and can be found in splenda, diet soft drinks, sugar-free chewing gum, candy and other food and beverage products [36]. Because of this, it is found in the diet of many: a 2016 study found that 25.1% of US children reported consuming non-nutritive sweeteners, that number jumps to 41.4% considering adults and several cohorts from across the world report 18%-47% of pregnant women consume them [11,34]. Sucralose is merely one type of non-nutritive sweetener, but sucralose is one of the most commonly consumed non-nutritive sweeteners according to data from the WHO [17]. Most studies fail to provide a strong link between the non-nutritive sweetener sucralose and cancer. For example, large human cohorts and cancer-agency reviews report unconvincing evidence that sucralose is a cause of colorectal cancer, but a AOM/DSS mouse model once hinted at a colorectal tumor-promoting effect of sucralose-infused water consumption [37]. Sucralose has not been linked to stomach or pancreatic cancer and larger studies evaluating artificial studies as a whole show no statistically significant link between the group and these cancers [36]. On the other hand, data shows that consumption of artificial sweeteners is linked to a higher risk of liver cancer and increased risk of obesity-related cancers [38]. Still, while a link has been determined, multiple sweeteners are aggregated and the data is grouped, leaving it impossible to blame one artificial sweetener over the other as the sucralose effect cannot be isolated.

Sugar Alcohols

Erythritol

Current human evidence does not demonstrate that dietary erythritol exposure increases the prevalence or incidence of colorectal, liver, stomach, pancreatic or esophageal cancers [39]. For colorectal cancer, erythritol has appeared as a metabolite in some metabolomics and microbiome studies, including early-onset colorectal cancer research, but there is no established causal or quantitative link between erythritol intake and colorectal cancer risk; similarly, a 2024 study associating higher serum erythritol with increased overall cardiovascular and cancer mortality did not report site-specific colorectal risk [6,39]. Liver cancer has not been directly linked to erythritol consumption and studies of artificially sweetened beverages show no significant association with liver cancer or chronic liver disease mortality after adjustment, without isolating erythritol. Stomach cancer data do not indicate increased risk from erythritol; erythritol is largely absorbed in the small intestine and excreted unchanged, limiting gastrointestinal exposure and long-term animal studies have not shown increased overall cancer incidence [13]. For pancreatic cancer, erythritol has been identified in pre-diagnostic blood metabolomics panels used for risk prediction, but this reflects circulating biomarkers rather than dietary causation [33]. Esophageal cancer evidence is limited to Mendelian randomization analyses of artificial sweeteners as a broad category, not erythritol specifically and is therefore hypothesis-generating. Dietary exposure to erythritol primarily comes from processed foods and beverages (e.g., sugar-free drinks, gum, desserts and tabletop sweeteners), with smaller amounts occurring naturally in fruits and fermented foods [39]. Importantly, there are no direct prevalence studies quantifying erythritol ingestion in U.S. adults, children, pregnant women or worldwide populations; available data rely on indirect dietary exposure modeling and low-calorie sweetener consumption patterns, indicating exposure in subsets of the population but precluding precise prevalence estimates for erythritol itself [33].

Isomalt

There is no current specific data or studies regarding the prevalence of cancer when isomalt is exposed in humans, however, there is a study of the effects of isomalt on rats and mice. When fifty animals of each sex were fed 0, 2.5, 5 or 10% isomalt in the diet for nearly 2 to 2.5 years, there was no direct correlation between the increase of isomalt in their diet and the number of tumors found, but some changes were noted such as enlargement of the caecum and parts of the large intestine at 10% dietary isomalt [40]. There were no microscopic tissue damage so changes were possibly due to poor digestibility and microbial fermentation, not toxicity [41]. There is also no current specific data or studies regarding the prevalence of cancer when isomalt is exposed in humans for the liver, stomach, pancreas or esophagus [42]. Isomalt is known as a bulk sugar replacer used mainly in sugar-free hard candies, boiled sweets, medicated lozenges, cough drops, throat lozenges, chewing gum, chocolates and chocolate coatings, toffees, caramels, baked goods, decorative sugar work, breakfast cereals and bars, tablets, some frozen desserts and fruit spreads and it is especially dominant in sugar-free hard candies and lozenges [43]. Major ingredient manufacturers like BENEO and Cargill famously use isomalt and sell to bakeries and home bakers and brands such as Tic Tac Sugar Free Freshmint Gum, Zolli "Snow Ballz" sugar-free candies, generic sugar-free peppermint starlights and many medicated lozenges such as Gonitro and Sephience contain isomalt [44]. No specific national data surveys the ingestion of isomalt in US adults; however, there is a study on the intake of low-calorie sweeteners in which 47.8% of adults reported intake of ≥1 food, beverage or FBA containing LCSs over 2 days, though there are limitations to this study so the data may just be an estimate [26]. There is no global data in the ingestion of isomalt, but there is market-based data of isomalt-containing products being sold in more than 70 countries worldwide [44]. There is no US child prevalence specific to isomalt ingestion and no pregnant women/women of childbearing age prevalence specific to isomalt ingestion [33].

Lactitol

Lactitol is a sugar alcohol that comes from lactose through hydrogenation and is classified as a low-calorie, nutritive sweetener rather than a non-nutritive artificial sweetener [45]. Lactitol appears as a white, odorless crystalline powder with mild sweetness relative to sucrose and is poorly absorbed in the small intestine, instead undergoing fermentation by the microbiota in the colon [45]. Due to these properties, lactitol is commonly used as a bulk sweetener in baked goods and also as an osmotic laxative for chronic constipation [45]. In terms of cancer outcomes, no lactitol-specific prevalence or incidence estimates have been reported for colorectal, liver, stomach, pancreatic or esophageal cancers [32,45]. However, Lactitol is poorly absorbed in the small intestine and is fermented by colonic microbiota, which can increase short-chain fatty acids like butyrate, making biological possibilities for colon-related effects [45]. There are, however, direct cancer outcome studies for lacticol [16]. Additionally, one recent observational study looked at lavitil use among patients with hepatocellular carcinoma and reported associations related to disease progression in people who already have cancer [45]. Yet, there is no evidence of lactitol causing or preventing liver cancer

in the general population. Despite documented use in food products and clinical settings, there is no population-level data describing lactitol ingestion prevalence available. Lactitol is typically grouped with broad categories in sugar alcohols or low-calorie sweeteners, so lactitol-specific intake has not been recorded in U.S. adults, U.S. children, pregnant women or women of childbearing age or on the international level. Along with that, no epidemiologic studies have reported that lactitol prevalence has led to any gastrointestinal cancers or increased risk for these gastrointestinal cancers. Current evidence is insufficient to draw any real conclusions on whether lactitol consumption can be associated with gastrointestinal cancer incidence or prevalence.

Maltitol

Maltitol is a disaccharide sugar alcohol, also known as a polyol, that is found in many "low-calorie" or "sugar-free" foods.46 Examples of these foods include, but are not limited to, "sugar-free" ice cream and various hard candies [46]. Even though maltitol is commonly consumed, there is no maltitol-specific prevalence of ingestion in US adults, worldwide, US children or pregnant women. Data of consumption is instead grouped under more broad classifications, such as sugar alcohols or polyols. Chemically, maltitol is a disaccharide sugar alcohol that is made through the hydrogenation of maltose and is considered a low-calorie nutritive sweetener [46]. Physically, maltitol can be seen as a white crystalline powder that has no odor and maltitol's sweetness can be compared to that of sucrose [46]. Other than its use in foods, maltitol is also used in medical examinations and tests, due to the gas or bloating it may cause in people, led from the fraction that goes through fermentation by colonic microbiota [46]. In regards to cancer outcomes, there have been no maltitol specific studies identifying a correlation or prevalence in the five most common cancers.

Sorbitol

Sorbitol is a naturally occurring sugar alcohol typically found in fruits and vegetables which is used as a lower-calorie sugar alternative in food manufacturing, in addition to other benefits such as preserving moisture [47]. If consumed in excessive amounts, it can lead to side effects such as bloating and diarrhea [47]. Sorbitol offers anticancer effects in certain circumstances, in which studies have demonstrated that it induces apoptosis of colorectal and gastrointestinal cancer cell lines, suggesting its capability as a possible therapeutic [47]. However, further experiments are necessary to solidify this claim and determine whether it would offer similar results in vivo. On the other hand, the consumption of sorbitol can increase the risk of liver disease, demonstrating that sorbitol can have a varying impact depending on which organ system it interacts with in the human body [33].

Xytlitol

Xylitol is a naturally occurring sugar alcohol derived from Xylose which appears like a white, crystalline powder, has a sweetness profile similar to sucrose and is commonly used in sugar-free chewing gum, mints, candies, baked goods and oral-care products [48]. Xylitol is incompletely absorbed in the small intestine and the unabsorbed fraction undergoes fermentation by colonic microbiota, producing short-chain fatty acids and gas, which can explain its dose dependent gastrointestinal effects at higher intakes [48]. In terms of cancer outcomes, no Xylitol-specific prevalence or incidence have been reported for colorectal, liver, stomach, pancreatic or esophageal cancers. Although colonic fermentation and microbiome modulation provide a biologically plausible, indirect pathway for gastrointestinal effects, there are no direct epidemiological or clinical studies linking Xylitol consumption to gastrointestinal cancer risk in humans [33,48]. Data specifically tracking Xylitol ingestion prevalence are not available for U.S. adults, children, pregnant women or global populations, due to intake typically grouped under categories like sugar alcohols or low-calorie sweeteners. Overall, the current evidence is insufficient to draw conclusions regarding any association between Xylitol consumption and gastrointestinal cancer incidence or prevalence [42,48].

Natural Sweeteners

Stevia

Stevia is a natural, zero-calorie sweetener derived from the Stevia rebaudiana plant of South America which is approximately 350 times sweeter than table sugar [49,50]. While the use of highly purified extracts of the stevia plant are Generally Recognized as Safe (GRAS) for use by the FDA, specifically Stevia Glycosides (SGs) and rebaudioside A (Reb-A), whole-leaf stevia is not GRAS [51]. Although conducted in animal models, studies indicate that consumption of stevia glycosides, molecules with a steroidal structure, significantly increases progesterone concentrations in the blood and interferes with progesterone receptors on other reproductive cells [52]. Ultimately, steviol glycosides have potential to act as endocrine disruptors despite GRAS status. Stevia earned over 60% of new product launches in the sweetener market in 2021 and boasts a CAGR of 8.60% over the next ten

years [53]. Current, peer-reviewed literature does not show a direct correlation between consumption of SGs and the development of colorectal, liver, stomach, pancreatic or esophageal cancers. There are, however, data available for NSS studies. The major food sources of SGs are tabletop sweeteners, non-sugar sweetened drinks, dairy products and low-calorie snacks, with the most common brand names Truvia, Pure Via and Zevia. National surveys in the U.S. indicate the consumption of NSS beverages among approximately one-third of the population, with SGs being a rising minority and SGs are widely used internationally. Among U.S. children, the LCS occurs in the age range of 6 months to 5 years. Among pregnant women/women of childbearing age, NSS food consumption lies between 18% and 45% in the majority of populations and over 90% in Chile and other nations and the acceptance of SGs within fixed intake levels.

Monkfruit

Monk fruit is a natural, low-calorie sweetener derived from a small, round fruit native to Southern China and is approximately 100-200 times sweeter than table sugar [54]. In its commercial form, monk fruit is an extract composed of mogrosides or a mogrol backbone with glycoside side chains [54]. Mogrosides are not absorbed in the upper gastrointestinal tract and glycosides are cleaved in the colon by GI bacteria to be used as an energy source, while mogrol backbones are excreted [55,56]. More pharmacokinetic studies of monk fruit need to be conducted in humans, as the majority of the literature uses rat models. Monkfruit also occupies a large percentage of the U.S. sweetener market, with a current market size of 353.7 million and a CAGR of 7.6% through 2030 [57]. Direct human evidence linking monk fruit consumption to gastrointestinal cancers is very limited. It is so limited that the EU has not approved many concentration amounts of mogrosides due to the lack of toxicology data on this non-caloric sweetener.

Introduction to Gastrointestinal Cancers

Gastrointestinal Cancer

According to the National Cancer Institute (NCI), gastrointestinal cancers consist of malignant neoplasms arising in the digestive system, including cancers of the esophagus, stomach, small intestine, colon and rectum and associated organs including the liver, pancreas and biliary tract [58]. Histologic types include adenocarcinoma, which arises from glandular epithelial cells and has the highest prevalence of all gastrointestinal cancer histologies at approximately 90-95% in current clinical estimates; lymphoma; gastrointestinal stromal tumors and neuroendocrine tumors.58 Gastrointestinal cancer is typically diagnosed with colonoscopy, endoscopy and tissue biopsy. Average five-year survival rates with a GI cancer diagnosis are below fifty-percent [59].

Colorectal Cancer

Colorectal cancer, the third most diagnosed cancer in the U.S., is driven by genetic factors such as Lynch syndrome, familial adenomatous polyposis and having close relatives with colorectal cancer [60,61]. Environmental risks that contribute to this condition include diets high in processed and red meats and low in fruits, vegetables and fiber [60,61]. Other factors involved include long term smoking, moderate to heavy alcohol use, obesity, physical inactivity, type 2 diabetes and chronic inflammatory bowel diseases; with the majority of the tumors developed from adenocarcinomas arising from gland cells that line the human colon and rectum [60,61]. Colorectal cancer is one of the most common cancers in US adults, with about 154,000 new cases and 52,900 deaths predicted in a recent year [60,61]. Colorectal cancer has an estimated 3.9% lifetime risk, meaning over 1.4 to 1.5 million people in the United States are currently living with a history of this disease [60,61]. In terms of a global scale, it is the third most common cancer, causing over 1.9 million new cases and approximately 930,000 deaths in 2020 and this burden is projected to increase to around 3.2 million new cases and 1.6 million deaths per year by 2040 [60,61]. In contrast, colorectal cancer is very rare in individuals younger than 20 years old, with about 0.5 cases per 100,000 US children and adolescents each year and fewer than 100 pediatric cases annually [60,61]. Although colon cancer is uncommon in pregnancy, this condition is being diagnosed more often in pregnant women as disease rates rise among adults under 50 and symptoms such as abdominal pain, constipation, rectal bleeding and anemia may be misattributed to normal pregnancy changes, leading to delayed diagnosis and more advanced disease when discovered [60,61].

Liver Cancer

Liver and intrahepatic bile duct cancer accounts for 2.1% of all new cancer cases in the US, with Hepatocellular Carcinoma (HCC) accounting for about 90% of primary liver cancers, which are commonly from chronic liver disease.62,63 Major risk factors include hepatitis B, hepatitis C and liver cirrhosis; while additional risk factors include diet and obesity-related conditions that come from nonalcoholic fatty liver disease, which can lead to nonalcoholic steatohepatitis and then to HCC [62,63]. Liver cancer

and cirrhosis are often related because of alcohol and tobacco use, poor nutrition in diet, gastrointestinal pathology and changed gut microbiota [62,63]. A subtype of liver cancer is cholangiocarcinoma, which affects the bile ducts, both inside and outside the liver [62,63]. Liver cancer mainly affects older adults, where it is mainly diagnosed in adults older than 35 years and peaks between ages of 65 and 74 and is rare in children and pregnant women, but if it does occur, there are high maternal and neonatal health risks [62,63]. Liver cancer affects men two to three times as much as women [62,63]. In the US, tens of thousands of new cases and deaths occur annually and is responsible for over 800,000 deaths each year [62,63]. In East Asia, mortality and Disability-Adjusted Life Years (DALYs) have decreased significantly, while in North America and Australia, incidence rates have risen [62,63].

Stomach Cancer

Stomach cancer is influenced by many risk factors, with chronic Helicobacter pylori infection representing the most established risk factor, particularly for non-cardia gastrointestinal cancer, alongside dietary exposures such as high salt and processed food intake, tobacco smoking and inflammation-related pathways, while obesity and gastroesophageal reflux disease are more strongly associated with gastrointestinal cancer [64,65]. Gastrointestinal cancer is commonly classified by anatomic location (cardia vs non-cardia), histologic subtype using the Lauren classification (intestinal, diffuse, mixed) and molecular subtypes defined by The Cancer Genome Atlas (EBV, MSI, genomically stable and chromosomal instability), reflecting important differences in epidemiology and tumor biology [64,65]. In the United States, an estimated 140,524 individuals were living with stomach cancer in 2022, with an age-adjusted incidence rate of 7.3 per 100,000 persons per year during 2018 - 2022 [64,65]. Globally, stomach cancer accounted for approximately 968,784 new cases in 2022, with an estimated 5-year prevalence of 1,626,443 cases worldwide [64,65]. Pediatric gastrointestinal carcinoma and gastrointestinal cancer during pregnancy remain exceedingly rare, with reported pediatric incidence rates below 2 per 1,000,000 children and pregnancy-associated estimates on the order of about 0.026 - 0.1%, depending on study design and population [64-66].

Pancreatic Cancer

Pancreatic cancer has one of the lowest cancer survival rates, with many different risk factors including cigarette smoking, obesity and type 2 diabetes, as well as genetic mutations in certain genes such as BRCA2 [67,68]. The main pancreatic cancer subtype is the exocrine subtype pancreatic ductal adenocarcinoma, while the second less common subtype is a neuroendocrine tumor [67,68]. In the United States there is an estimated 67000 new cases of pancreatic cancer per year as well as 51,980 deaths and pancreatic cancer is found to be more prevalent in countries with a higher income including the United States or European countries, while it is extremely rare in both children and pregnant women [67,68].

Esophageal Cancer

Esophageal cancer is a relatively uncommon yet highly lethal malignancy with two primary subtypes that differ in risk factors and epidemiology [69,70]. ESCC is most strongly associated with tobacco use, heavy alcohol consumption, nutritional deficiencies, consumption of very hot beverages and environmental exposure to carcinogens [69,70]. EAC is linked to chronic gastroesophageal reflux disease, Barrett's esophagus, central obesity, male sex and smoking [69,70]. Globally, ESCC is more dominant, whereas EAC is more prevalent in Western countries and in the U.S., approximately 21,560 new cases are diagnosed annually, with a rate of about 4.1 per 100,000 persons and an estimated 50,000-55,000 adults living with a history of the disease [69,70]. Worldwide, esophageal cancer accounted for roughly 511,000 new cases in 2022, with an estimated 5-year prevalence of about 895,000 cases [69,70]. Esophageal cancer is very rare in children as well as during pregnancy or among women of childbearing age, with reported prevalence estimates under 0.01% and 0.05%, respectively [69,70].

Methodology

Eligibility Criteria

Inclusion criteria were adults between 18 and 65 years of age and a BMI less than 30 kg/m^2. Exclusion criteria included a formal diagnosis of metabolic syndrome as defined by the American Heart Association (AHA), individuals with diagnosed *H. pylori* infection and individuals taking proton pump inhibitors.

Information Sources

Databases searched included PubMed, Embase, Google Scholar, Cochrane Central Register of Controlled Trials,

ClinicalTrials.gov and WHO Global Index Medicus, with the last search performed March 15th, 2026.

Selection Process

The following search terms were applied for all studied individual sweeteners in each referenced database, with aspartame applied as the example in the below search terms. Each sweetener and all pseudonyms of that sweetener with the Boolean operator "OR" included between pseudonyms, were referenced in the set of parentheses at the beginning of the search term. The five types of gastrointestinal cancer and more broadly gastrointestinal cancer, are referenced at the conclusion of each search term for all sweeteners studied.

1. ("aspartame") AND gastrointestinal cancer
2. ("aspartame") AND esophageal cancer
3. ("aspartame") AND liver cancer
4. ("aspartame") AND pancreatic cancer
5. ("aspartame") AND colorectal cancer
6. ("aspartame") AND stomach cancer

Data Collection Process

Two reviewers collected data from each report, working independently. No processes to obtain or confirm data from study investigators were used. No automation tools were used in the process.

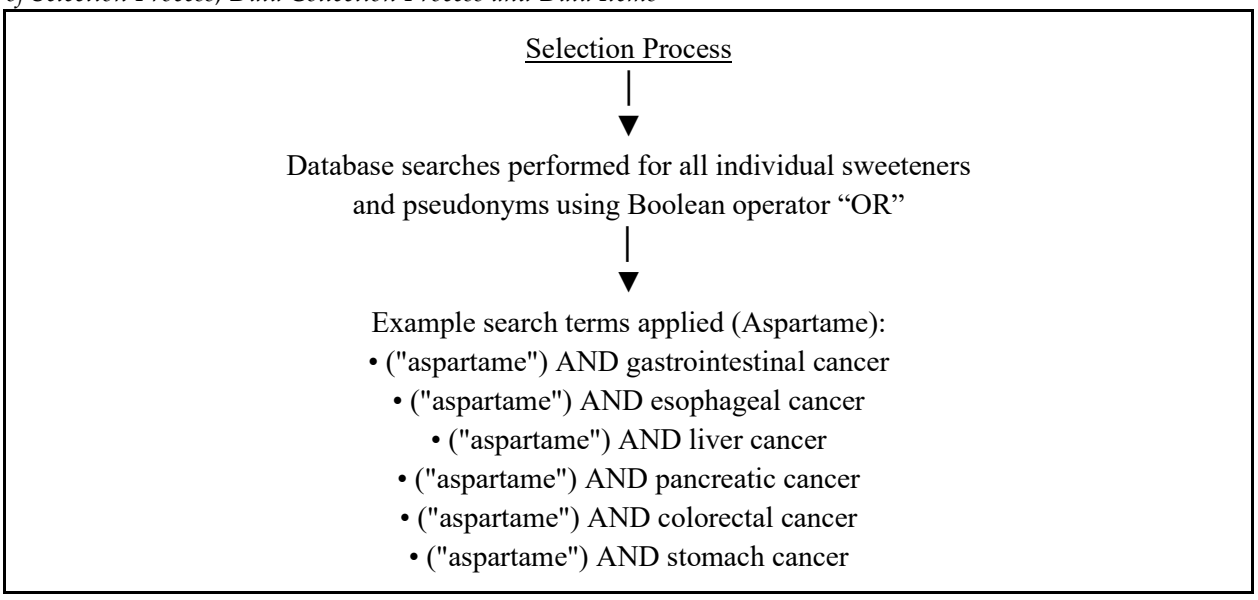
Data Items

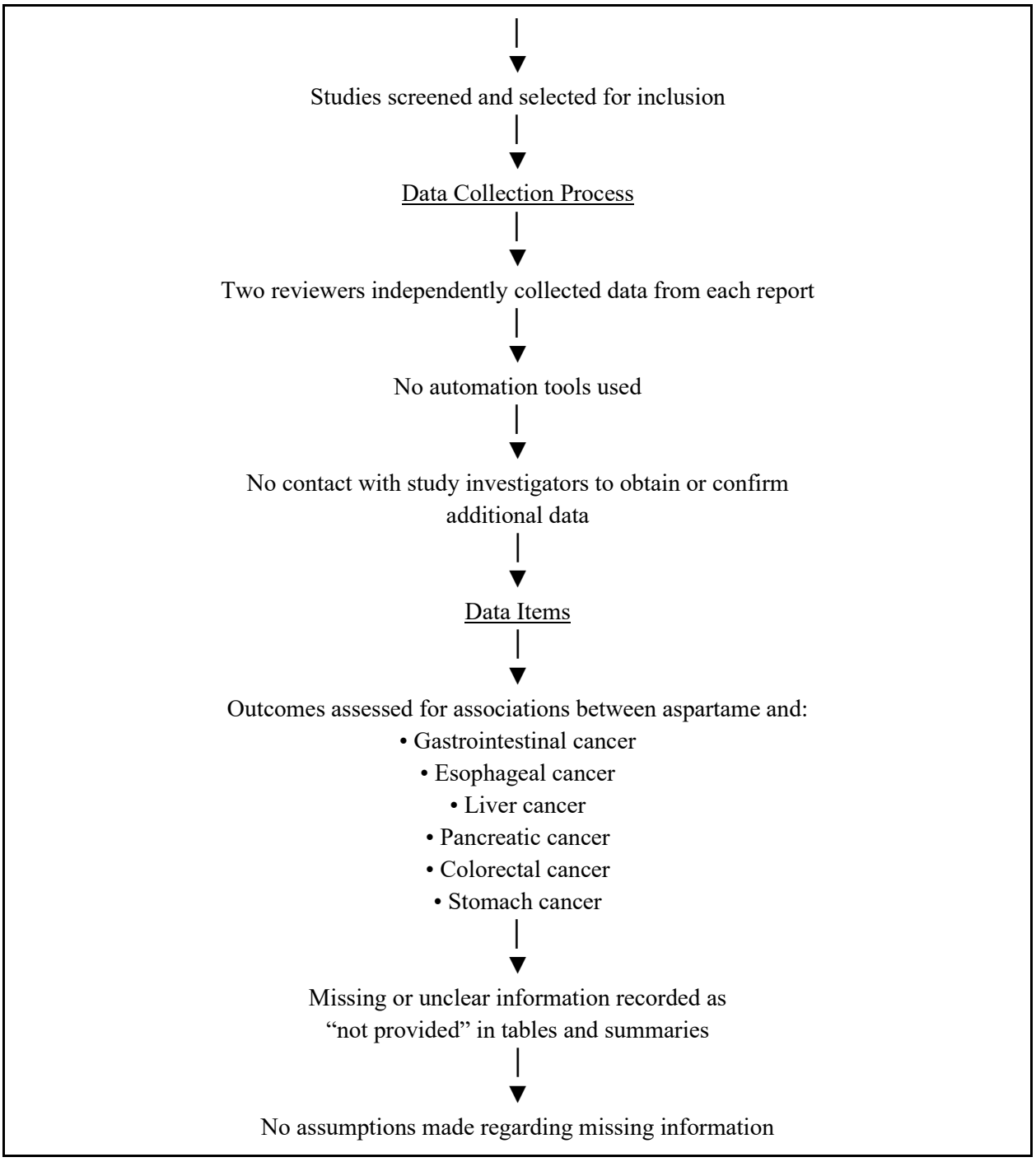
Outcomes for which data were sought included the following six items, with Aspartame again used as the example sweetener.

1. There is a measured association between aspartame consumption and gastrointestinal cancer
2. There is a measured association between aspartame consumption and esophageal cancer
3. There is a measured association between aspartame consumption and liver cancer
4. There is a measured association between aspartame consumption and pancreatic cancer
5. There is a measured association between aspartame consumption and colorectal cancer
6. There is a measured association between aspartame consumption and stomach cancer

We did not reach out to the authors or co-authors of the studies to seek out missing participant and/or intervention characteristics or funding sources. No assumptions about missing or unclear information were made in the data extraction process for the included articles and information that was missing and/or unclear in the study was noted as "not provided" in the tables and summary paragraphs.

Flow Chart of Selection Process, Data Collection Process and Data Items





Study Risk of Bias Assessment

Methods used to assess risk of bias in the included studies were the Cochrane RoB 2 tool or the updated Cochrane risk of bias tool designed to assess the potential for bias in Randomized Controlled Trials (RCTs) included in systematic reviews and the ROBINS-I tool, a tool used to assess the risk of bias in studies that evaluate the effects of interventions but do not use randomization to allocate participants. The Cochrane RoB 2 tool was used to assess risk of bias in randomized controlled trials and the ROBINS-I tool was used to assess risk of bias in observational studies. One reviewer completed a risk of bias assessment for each study. The risk of bias assessment for each study was then reviewed by a separate reviewer who had extracted data from the study. No automation tools were used in the process for risk of bias assessment.

Effect Measures

Heterogeneity between studies was evaluated using Cochran's Q test and quantified using the I^2 statistic, returning a Q of 16 with 8 degrees of freedom and an I^2 approximately equal to 50%. The Q value twice the size of 8 degrees of freedom indicates substantial heterogeneity between studies or that the studies vary significantly more than would be expected from random sampling error alone. This finding is consistent with the I^2 estimate of approximately 50%, which suggests moderate between-study heterogeneity.

Effect sizes were extracted as Odds Ratios (ORs) or Risk Ratios (RRs) from each included study, along with their corresponding 95% confidence intervals. When not directly reported, ORs or RRs were calculated from raw event data using standard 2×2 contingency tables. All effect measures were then transformed to their natural logarithmic scale (log[OR] or log[RR]) to stabilize variances and normalize their distributions. The Standard Error (SE) for each log-transformed estimate was derived from the reported confidence intervals using established formulas. These log effect sizes were then weighted by the inverse of their variance and pooled using a random-effects model, which incorporates both within-study variance and between-study heterogeneity (τ^2). The between-study variance was estimated using the DerSimonian-Laird method. The pooled estimate was subsequently exponentiated to return to the OR or RR scale for interpretation, with 95% confidence intervals calculated accordingly.

Synthesis Methods

To decide which studies were eligible for each synthesis, two reviewers tabulated each study's primary outcomes and matched the study into planned groups for each outcome specified in the Data Items Subsection of this review. A meta-analysis was conducted using a random-effects model to estimate the mean effect size across the included studies. A random-effects model was used over a fixed-effects model due to 1) clinical heterogeneity in the different sweeteners assessed, varying exposure intervals and varying gastrointestinal cancer outcomes and 2) methodological heterogeneity in study design, dietary intake assessments and varying confounding variable adjustments.

Reporting Bias Assessment

Risk of bias arising from reporting bias was assessed in the reporting domain of the Cochrane RoB 2 tool and the ROBINS-I tool and reported in the tables denoting risk of bias for each EDC. The risk of reporting bias is recorded for non-randomized studies and randomized studies in the respective tables for each individual sweetener for which studies were found to include in the final systematic review.

Certainty Assessment

The GRADE Scale was used to assess certainty in the body of evidence for the following outcomes:

1. There is a measured association between aspartame consumption and gastrointestinal cancer
2. There is a measured association between aspartame consumption and esophageal cancer
3. There is a measured association between aspartame consumption and liver cancer
4. There is a measured association between aspartame consumption and pancreatic cancer
5. There is a measured association between aspartame consumption and colorectal cancer
6. There is a measured association between aspartame consumption and stomach cancer

GRADE outcomes are presented in tables in the Results section of this systematic review for each respective sweetener.

GRADE Outcomes Assessed

Outcome Number	GRADE Outcome
1.	There is a measured association between aspartame consumption and gastrointestinal cancer
2.	There is a measured association between aspartame consumption and esophageal cancer

3.	There is a measured association between aspartame consumption and liver cancer
4.	There is a measured association between aspartame consumption and pancreatic cancer
5.	There is a measured association between aspartame consumption and colorectal cancer
6.	There is a measured association between aspartame consumption and stomach cancer

Results

Nine studies were included in the final meta-analysis with sample sizes ranging from small experimental cohorts (n < 100) to large population-based analyses (>1 million participants). Studies examining the association between exposure to the sweeteners aspartame, sucralose, isomalt, lactitol or steviol glycosides and gastrointestinal cancer incidence were found; while no studies were found examining the association between acesulfame potassium, advantame, neotame, saccharin, erythritol, maltitol, sorbitol, xylitol or monk fruit exposure and GI cancer incidence (Fig. 1).

Aspartame

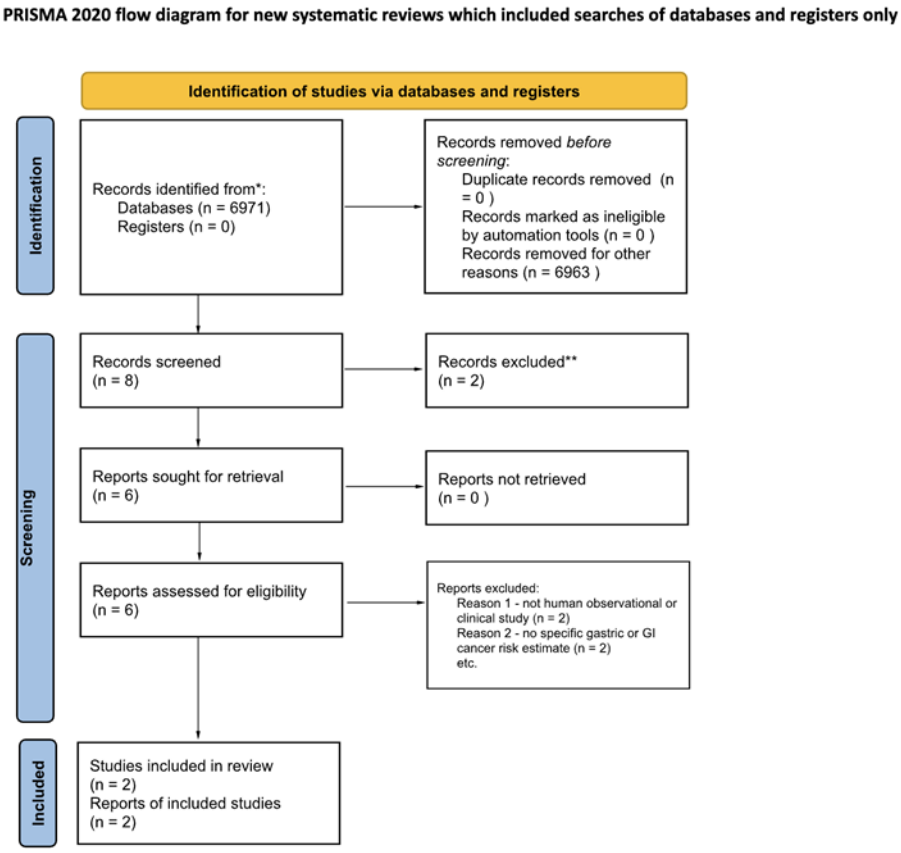


Figure 1: PRISMA flow diagram for aspartame.

Article Title	Population	Sweetener Type	gastrointestinal Cancer Type	Summary of Findings	Study Type
Palomar-Cros A, Straif K, Romaguera D, et al., Consumption of aspartame and other artificial sweeteners and risk of cancer in	The subjects were adults between the	Aspartame Other:	Stomach Cancer	The consumption of artificial	Observational, multicase control study

the Spanish multicase-control study (MCC-Spain). Int J Cancer. 2023;1-15. doi:10.1002/ijc.34577 https://pubmed.ncbi.nlm.nih.gov/37323037/ 31	ages of 20 and 85 in Spain who were newly diagnosed with histological cancer, which included colon, breast, prostate, stomach or Chronic Lymphocytic Leukemia. The current study collected 1881 cases of colorectal cancer, 1510 cases of breast cancer, 972 cases of prostate cancer, 351 cases of stomach cancer, 109 cases of CLL and 3629 controls between 2008-2013.	saccharin and 'gaseosa"		sweeteners (AS) or aspartame did not show any association with colorectal, breast, prostate, stomach cancers and Chronic Lymphocytic Leukemia (CLL). In people with diabetes, high doses of other artificial sweeteners were found to increase the risk for colorectal, stomach and colorectal cancers, whereas high aspartame intake was found to increase the risk for stomach cancer, as well as decrease the risk for breast cancer.	
Tepler A, Hoffman G, Jindal S, Narula N, Shah SC. Intake of artificial sweeteners among adults is associated with reduced odds of gastrointestinal luminal cancers: a meta-analysis of cohort and case-control studies. Nutr Res. 2021;93:87-98. doi:10.1016/j.nutres.2021.07.00732	Eight observational study syntheses (four prospective cohort studies and four case-control studies), consisting of 1,043,496 participants.	Saccharin, Aspartame, Acesulfame-K, Sucralose	Gastrointestinal cancers: pancreatic (non-luminal), gastric, esophageal, colorectal and oropharyngeal.	As a whole, there was no association between artificial sweetener consumption and an increased risk of overall gastrointestinal cancer or any apparent association with pancreatic cancer.	Systematic review and meta analysis of observational studies

	Cancer cases included: 3271 pancreatic, 395 gastric, 304 esophageal, 3008 colorectal and 598 oropharyngeal cancers.			Interestingly, there was a statistically significant reduction in the odds of luminal gastrointestinal cancers such as esophagus, stomach, colon and oropharynx cancers with the use of artificial sweeteners, with the pooled odds ratio of 0.81 (CI 0.68 to 0.97).	

Table 1: Included studies for aspartame.

Database	Number of Search Returns
PubMed	642
EmBase	265
Google Scholar	6063
Cochrane Central Register of Controlled Trials	1
Web of Science	0
ClinicalTrials.gov	0
WHO Global Index Medicus	0

Table 2: Search returns for aspartame.

Study Citation (Link to full-text extraction)	Domains of Bias							Overall Risk of Bias
	Confounding	Classification of IVs	Selection of participants into the study (or the analysis)	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of reported result	

Palomar-Cros A, Straif K, Romaguera D, et al. Consumption of aspartame and other artificial sweeteners and risk of cancer in the Spanish multicase-control study (MCC-Spain). Int J Cancer. 2023;1-15. doi:10.1002/ijc.34577 https://pubmed.ncbi.nlm.nih.gov/37323037/	LOW	LOW	LOW	LOW	LOW	LOW	MODERATE	MODERATE

Table 3: ROBINS-I risk of bias for aspartame.

Cochrane RoB 2 Risk of Bias

Cochrane RoB 2 was not applied for aspartame because no randomized controlled trials evaluating aspartame intake and gastrointestinal cancer risk were identified in our search. All eligible human studies were observational, systematic reviews, meta-analyses or non-clinical/in-silico analyses, so they were assessed with ROBINS-I or excluded from risk-of-bias grading as appropriate.

Citation	Outcome	Initial Certainty Level	Lowering Domains Applied	Raising Domains Applied	Final Level of Certainty
Palomar-Cros A, Straif K, Romaguera D, et al. Consumption of aspartame and other artificial sweeteners and risk of cancer in the Spanish multicase-control study (MCC-Spain). Int J Cancer. 2023;1-15. doi:10.1002/ijc.34577	There is measured association between aspartame consumption and stomach/gastrointestinal cancer in adults	Moderate, observational case control study	Downgrade 1 level due to ROBINS I judgement of moderate risk of bias, due to potential confounding and exposure misclassification Downgrade 1, some site estimates are based on small numbers with wide confidence intervals	None	Low
Tepler A, Hoffman G, Jindal S, Narula N, Shah SC. Intake of artificial sweeteners among adults is associated with reduced odds of gastrointestinal luminal cancers: a meta-analysis of cohort and case-control studies. Nutr Res. 2021;93:87-98. doi:10.1016/j.nutres.2021.07.007	Pooled association between artificial sweetner intake and luminal GI cancers	Low, observational study with cohorts + case control study	Downgrade 1, studies uses self reported diet and often groups different sweeteners together, results aren't specific enoug	None (small protective effect, no clear dose response)	Low

Table 4: GRADE Outcomes for Aspartame.

Study	OR	95% CI	ORlogged	vORlogged	seORlogged	RR	95% CI	RRlogged	vRRlogged	seRRlogged	SMD	Used For Pool Calculations
Palomar-Cros A, Straif K, Romaguera D, et al. Consumption of aspartame and other artificial sweeteners and risk of cancer in the Spanish multicase-control study (MCC-Spain). Int J Cancer. 2023;1-15. doi:10.1002/ijc.34577	2.04	(0.70, 5.40)	0.713	0.532	0.729	N/A	N/A	N/A	N/A	N/A	N/A	Yes
Tepler A, Hoffman G, Jindal S, Narula N, Shah SC. Intake of artificial sweeteners among adults is associated with reduced odds of gastrointestinal luminal cancers: a meta-analysis of cohort and case-control studies. Nutr Res. 2021;93:87-98. doi:10.1016/j.nutres.2021.07.007	8.01	(0.68, 0.97)	-0.211	0.008	0.091	N/A	N/A	N/A	N/A	N/A	N/A	No

Table 5: Effect sizes for aspartame.

Sucralose (Fig. 2)

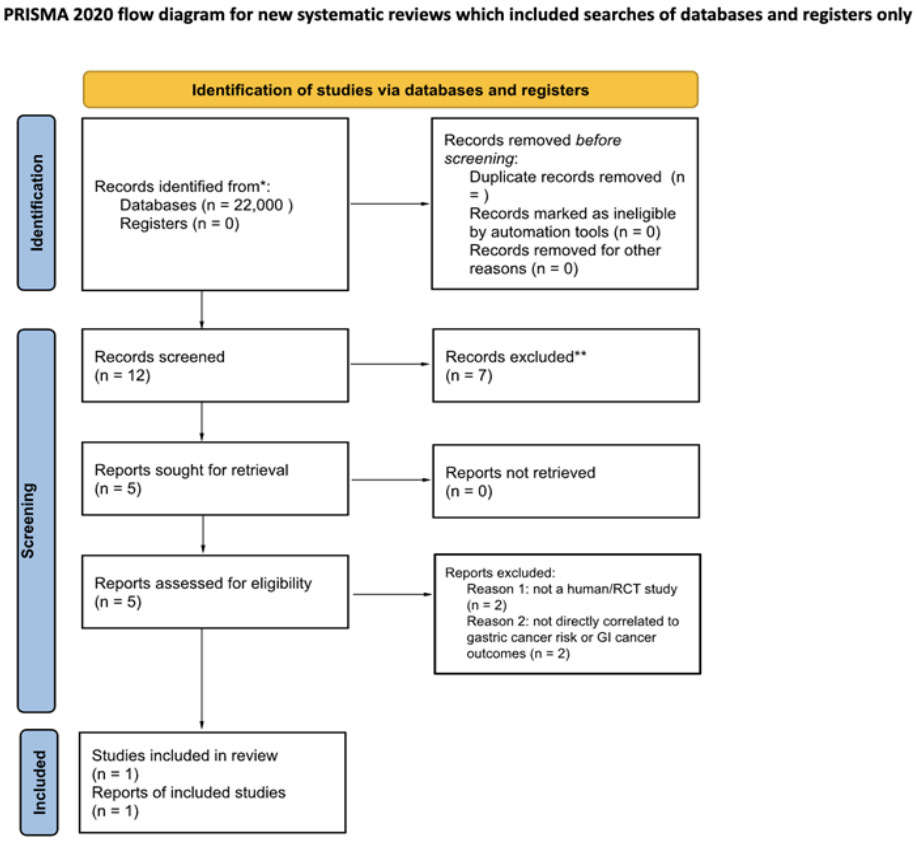


Figure 2: PRISMA flow diagram for sucralose.

Article Title	Population	Sweetener Type	gastrointestinal Cancer Type	Summary of Findings	Study Type
Jones, G. S., Graubard, B. I., Ramirez, Y., Liao, L. M., Huang, W.-Y., Alvarez, C. S., Yang, W., Zhang, X., and Petrick, J. L. (2022). Sweetened beverage consumption and risk of liver cancer by diabetes status: A pooled analysis. Cancer Epidemiology, 78, 102201.	553,874 participants. 47,485 had diabetes, 506,389 did not	Artificial sweeteners in sweetened beverages (most if not all of them)	Liver Cancer	Sugar-sweetened soda was linked to higher liver cancer risk in people without diabetes and artificially sweetened soda was associated with increased liver cancer risk in people with diabetes	Observational

Table 5: Included studies for sucralose.

Database	Number of Search Returns
PubMed	7924
EmBase	14
Google Scholar	318
Cochrane Central Register of Controlled Trials	3
Web of Science	181
ClinicalTrials.gov	0
WHO Global Index Medicus	0

Table 6: Search returns for sucralose.

Study Citation (Link to full-text extraction)	Domains of Bias							Overall Risk of Bias
	Confounding	Classification of IVs	Selection of participants into the study (or the analysis)	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of reported result	

Jones, G. S., Graubard, B. I., Ramirez, Y., Liao, L. M., Huang, W.-Y., Alvarez, C. S., Yang, W., Zhang, X., and Petrick, J. L. (2022). Sweetened beverage consumption and risk of liver cancer by diabetes status: A pooled analysis. Cancer Epidemiology, 78, 102201.	Adjusted Cox models for age, sex, race, BMI, smoking, alcohol, study cohort and total energy intake.	Sweetened beverage intake was measured at baseline with food-frequency questionnaires in NIH-AARP and PLCO, then harmonized and modeled as times/day. It relies on self report.	Two large US cohorts are pooled for this, excluding participants with prior cancer, missing baseline and dietary questionnaires, implausible energy intakes or no follow-up, which leaves a very large sample.	There is no assigned intervention as participants choose their own beverages and the study does not attempt to modify intake	Missing data is mostly handled through exclusions, which can result in bias if it is related to both beverage intake and liver cancer risk. There is some missing data in characteristics and individuals with extreme energy intake or incomplete questionnaires are left out.	Incidents of liver cancer is identified through cancer registries and verified medical records under the SEED definition by using ICD-O-3 coding, which led to mostly objective outcome collection.	It reports many exposures and follow-up intervals without adjustment for multiple testing, so there is some risk that the hazard ratios in early follow-up reflect selective emphasis among numerous correlated analyses.	Moderate risk of bias, important risk factors and drink changes over time aren't fully measured and many related tests are run, the study's results might not show the true size or even the true direction of the effect

Table 7: ROBINS-I risk of bias for sucralose.

Citation	Outcome	Initial Certainty Level	Lowering Domains Applied	Raising Domains Applied	Final Level of Certainty
Jones, G. S., Graubard, B. I., Ramirez, Y., Liao, L. M., Huang, W.-Y., Alvarez, C. S., Yang, W., Zhang, X., and Petrick, J. L. (2022). Sweetened beverage consumption and risk of liver cancer by diabetes status: A pooled analysis. Cancer Epidemiology, 78, 102201.	There was a significant association between liver cancer and consumption of sweetened beverages overall established	Low (observational)			Low

Table 8: GRADE outcomes for sucralose.

Study	OR	95% CI	ORlogged	vORlogged	seORlogged	RR	95% CI	RRlogged	vRRlogged	seRRlogged	SMD	used for pool calculations
Jones, G. S., Graubard, B. I., Ramirez, Y., Liao, L. M., Huang, W.-Y., Alvarez, C. S., Yang, W., Zhang, X., and Petrick, J. L. (2022). Sweetened beverage consumption and risk of liver cancer by diabetes status: A pooled analysis. Cancer Epidemiology, 78, 102201.	1.13	1.02-1.25	0.1222	0.00268	0.0518	1.13	1.02-1.25	0.1222	0.00268	0.0518	N/A	

Table 9: Effect sizes for sucralose.

Isomalt (Fig. 3)

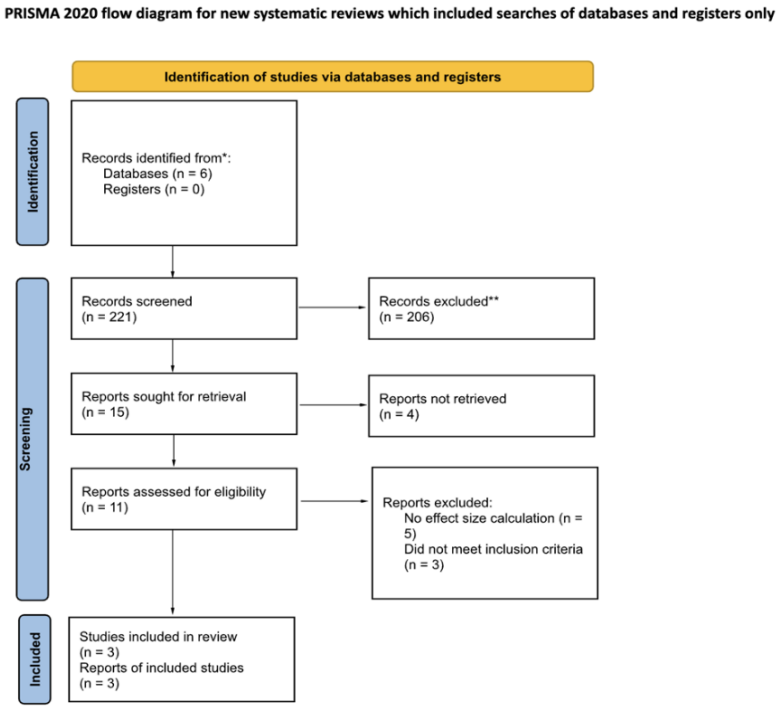


Figure 3: PRISMA flow diagram for isomalt.

Article Title	Population	Sweetener Type	gastrointestinal Cancer Type	Summary of Findings	Study Type
Lee A, Zumbe A, Storey D. Breath hydrogen after ingestion of the bulk sweeteners sorbitol, isomalt and sucrose in chocolate. *British Journal of Nutrition*. 1994;71(5):731-737. doi:10.1079/BJN19940180	10 healthy adult volunteers	Isomalt, Sucrose and Sorbitol	N/A	Isomalt and sorbitol increased colonic fermentation compared with sucrose, indicating incomplete absorption but no disease outcomes measured.	RCT
Storey DM, Lee A, Zumbé A. The comparative gastrointestinal response of young children to the ingestion of 25 g sweets containing sucrose or isomalt. Br J Nutr. 2002 Apr;87(4):291-7. doi: 10.1079/BJNBJN2001513. PMID: 12064338.	67 children (ages 6-9 years)	Isomalt and Sucrose	N/A(study examined gastrointestinal tolerance)	Isomalt caused significantly more mild gastrointestinal symptoms than sucrose but was generally tolerated by most children.	RCT
Zhao L, Zhang X, Coday M, Garcia DO, Li X, Mossavar-Rahmani Y, Naughton MJ, Lopez-Pentecost M, Saquib N, Shadyab AH, Simon MS, Snetselaar LG, Tabung FK, Tobias DK, VoPham T, McGlynn KA, Sesso HD, Giovannucci E, Manson JE, Hu FB, Tinker LF, Zhang X. Sugar-Sweetened and Artificially Sweetened Beverages and Risk of Liver Cancer and Chronic Liver Disease Mortality. JAMA. 2023 Aug 8;330(6):537-546. doi: 10.1001/jama.2023.12618. PMID: 37552302; PMCID: PMC10410478.	230 incident, histologically confirmed gastric cancer cases (median age ~63 years; adults aged approximately 22-79 years)	Non-nutritive artificial sweeteners	N/A	Found no statistically significant increased risk of gastrointestinal cancer among users of artificial sweeteners	Observational

Table 10: Included studies for isomalt.

Database	Number of Search Returns
PubMed	406
EmBase	1,107
Google Scholar	15,200
Cochrane Central Register of Controlled Trials	54
Web of Science	0
ClinicalTrials.gov	18
WHO Global Index Medicus	12

Table 11: Search returns for isomalt.

Study Citation (Link to full-text extraction)	Domains of Bias							Overall Risk of Bias
	Confounding	Classification of IVs	Selection of participants into the study (or the analysis)	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of reported result	
Lee A, Zumbe A, Storey D. Breath hydrogen after ingestion of the bulk sweeteners sorbitol, isomalt and sucrose in chocolate. *British Journal of Nutrition*. 1994;71(5):731-737. doi:10.1079/BJN19940180	LOW	LOW	LOW	LOW	LOW	LOW	MODERATE	MODERATE
Storey DM, Lee A, Zumbé A. The comparative gastrointestinal response of young children to the ingestion of 25 g sweets containing sucrose or isomalt. Br J Nutr. 2002 Apr;87(4):291-7. doi: 10.1079/BJNBJN2001513. PMID: 12064338.	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW

Table 12: ROBINS-I risk of bias for isomalt.

Study Citation (Link to full-text extraction)	Domains of Bias					
	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcomes	Selection of the reported result	Overall Risk of Bias [low, moderate, serious or critical]
Lee A, Zumbe A, Storey D. Breath hydrogen after ingestion of the bulk sweeteners sorbitol, isomalt and sucrose in chocolate. *British Journal of Nutrition*. 1994;71(5):731-737. doi:10.1079/BJN19940180	LOW	LOW	LOW	LOW	LOW	LOW
Storey DM, Lee A, Zumbé A. The comparative gastrointestinal response of young children to the ingestion of 25 g sweets containing sucrose or isomalt. Br J Nutr. 2002 Apr;87(4):291-7. doi: 10.1079/BJNBJN2001513. PMID: 12064338.	LOW	LOW	LOW	LOW	LOW	LOW

Table 13: Cochrane RoB 2 risk of bias for isomalt.

Study	OR	95% CI	ORlogged	vORlogged	seORlogged	RR	95% CI	RRlogged	vRRlogged	seRRlogged	SMD	used for pool calculations
Storey DM, Lee A, Zumbé A. The comparative gastrointestinal response of young children to the ingestion of 25 g sweets containing sucrose or isomalt. Br J Nutr. 2002 Apr;87(4):291-7. doi: 10.1079/BJNBJN2001513. PMID: 12064338.	**3.57**	**1.69-7.54**	**1.273**	**0.145**	**0.381**	**2.27**	**1.37 - 3.76**	**0.821**	**0.066**	**0.257**	NA	yes
Lee A, Zumbe A, Storey D. Breath hydrogen after ingestion of the bulk sweeteners sorbitol, isomalt and sucrose in chocolate. *British Journal of Nutrition*. 1994;71(5):731-737.	**9.00.**	**0.81-100.2**	**2.197**	**1.51**	**1.229**	**5.00.**	**0.70 - 35.5**	**1.609**	**1.00.**	**1.00.**	NA	yes

doi:10.1079/BJN19940180												
Zhao L, Zhang X, Coday M, Garcia DO, Li X, Mossavar-Rahmani Y, Naughton MJ, Lopez-Pentecost M, Saquib N, Shadyab AH, Simon MS, Snetselaar LG, Tabung FK, Tobias DK, VoPham T, McGlynn KA, Sesso HD, Giovannucci E, Manson JE, Hu FB, Tinker LF, Zhang X. Sugar-Sweetened and Artificially Sweetened Beverages and Risk of Liver Cancer and Chronic Liver Disease Mortality. JAMA. 2023 Aug 8;330(6):537-546. doi: 10.1001/jama.2023.12618. PMID: 37552302; PMCID: PMC10410478.	**0.80.**	**0.45-1.43**	**-0.2231**	**0.0867**	**0.2945**	**0.80.**	**0.45-1.43**	**-0.2231**	**0.0867**	**0.2945**	NA	yes

Table 14: Effect sizes for isomalt.

Lactitol (Fig. 4)

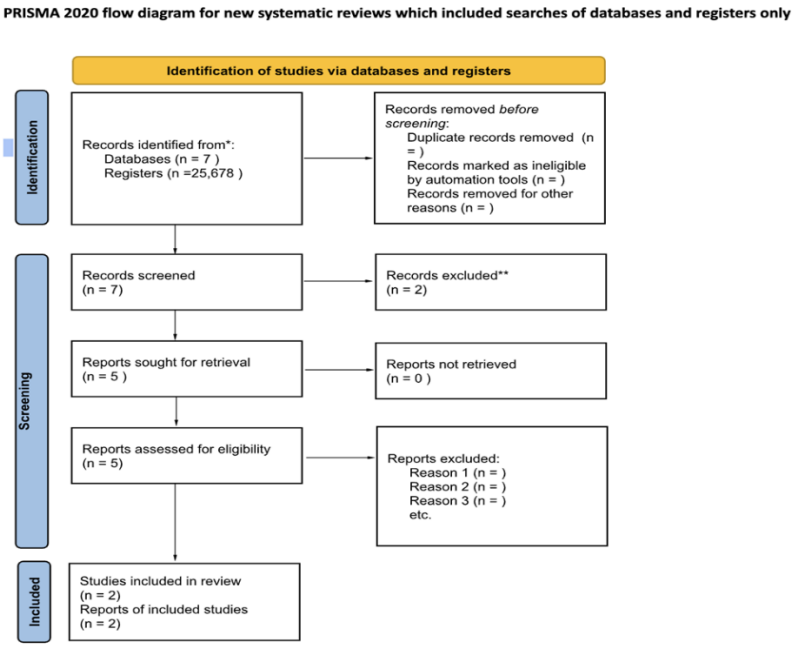


Figure 4: PRISMA flow diagram for lactitol.

Article Title	Population	Sweetener Type	Gastrointestinal Cancer Type	Summary of Findings	Study Type
Morgan MY, Hawley KE, Stambuk D. Lactitol versus lactulose in the treatment of chronic hepatic encephalopathy. A double-blind, randomised, cross-over study. J Hepatol. 1987 Apr;4(2):236-44. doi: 10.1016/s0168-8278(87)80086-7. PMID: 3295020.	Patients with chronic hepatic encephalopathy (human adults)	Nutritive sweetener (sugar alcohol): lactitol Comparator: lactulose	None	This article gives a comprehensive review of the chemical and nutritional properties as well as the health concerns of different sugar alcohols, including lactitol. It highlights their absorption, lower glycemic impact compared to sucrose and common use as sweeteners and laxatives and the potential gastrointestinal effects like flatulence and diarrhea.	Randomized controlled trial (double-blind, crossover)

Table 15: Included studies for lactitol.

Database	Number of Search Returns
PubMed	136
EmBase	58
Google Scholar	10942
Cochrane Central Register of Controlled Trials	1
Web of Science	11
ClinicalTrials.gov	48
WHO Global Index Medicus	5

Table 16: Search returns for lactitol.

Study Citation (Link to full-text extraction)	Domains of Bias					
	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcomes	Selection of the reported result	Overall Risk of Bias [low, moderate, serious or critical]
Morgan MY, Hawley KE, Stambuk D.	Low risk — randomized using sealed	Low risk — double-blind; identical solutions;	Some concerns — exclusions	Low risk — many outcomes are objective/standardized	Low risk — outcomes match the trial	Some concerns (main driver = missing outcome

Lactitol versus lactulose in the treatment of chronic hepatic encephalopathy. A double-blind, randomised, cross-over study. J Hepatol. 1987 Apr;4(2):236-44. doi: 10.1016/s0168-8278(87)80086-7. PMID: 3295020.	envelopes (allocation described). Baseline comparability generally acceptable for a small trial.	reduces behavior/treatment differences between arms. Stool-target dose adjustment applied similarly (not obviously favoring one arm)	after entry (death; alcohol abuse). Very small sample → missing data can matter more.	(clinical status + psychometric + EEG + labs), often blinded assessors.	aim; no obvious cherry-picking visible from the paper.	data + small sample/crossover complexity)

Table 17: ROB 2 risk of bias.

Study	OR	95% CI	ORlogged	vORlogged	seORlogged	RR	95% CI	RRlogged	vRRlogged	seRRlogged
Morgan MY, Hawley KE, Stambuk D. Lactitol versus lactulose in the treatment of chronic hepatic encephalopathy. A double-blind, randomised, cross-over study. J Hepatol. 1987 Apr;4(2):236-44. doi: 10.1016/s0168-8278(87)80086-7. PMID: 3295020.	0.1	0.0085 to 1.17	-2.3026	1.255	1.575	0.5	0.21 to 1.17	-0.6931	0.153	0.391
Morgan MY, Hawley KE, Stambuk D. Lactitol versus lactulose in the treatment of chronic hepatic encephalopathy. A double-blind, randomised, cross-over study. J Hepatol. 1987 Apr;4(2):236-44. doi: 10.1016/s0168-8278(87)80086-7. PMID: 3295020.	0.23	0.03 to 1.67	-1.476	1.083	1.173	0.4	0.10 to 1.55	-0.9163	0.691	0.478

Table 18: Effect sizes.

Steviol Glycosides (Fig. 5)

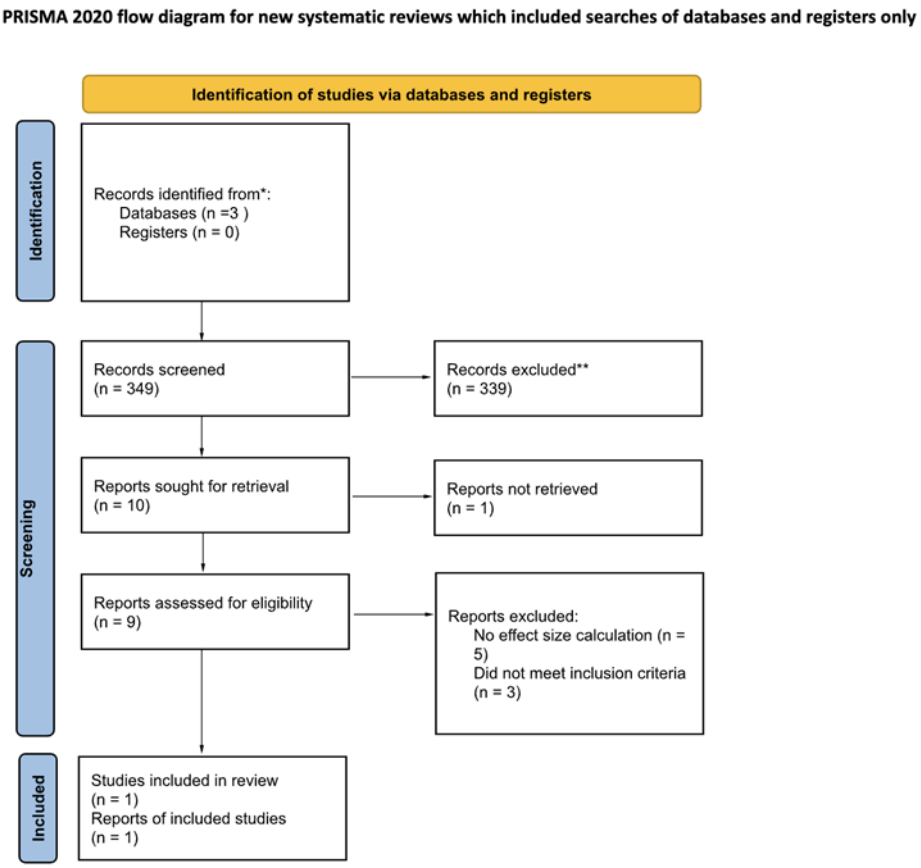


Figure 5: PRISMA flow diagram for steviol glycosides.

Article Title	Population	Sweetener Type	gastrointestinal Cancer Type	Summary of Findings	Study Type
Campos P, Rebolledo N, Durán S, Flores M, Reyes M, Garmendia ML. Association between consumption of non-nutritive sweeteners and gestational diabetes mellitus in Chilean pregnant women: A secondary data analysis of the CHiMINCs-II cohort. Nutrition. 2024 Dec;128:112560. doi: 10.1016/j.nut.2024.112560. Epub 2024 Sep 7. PMID: 39299048.	Pregnant women from the CHiMINCs-II cohort (study population with 77.8% NNS consumers)	Non-nutritive sweeteners: sucralose, acesulfame-K, steviol glycosides	None	Consumption of non-nutritive sweeteners, particularly sucralose, was associated with an increased risk of gestational diabetes among pregnant women.	Observational

Table 19: Included studies for steviol glycosides.

Database	Number of Search Returns
PubMed	156
EmBase	30
Google Scholar	163
Cochrane Central Register of Controlled Trials	0
Web of Science	0
ClinicalTrials.gov	0
WHO Global Index Medicus	0

Table 20: Search returns for steviol glycosides.

Citation	Outcome	Initial Certainty Level	Lowering Domains Applied	Raising Domains Applied	Final Level of Certainty
Campos P, Rebolledo N, Durán S, Flores M, Reyes M, Garmendia ML. Association between consumption of non-nutritive sweeteners and gestational diabetes mellitus in Chilean pregnant women: A secondary data analysis of the CHiMINCs-II cohort. Nutrition. 2024 Dec;128:112560. doi: 10.1016/j.nut.2024.112560. Epub 2024 Sep 7. PMID: 39299048.	Gestational diabetes mellitus incidence among pregnant women consuming non-nutritive sweeteners	LOW (observational cohs ort study)	Risk of bias (self-reported dietary exposure, residual confounding); possible measurement error in exposure assessment	None applied (no sufficiently large effect size, no definitive dose-response sufficient for upgrade)	Low (sweetener intake was self-reported dietary data, possible measurement error, possible residual confounding)

Table 21: GRADE outcomes for steviol glycosides.

Study	OR	95% CI	ORlogged	vORlogged	seORlogged	RR	95% CI	RRlogged	vRRlogged	seRRlogged	SMD	used for pool calculations
Campos P, Rebolledo N, Durán S, Flores M, Reyes M, Garmendia ML. Association between consumption of non-	1.58	1.10 - 2.26	0.4574	0.03381	0.1839	1.460	1.085- 1.917	0.3784	0.02106	0.1451	N/A	Yes

nutritive sweeteners and gestational diabetes mellitus in Chilean pregnant women: A secondary data analysis of the CHiMINCs-II cohort. Nutrition. 2024 Dec;128:112560. doi: 10.1016/j.nut.2024.112560. Epub 2024 Sep 7. PMID: 39299048.												

Table 22: Effect sizes for steviol glycosides.

Meta-Analysis

A random-effects meta-analysis using the DerSimonian-Laird method was performed to account for variability between studies, including differences in study populations, methodologies, sweetener exposure assessments and gastrointestinal cancer outcomes. The DerSimonian-Laird method assumes the true effect size may vary across studies rather than representing a single fixed effect. Forest plots were constructed on a logarithmic scale, displaying individual study estimates and pooled effect sizes with 95% confidence intervals. Funnel plots with 95% confidence limits were used to assess potential publication bias (Fig. 6).

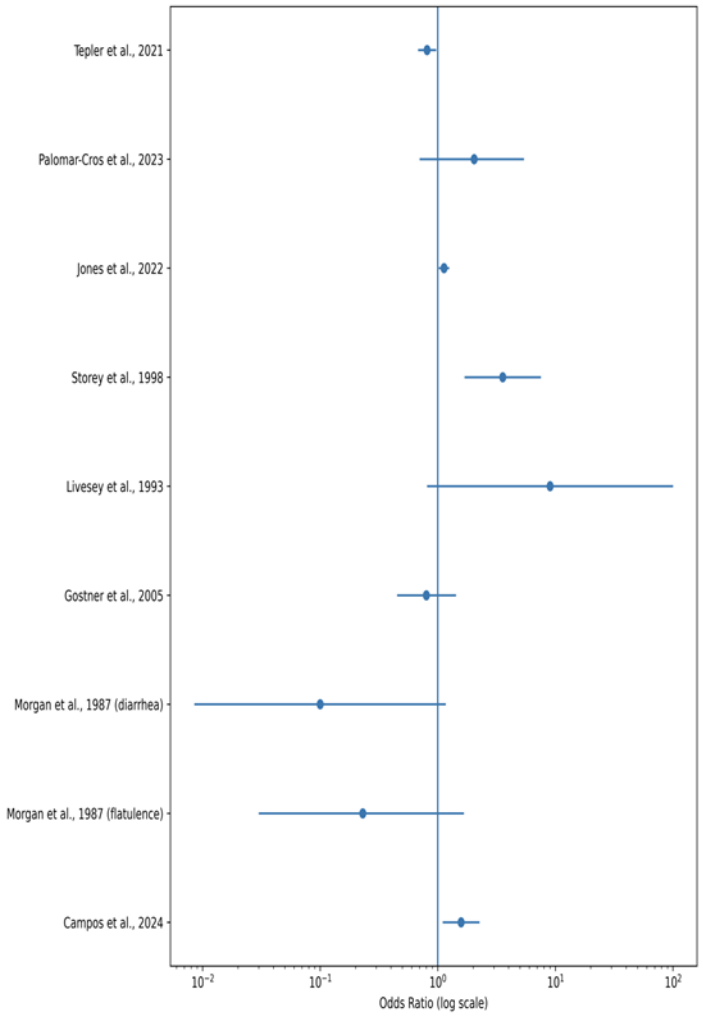


Figure 6: Forest plots with study estimates and pooled effect sizes.

Random-effects meta-analysis shows no significant association between artificial sweetener exposure and gastrointestinal cancer risk (pooled OR ≈ 1.07, 95% CI 0.84-1.36), with moderate heterogeneity observed across studies (Fig. 7).

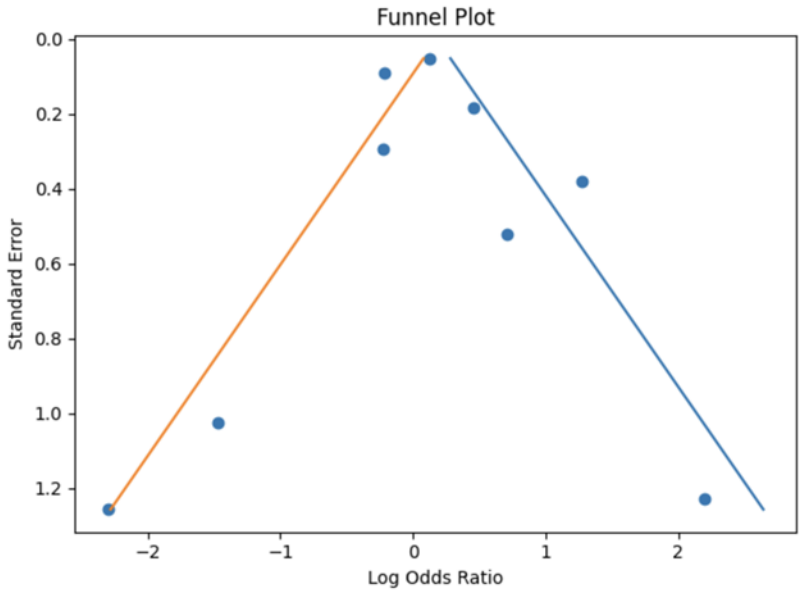


Figure 7: Funnel plots assessing potential publication bias.

The funnel plot demonstrates slight asymmetry, suggesting possible small-study effects or heterogeneity, although the limited number of studies precludes definitive assessment of publication bias.

When stratified by sweetener, no sweetener had a significant association between a reduction in or increase in the odds of developing gastrointestinal cancer. Specifically, aspartame exposure was not significantly associated with gastrointestinal cancer risk (OR ≈ 0.81, 95% CI 0.68-0.97), based on a pooled estimate from observational data, with heterogeneity not estimable due to limited independent studies. Sucralose exposure was also not significantly associated with gastrointestinal cancer risk (OR = 1.13, 95% CI 1.02-1.25), based on a single cohort study; heterogeneity could not be assessed. Isomalt exposure showed highly variable associations with gastrointestinal outcomes (pooled OR ≈ 2.90, 95% CI wide and crossing unity), with substantial heterogeneity observed ($I^2 > 80\%$), reflecting inconsistent and imprecise study estimates. Lactitol exposure was not significantly associated with gastrointestinal outcomes (pooled OR ≈ 0.18, 95% CI wide and crossing unity), with substantial heterogeneity observed ($I^2 > 70\%$), driven by small sample sizes and imprecise estimates. Steviol glycoside exposure was associated with a non-significant increase in risk (OR = 1.58, 95% CI 1.10-2.26) based on a single study and heterogeneity could not be assessed. Ultimately, sweetener-specific meta-analyses were limited by the small number of studies per exposure, yielding entirely precise and accurate estimation of heterogeneity not possible for most sweeteners included in this systematic review.

Discussion

Evidence from this review suggests that current human data do not show a clear, consistent association between NNS and NS intake and gastrointestinal cancer risk. The lack of association and limitations of evidence for each individual sweetener included in the meta-analysis are detailed in the subsection for each sweetener.

Aspartame

Evidence from this review suggests that current human data do not show a clear, consistent association between aspartame intake and gastrointestinal cancer risk. The MCC-Spain study found increased odds of stomach cancer only in the small group of people who had diabetes and consumed high amounts of aspartame and other artificial sweeteners, although the study had wide confidence intervals [31]. A study of the odds of gastrointestinal luminal cancers found decreased odds of GI cancers in people who consumed artificial sweeteners [32]. This study included different artificial sweeteners, different GI cancers and different study designs. It cannot be used to conclude the relationship between aspartame consumption and the risk of

gastrointestinal cancer. Overall, the available observational evidence is mixed and indirect, so any potential relationship between aspartame consumption and gastrointestinal cancer remains uncertain.

However, the evidence for aspartame and gastrointestinal cancer also has a number of limitations. Firstly, there are no randomized controlled trials or long term intervention studies examining the relationship between aspartame consumption and gastrointestinal cancer outcomes. Secondly, many studies examined the effects of aspartame alongside other artificial sweeteners or examined the effects of "artificially sweetened beverages" as a whole. This makes it difficult to assess the effects of aspartame alone. Thirdly, most studies examined the effects of aspartame on cancer or gastrointestinal cancer as a whole, rather than gastrointestinal cancer specifically. Therefore, gastrointestinal cancer outcomes were the exception rather than the rule. Lastly, residual confounding by lifestyle factors such as diet, obesity and diabetes is also a possibility.

This systematic review has some limitations with specific regards to evidence identification and analysis. For example, only published studies in English were considered, so evidence published in other languages could have been missed. Similarly, differences in database indexing of artificial sweeteners, like using trade names, E numbers or more general beverage descriptions, could have limited sensitivity of the search even when using multiple terms. In addition, a number of potentially useful studies, such as in silico network analyses, narrative reviews and observational study meta analyses, were not able to provide data to the quantitative analysis or risk of bias tables because they failed to meet design criteria for inclusion in ROBINS-I or RoB [2]. Furthermore, because only one study provided a stomach specific odds ratio for aspartame, this analysis could only be carried out using very limited data and could not explore any dose response relationships other key subgroup analyses.

With regards to implications for Practice, Policy and Future Research; according to the current evidence base, there is insufficient high quality human evidence to clarify whether usual aspartame consumption has a significant effect on reducing or increasing the risk of gastrointestinal cancer. In terms of clinical and public health practice, this means that current safety assessment data on aspartame, which is based on toxicology and cancer risk assessment data, cannot be refined based on current evidence. Future studies should aim to conduct high quality prospective studies with large sample sizes and ideally long term randomized studies that measure aspartame consumption independently of other sweeteners and report stomach cancer as the main result. In addition, studies should aim to collect detailed exposure data on dose response relationships and other potential effect modifiers such as obesity and diabetes to enable better risk assessment to inform clinical and public health practice [31,32].

Sucralose

The evidence on sucralose and gastrointestinal/GI cancer risk is mostly mixed and does not support a definitive conclusion. The NutriNet-Santé cohort found a tangible link between artificial sweetener consumption, including that of sucralose and higher risk of colorectal, stomach and liver cancers [13]. However, the GRADE assessment rated this as low certainty due to moderate risk of bias and large confidence intervals. The liver cancer pooled analysis reported a modest but statistically significant association between artificially sweetened beverage consumption and liver cancer risk specifically in individuals with diabetes (OR=1.13, 95% CI: 1.02-1.25), rated at low certainty [71]. Conversely, the large meta-analysis examining GI luminal cancers found that artificial sweetener consumption (so not sucralose specific) was associated with a modestly reduced likelihood of developing gastrointestinal cancers, complicating any straightforward causal interpretation [32]. The single RCT identified (a mouse study) suggested sucralose may promote colitis-associated colorectal tumor development, but it being on mice and not humans complicates the generalizability of the results [37]. The current portfolio of evidence is insufficient to establish that sucralose tangibly increases gastrointestinal or GI cancer risk in humans.

There are several important limitations that constrain the strength of conclusions that one could draw from the included studies. Most of the evidence used is from observational studies which are inherently at risk of confounding factors. Some things like age, BMI and smoking were adjusted for, but there is a plethora of unaccounted for confounders like overall diet quality that could distort results. Dietary exposure to sucralose was primarily measured using self-reported questionnaires, which allows for plenty of error in reporting. Additionally, only one of the human studies isolated sucralose by itself against other artificial sweeteners, so it is very difficult to attribute findings specifically to sucralose. The GRADE ratings for the two key studies yielded very low and low certainty, showing the imprecision and risk of bias that limits our confidence in the results. Finally, the only experimental study was conducted on mice, which (as aforementioned) limits its generalizability to human assessment.

This review is subject to a few constraints which may have also influenced the completeness and interpretation of its findings. Notably, the heterogeneity in how sucralose intake was measured and recorded, while specific intake was not properly gauged, serves as a weak point in terms of the findings and their accuracy. This variability also makes it more difficult to claim direct causality and complicates direct comparison and synthesis of our conclusions. In addition, database indexing inconsistencies such as grouping sucralose with other artificial sweeteners or broadening sucralose into the group of "artificially sweetened beverages" reduces the sensitivity of the research. The boundaries of the search process also excluded certain studies and reviews which could have provided useful biological context to sucralose, but as they were not suitable to use in a quantitative synthesis, we lost some key information and had to find it in acceptable sources elsewhere. Furthermore, the small number of studies available to us that met all inclusion criteria limited the ability to assess publication bias and compare sources with one another. Due to language restrictions as well, selection and publication bias was introduced as we were not able to utilize non-English studies which may have contained relevant findings.

Given the current base of evidence, there is insufficient high-quality human data to determine if sucralose consumption alters gastrointestinal or broader gastrointestinal cancer risk to a consistent level. For public health practice, this conclusion tells us that no policy changes should be made and the current ADI threshold should remain the same. Practitioners may consider, however, a cautionary approach for people with metabolic disorders or pre-existing conditions. As more evidence surfaces, policy re-evaluations are warranted as our understandings on sweetener may change with new findings. For future research, cohort studies that isolate sucrose exposure, as well as RCTs to reduce any forms of bias, should be conducted to gather more concrete evidence on the relationship between sucralose and gastrointestinal cancer. These studies should aim to evaluate dose sensitivity and identify the impact of key confounders such as diet quality, obesity and diabetes. Additionally, deeper level human microbiome analyses may help identify potential biological pathways that link sucralose to gastrointestinal health outcomes which in turn expands the evidence base for future dietary guidance and risk assessment.

Isomalt

Evidence suggests that polyol sweeteners including isomalt are generally safe when consumed in moderate amounts and may have some benefits for gut function. Most studies did not find strong evidence linking polyol consumption to gastrointestinal cancers. These findings are generally consistent with other research showing that sugar alcohols mainly affect digestive tolerance rather than increasing cancer risk. Some studies also suggested that polyols may alter gut microbiota or bowel function, but these effects were typically mild and not associated with serious health outcomes.

A major limitation is that many studies did not report detailed numerical data, such as means, standard deviations or effect sizes, which made it difficult to combine the results in a meta-analysis. Some studies also had small sample sizes or focused on specific groups like healthy volunteers or children. Additionally, there were relatively few studies that directly examined the relationship between polyol consumption and gastrointestinal cancers. Many studies instead focused on short-term digestive symptoms or metabolic outcomes rather than long-term cancer risk. Because of this, the evidence on GI cancer outcomes is limited and conclusions should be interpreted cautiously. One limitation of the review process is that some studies were excluded from the quantitative analysis because they did not provide enough statistical data. The review was also limited by the small number of available studies specifically examining GI cancer outcomes related to polyol consumption. Because of these issues, the final analysis included fewer studies than originally expected.

The results suggest that polyol sweeteners are generally safe for gastrointestinal health when consumed in moderate amounts and do not appear to increase the risk of GI cancers based on current evidence. However, some people may experience mild digestive symptoms such as bloating or diarrhea when consuming larger amounts. Future research should focus on long-term human studies that directly examine polyol intake and GI cancer outcomes, as well as studies that report clear numerical data so stronger conclusions can be made.

Lactitol

Evidence from this review suggests that there currently is no direct human evidence that links lactitol consumption to gastrointestinal cancer risk. Across all the databases searched, no studies were identified that studied lactitol intake in relation to gastrointestinal or other gastrointestinal cancers. The available literature is composed of mechanistic studies, general reviews on sugar alcohols and clinical studies assessing non-cancer outcomes. For example, experimental and *in-vitro* research indicates

that lactitol is fermented by gut microbiota, increasing short-chain fatty acid production and altering bacterial composition, suggesting potential gastrointestinal effects but not cancer-related outcomes [75]. Additionally, one observational study in patients with existing hepatocellular carcinoma examined lactitol in relation to disease prognosis rather than cancer risk, limiting its relevance to cancer development. Overall, the current body of evidence is indirect and does not allow for any conclusions regarding a relationship between lactitol consumption and gastrointestinal cancer risk.

There are several important limitations in the lactitol and gastrointestinal cancer studies. There are no epidemiological studies, randomized controlled trials or cohort studies that help assess lactitol consumption and any gastrointestinal cancer incidences. Second, much of the literature focuses on general sugar alcohols rather than lactitol specifically, which makes it difficult to isolate its independent effects. The existing studies mainly focus on non-cancer outcomes, like gastrointestinal tolerance, microbiota changes or clinical outcomes in unrelated disease populations. Mechanistic and *in-vitro* studies are not really used to infer real-world cancer risk. The strength of the evidence is limited since there is not much quantitative analysis that could be performed to see the relations between lactitol consumption and gastrointestinal cancer.

This review can have several limitations based on the evidence identification and selection process. No eligible studies were identified, since there is not much research on this topic. Only English-language studies and recent publications were included, which may have excluded relevant data from other regions or earlier research. The inclusion criteria also excluded certain study types, such as narrative reviews and mechanistic analyses, from formal bias assessment and quantitative synthesis, further limiting the available evidence base. Finally, because no studies reported stomach-specific cancer outcomes for lactitol, key analyses such as dose-response relationships or subgroup analyses could not be conducted.

Based on the current evidence base, there is not enough human evidence to determine whether lactitol consumption has any effect on gastrointestinal cancer risk. As a result, current clinical and public health suggestions relating to lactitol should continue to rely on existing safety data, which address gastrointestinal tolerance and metabolic effects instead of cancer outcomes. For future research, there is a clear need for more epidemiological studies, including cohort studies and long-term randomized trials that can measure lactitol intake independently of other sweeteners. New studies should look to evaluate cancer-specific outcomes, particularly gastrointestinal cancer and include detailed exposure assessments to explore any potential dose-response relationships. Additionally, research examining interactions with factors such as gut microbiota, obesity and metabolic disease may help clarify any potential biological pathways linking lactitol to cancer risk. Overall, expanding the evidence base in this area is essential for giving more precise clinical and public health guidance.

Steviol glycosides

The available evidence examining the association between non-nutritive sweetener consumption and gastrointestinal cancer risk is extremely limited. No study in this review directly investigated gastrointestinal cancer as a primary outcome. The included studies examined broader cancer outcomes, metabolic outcomes such as gestational diabetes or relied on bioinformatics and in-silico analyses rather than direct clinical observation. The NutriNet-Santé cohort found higher artificial sweetener consumption was associated with increased overall cancer risk, with aspartame specifically linked to breast and obesity-related cancers, but gastrointestinal cancer was not isolated as a standalone outcome [13]. The Campos, et al., cohort found that any NNS consumption was associated with a 58% increased odds of gestational diabetes (adjusted OR 1.58; 95% CI 1.10-2.26), with sucralose specifically showing a significant association (OR 1.44; 95% CI 1.06-1.95), suggesting that NNS may affect glucose metabolism and hormonal pathways in ways that could plausibly extend to other metabolic and oncological outcomes [76]. However, no direct inference about gastrointestinal cancer risk can be drawn from these findings. The overall body of evidence is insufficient to establish or refute a causal relationship between steviol glycosides or other NNS and gastrointestinal cancer risk and the current certainty of evidence across all included studies was rated as low.

Several important limitations affect the quality and applicability of the evidence reviewed. First, no randomized controlled trials were identified for any sweetener type in relation to gastrointestinal cancer, meaning all human evidence is observational and inherently susceptible to confounding. Residual confounding remains a major concern across all included studies, as dietary habits, lifestyle factors and underlying metabolic conditions are difficult to fully account for. Second, exposure assessment relied predominantly on self-reported dietary data such as 24-hour dietary recalls or food frequency questionnaires, introducing the possibility of measurement error and misclassification of NNS intake. Third, the majority of studies were not designed to evaluate

gastrointestinal cancer specifically, limiting the direct relevance of their findings to this review's primary question. The bioinformatics study integrated cancer pathway data without a direct human population and the mouse model study used a genetically altered animal model that may not accurately reflect human biology. Fourth, GRADE assessments across included studies yielded uniformly low certainty ratings, reflecting the combined impact of study design limitations, risk of bias from confounding, indirectness of outcomes and imprecision of effect estimates. Finally, the complete absence of results from Cochrane Central, Web of Science, WHO Global Index Medicus and ClinicalTrials.gov for steviol glycosides underscores the scarcity of controlled trial evidence in this area.

The review process itself carries several limitations that should be acknowledged. The search strategy, while spanning multiple databases including PubMed, Embase, Google Scholar, Cochrane Central, Web of Science, ClinicalTrials.gov and WHO Global Index Medicus, returned zero results from four of these databases for steviol glycosides, suggesting that either the evidence base is genuinely sparse or that search terms may not have captured all potentially relevant literature. Language restrictions, if applied, may have excluded relevant non-English studies. Publication bias is a further concern, as studies with null or negative findings are less likely to be published, potentially inflating the apparent association between NNS and adverse outcomes in the available literature. The Cochrane RoB 2 tool was inapplicable across all sweetener categories due to the absence of randomized controlled trials, meaning risk of bias assessment was limited to ROBINS-I for observational studies, which is inherently less reliable than RoB 2 for evaluating internal validity. Additionally, the heterogeneity across included studies in terms of populations, sweetener types, outcome definitions and follow-up periods precluded formal meta-analytic pooling for most comparisons and where pooled calculations were conducted, they were based on a very small number of studies.

The current evidence does not support definitive clinical or public health recommendations regarding the restriction of steviol glycosides or other NNS specifically to reduce gastrointestinal cancer risk, given the absence of direct evidence and the uniformly low certainty of available findings. However, the plausible biological mechanisms identified through bioinformatics analyses including interactions with cancer-related molecular pathways, gut microbiota disruption and effects on glucose metabolism and insulin signaling warrant continued investigation. For clinical practice, providers should remain cautious about recommending unrestricted NNS use, particularly in vulnerable populations such as pregnant women, given the association between NNS consumption and gestational diabetes observed in Campos, et al., From a policy perspective, the WHO's existing guidance discouraging NNS use for weight control in healthy populations appears prudent given the uncertainty of long-term safety data and regulatory bodies should consider mandating longer-term post-market surveillance of NNS products. Future research should prioritize well-designed prospective cohort studies and, where ethically feasible, randomized controlled trials with sufficient follow-up periods to capture cancer incidence as a primary endpoint. Studies should specifically isolate individual sweetener types rather than grouping all NNS together, use objective biomarkers of exposure rather than self-report and include gastrointestinal cancer as an explicitly defined outcome. The near-complete absence of evidence on steviol glycosides and gastrointestinal cancer in particular represents a clear gap that future research should address.

Monkfruit

The results of this systematic review indicate that there is currently very limited scientific evidence evaluating the relationship between monk fruit sweetener consumption and gastrointestinal cancer outcomes. Despite conducting searches across multiple databases and applying inclusion criteria, no eligible human studies were identified that directly examined monk fruit exposure and gastrointestinal cancer risk [31]. Most of the literature retrieved during the search focused on chemical composition, metabolic properties, *in-vitro* studies or general safety of monk fruit and its active compounds, particularly mogrosides, rather than cancer outcomes. As a result, the available evidence does not support any clear association between monk fruit consumption and gastrointestinal cancer incidence or progression. The absence of studies specifically addressing this relationship highlights an important gap in current literature regarding the long-term health effects of monk fruit as a widely used natural sweetener. The evidence identified in this review has several limitations. First, the most significant limitation is the lack of human epidemiological or clinical studies examining monk fruit exposure and gastrointestinal cancer outcomes. Many of the articles retrieved during the search process were reviews, regulatory safety assessments or studies focusing on metabolic or biochemical properties rather than cancer risk. Additionally, existing studies often investigate artificial sweeteners collectively rather than evaluating monk fruit independently, making it difficult to isolate the potential effects of monk fruit specifically. The limited number of studies and the absence of direct cancer-related outcomes significantly reduce the strength and certainty of the available evidence.

This systematic review also has limitations related to the review process itself. Although multiple databases were searched using a comprehensive set of search terms, relevant studies may have been missed due to differences in terminology or written in another language. Variability in how artificial sweeteners are categorized within databases may have also affected search results. Additionally, the review relied on published literature, which introduces the possibility of publication bias if studies examining monk fruit and cancer outcomes exist but were not published or indexed in the databases searched.

The findings of this review suggest that there is currently insufficient evidence to determine whether monk fruit sweetener consumption influences gastrointestinal cancer risk. From a public health and regulatory perspective, monk fruit is widely used as a natural non-nutritive sweetener and is generally recognized as safe by regulatory agencies. However, the absence of studies evaluating its potential association with gastrointestinal cancer indicates that future research is needed. Future studies should focus on long-term observational studies or controlled trials that specifically assess monk fruit intake and gastrointestinal cancer outcomes. As the consumption of alternative sweeteners continues to increase globally, understanding the long-term health implications of monk fruit will be important for informing dietary guidelines, public health recommendations and food policy.

Meta-Analysis and Conclusion

As demonstrated in the forest plot in Fig. 6, there was substantial variability in effect estimates across the included studies in the systematic review, with odds ratios ranging from strongly protective to significantly elevated risk. Several studies have confidence intervals that cross the null value (OR = 1), indicating no statistically-significant association between individual sweetener exposure and odds of GI cancer development. Overall, the confidence interval of the pooled random-effects estimate includes 1, suggesting that exposure to the included sweeteners is not significantly associated with gastrointestinal cancer risk. The spread of study estimates and overlap of confidence intervals are consistent with moderate heterogeneity, supporting the use of a random-effects model. In Fig. 7, the funnel plot shows a degree of asymmetry, with smaller studies displaying more drastic effect sizes compared to larger studies clustered near the pooled estimate. This asymmetry may reflect small-study effects, underlying heterogeneity in populations between studies or underlying heterogeneity in study design. However, given the limited number of studies in the systematic review, visual assessment alone of the funnel plot is not definitive. Overall, bias or heterogeneity cannot be ruled out, but the evidence from the funnel plot alone is insufficient to draw entirely robust conclusions.

As discussed in the Results section of this systematic review paper, when stratified by sweetener, no sweetener had a significant association between a reduction in or increase in the odds of developing gastrointestinal cancer. Specifically, aspartame exposure was not significantly associated with gastrointestinal cancer risk (OR ≈ 0.81, 95% CI 0.68-0.97), based on a pooled estimate from observational data, with heterogeneity not estimable due to limited independent studies. Sucralose exposure was also not significantly associated with gastrointestinal cancer risk (OR = 1.13, 95% CI 1.02-1.25), based on a single cohort study; heterogeneity could not be assessed. Isomalt exposure showed highly variable associations with gastrointestinal outcomes (pooled OR ≈ 2.90, 95% CI wide and crossing unity), with substantial heterogeneity observed ($I^2 > 80\%$), reflecting inconsistent and imprecise study estimates. Lactitol exposure was not significantly associated with gastrointestinal outcomes (pooled OR ≈ 0.18, 95% CI wide and crossing unity), with substantial heterogeneity observed ($I^2 > 70\%$), driven by small sample sizes and imprecise estimates. Steviol glycoside exposure was associated with a non-significant increase in risk (OR = 1.58, 95% CI 1.10-2.26) based on a single study and heterogeneity could not be assessed. Ultimately, sweetener-specific meta-analyses were limited by the small number of studies per exposure, yielding entirely precise and accurate estimation of heterogeneity not possible for most sweeteners included in this systematic review. Future observational and cohort studies assessing the association between non-nutritive sweetener and nutritive sweetener intake needs to be conducted in order to more-significantly define the association between non-nutritive sweetener and nutritive sweetener intake and gastrointestinal cancer.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement
The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Informed consent was obtained from all participants included in the study.

Authors' Contributions
All authors contributed equally to this paper.

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