

Potential Health Risks of Artificial Sweeteners

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Keywords

nonnutritive sweeteners, artificially sweetened beverages, sweetening agents, artificial sweeteners

Abstract

Artificial sweeteners are widely used worldwide, yet their potential health effects remain a topic of debate. Recent studies suggest that artificial sweeteners, both nutritive and nonnutritive, may stimulate appetite, leading to increased caloric intake, a higher body mass index, and a greater risk of obesity. These metabolic changes are associated with an elevated risk of type 2 diabetes and cardiovascular diseases. Moreover, emerging preclinical evidence indicates that artificial sweeteners may influence cancer biology, potentially affecting tumor progression. This review examines the impact of artificial sweeteners on metabolic health, cardiovascular risk, and carcinogenesis, emphasizing the need for further research to clarify their long-term safety and health implications.

AS: artificial sweeteners

ASB: artificially sweetened beverages

INTRODUCTION

The negative health impacts of excessive sugar consumption have been widely researched, meta-analyzed, and recognized as significant risk factors by public health authorities (1). The World Health Organization (WHO), for instance, recommends that less than 5% of daily energy intake should come from free sugars (2). In response to these concerns, artificial sweeteners (AS) were introduced as sugar alternatives, providing sweetness without the caloric content of sugar (3).

The global market for AS is currently valued at US\$7.2 billion, with an expected annual growth rate of 5%, reaching \$9.7 billion by 2028. AS are found in more than 23,000 products worldwide, particularly in ultraprocesed foods like artificially sweetened beverages (ASB), snacks, low-calorie ready-to-eat meals, and dairy products. They are also popular as tabletop sugar substitutes.

Acceptable daily intake levels for various AS have been established by regulatory bodies like the European Food Safety Authority (EFSA), the US Food and Drug Administration, and the Joint Expert Committee on Food Additives. However, these sweeteners remain controversial, and the WHO recommends against their use (4). This review explores the available data linking AS and disease (**Figure 1**).

ARTIFICIAL SWEETENERS

Several AS, including saccharin, neotame, advantame, aspartame, acesulfame K (ACE-K), and sucralose, are commonly used as food additives worldwide. Additionally, sugar alcohols like xylitol, sorbitol, and erythritol are popular plant-derived sweeteners. Aspartame, made from methanol and two amino acids (aspartate and tryptophan), is approximately 200 times sweeter than sucrose (5). Aspartame breaks down into methanol and amino acids during metabolism, contributing 4 kcal/g, though its caloric impact is negligible because of its potency (6).

Saccharin, the oldest AS, is 300 times sweeter than sucrose and is heat stable. It is used in drinks, gum, baked goods, and canned fruits (7) and is excreted unchanged via the kidneys (7).

Neotame and advantame, both aspartame analogs, are noncaloric and significantly sweeter than sugar; neotame is 7,000–13,000 times sweeter (8, 9). Neotame is metabolized and excreted within 72 h, while advantame is eliminated mostly unchanged in feces (8, 9).

ACE-K, a heat-stable sweetener, is 200 times sweeter than sucrose. It is often blended with other sweeteners to reduce its bitter aftertaste at high concentrations. ACE-K is not metabolized and is excreted through the kidneys (4).

Sucralose, produced through the chlorination of sucrose, is 600 times sweeter than sugar and stable under heat (10). Sucralose is not metabolized by the body and is excreted mostly in feces, with a small portion eliminated in urine (10).

Artificial Sweeteners, Taste Receptors, and Insulin Secretion

The cephalic phase of insulin secretion is the initial insulin release triggered by food stimuli, particularly via receptors in the head and oropharynx (11). This response lasts around 10 min, priming the body for food intake (12).

The sweet taste receptors T1R2 and T1R3 are found in both the oral cavity and the pancreas, where they influence insulin secretion (13). In rodent studies, physiological saccharin levels had no effect (14), but higher concentrations of saccharin, sucralose, and ACE-K significantly increased insulin secretion (15).

A study in fasted, healthy individuals examined the impact of various taste stimuli on plasma insulin and glucose (12). Participants rinsed their mouths with different solutions for 45 s without swallowing, and blood samples were taken at 3, 5, 7, and 10 min. Sucrose and saccharin notably

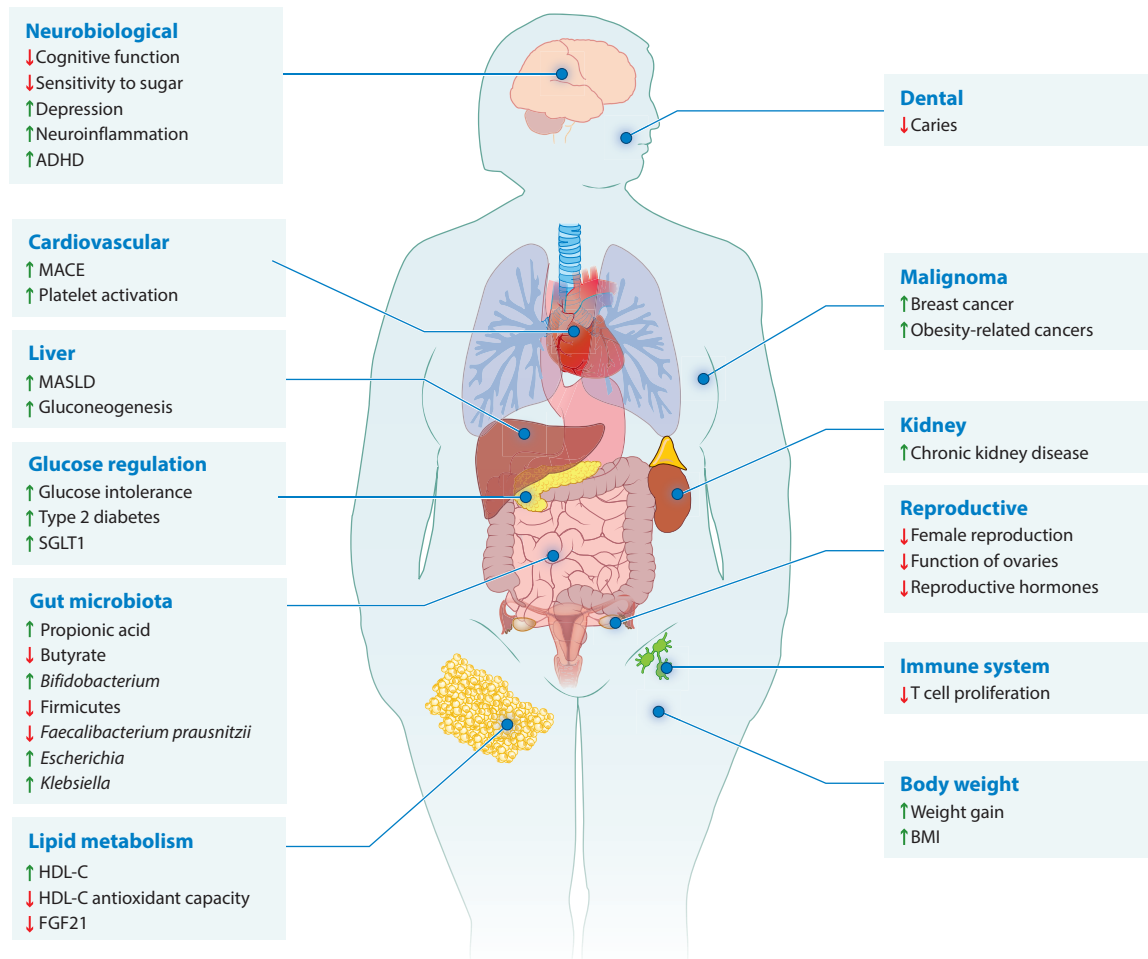


Figure 1

Schematic representation of the potential effects of artificial sweeteners on health and disease. Key physiological influences of artificial sweeteners include their impact on glucose metabolism, cardiovascular function, gut microbiome composition, kidney function, neurobehavioral effects, the reproductive system, and malignancies. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; FGF21, fibroblast growth factor 21; HDL-C, high-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MASLD, metabolic dysfunction-associated steatotic liver disease; SGLT1, sodium-glucose cotransporter 1.

increased plasma insulin; saccharin was the only sweetener to trigger a cephalic-phase insulin response.

Intestinal Glucose Absorption and Incretin Secretion

The sweet taste receptors T1R2 and T1R3 are also found in the intestine, where they influence glucose absorption and the secretion of incretins. Some studies suggest that AS, particularly sucralose, increase glucose absorption by upregulating sodium-glucose transport proteins in the intestine (16). However, human studies have reported inconsistent results regarding the effect of AS on incretin secretion. For instance, sucralose infusion did not increase glucose absorption or glucagon-like peptide 1 (GLP-1) secretion in healthy subjects, but it did stimulate GLP-2 secretion, which plays a role in gastrointestinal health (17).

Artificial Sweeteners and the Microbiome

NNS: nonnutritive artificial sweeteners

BMI: body mass index

The impact of nonnutritive artificial sweeteners (NNS) on gut microbiota is an increasingly relevant topic in nutritional science. Recent research has revealed diverse outcomes depending on the type of sweetener, dosage, and study design.

A 2014 study explored the effects of chronic low-dose aspartame consumption in an obese animal model (18). Male Sprague-Dawley rats were fed either a standard or a high-fat diet, with aspartame administered in drinking water, for 8 weeks. Fecal analyses revealed that aspartame increased overall bacterial counts, including Enterobacteriaceae and *Clostridium leptum*. While a high-fat diet decreased Bacteroidetes and increased Firmicutes, aspartame supplementation mitigated the increase in Firmicutes without significantly affecting Bacteroidetes.

A subsequent study investigated the effects of aspartame on pregnant female Sprague-Dawley rats fed a high-fat/sucrose diet (19). Offspring from aspartame-supplemented dams exhibited increased body fat and altered glucose tolerance compared with those from dams fed the high-fat/sucrose diet alone. Maternal microbiota showed higher levels of *Akkermansia muciniphila* and Enterobacteriaceae, with decreased Enterococcaceae and increased *Clostridium* cluster IV following aspartame treatment. Transplantation of microbiota from offspring feces into germ-free mice led to increased body fat and impaired glucose tolerance. Notably, both male and female mice exhibited elevated concentrations of Porphyromonadaceae.

A 2015 cross-sectional study was the first to investigate the effects of high-intensity sweeteners on human gut microbiota (20). The study involved 31 healthy individuals, of whom 7 consumed aspartame and 7 consumed ACE-K. The study found no significant differences in body mass index (BMI), dietary intake, or total bacterial count between sweetener users and nonusers. However, the sweetener consumers exhibited a reduction in microbial diversity.

A pivotal study demonstrated that NNS induce glucose intolerance by altering both human and mouse gut microbiota composition and function (21). These metabolic disruptions were reversible with antibiotic treatment and transmissible to germ-free mice via fecal transplants from NNS-consuming humans or mice. Similar microbiota changes observed in healthy human subjects established a link between NNS consumption, dysbiosis, and metabolic dysfunction. Notably, all three groups of NNS-consuming mice in this study [i.e., 10-week-old C57BL/6 male mice, and Swiss Webster mice in one arm, subjected to different dietary regimes combining normal chow or a high-fat diet with drinking solutions containing various NNS (saccharin, sucralose, aspartame) with glucose, sucrose, or water as control] developed significant glucose intolerance, underscoring the robust effect of NNS on metabolic health (21).

The PREDICT 1 study (22) conducted deep metagenomic sequencing of 1,203 gut microbiomes from 1,098 participants, who provided detailed dietary information and extensive cardiometabolic blood marker measurements. The analysis revealed significant associations between specific microbes and various dietary components, particularly healthy and plant-based foods. Notably, certain microbes, such as *Prevotella copri* and *Blastocystis* species, were linked to improved postprandial glucose metabolism.

A randomized, double-blind crossover trial investigated the impact of sucralose and aspartame on gut microbiota in 17 healthy participants over 12 weeks (23). After consuming realistic daily amounts of aspartame or sucralose, the participants demonstrated no significant changes in microbiota composition or short-chain fatty acids (SCFAs).

Another study examined the effects of various substances on the production of SCFAs and the composition of the gut microbiome (24). Acetic acid levels rose with maltodextrin and aspartame but decreased with dishwashing detergent and sodium sulfite. Propionate increased with several additives, while butyrate and branched-chain fatty acids decreased with substances like

cinnamaldehyde and aspartame. Microbiome diversity increased with stevia but decreased with dishwashing detergent and cinnamaldehyde, which also significantly altered community structure, promoting *Escherichia* and *Shigella* and reducing beneficial bacteria like *Faecalibacterium*. Maltodextrin and aspartame supported *Bifidobacterium* growth, whereas additives like sodium sulfite inhibited it.

In an open-label, randomized clinical trial with 47 healthy volunteers, participants consumed either sucralose or water daily for 10 weeks (25). This study found a decrease in *Lactobacillus acidophilus* and an increase in *Blautia coccooides* in the sucralose group.

In 2022, a multiarm randomized controlled trial conducted by Suez et al. (26) yielded mixed results regarding the effects of aspartame and other NNS on human metabolic health and microbiota. This study involved 120 participants divided into four groups, which received aspartame, saccharin, sucralose, or stevia, and two control groups, which received either glucose or no supplement. Each NNS group received 0.24 g of aspartame and 5.76 g of glucose daily, administered via sachets three times a day. The trial lasted 14 days, with a 7-day baseline period and a 7-day postsupplementation follow-up. All NNS significantly altered the gut microbiota and their functionality, though specific bacterial changes were not described in detail. Aspartame also affected the oral microbiota, reducing the prevalence of *Porphyromonas* and *Prevotella nanceiensis*.

Research on AS and their effects on gut microbiota has produced mixed and sometimes contradictory results. While some studies suggest that AS consumption alters microbial diversity and composition, potentially leading to dysbiosis and metabolic disturbances, others report minimal or no significant impact. These inconsistencies may arise as a result of differences in study design and individual microbiome variability. Given the crucial role of gut microbiota in metabolic and overall health, further well-controlled, long-term studies, using typically consumed doses, are needed to clarify how AS influence microbial balance, metabolic pathways, and disease risk.

Artificial Sweeteners and Glucose Regulation

One of the key metabolic effects linked to AS is their negative impact on glucose regulation. Several mechanisms have been proposed to explain aspartame's negative effects on glucose homeostasis and hormonal regulation, beyond its influence on GLP-1 and other gut hormones (27). One hypothesis links aspartame with increased levels of propionate, an SCFA in the colon (18). Elevated propionate may enhance gluconeogenesis in the liver, leading to higher hepatic glucose production and hyperglycemia. Another theory involves intestinal alkaline phosphatase (IAP), which is linked to a reduced risk of metabolic syndrome in mice. Aspartame's breakdown product, phenylalanine, inhibits IAP (28). Gul et al. (29) showed that mice on a high-fat diet with aspartame had lower IAP levels, gained more weight, and exhibited greater glucose intolerance than those on a high-fat diet with water.

Human studies on glucose homeostasis present conflicting results. Pepino et al. (30) found that ingestion of sucralose in obese, insulin-sensitive individuals led to increased plasma glucose and insulin after a glucose load compared with ingestion of water. In contrast, Anton et al. (31) reported no compensatory overeating after stevia or aspartame consumption in healthy and obese individuals, with the stevia group showing lower postprandial glucose levels. O'Connor et al. (32) observed no reduction in diabetes risk when substituting ASB for sugar-sweetened beverages (SSB), but replacing them with nonnutritive sweetened beverages (NNSB) did reduce risk. ASB refer to beverages containing synthetic NNS, whereas NNSB represent a broader category that includes both artificial and naturally derived sweeteners like steviol glycosides and monk fruit extract. Additionally, a prospective study comparing aspartame, stevia, monk fruit, and sucrose found that, although sucrose caused a greater initial spike in glucose and insulin, total glucose and insulin responses over 3 h were similar across the groups (33).

SSB: sugar-sweetened beverages

NNSB: nonnutritive sweetened beverages

FGF21: fibroblast growth factor 21

HDL-C: high-density lipoprotein cholesterol

Debras et al. (34) analyzed data from 105,588 participants in the NutriNet-Santé study to assess the relationship between AS intake and risk of type 2 diabetes (T2D). Over a median follow-up of 9.1 years, higher consumers of AS had a significantly greater risk of developing T2D compared with nonconsumers [hazard ratio (HR), 1.69]. Despite potential reverse causality, sensitivity analyses suggest that these findings support growing concerns about the safety of AS as sugar substitutes.

Artificial Sweeteners and Body Weight

The impact of AS on body weight and diabetes remains contentious, as studies show conflicting evidence (35). While some rodent studies have shown that AS can promote body weight gain and fat accumulation, these effects appear to be independent of caloric intake and more closely related to changes in energy efficiency (36, 37).

Research by Feijó et al. (38) demonstrated that the consumption of saccharin or aspartame in rodents was associated with increased weight gain and adiposity, independently of caloric intake. Similarly, a study by Mitsutomi et al. (39) found that mice supplemented with sucrose developed hyperglycemia, increased weight gain, and higher adiposity levels after 4 weeks. However, the mice in the AS group exhibited a significant increase in adiposity.

Human trials on NNS have shown inconclusive effects on body weight, HbA1c, and diabetes management. However, large-scale cohort studies suggest a dose-dependent link between NNS intake and higher BMI (40, 41). A study by Azad et al. (42) showed that maternal consumption of ASB during pregnancy is linked to higher infant BMI. This study, which involved 3,033 healthy mothers followed from 2009 to 2012, assessed dietary intake and found that daily consumption of ASB during pregnancy doubled the risk of the child being overweight by age 1 year. In a cohort study of 1,454 participants followed from 1984 to 2012, those who reported AS consumption had a significantly higher BMI and waist circumference compared with nonconsumers (43). Additionally, a recent meta-analysis of 11 studies reported a relative risk of obesity of 1.18 [95% confidence interval (CI), 1.10–1.27] for individuals consuming NNSB, compared with a higher relative risk of 1.59 (95% CI, 1.22–2.08) for those consuming ASB (44).

Artificial Sweeteners and Lipid Metabolism

AS appear to influence lipid metabolism (45). Studies in obese nonhuman primates have shown that fibroblast growth factor 21 (FGF21), a hepatokine involved in glucose and lipid metabolism (46), reduces food intake, decreases body weight, and improves lipid profiles while increasing adiponectin levels (47, 48). While glucose and fructose induce FGF21 expression via carbohydrate response element-binding proteins, AS do not (49). Additionally, sucralose promotes hepatic steatosis in rodents through mechanisms involving increased reactive oxygen species generation and endoplasmic reticulum stress (50).

Some studies report an association between long-term consumption of AS and higher levels of high-density lipoprotein cholesterol (HDL-C) (45). However, AS may impair the antioxidant capacity of HDL-C, reducing its cardioprotective properties (51).

Artificial Sweeteners and Cardiovascular Risks

Recent research exploring the complex relationship between NNS and cardiovascular disease (CVD) suggests a potentially harmful association (52). A pivotal study by Mullee et al. (53) involving more than 450,000 individuals from European cohorts found a significant positive correlation between high intake of NNSB and CVD mortality. Consumption of two or more servings of NNSB daily was associated with a 52% higher risk of CVD mortality (relative risk, 1.52). Another

study found a link between higher intake of ASB and increased CVD risk, even among physically active individuals (54).

Erythritol has been linked to an increased risk of atherothrombosis and major adverse cardiovascular events (MACE). Metabolomic analyses of US and European cohorts undergoing cardiac evaluation found an association between higher circulating erythritol levels and an elevated MACE risk (55). Erythritol also enhances platelet reactivity and thrombosis formation *in vitro* and *in vivo*; a pilot intervention study confirmed sustained elevation of plasma erythritol levels following ingestion (55). Xylitol has also been linked to MACE risk and increased platelet reactivity (56). A French study found that overall AS intake is associated with an elevated risk of CVD, particularly cerebrovascular events and coronary heart disease (57). A prospective study (58) that followed 39,786 persons found no significant relationship between soft drink consumption and stroke risk in men. However, in women, daily consumption of NNSB was strongly associated with ischemic stroke. Similarly, the Women's Health Initiative found that postmenopausal women consuming two or more ASB daily had a 30% higher risk of cardiovascular events (59).

In another meta-analysis (60), 2 of 16 studies demonstrated a significant direct association between ASB consumption and stroke. Another 10 studies reported a significant association between ASB intake and T2D [pooled risk estimate, 1.32 (95% CI, 1.11–1.56)], while 4 studies suggested that ASB contribute to the development of hypertension [pooled risk estimate, 1.14 (95% CI, 1.10–1.18)]. These findings suggest that ASB consumption may influence stroke risk both directly and indirectly through their association with T2D and arterial hypertension. A 2021 meta-analysis also linked NNSB to a 17% increased CVD risk and 14% higher all-cause mortality (61). Similarly, a Harvard meta-analysis (62) comprising six studies spanning 16 million person-years found that each additional daily ASB serving raised CVD risk, with high consumers facing a 32% greater risk of adverse cardiovascular outcomes.

Although the evidence indicates a linear association between consumption of NNS and increased risk of CVD, it is crucial to recognize that most of these findings are derived from observational studies (63). It remains unclear whether higher intake of NNS actively contributes to increased CVD risk, or whether individuals already at elevated risk for CVD are more likely to consume NNS in an effort to make healthier dietary choices. In this context, it is worth considering that patients with a high underlying CVD risk profile may be inherently more inclined to use AS, potentially confounding the observed associations.

Artificial Sweeteners and Cancer

Despite the overall consensus on the safety of AS (4), some studies have reported conflicting results. Recent research suggests that high doses of sucralose can affect the immune system (64), particularly by reducing T cell proliferation and function. In mice, sucralose intake dampened T cell responses in cancer and autoimmune models, suggesting potential therapeutic uses in autoimmune conditions (65). However, these effects were observed at high doses that are not typically consumed through diet; therefore, further clinical studies are needed to confirm whether these findings are applicable to humans.

While some animal studies, such as those by Soffritti et al. (66), have suggested a potential link between aspartame and cancers like lymphoma and leukemia in rats, these findings have been criticized. EFSA dismissed these results on the basis of methodological concerns, including high infection rates in the animals and uncertainties in diagnosing the tumors (67).

The NutriNet-Santé cohort study found that higher intake of AS, particularly aspartame and ACE-K, is associated with an increased risk of overall, breast, and obesity-related cancers (68). Similarly, a US study (69) found a 30% higher risk of non-Hodgkin lymphoma among consumers

MACE: major adverse cardiovascular events

with moderate aspartame intake. However, this study observed no consistent association at higher consumption levels. In another study (70), postmenopausal women who consumed three or fewer servings of NNSB per month had a significantly lower risk of liver cancer (HR, 1.85; 95% CI, 1.16–2.96) and chronic liver disease mortality (HR, 1.68; 95% CI, 1.03–2.75) than women who drank one or more servings per day.

Other studies have yielded different results. A Spanish study (71) involving 3,629 cancer cases and controls found no overall association between AS and cancer risk. However, in participants with diabetes, higher consumption of NNSB was linked to an increased risk of colorectal and stomach cancers. Aspartame was associated with a higher risk of stomach cancer but a lower risk of breast cancer. These findings, particularly in diabetic subgroups, are intriguing but should be interpreted cautiously because of the studies' small sample sizes and potential confounders.

In contrast, a larger study by Lim et al. (72), involving 437,984 individuals, found no increased risk for hematopoietic malignancies, even at very high levels of aspartame intake. Similarly, case–control studies of brain tumors in both children and adults found no significant association between maternal or childhood aspartame use and brain cancer risk (73). Additionally, recent studies have raised concerns that measurements of AS may not fully capture overall dietary exposure, potentially underestimating their true health risks (74, 75).

In summary, while certain studies suggest a weak association between AS and cancer, particularly in specific subgroups, most evidence does not support a clear or consistent link (76). Numerous studies using different test systems have extensively evaluated AS for their potential genotoxicity (77), consistently finding that low- and no-calorie sweeteners exhibit neither genotoxic (77) nor procancerogenic (77) effects. Systematic reviews of epidemiological data further support the absence of a significant association between AS consumption and cancer risk in nonrandomized controlled trials and observational studies (4, 78).

Recent studies have highlighted the complex effects of AS on immunity and health. Zani et al. (65) demonstrated that sucralose, unlike sodium saccharin, suppresses T cell proliferation and differentiation, increasing susceptibility to infection in mice while impairing antitumor immunity in lymphoma and pancreatic cancer models (79). However, sucralose also mitigates T cell–mediated autoimmunity in models of type 1 diabetes and colitis. Notably, long-term sucralose exposure in healthy mice had no impact on metabolic parameters, underscoring its nuanced role in immune modulation.

Artificial Sweeteners and Neurobiological Effects

Excessive sugar consumption has been proposed to impair cognitive function and increase the risk of dementia (80). Studies have shown that chronic high sugar intake can negatively affect memory, mood, object recognition, and concentration (37, 66, 81). Animal studies have shown that diets high in fructose can trigger neuroinflammation and neuronal loss in the hippocampus, a mechanism that may contribute to the neurological and psychiatric impairments linked to sugar consumption (82). Beecher et al. (83) found that adolescent mice consuming sucrose for 12 weeks experienced impaired adult episodic and spatial memory along with reduced hippocampal cell proliferation. Similarly, rats exposed to high-fructose corn syrup early in life displayed long-lasting cognitive and emotional changes in adulthood, with protein abnormalities in the nucleus accumbens (81). In mice, prenatal exposure to sucrose resulted in offspring with attention and impulsivity problems, which are key characteristics of attention-deficit/hyperactivity disorder (84). A recent human study reported the same findings (85). Research on maternal sugar consumption in rats has shown that high-sucrose or high-fructose diets consumed during pregnancy or breastfeeding are associated with cognitive deficits and hippocampal changes in offspring (86). Human studies

support these findings, showing that maternal consumption of sugary drinks correlates with poorer childhood cognitive performance and social-emotional development (87, 88). These effects suggest that early-life exposure to sugar may pose a critical risk to cognitive development, especially during vulnerable periods such as pregnancy, childhood, and adolescence.

Additional studies have shown that ASB contribute to cognitive decline over time (89). A systematic review found that most studies involving middle-aged and older adults showed negative associations between ASB consumption and cognitive performance (90). The detrimental effects were even more pronounced in diabetic populations (91). While some researchers argue that sugars may improve cognition (92), especially in elderly individuals or those with Alzheimer's disease (93), these effects are typically observed only in short-term studies following fasting, so they may not reflect the long-term impacts of chronic sugar consumption (94).

The gut microbiome plays a crucial role in the effects of sugar on cognition and mood (95). High-sugar diets can disrupt gut microbiota, leading to increased gut permeability and inflammation, which are associated with cognitive decline (96). Dalenberg et al. (97) showed that consuming sucralose alongside carbohydrates quickly disrupts glucose metabolism and leads to a long-term reduction in the brain's sensitivity to sweet taste, while perceptual sensitivity remains unchanged. This finding points to a potential dysregulation of the gut-brain axis in controlling glucose metabolism. Overall, the evidence suggests that chronic sugar intake, particularly from ASB, may have lasting adverse effects on cognition and mood, especially in vulnerable populations such as children and the elderly.

Artificial Sweeteners and Kidney Function

A systematic review and meta-analysis assessed the link between consumption of SSB and chronic kidney disease (CKD) (98). Five studies examining SSB found a pooled relative risk of CKD of 1.58 (95% CI, 1.00–2.49). For ASB, the pooled relative risk was 1.33 (95% CI, 0.82–2.15), indicating a potential but inconclusive association between ASB and CKD (98).

Artificial Sweeteners and the Reproductive System

Research suggests that AS have a negative effect on the female reproductive system (99). In a murine model, AS including aspartame negatively affected ovary function and the feedback mechanism of reproductive hormones by altering the hypothalamic-pituitary-gonadal axis (100).

OUTLOOK FOR FUTURE STUDIES ON ARTIFICIAL SWEETENERS

Research on AS highlights both their role in weight management and their potential health risks. While short-term studies prevail, the long-term impact of AS on metabolism, CVD, and organ function remains uncertain. Some studies have linked AS to increased BMI and metabolic dysfunction, but the causality is unclear, underscoring the need for long-term research in diverse populations.

AS are not biologically inert; they influence insulin secretion, incretin release, and glucose absorption via sweet taste receptors. High doses of AS such as sucralose may alter immune responses, potentially affecting autoimmune and inflammatory conditions. AS also influence hunger hormones like ghrelin and leptin, although the findings on appetite regulation are inconsistent.

Emerging research links AS to gut microbiome imbalances, which may contribute to glucose intolerance and metabolic issues. Studies in animals and humans have reported effects from sweeteners like saccharin and sucralose, warranting further investigation. Personalized nutrition, encompassing genetic, microbiome, and lifestyle factors, may optimize the use of AS while minimizing their risks.

CONCLUSIONS

AS offer a potential solution for reducing sugar intake and managing caloric consumption, but their long-term health effects remain a topic of debate. Emerging evidence suggests that AS may affect metabolic pathways, immune function, and the gut microbiome, all of which warrant further investigation. Long-term studies are critical for establishing the safety and efficacy of AS in diverse populations, and deeper exploration into the molecular mechanisms behind their effects could help clarify their role in human health. In the future, integrating insights from long-term clinical studies, microbiome research, and personalized nutrition approaches will be essential for a full understanding of the health implications of AS and for guiding public health recommendations.

SUMMARY POINTS

1. Artificial sweeteners (AS) are widely consumed, yet their long-term health effects remain a growing concern.
2. Emerging evidence suggests that AS negatively affect gut microbiome composition and function.
3. AS influence insulin secretion and may contribute to the progression of cardiovascular diseases.
4. Some studies indicate that AS could affect tumor development and progression, warranting further investigation.

DISCLOSURE STATEMENT

The authors are not aware of any memberships, affiliations, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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