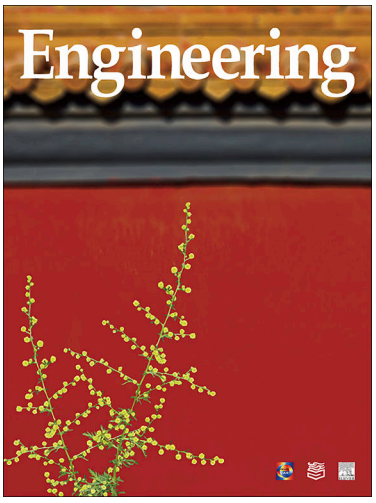
Journal Pre-proofs



Review

Artificial Sweeteners and Host Response Variability: Insights from the Gut Microbiota for Precise Application

Jie Cai, Qingping Wu, Alaa El-Din Ahmed Bekhit, Juan Wang, Yu-Long Li, Rong Huang, Fen Zhang, Hang Xiao, Zhenjun Zhu, Yu Ding

PII: S2095-8099(26)00262-6
DOI: https://doi.org/10.1016/j.eng.2026.05.004
Reference: ENG 2339

To appear in: *Engineering*

Received Date: 23 August 2025
Revised Date: 5 March 2026
Accepted Date: 8 May 2026

Please cite this article as: J. Cai, Q. Wu, A.E-D. Ahmed Bekhit, J. Wang, Y-L. Li, R. Huang, F. Zhang, H. Xiao, Z. Zhu, Y. Ding, Artificial Sweeteners and Host Response Variability: Insights from the Gut Microbiota for Precise Application, *Engineering* (2026), doi: https://doi.org/10.1016/j.eng.2026.05.004

Research
Development of Gut Microbiome-Targeted Foods and Drugs—Review

Artificial Sweeteners and Host Response Variability: Insights from the Gut Microbiota for Precise Application

Jie Cai [a,b,c], Qingping Wu [b,c], Alaa El-Din Ahmed Bekhit [d], Juan Wang [e], Yu-Long Li [f], Rong Huang [a,b,c], Fen Zhang [a], Hang Xiao [g], Zhenjun Zhu [a,*], Yu Ding [a,*]

[a]*State Key Laboratory of Bioactive Molecules and Drug ability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, Department of Food Science and Engineering, College of Life Science and Technology, Jinan University, Guangzhou 510632, China*

[b]*Institute of Microbiology, Guangdong Academy of Sciences, State Key Laboratory of Applied Microbiology Southern China, Guangdong Provincial Key Laboratory of Microbial Safety and Health, National Health Commission Science and Technology Innovation Platform for Nutrition and Safety of Microbial Food, Key Laboratory of Big Data Technologies for Food Microbiological Safety, State Administration for Market Regulation; Guangzhou 510070, China*

[c]*Food and Drug Laboratory, Guangdong Detection Center of Microbiology, Guangzhou 510070, China*

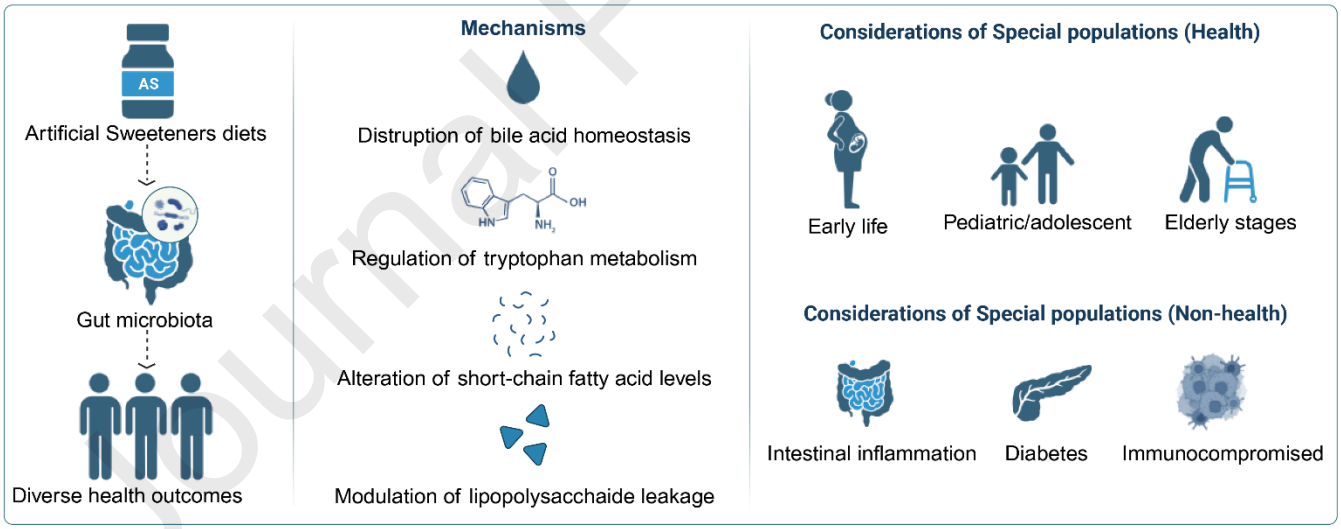
[d]*Department of Food Science, University of Otago, Dunedin 9054, New Zealand*

[e]*College of Food Science, South China Agricultural University, Guangzhou 510642, China*

[f]*Department of Emergency Medicine, University of Nebraska Medical Center, Omaha NE 68198, USA*

[g]*Department of Food Science, University of Massachusetts, Amherst MA 01003, USA*

*Corresponding Authors.
E-mail addresses: dingyu@jnu.edu.cn (Y. Ding), zzj1904@jnu.edu.cn (Z. Zhu).



Highlights

- Evidence of artificial sweeteners on health through gut microbiota is summarized
- AS effects on health via gut microbiota is through four potential mechanisms
- AS effects vary in special populations with distinct physiological needs
- Insights support precise application of ASs to balance benefits and risks

ABSTRACT Artificial sweeteners (ASs) are widely used as sugar substitutes, valued for their low-calorie content and minimal impact on blood glucose levels, which aligns with current dietary demands. However, recent studies have raised concerns about their potential effects on gut microbiota homeostasis and subsequent health outcomes, making a comprehensive evaluation of their impacts increasingly relevant. This article

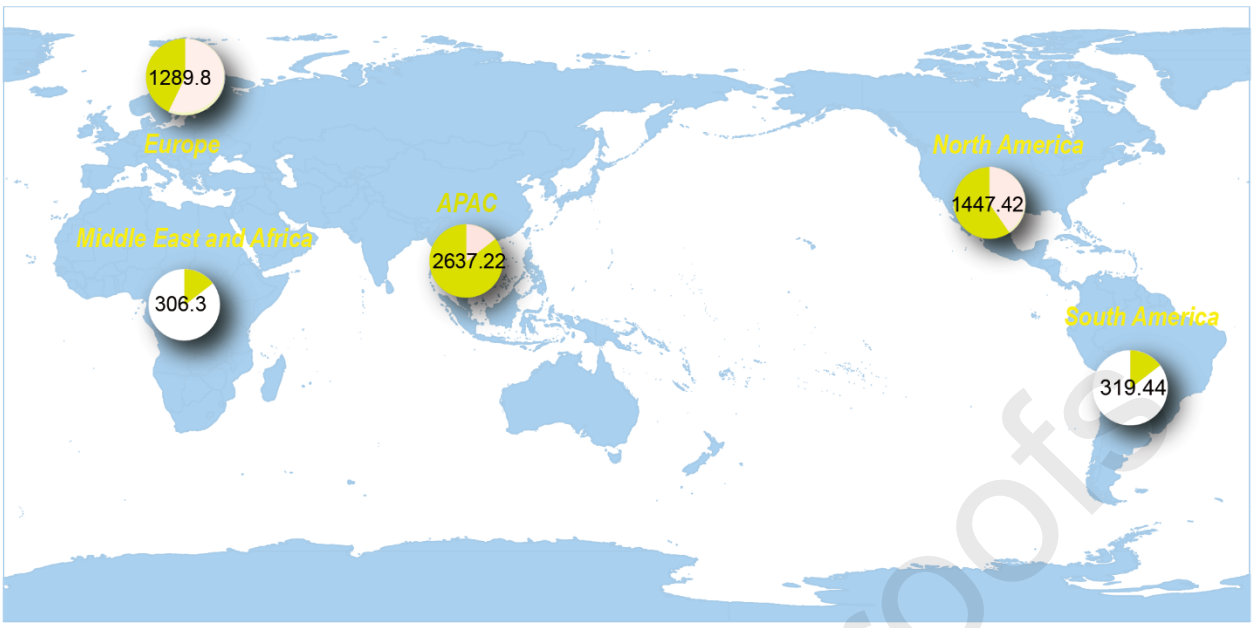
systematically reviews recent findings from cohort studies, clinical trials, and animal experiments, providing a synthesis of current knowledge on ASs. We discuss the controversies surrounding the health effects of ASs and explore the potential mechanisms through the lens of gut microbiota, with particular attention to special populations that have distinct physiological needs. Key findings suggest that gut microbiota may mediate the effects of ASs on host health through four potential mechanisms: disruption of bile acid homeostasis, regulation of tryptophan metabolism, alteration of short-chain fatty acid levels, and modulation of lipopolysaccharide leakage. Notably, the effects of ASs may be more complex in special populations due to their unique physiological states (e.g., developmental stages, metabolic fragility, or immune dysregulation), which necessitate targeted investigation. Such evidence underscores the need for a balanced assessment of ASs, taking into account both their practical benefits and the nuances of their biological effects across diverse populations. A more thorough understanding of these mechanisms may help inform evidence-based dietary strategies for optimizing the use of ASs while minimizing potential adverse effects, particularly in context-specific scenarios.

KEYWORDS Artificial sweetener, Gut microbiota, Bile acid, Tryptophan metabolite, Short-chain fatty acid

1. Introduction

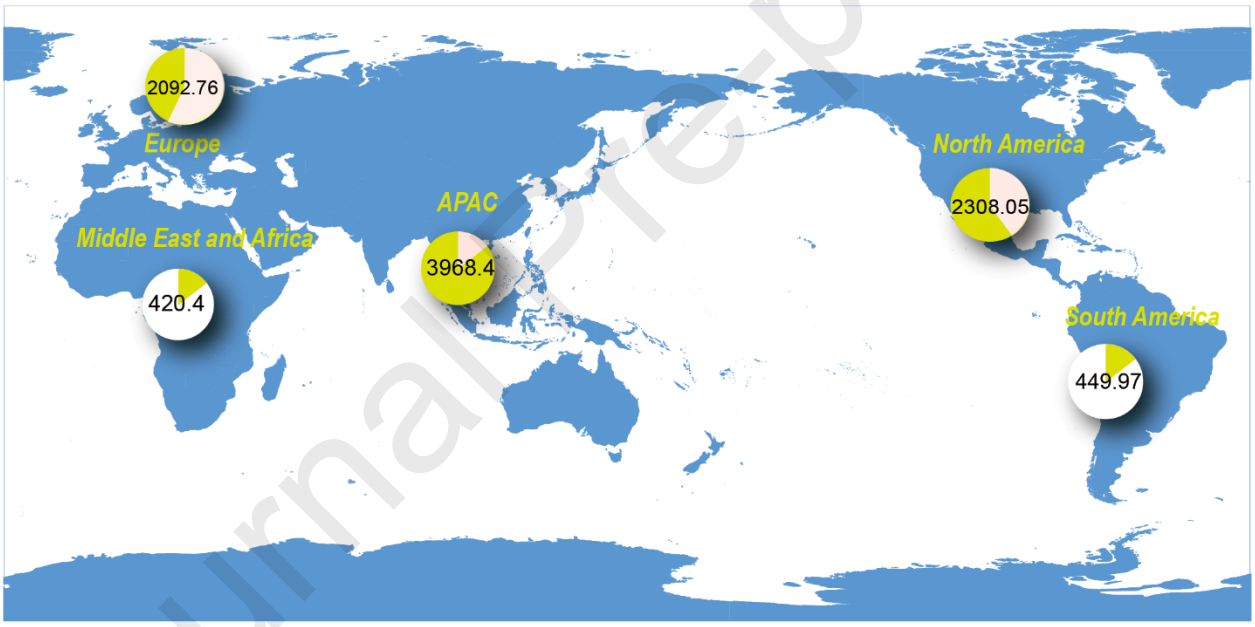
Excessive sugar intake is a major contributor to the global obesity epidemic and the rising prevalence of noncommunicable diseases (NCDs). To address these concerns, artificial sweeteners (ASs), primarily saccharin, aspartame, sucralose, and acesulfame K (Ace-K), have been widely adopted as sugar substitutes, primarily attributed to their low-calorie properties and suitability in dietary management. Currently, they continue to gain traction, with consumption prevalence reaching 25.1% in children and 41.4% in adults in the United States [1], and environmental monitoring detecting high concentrations of ASs in wastewater, reflecting their extensive routine use [2]. The market is projected to expand further from 2022 to 2027 (Fig. 1 [3]). However, discussions around their long-term effects have evolved, particularly following the World Health Organization's 2023 guidance on limiting AS use for weight control and NCD prevention, sparking renewed scientific dialogue [4].

A



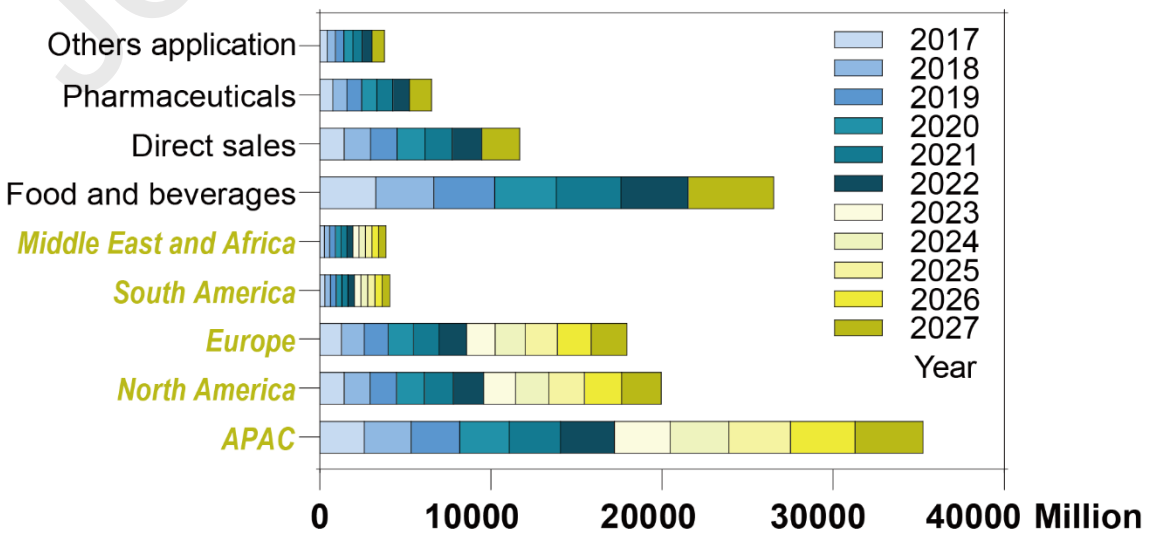
The Global Market Size of Artificial Sweeteners in 2017

B



Projected Global Market Size of Artificial Sweeteners in 2027

C



Historic Market Size (2017–2021) and Forecast (2022–2027)

Fig. 1. Global market size statistics for 5 types of artificial sweeteners, including saccharin, aspartame, Ace-K, sucralose, and neotame, from Infiniti Research [3]. (a) The global market size of artificial sweeteners in 2017; (b) Projected global market size of artificial sweeteners in 2027; (c) Historic market size (2017 – 2021) and forecast (2022 – 2027). The global artificial sweetener market was valued at 6000.18 million USD in 2017 and is estimated to grow to 9239.58 million USD in 2027. Food and beverages were the largest segment in 2017 and continued to be the largest segment of the market from 2022 – 2027. APAC: Asia & Pacific.

Central to this dialogue is the unresolved question of whether AS-induced physiological responses are primarily driven by the intrinsic structural properties of the sweeteners or by the host's specific physiological context. A growing body of research highlights the gut microbiota as a key mediator in AS-related physiological effects [5,6], revealing that different ASs exert distinct microbial perturbations based on their chemical structures. For instance, as a structural archetype, sucralose, a chlorinated disaccharide that remains stable and reaches the colon intact, preferentially depletes *Lactobacillus* and *Ruminococcus*, disrupting bile acid (BA) metabolism and SCFA production [7,8]. In contrast, aspartame, a peptide-based sweetener rapidly metabolized in the upper gastrointestinal tract, enriches specific *Bacteroides* species and alters tryptophan metabolism, leading to elevated indoxyl sulfate production [6]. Furthermore, baseline microbiota composition acts as a susceptibility determinant, with individuals harboring high *Bacteroides* abundance demonstrating resilience to AS-induced perturbations, whereas those with lower microbial diversity experience more pronounced metabolic and immune alterations [5,6]. Such influences could potentially alter pathways involving BAs, tryptophan metabolism, short-chain fatty acids (SCFAs), and lipopolysaccharides (LPS) [9,10].

In light of these findings, the present review synthesizes recent evidence from cohort studies, clinical trials, and animal experiments to critically evaluate ASs. It examines the current understanding of their physiological impacts and analyzes the underlying mechanisms from the perspective of gut microbiota and three core host physiological axes, with specific attention to populations with distinct physiological needs. In this review, we propose a hierarchical framework in which the intrinsic chemical properties of ASs determine their microbial accessibility and perturbation potential, whereas host-specific physiological context and baseline gut microbiota configurations govern how these perturbations are translated into metabolic and immune outcomes. Under this paradigm, ASs act as defined perturbational inputs, while host microbial ecology and physiology shape the direction, magnitude, and persistence of biological responses. These insights aim to inform evidence-based discussions on AS usage guidelines and support the development of tailored nutritional approaches to optimize their application.

2. The evolving understanding of artificial sweeteners: Integrating evidence and controversies

Historically, ASs were considered safe alternatives to sugar, with no impact on postprandial glycemic responses or weight gain. However, recent studies have highlighted health risks associated with foods containing ASs, drawing from epidemiological evidence, clinical intervention, and animal model studies (Tables S1 – S3 in Appendix A). Before examining specific metabolic pathways, it is essential to summarize the foundational microbial shifts induced by ASs.

2.1. Epidemiological evidence linking artificial sweeteners to chronic diseases

Observational studies in nutritional epidemiology have identified worrisome associations between ASs intake and metabolic syndrome (MetS)-related conditions, including obesity, type 2 diabetes (T2DM), and non-alcoholic fatty liver disease (NAFLD) (Table S1 in Appendix A). For instance, a large cohort study involving 105,588 individuals reported a significantly elevated risk of T2DM (hazard ratio: 1.69) in those consuming ASs daily [9]. Additionally, higher ASs intake has been associated with a greater likelihood of developing cardiovascular disease (CVD), with one study noting a hazard ratio of 1.32 for CVD incidence among frequent consumers [11]. Similarly, ASs have been implicated in chronic kidney disease (CKD) [10]. Emerging studies have pointed to a possible association between ASs and cancer, particularly obesity-related malignancies (hazard ratio: 1.13) [12,13]. Furthermore, ASs have been linked to neurological conditions, including Alzheimer's disease (AD) [14] and depression [15], possibly through mechanisms involving gut-brain axis dysregulation and neuroinflammation. Notably, a U-shaped association between AS intake and mortality has been reported, indicating potential complexities in their long-term health effects [16,17]. Collectively, these observations raise concerns about chronic health risks linked to ASs, which, despite being promoted as sugar substitutes, have been associated with MetS, CVD, CKD, cancer, and neurological diseases.

2.2. Mechanistic insights from clinical and animal studies

Clinical intervention studies have further corroborated these associations, indicating that ASs may impair glucose tolerance [5,6] and modulate immune responses [18] (Table S2 in Appendix A). For instance, a recent randomized controlled trial with 20 participants showed that intake of sucralose (34%) and saccharin (20%) of the FDA-approved daily limits led to notable changes in the composition of previously healthy gut microbiota [6]. These changes, accompanied by impaired glucose tolerance and elevated postprandial blood glucose levels, were mediated by AS-induced gut microbiome dysbiosis, as evidenced by fecal microbiota transplantation into germ-free mice. Moreover, evidence primarily from rodent models indicates that ASs can alter the microbial ecology, which may in turn influence glucose metabolism, insulin sensitivity, immune function, and even cognitive abilities, suggesting a potential link between these changes and host physiological and

cognitive functions (Table S3 in Appendix A). These findings imply that the disruption of gut microbiota plays a central role in the adverse effects induced by ASs.

However, these apparent discrepancies likely reflect the complex interplay of multiple confounding variables rather than inherent contradictions. Specifically: ① AS type determines distinct microbial targets and metabolic consequences; for example, sucralose preferentially depletes *Lactobacillus* and *Ruminococcus*, leading to reduced BA metabolism and SCFA production [7,8], while saccharin selectively enriches *Bacteroides* species and reduces *Prevotella*, resulting in elevated indoxyl sulfate production via altered tryptophan metabolism [6]. ② Dose and duration modulate microbial responses; short-term saccharin exposure (28 days) can transiently increase acetate, propionate, and butyrate production [5,19], whereas long-term sucralose exposure (6 months) induces chronic dysbiosis characterized by SCFA depletion, reduced BA metabolism, and disrupted intestinal barrier function [7,8,20]. ③ Mode of consumption introduces dietary matrix effects; commercial AS formulations containing additional carbohydrates (e.g., 5% saccharin with 95% glucose) produce different microbial outcomes compared to isolated AS administration [5], highlighting the need to consider AS within their typical dietary contexts. These context-dependent dynamics underscore the necessity of moving beyond generalized safety assessments toward population- and exposure-tailored evaluation frameworks.

3. AS-induced alterations in gut microbiota composition: A foundational mechanism for downstream health effects

3.1. AS-mediated gut microbiota dysbiosis as a central mediator

Chronic AS consumption fundamentally reshapes the taxonomic and functional architecture of the gut microbiome, establishing a dysbiotic state that serves as the proximal driver of downstream metabolic, immune, and neurological perturbations. Across multiple AS classes, including saccharin, sucralose, aspartame, and Ace-K, consistent patterns emerge: depletion of beneficial commensal taxa and expansion of opportunistic or pro-inflammatory groups (Fig. 2).

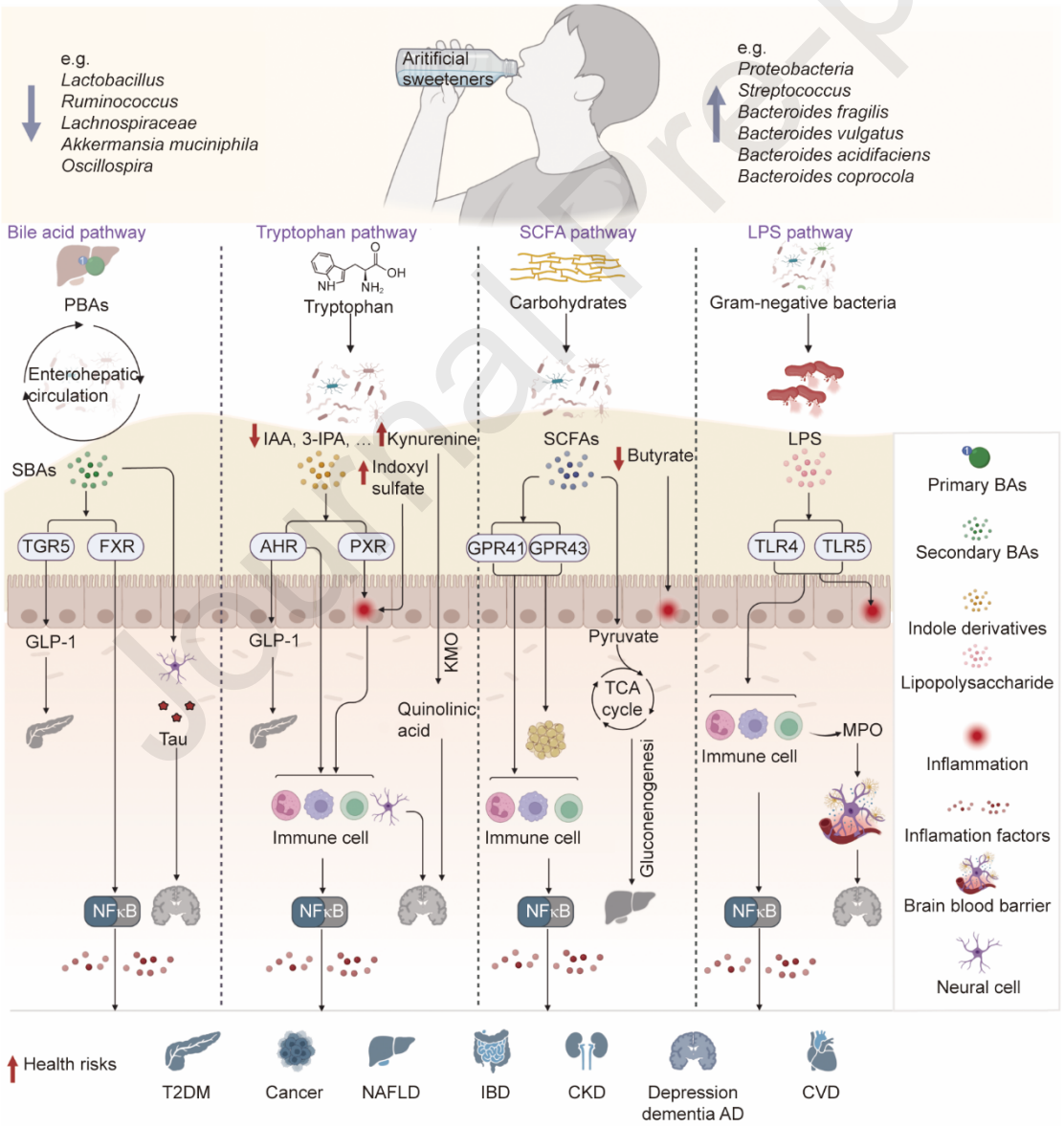


Fig. 2. Gut microbiota-derived metabolites mediate artificial sweetener-induced health risks. ASs affect host health through BA metabolism,

tryptophan metabolism pathways, SCFAs metabolism pathways, and LPS pathways. First, disrupted enterohepatic circulation reduces SBA production; diminished TGR5 and FXR receptor activation suppresses GLP-1 secretion from enteroendocrine cells and promotes hepatic NF-κB-driven inflammation, thereby elevating risk for T2DM, NAFLD, and CVD. Second, altered tryptophan catabolism shifts flux away from indole derivatives (IAA, IPA) toward the kynurenine–KMO–quinolinic acid branch; reduced AHR/PXR activation impairs mucosal immune tolerance, while elevated quinolinic acid crosses the blood–brain barrier and activates neuroinflammatory cascades associated with depression, dementia, and Alzheimer's disease. Third, SCFA depletion, particularly butyrate, which reduces GPR41/GPR43 signaling in colonocytes, impairing mitochondrial pyruvate entry into the TCA cycle, promoting gluconeogenesis, and suppressing intestinal immune cell homeostasis, with downstream consequences for IBD, CKD, and metabolic disease. Fourth, expansion of Gram-negative bacteria elevates luminal LPS, activating TLR4/TLR5 on epithelial and immune cells; systemic LPS translocation triggers chronic NF-κB-mediated inflammation and enables direct CNS injury via disruption of the blood–brain barrier. Collectively, these four axes converge on shared inflammatory endpoints, including NF-κB activation, immune cell dysregulation, and organ-level pathology, underscoring the pleiotropic health risks of chronic AS exposure illustrated at the base of Fig. 2. PBAs: primary bile acids, SBAs: secondary bile acids, FXR: farnesoid X receptor, TGR5: Takeda G-protein-coupled receptor 5, NF-κB: nuclear factor kappa B, GLP-1; glucagon-like peptide-1, IAA: indole-3-acetic acid, 3-IPA: 3-indolepropionic acid, AHR: aryl hydrocarbon receptor, PXR: pregnane X receptor, KMO: kynurenine 3-monooxygenase, GPR: G protein-coupled receptors, TLR: toll-like receptor, T2DM: type 2 diabetes, IBD: inflammatory bowel disease.

ASs selectively suppress key beneficial commensal taxa critical for maintaining intestinal homeostasis. Most notably, *Lactobacillus* depletion is consistently observed across multiple ASs: saccharin [8,19], sucralose [7,8], and Ace-K [21], all of which significantly reduce *Lactobacillus* abundance. Similarly, Ruminococcus and related Ruminococcaceae family members are depleted by saccharin [7,20], sucralose [7,22], Ace-K [21,23], and neotame [24], representing one of the most consistent microbial shifts induced by AS consumption. Lachnospiraceae family members, major butyrate producers including *Lachnoclostridium*, are also reduced by sucralose [22], Ace-K [23], and neotame [24]. Long-term AS exposure (≥11 weeks) further depletes *Akkermansia muciniphila*, a mucin-degrading bacterium essential for maintaining intestinal barrier integrity [8]. Additional taxa showing depletion include *Oscillospira* [20,22], *Dorea* [20], and *Adlercreutzia* [20]. These commensal bacteria collectively constitute the core functional guilds responsible for producing SCFAs, maintaining epithelial barrier function, and preventing pathogen colonization through competitive exclusion and bacteriocin production [25,26]. Their depletion compromises colonization resistance, the microbiota's intrinsic capacity to prevent pathogen establishment, thereby increasing susceptibility to enteric infections [26,27].

Conversely, AS exposure promotes the expansion of potentially pathogenic and pro-inflammatory taxa. Notably, ASs increase *Proteobacteria* phylum abundance, and sucralose elevates multiple Proteobacteria classes, including Alphaproteobacteria, Betaproteobacteria, Gammaproteobacteria, Deltaproteobacteria, and Epsilonproteobacteria in Crohn's disease models [28], while also increasing overall *Proteobacteria* levels in colitis models [29]. *Streptococcus* expansion is observed following saccharin [8] and sucralose [8,22] exposure. Concurrently, specific *Bacteroides* species undergo selective enrichment: saccharin increases *Bacteroides fragilis* and *Bacteroides vulgatus* [5], while aspartame enriches *Bacteroides fragilis*, *Bacteroides acidifaciens*, and *Bacteroides coprocola* [6]. Additional pro-inflammatory taxa showing expansion include *Prevotella*, *Fusibacter* [8], *Alistipes* [19], and *Mucispirillum* [19,21]. These compositional shifts collectively favor a pro-inflammatory microbial community structure characterized by elevated endotoxin production potential and reduced beneficial metabolite synthesis capacity.

These AS-induced shifts in microbial community structure translate into profound alterations in four key metabolite classes: SCFAs, BAs, tryptophan-derived metabolites, and LPS. The depletion of SCFA-producing taxa reduces butyrate and propionate levels [8,20], while loss of BA-metabolizing bacteria disrupts secondary BA biosynthesis [7]. Tryptophan metabolism is redirected toward pro-inflammatory pathways, decreasing beneficial indole derivatives and increasing indoxyl sulfate [6,8]. Concurrently, expansion of Gram-negative Proteobacteria upregulates LPS biosynthesis genes [8,20]. The subsequent sections detail how each metabolite class mediates AS-induced pathophysiology: BA alterations impair TGR5/FXR signaling, tryptophan metabolite shifts dysregulate AHR/PXR pathways, SCFA depletion compromises colonocyte energy metabolism and barrier integrity, and LPS accumulation drives TLR4/TLR5 – NF-κB inflammatory cascades (Fig. 2).

3.2. Disruption in bile acid enterohepatic circulation homeostasis

Impaired enterohepatic circulation of BAs has been identified as a major contributor to the pathogenesis of metabolic and gastrointestinal disorders [30]. Ace-K treatment in Crohn's disease mice has been demonstrated to notably raise levels of the PBAs – cholic acid (CA) while simultaneously lowering the concentrations of SBAs-deoxycholic acid (DCA) [21]. In contrast, long-term consumption of sucralose (0.1 $mg \cdot mL^{-1}$ in drinking water for 11 weeks) resulted in elevated levels of DCA in feces, blood, and liver, and concurrently reduced the contents of taurine-conjugated BA and free BAs in the liver [7,31]. However, these contrasting findings should not be overinterpreted as inherently opposite actions of Ace-K and sucralose on BA metabolism. A key difference is that Ace-K was evaluated in a Crohn's disease model, whereas sucralose was tested in healthy mice. Since disease-associated inflammation can substantially alter gut microbial ecology, bile salt hydrolase/7α-dehydroxylation capacity, and enterohepatic BA circulation, the direction and magnitude of BA changes induced by ASs may be highly context dependent [7,31,32]. At present, whether the observed divergence is primarily driven by sweetener chemistry or by the host's pathological background remains unresolved. This unresolved issue should be considered a critical knowledge gap in the field.

Besides, BAs act as signaling molecules through FXR and TGR5, which regulate various physiological processes, including

inflammation and metabolism [30]. A previous study has shown that consumption of sucralose (0.1 mg·mL^{-1} in drinking water) inhibits FXR expression [7], which is involved in the formation of metabolic diseases such as T2DM and NAFLD [33,34]. Additionally, ASs may influence the secretion of GLP-1 by TGR5 signaling pathways, potentially contributing to the development of T2DM and NAFLD. Given that TGR5 and FXR regulate NF-κB activity [35], their suppression further links ASs to inflammation (Fig. 2, bile acid pathway). Further studies have highlighted a potential link between certain BAs, such as DCA and neurological conditions. DCA can cross the blood-brain barrier and activate microglia, causing neuroinflammation and Tau hyperphosphorylation [36] (Fig. 2, bile acid pathway). These findings underscore the need to account for gut microbiome–mediated BA regulation when assessing the physiological effects of AS.

3.3. Alteration in tryptophan metabolite levels

Gut tryptophan metabolism is a multifaceted, tightly controlled process encompassing three principal pathways: Indole derivatives, serotonin pathway, and kynurenine pathway [37]. AS exposure consistently reduces microbiota-derived indole metabolites such as IAA and 3-IPA [8,19], leading to impaired activation of AHR and PXR. These receptors normally promote epithelial integrity, immune tolerance, and neuronal protection through transcriptional programs involving CYP enzymes and detoxification pathways [38–41]. Loss of this signaling axis facilitates NF-κB activation and may contribute to IBD, MetS, and neurobehavioral alterations [8,19] (Fig. 2, tryptophan pathway). Additionally, saccharin exposure has been associated with an increased production of the uremic toxin indoxyl sulfate, a tryptophan-derived metabolite linked to intestinal and systemic pathology [6]. Indoxyl sulfate disrupts intestinal barrier integrity by promoting mitophagy through the dynamin-related protein 1—interferon regulatory factor 1 axis, leading to mitochondrial dysfunction and increased epithelial permeability. This barrier disruption amplifies systemic inflammation and has been implicated in the pathogenesis of CVD and CKD, in part through activation of the AHR–NF-κB signaling pathway [42,43] (Fig. 2, tryptophan pathway).

In parallel, the kynurenine pathway, one of the principal routes of tryptophan metabolism regulated by indoleamine 2,3-dioxygenase (IDO) [44], is also profoundly affected by AS-induced dysbiosis [6,8,20]. For example, sucralose administration increased the levels of kynurenine and a higher kynurenine/tryptophan ratio [6,8]. Quinolinic acid, a potent neurotoxin, is synthesized from kynurenine via the enzyme kynurenine 3-monooxygenase [45]. It contributes to excitotoxicity in the brain by over-activating NMDA receptors, potentially leading to neuronal death. ASs, such as saccharin, have been shown to increase the levels of quinolinic acid [20], suggesting a potential mechanistic nexus that warrants investigation in the context of neurodegenerative diseases, such as AD and depression (Fig. 2, tryptophan pathway). Together, these findings underscore how AS-driven microbial perturbations reprogram tryptophan metabolism toward pro-inflammatory and neuroactive outputs.

3.4. Alteration in short-chain fatty acid levels

SCFAs exert broad physiological effects by activating GPRs, thereby influencing energy metabolism, glucose regulation, and immune function [46]. Emerging evidence indicates that ASs, such as saccharin, sucralose, and Ace-K, exert bidirectional modulation of SCFA levels, a process governed by host-specific physiological variables, including baseline microbial diversity, intestinal permeability, metabolic status, and duration of exposure. These factors collectively determine whether elevated SCFAs act as beneficial metabolic signals or as contributors to energy overaccumulation and inflammation [47,48]. Specifically, baseline microbial diversity and community structure influence the abundance of SCFA-producing taxa and microbial cross-feeding capacity, thereby affecting whether AS exposure leads to transient increases in SCFA production or reduced SCFA biosynthesis under dysbiosis [5,6,8,24]. In parallel, intestinal permeability and host metabolic status shape the downstream consequences of altered SCFA levels by determining whether SCFAs predominantly support barrier integrity and anti-inflammatory signaling or instead contribute to endotoxin-associated inflammation and metabolic stress [25,47,48]. For instance, short-term exposure to AS may enhance the proliferation of SCFA-producing taxa, resulting in elevated SCFA concentrations [5,6]. Elevated SCFA levels under AS exposure have been linked to enhanced gluconeogenesis, driven by the upregulation of key intermediates like pyruvate, associated with altered carbohydrate fermentation and host glucose metabolic intermediates [21,49]. Increased pyruvate levels may lead to excessive glucose production and energy overaccumulation, thereby impairing glucose regulation and promoting insulin resistance [50] (Fig. 2, SCFA pathway). Besides, acetate can also feed into the TCA cycle, generating excess ATP and promoting hepatic lipogenesis and adiposity [51]. This evidence suggests that ASs may potentially impact host health through elevated SCFA levels. Although SCFAs are generally considered beneficial, this is not always the case, as high levels of SCFAs have been reported to exert certain adverse effects. In healthy individuals, SCFAs exert anti-inflammatory and immunomodulatory properties through the activation of G protein-coupled receptors such as GPR41 and GPR43 [25] (Fig. 2, SCFA pathway). However, consistent with findings observed under AS exposure, one study reported that treatment with di-(2-ethylhexyl) phthalate led to elevated SCFA levels and upregulation of Gpr41 and Gpr43 expression in the colon, which in turn enhanced caloric extraction from the diet and promoted hepatic steatosis and weight gain in mice [52]. Besides, high levels of SCFAs can limit the effectiveness of cancer drugs [53]. Thus, the physiological effects of SCFAs appear to depend on the host's health status and specific contextual factors, emphasizing the need for nuanced evaluation of their roles in AS-related pathways.

In contrast, chronic exposure to sucralose may induce gut microbial dysbiosis, thereby impairing the expression or activity of enzymes essential for SCFA biosynthesis [8,24]. A study in humans showed that 21 days of sucralose intake at 180 mg·d^{-1} increased SCFAs (propionate, butyrate, and valerate) production [6], whereas 11 weeks of intake at the same concentration

reduced SCFAs (propionate and butyrate) levels in mice [8]. As a key energy source for colonocytes, butyrate supports mucosal integrity by upregulating tight junction proteins such as occludin and ZO-1 [54] (Fig. 2, SCFA pathway). Its depletion facilitates the translocation of endotoxins like LPS into circulation, initiating inflammatory cascades that contribute to insulin resistance and metabolic disorders such as MetS and NAFLD [8,24]. Collectively, while ASs may transiently enhance SCFA production by stimulating microbial fermentation, sustained intake appears to disrupt microbial and metabolic homeostasis. Notably, SCFA is more susceptible to interference when the diversity of host microbiota decreases, and intestinal permeability increases [55]. These findings underscore the necessity of elucidating the long-term consequences of AS consumption and the host factors that modulate their divergent physiological effects.

3.5. Lipopolysaccharide leakage

Emerging research indicates that ASs markedly enhance the expression of genes responsible for LPS biosynthesis in gut Gram-negative bacteria [20,21,56]. Elevated LPS levels compromise bacterial outer membrane stability, facilitating its translocation across the intestinal epithelium and promoting endotoxemia, a critical contributor to systemic inflammation and metabolic disorders [57]. LPS-mediated disruption of the intestinal barrier also triggers innate immune activation via TLR signaling, subsequently inducing NF-κB pathway activation and upregulation of pro-inflammatory cytokines, including IL-6, IL-17, TNF-α, and IL-1β [56]. Sucralose has been reported to increase the expression of TLRs, notably TLR4 and TLR5, in intestinal epithelial cells [56] (Fig. 2, LPS pathway). This upregulation may enhance the cellular sensitivity to their respective ligands, such as TLR4, thereby potentiating the inflammatory signaling pathways triggered by LPS exposure [58]. The sustained elevation of cytokines promotes a persistent inflammatory state, a key driver of various pathological conditions, including metabolic disorders and autoimmune conditions [59] (Fig. 2, LPS pathway). Meanwhile, this dysregulated inflammatory response impacts immune cells, including neutrophils, lymphocytes, and T cells, contributing to increased production of myeloperoxidase (MPO) [60]. Sucralose exposure has been shown to increase MPO activity in neutrophils, leading to elevated oxidative stress and tissue damage in the colon [29]. Elevated MPO levels have been associated with CVD, as they promote atherosclerosis by oxidizing low-density lipoprotein and generating foam cells [61] (Fig. 2, LPS pathway). Notably, these pro-inflammatory mediators are not only implicated in metabolic disorders like diabetes and obesity but also contribute to the pathogenesis of autoimmune diseases, gastrointestinal disorders, and even neurodegenerative conditions. This suggests that the impact of ASs extends beyond metabolic dysfunction to encompass broader immunological effects. A thorough understanding of these mechanisms is crucial for developing interventions aimed at reducing the adverse health effects of AS consumption and promoting gut and immune homeostasis.

4. Artificial sweeteners and host physiological axes: Implications for special populations and disease states

Over the past decade, a growing body of research has investigated AS effects in vulnerable groups, including individuals at different stages of life (e.g., early life, the elderly) and those with chronic conditions (e.g., diabetes, IBD). These studies have revealed that gut microbiota, immune function, and metabolic homeostasis, dynamic factors shaped by both developmental transitions and disease pathophysiology, play pivotal roles in mediating responses to ASs (Table S1 in Appendix A). We synthesize current evidence through a novel, integrated framework centered on three core host physiological axes: immune competence, metabolic state, and developmental/epigenetic plasticity (Fig. 3). This framework transcends traditional boundaries between life stages and disease states, enabling a more holistic analysis of how ASs interact with gut microbiota to modulate host physiology across interconnected vulnerable populations.

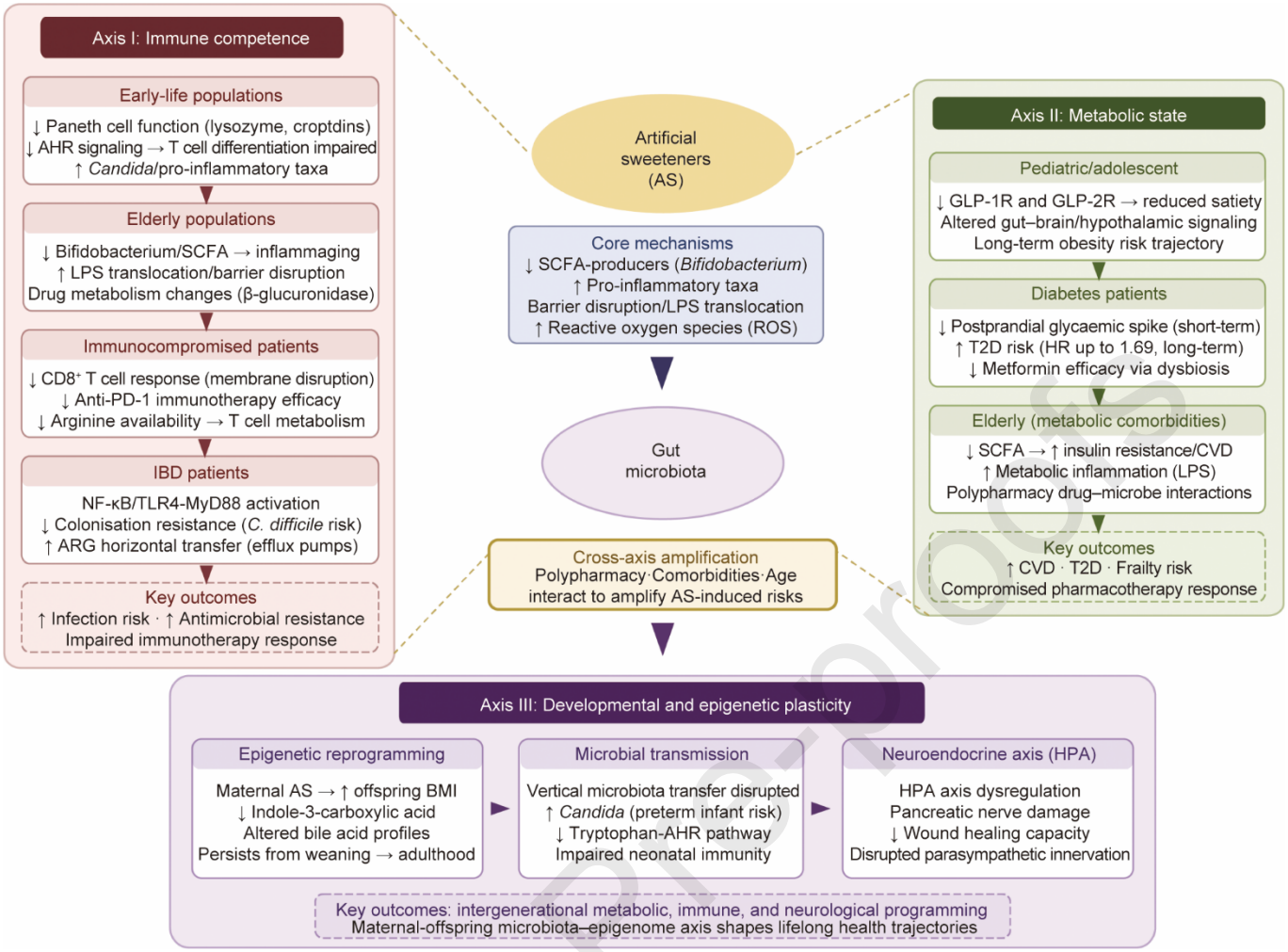


Fig. 3. Artificial sweeteners modulate host physiology via gut microbiota across three core physiological axes. Artificial sweeteners (ASs) perturb gut microbiota composition and diversity through multiple mechanisms, including depletion of SCFA-producing commensals, expansion of pro-inflammatory taxa, disruption of intestinal barrier integrity, and increased reactive oxygen species (ROS) production, with consequent LPS translocation. Downstream effects are channelled through three context-dependent physiological axes. Axis I (immune competence) encompasses populations with dynamic or impaired immunity: early-life individuals (impaired Paneth cell function, AHR-mediated T cell differentiation, increased *Candida* colonization), the elderly (immunosenescence, inflammaging, altered drug metabolism via β-glucuronidase), immunocompromised patients (blunted $CD8^+$ T cell responses, diminished anti-PD-1 immunotherapy efficacy, reduced arginine availability), and IBD patients (NF-κB/TLR4–MyD88 pathway activation, loss of colonization resistance, and horizontal ARG transfer via efflux pump upregulation). Axis II (metabolic state) integrates paediatric and adolescent populations (GLP-1R and GLP-2R downregulation, hypothalamic signaling disruption, long-term obesity risk), patients with diabetes (short-term glycaemic benefit versus long-term increased type 2 diabetes mellitus (T2D) risk and reduced metformin efficacy), and elderly individuals with metabolic comorbidities (worsened insulin resistance and CVD risk via reduced SCFA production, metabolic inflammation, and polypharmacy drug–microbe interactions). Axis III (developmental and epigenetic plasticity) highlights the maternal–offspring axis, encompassing epigenetic reprogramming (altered offspring BMI, reduced indole-3-carboxylic acid and bile acids (BAs) profiles persisting into adulthood), disrupted vertical microbial transmission (increased *Candida* colonization in preterm infants, impaired tryptophan–AHR signaling and neonatal immunity), and hypothalamic – pituitary – adrenal (HPA) axis dysregulation (pancreatic nerve damage, impaired wound healing, disrupted parasympathetic innervation of pancreatic islets). Cross-axis amplification occurs when comorbidities, polypharmacy, and age-related physiological changes interact synergistically with AS-induced perturbations. ARG: antimicrobial resistance gene; GLP-1R/2R: glucagon-like peptide-1/2 receptor.

4.1. Immune competence axis: From developmental vulnerability to age-related and disease-associated immune dysregulation

The immune competence axis encompasses populations with dynamic or impaired immune function, including early-life individuals, the elderly, immunocompromised patients, and those with inflammatory IBD (Fig. 3, Axis I). The gut microbiota is a key regulator of immune development and function; thus, AS-induced microbial perturbations can disproportionately affect immune responses in these groups, either by disrupting immature immune networks (early life), exacerbating age-related immune decline (elderly), or amplifying pre-existing inflammation (IBD/immunocompromised states).

4.1.1. Early-life populations: Immune development and microbial programming

In early development, gut microbiota and immune networks are still being established, making them highly sensitive to

dietary perturbations like ASs. Maternal AS consumption during pregnancy can disrupt offspring immune function via microbial and epigenetic mechanisms, representing a critical intergenerational link. For instance, maternal sucralose intake impairs Paneth cell function in offspring by reducing lysozyme expression and antimicrobial peptides (cryptdin-1 and cryptdin-5), leading to increased intestinal inflammation and the expansion of pro-inflammatory taxa [62,63]. This early-life dysbiosis often persists into adulthood and is associated with altered microbial metabolites (e.g., reduced indole-3-carboxylic acid and BAs) [64].

ASs also interfere with tryptophan metabolism, a key pathway for neonatal immune development. High-dose sucralose disrupts AHR signaling, mediated by microbiota-derived tryptophan metabolites, thereby impairing T cell proliferation and differentiation [65,66]. This leads to altered intestinal lymphocyte composition (increased $CD3^+/CD4^+$ T cells, reduced $CD8^+$ T cells in Peyer's patches) and elevated mucosal infiltration [67], while AHR – NF-κB crosstalk amplifies inflammatory potential [68]. Additionally, prenatal AS exposure alters fungal microbiota development (e.g., increased *Candida* species) [69,70], which can damage the infant's immune system, particularly in preterm newborns [71]. These findings highlight that AS-induced perturbations during immune development may have long-lasting consequences for offspring's health.

4.1.2. Elderly populations: Immunosenescence and comorbid immune vulnerability

Aging is characterized by immunosenescence (e.g., declined T-cell function, altered macrophage polarization) and reduced gut microbiota diversity, rendering the elderly highly susceptible to AS-mediated disturbances [72,73]. ASs may further deplete SCFA-producing taxa [74], impairing intestinal barrier repair (via reduced ZO-1 expression) and exacerbating inflammaging [74]. Compromised barrier integrity also enables translocation of AS-induced microbial byproducts (e.g., LPS), worsening age-related chronic diseases.

Beyond immune decline, AS-induced immune perturbations may weaken pathogen resistance and wound healing in a population already at elevated infection risk [73]. Additionally, polypharmacy (e.g., antidiabetics, statins) in the elderly raises concerns about AS-microbe-drug interactions; specifically, AS-induced shifts in gut microbial enzyme activity (e.g., β-glucuronidase) may alter drug metabolism and therapeutic efficacy [73,75]. Observational data link AS consumption to increased frailty and depression risk in the elderly [76,77], underscoring the need to integrate immune competence and comorbidities into risk assessments.

4.1.3. Immunocompromised individuals: Synergistic immune dysfunction

Individuals with compromised immune function (e.g., chemotherapy recipients, organ transplant patients) face unique risks from AS exposure, as pre-existing microbiota instability and impaired intestinal barrier function amplify AS-induced perturbations [78]. Sucralose (at doses equivalent to the FDA and EFSA acceptable daily intake in humans, achieved via $0.17 – 0.72\ mg \cdot mL^{-1}$ in mouse drinking water), a widely used AS, has been shown to directly disrupt T cell membrane organization and signaling, blunting $CD8^+$ T cell responses to infections and tumors [65]. In cancer patients receiving anti-PD-1 immunotherapy, sucralose alters microbial composition, reduces microbiota-accessible arginine levels, and impairs T cell metabolism, diminishing immunotherapy efficacy (reversible via amino acid supplementation or fecal microbiota transfer) [78]. These effects are context-dependent: while AS-induced immune suppression may be detrimental in infection/cancer settings, it could potentially mitigate autoimmunity [65]. However, for immunocompromised populations, the synergy between direct T cell suppression and microbiota-driven immune impairment necessitates targeted dietary guidance.

4.1.4. Patients with IBD: Inflammation, barrier disruption, and antimicrobial resistance

IBD is characterized by gut dysbiosis, barrier dysfunction, and chronic inflammation, conditions that enhance AS sensitivity. Despite ASs being perceived as "healthier" alternatives to sugar, clinical guidelines recommend limiting their intake in Crohn's disease and ulcerative colitis patients [79]. Preclinical studies confirm sucralose exacerbates DSS-induced colitis via NF-κB activation (upregulating pro-inflammatory cytokines) and downregulates barrier proteins (claudins, MUC-2, TFF3), increasing gut permeability [56,80]. Sucralose also accelerates colitis-associated colorectal cancer via TLR4/5 – MyD88 – NF-κB pathways and elevated fecal β-glucuronidase (enhancing BA toxicity) [81].

Beyond direct inflammatory effects, AS-mediated dysbiosis critically impairs gut colonization resistance, the ability of commensal microbiota to prevent pathogen invasion and establishment. Colonization resistance relies on microbial diversity, niche competition, and production of inhibitory metabolites (e.g., SCFAs, bacteriocins) that limit pathogen growth. In IBD patients, baseline colonization resistance is already compromised due to reduced microbiota diversity and inflammation; AS exposure further disrupts this balance by depleting key commensal taxa that produce SCFAs and bacteriocins [74,82]. This loss of protective microbiota creates ecological niches that facilitate colonization by enteric pathogens such as *Clostridioides difficile*, *Escherichia coli*, and Salmonella enterica, a major concern in IBD, where recurrent infections drive disease flares and complications [83]. For example, in murine models, sucralose exposure reduced levels of *Lactobacillus* and *Ruminococcus*, correlating with increased *C. difficile* spore germination and colonization [84]. These findings highlight a critical but understudied link: AS-induced dysbiosis not only worsens inflammation but also undermines the gut's first line of defense against pathogens, amplifying infection risk in vulnerable IBD patients.

First, ASs facilitate conjugative plasmid transfer, a primary route for antimicrobial resistance gene (ARG) dissemination,

by increasing bacterial cell membrane permeability, promoting cell-to-cell contact, and upregulating conjugation-related genes. In vitro studies show saccharin, sucralose, aspartame, and Ace-K promote horizontal ARG transfer between commensal and pathogenic bacteria via increased membrane permeability, reactive oxygen species production, SOS response activation, and efflux pump upregulation [85–87]. For example, Ace-K enhances AcrAB – TolC efflux pump activity in *Escherichia coli* and *Klebsiella pneumoniae*, contributing to multidrug resistance [88]. Notably, horizontal transfer of antimicrobial resistance genes in inflamed gut environments is frequently mediated by bacteriophages, which constitute a major genetic reservoir within the human gut microbiome [89]. ASs have also been implicated in triggering the transition of prophages from lysogeny to the lytic cycle, inducing prophage excision and phage release from host bacteria [90]. Although the direct contribution of AS to phage-mediated gene transfer in clinical settings remains to be fully elucidated, AS-associated dysbiosis and inflammation may create ecological conditions that facilitate phage-driven genetic exchange and destabilize the gut ecosystem [90,91]. These findings underscore the need for cautious AS use in IBD, given their potential to worsen inflammation and antimicrobial resistance.

4.2. Metabolic state axis: Obesity, diabetes, and age-related metabolic comorbidities

The metabolic state axis integrates populations with altered metabolic homeostasis, including children/adolescents (at risk of obesity), patients with diabetes, and elderly individuals with metabolic comorbidities (e.g., diabetes, CVD) (Fig. 3, axis II). ASs are widely used to manage weight and glycemia, but their effects are modulated by microbial-metabolic crosstalk, with context-dependent benefits and risks.

4.2.1. Pediatric and adolescent populations: Developmental metabolic plasticity and obesity risk

Global trends show a doubling of overweight/obesity prevalence in children/adolescents between 1990 and 2021, coinciding with increased AS intake [92–94]. Evidence on ASs and BMI remains conflicting: meta-analyses of prospective cohorts suggest smaller BMI gains compared to sugar [95], while other studies report no significant impact [96]. However, this population's unique metabolic plasticity, coupled with maturing gut microbiota and gut-brain axis, renders them sensitive to long-term AS-induced perturbations.

ASs may influence appetite regulation via microbial-metabolic pathways: sucralose alters the hypothalamic functional connections with motivation/somatosensory brain regions, increasing hunger compared to sugar or water [97]. Mechanistically, ASs reduce satiety by downregulating GLP-1R and GLP-2R [23], while gut microbiota maturation amplifies dietary influences on metabolic trajectories [98,99]. Since childhood dietary habits persist into adulthood, AS exposure during this stage may shape long-term metabolic health beyond immediate BMI effects.

4.2.2. Patients with diabetes: Glycemic management vs long-term microbial-metabolic risks

ASs can reduce acute postprandial glycemic spikes [4], aligning with clinical recommendations. However, epidemiological data link habitual AS intake to an increased T2D risk (hazard ratios up to 1.69), though confounding dietary/lifestyle factors limit interpretation [9,100]. A key mechanism involves AS-induced gut microbial shifts: alterations in glucose-metabolizing taxa and pro-inflammatory genera may progressively impair insulin sensitivity [6,101]. Critically, first-line antidiabetic drugs like metformin rely on gut microbial function for efficacy [102], suggesting that AS-induced dysbiosis could diminish therapeutic responses. Thus, while ASs offer short-term glycemic benefits, their long-term impacts on microbial-metabolic pathways and drug responsiveness require further investigation, including dose-dependent effects and susceptibility biomarkers.

4.2.3. Elderly populations with metabolic comorbidities: Amplified risks of dysmetabolism

Elderly individuals frequently present with metabolic comorbidities (diabetes, CVD), which interact with age-related physiological changes to modify AS responses [72]. Reduced gut microbiota diversity exacerbated by ASs impairs SCFA production, worsening insulin resistance and CVD risk [74]. AS-induced microbial byproducts (e.g., LPS) may also contribute to metabolic inflammation, amplifying comorbidity progression. Additionally, polypharmacy in this group raises concerns about AS-microbe-drug interactions affecting antidiabetic or lipid-lowering medications [73,75]. Observational data linking AS consumption to frailty [76] further highlights the need to integrate metabolic state and age-related vulnerabilities in risk-benefit analyses.

4.3. Developmental and epigenetic plasticity axis: Maternal-offspring transmission and lifelong programming

The developmental and epigenetic plasticity axis focuses on early life and the maternal-offspring axis, periods of heightened susceptibility to AS-induced epigenetic reprogramming and microbial programming, with long-lasting intergenerational effects (Fig. 3, axis III).

Maternal AS consumption during pregnancy and lactation influences offspring health via epigenetic modifications and gut microbiota transmission. Sucralose exposure during pregnancy induces epigenetic reprogramming in offspring, altering metabolic phenotypes (e.g., increased BMI) [103,104]. This is mediated by microbial perturbations: maternal sucralose intake

disrupts the offspring's gut microbiota balance, reduces Paneth cell function, and downregulates microbiota-derived metabolites (indole-3-carboxylic acid and BAs) [62,64]. These changes persist from weaning into adulthood, highlighting the lifelong impact of early-life AS exposure.

Beyond metabolism, maternal AS intake affects the HPA-axis in offspring, leading to pancreatic nerve damage, delayed wound healing [105], and disrupted parasympathetic innervation of pancreatic islets [106]. The tryptophan-AHR pathway, critical for neonatal immune development, also plays a role: maternal AS exposure disrupts AHR signaling, compromising offspring immunity [107]. Additionally, prenatal AS exposure alters vertical transmission of fungal microbiota (e.g., increased *Candida* species) [69,70], which can impair immune development in preterm infants [71].

Notably, the maternal-offspring axis represents a key intergenerational link for AS effects: microbial and epigenetic changes induced by maternal AS consumption are transmitted to offspring, thereby programming their long-term health trajectories. This underscores the importance of dietary guidance for pregnant and lactating individuals, as early-life programming has implications for metabolic, immune, and neurological health across generations.

5. Concluding remarks and future perspectives

The evidence synthesized AS-induced alterations in BA profiles, tryptophan-derived metabolites, SCFA levels, and LPS dynamics converges on three core host physiological axes, including immune competence, metabolic state, and developmental/epigenetic plasticity (Fig. 4), each integrating populations with shared susceptibility mechanisms despite differences in age or disease state. For instance, the immune competence axis encompasses early-life individuals with maturing immune networks, elderly populations experiencing immunosenescence, immunocompromised patients, and IBD patients with chronic inflammation, all of whom share heightened vulnerability to AS-induced immune and microbial perturbations. Similarly, the metabolic state axis integrates pediatric obesity risk, diabetes management challenges, and age-related metabolic comorbidities through common dysregulation of glucose-lipid homeostasis and microbial-metabolic crosstalk. This axis-based framework transcends traditional demographic categorization, revealing that AS responses are governed by physiological state rather than age or diagnosis alone. Such mechanistic heterogeneity challenges one-size-fits-all safety paradigms and necessitates a shift toward population-tailored dietary guidance informed by host-microbiota-physiological axis interactions.

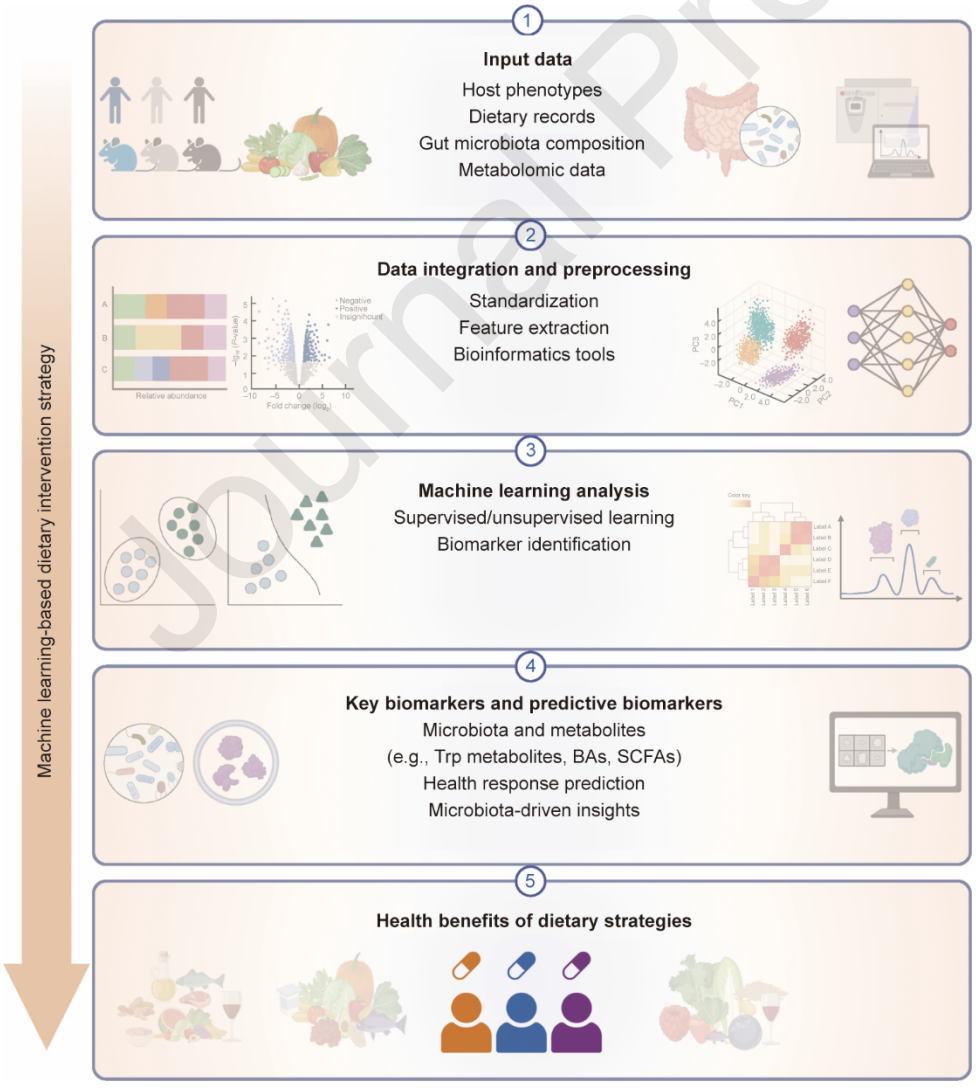


Fig. 4. Integrating machine learning to assess and mitigate health risks associated with artificial sweeteners. Data acquisition from multi-omics sources such as metagenomics, metabolomics, and dietary records, followed by data preprocessing and feature extraction to identify critical patterns. Machine learning models are applied to analyze these patterns, uncover biomarkers (e.g., microbial taxa or metabolites), and predict individual responses to ASs consumption. Insights from these analyses inform precision dietary interventions aimed at mitigating adverse health effects while advancing our understanding of the long-term effects of ASs on host health. Trp: tryptophan.

Several considerations remain to be addressed. Current research often aggregates different AS types, overlooking potential variations in how sucralose, aspartame, Ace-K, or saccharin interact with microbial communities. Additionally, large-scale studies focusing on population-specific responses are still scarce. Moving forward, prioritizing targeted investigations into these population groups will be pivotal. Regulatory efforts should focus on enhancing labeling transparency to support informed choices, particularly for special needs populations. It is also worth noting that natural sugar substitutes warrant similar scrutiny. High-fat diets, for example, can induce sorbitol intolerance following antibiotic-induced *Clostridia* depletion, exacerbating intestinal inflammation and disrupting homeostasis [82]; trehalose has been linked to enhanced *C. difficile* virulence [83]; and erythritol has been associated with increased cardiovascular risk [84]. These observations emphasize the need for systematic evaluation of all sugar substitutes, both artificial and natural, through the lens of host-microbiota interactions. Ultimately, the goal is not to overstate risks but to develop a contextual understanding that maximizes the practical benefits of ASs (such as aiding glycemic control in diabetes) while mitigating potential adverse effects. By centering population-specific microbiota profiles in future research, we can refine dietary strategies to enable the effective and safe use of ASs as part of personalized nutritional management.

Probiotic supplementation, dietary fiber enrichment, and personalized dietary adjustments represent feasible interventions to restore microbial balance and counteract AS-induced dysbiosis, particularly in vulnerable populations (e.g., elderly, immunocompromised, IBD patients) where baseline microbiota instability amplifies susceptibility. Early microbial intervention in these groups holds translational promise for the reduction of AS-related metabolic and immune perturbations [108,109].

As conceptualized in Fig. 4, precision application of ASs can be operationalized as a stepwise integration of three contextual inputs: ① host physiological status (immune competence, metabolic state, developmental stage); ② microbiota-derived metabolic readouts (BA composition, indole derivatives, SCFA profiles, LPS burden); and ③ dietary or pharmacological co-exposures. This framework yields stratified assessments that identify populations who may benefit from AS use (e.g., glycemic control in diabetes) versus those requiring heightened caution, monitoring, or dietary alternatives. Notably, habitual dietary patterns further modulate AS–microbiota interactions: high-fiber diets, prevalent in many Asian populations, support microbial diversity and SCFA production, potentially buffering AS-induced perturbations, whereas high-fat Western-style diets may exacerbate microbial instability and inflammatory signaling. Given the global heterogeneity in AS consumption (Fig. 1), integrating cultural dietary context represents a critical future direction for refining risk assessment.

The goal is not to overstate risks but to develop a contextual understanding that maximizes AS benefits (e.g., aiding glycemic control) while mitigating adverse effects. By centering population-specific microbiota profiles in future research and regulatory frameworks, we can refine dietary strategies to enable the effective and safe use of ASs as part of personalized nutritional management.

Author contributions

Jie Cai: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Qingping Wu:** Project administration, Supervision. **Alaa El-Din Ahmed Bekhit:** Writing – review & editing. **Juan Wang:** Resources, Writing – review & editing. **Yu-Long Li:** Writing – review & editing. **Rong Huang:** Visualization. **Fen Zhang:** Writing – review & editing. **Hang Xiao:** Writing – review & editing. **Zhenjun Zhu:** Conceptualization, Funding acquisition, Supervision, Visualization, Writing – review & editing. **Yu Ding:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the Guangdong Basic and Applied Basic Research Foundation (2025A1515011242 and 2023A1515010744), the National Natural Science Foundation of China (32202014), and the State Key Laboratory of Applied Microbiology Southern China (SKLAM002-2022).

References

[1] Sylvetsky AC, Jin Y, Clark EJ, Welsh JA, Rother KI, Talegawkar SA. Consumption of low-calorie sweeteners among children and adults in the United States. J Acad Nutr Diet 2017;117(3):441–8.e2.

[2] Li D, Zheng Q, Wang Z, Ren Y, Thomas KV, Thai PK. Young population consume twice as much artificial sweetener than the general population—a wastewater-based assessment in China. Sci Total Environ 2022;839:156200.

[3] Market Data Forecast. Global artificial sweetener market by type (aspartame, acesulfame-K, monosodium glutamate, saccharin, and sodium benzoate), by application (bakery items, dairy products, confectionery, beverages, and other), by distribution channel (supermarkets & hypermarkets, departmental stores, convenience stores, and others) and by regional analysis (North America, Europe, Asia Pacific, Latin America, and Middle East & Africa)—global industry analysis, size, share, growth, trends, and forecast (2022–2027). Report. Hyderabad: Market Data Forecast; 2022.
[4] World Health Organization (WHO). Use of non-sugar sweeteners: WHO guideline. Report. Geneva: World Health Organization; 2023
[5] Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 2014;514(7521):181–6.
[6] Suez J, Cohen Y, Valdés-Mas R, Mor U, Dori-Bachash M, Federici S, et al. Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. Cell 2022;185(18):3307–3328.e19.
[7] Chi L, Yang Y, Bian X, Gao B, Tu P, Ru H, et al. Chronic sucralose consumption inhibits farnesoid X receptor signaling and perturbs lipid and cholesterol homeostasis in the mouse livers, potentially by altering gut microbiota functions. Sci Total Environ 2024;919:169603.
[8] Shi Z, Lei H, Chen G, Yuan P, Cao Z, Ser HL, et al. Impaired intestinal Akkermansia muciniphila and aryl hydrocarbon receptor ligands contribute to nonalcoholic fatty liver disease in mice. mSystems 2021;6(1):e00985-e20.
[9] Debras C, Deschasaux-Tanguy M, Chazelas E, Sellem L, Druesne-Pecollo N, Esseddik Y, et al. Artificial sweeteners and risk of type 2 diabetes in the prospective nutrinet-santé cohort. Diabetes Care 2023;46(9):1681–90.
[10] Heo GY, Koh HB, Park JT, Han SH, Yoo TH, Kang SW, et al. Sweetened beverage intake and incident chronic kidney disease in the UK Biobank study. JAMA Netw Open 2024;7(2):e2356885.
[11] Chazelas E, Debras C, Srour B, Fezeu LK, Julia C, Hercberg S, et al. Sugary drinks, artificially-sweetened beverages, and cardiovascular disease in the nutrinet-santé cohort. J Am Coll Cardiol 2020;76(18):2175–7.
[12] Debras C, Chazelas E, Srour B, Druesne-Pecollo N, Esseddik Y, Szabo de Edelenyi F, et al. Artificial sweeteners and cancer risk: results from the NutriNet-Santé population-based cohort study. PLoS Med 2022;19(3):e1003950.
[13] Pan H, Feng C, Zhou Z, Huang J, Deng J, Zhou Y, et al. The causal association between artificial sweeteners and the risk of cancer: a Mendelian randomization study. Food Funct 2024;15(8):4527–37.
[14] Chen Y, Zhang Y, Yang H, Li H, Zhou L, Zhang M, et al. Associations of sugar-sweetened, artificially sweetened, and naturally sweet juices with Alzheimer's disease: a prospective cohort study. Geroscience 2024;46(1):1229–40.
[15] Castro A, Gili M, Visser M, Penninx BWJH, Brouwer IA, Montaño JJ, et al. Soft drinks and symptoms of depression and anxiety in overweight subjects: a longitudinal analysis of an european cohort. Nutrients 2023;15(18):3865.
[16] Liu D, Li ZH, Shen D, Zhang PD, Song WQ, Zhang WT, et al. Association of sugar-sweetened, artificially sweetened, and unsweetened coffee consumption with all-cause and cause-specific mortality: a large prospective cohort study. Ann Intern Med 2022;175(7):909–17.
[17] Cyphert EL, Liu C, Morales AL, Nixon JC, Blackford E, Garcia M, et al. Effects of long-term high-dose aspartame on body mass, bone strength, femoral geometry, and microbiota composition in a young and aged cohort of male and female mice. 2024. bioRxiv:573970
[18] Skurk T, Krämer T, Marcinek P, Malki A, Lang R, Dunkel A, et al. Sweetener system intervention shifted neutrophils from homeostasis to priming. Nutrients 2023;15(5):1260.
[19] Zhang X, Gu J, Zhao C, Hu Y, Zhang B, Wang J, et al. Sweeteners maintain epithelial barrier function through the mir-15b/reck/mmp-9 axis, remodel microbial homeostasis, and attenuate dextran sodium sulfate-induced colitis in mice. J Agric Food Chem 2022;70(1):171–83.
[20] Bian X, Tu P, Chi L, Gao B, Ru HY, Lu K, et al. Saccharin induced liver inflammation in mice by altering the gut microbiota and its metabolic functions. Food Chem Toxicol 2017;107:530–9.
[21] Bian X, Chi L, Gao B, Tu P, Ru H, Lu K. The artificial sweetener acesulfame potassium affects the gut microbiome and body weight gain in CD-1 mice. PLoS One 2017;12(6):e0178426.
[22] Zheng Z, Xiao Y, Ma L, Lyu W, Peng H, Wang X, et al. Low dose of sucralose alter gut microbiome in mice. Front Nutr 2022;9:848392.
[23] Hanawa Y, Higashiyama M, Kurihara C, Tanemoto R, Ito S, Mizoguchi A, et al. Acesulfame potassium induces dysbiosis and intestinal injury with enhanced lymphocyte migration to intestinal mucosa. J Gastroenterol Hepatol 2021;36(11):3140–8.
[24] Chi L, Bian X, Gao B, Tu P, Lai Y, Ru H, et al. Effects of the artificial sweetener neotame on the gut microbiome and fecal metabolites in mice. Molecules 2018;23(2):367.
[25] Mann ER, Lam YK, Uhlig HH. Short-chain fatty acids: linking diet, the microbiome and immunity. Nat Rev Immunol 2024;24(8):577–95.
[26] Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. Cell 2016;167(5):1339–1353.e21.
[27] Ducarmon QR, Zwittink RD, Hornung BVH, van Schaik W, Young VB, Kuijper EJ. Gut microbiota and colonization resistance against bacterial enteric infection. Microbiol Mol Biol Rev 2019;83(3):e00007-19.
[28] Rodriguez-Palacios A, Harding A, Menghini P, Himmelman C, Retuerto M, Nickerson KP, et al. The artificial sweetener Splenda promotes gut proteobacteria, dysbiosis, and myeloperoxidase reactivity in Crohn's disease-like ileitis. Inflamm Bowel Dis 2018;24(5):1005–20.
[29] Wang X, Guo J, Liu Y, Yu H, Qin X. Sucralose increased susceptibility to colitis in rats. Inflamm Bowel Dis 2019;25(2):e3–e4.
[30] Fuchs CD, Trauner M. Role of bile acids and their receptors in gastrointestinal and hepatic pathophysiology. Nat Rev Gastroenterol Hepatol 2022;19(7):432–50.
[31] Shi Z, Chen G, Cao Z, Wu F, Lei H, Chen C, et al. Gut microbiota and its metabolite deoxycholic acid contribute to sucralose consumption-induced nonalcoholic fatty liver disease. J Agric Food Chem 2021;69(13):3982–91.
[32] Rimal B, Collins SL, Tanes CE, Rocha ER, Granda MA, Solanki S, et al. Bile salt hydrolase catalyses formation of amine-conjugated bile acids. Nature 2024;626(8000):859–63.
[33] Dalenberg JR, Patel BP, Denis R, Veldhuizen MG, Nakamura Y, Vinke PC, et al. Short-term consumption of sucralose with, but not without, carbohydrate impairs neural and metabolic sensitivity to sugar in humans. Cell Metab 2020;31(3):493–502.e7.
[34] Chi L, Yang Y, Bian X, Gao B, Tu P, Ru H, et al. Chronic sucralose consumption inhibits farnesoid X receptor signaling and perturbs lipid and cholesterol homeostasis in the mouse livers, potentially by altering gut microbiota functions. Sci Total Environ 2024;919:169603.
[35] Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab 2019;30:72–130.
[36] Chen Y, Li Y, Fan Y, Chen S, Chen L, Chen Y, et al. Gut microbiota-driven metabolic alterations reveal gut-brain communication in Alzheimer's disease model mice. Gut Microbes 2024;16(1):2302310.
[37] Agus A, Planchais J, Sokol H. Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe 2018;23(6):716–24.
[38] Zhang Y, Tu S, Ji X, Wu J, Meng J, Gao J, et al. Dubosiella newyorkensis modulates immune tolerance in colitis via the L-lysine-activated AhR-IDO1-Kyn pathway. Nat Commun 2024;15(1):1333.
[39] Jia D, Wang Q, Qi Y, Jiang Y, He J, Lin Y, et al. Microbial metabolite enhances immunotherapy efficacy by modulating T cell stemness in pan-cancer. Cell 2024;187(7):1651–1665.e21.
[40] Yong CC, Sakurai T, Kaneko H, Horigome A, Mitsuyama E, Nakajima A, et al. Human gut-associated Bifidobacterium species salvage exogenous indole, a uremic toxin precursor, to synthesize indole-3-lactic acid via tryptophan. Gut Microbes 2024;16(1):2347728.
[41] Jin J, Wahlang B, Thapa M, Head KZ, Hardesty JE, Srivastava S, et al. Proteomics and metabolic phenotyping define principal roles for the aryl hydrocarbon receptor in mouse liver. Acta Pharm Sin B 2021;11(12):3806–19.
[42] Candellier A, Issa N, Grissi M, Brouette T, Avondo C, Gomila C, et al. Indoxyl-sulfate activation of the AhR-NF-κB pathway promotes interleukin-6 secretion and the subsequent osteogenic differentiation of human valvular interstitial cells from the aortic valve. J Mol Cell Cardiol 2023;179:18–29.

[43] Huang Y, Zhou J, Wang S, Xiong J, Chen Y, Liu Y, et al. Indoxyl sulfate induces intestinal barrier injury through IRF1-DRP1 axis-mediated mitophagy impairment. Theranostics 2020;10(16):7384–7400.
[44] Stone TW, Williams RO. Modulation of T cells by tryptophan metabolites in the kynurenine pathway. Trends Pharmacol Sci 2023;44(7):442–456.
[45] Xue C, Li G, Zheng Q, Gu X, Shi Q, Su Y, et al. Tryptophan metabolism in health and disease. Cell Metab 2023;35(8):1304–1326.
[46] Mann ER, Lam YK, Uhlig HH. Short-chain fatty acids: linking diet, the microbiome and immunity. Nat Rev Immunol 2024;24(8):577–95.
[47] Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science 2018;359(6380):1151–6.
[48] Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 2016;165(6):1332–45.
[49] Onodera T, Wang MY, Rutkowski JM, Deja S, Chen S, Balzer MS, et al. Endogenous renal adiponectin drives gluconeogenesis through enhancing pyruvate and fatty acid utilization. Nat Commun 2023;14(1):6531.
[50] Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest 2016;126(1):12–22.
[51] De Mets F, Van Melderen L, Gottesman S. Regulation of acetate metabolism and coordination with the TCA cycle via a processed small RNA. Proc Natl Acad Sci USA 2019;116(3):1043–52.
[52] Su H, Yuan P, Lei H, Zhang L, Deng D, Zhang L, et al. Long-term chronic exposure to di-(2-ethylhexyl)-phthalate induces obesity via disruption of host lipid metabolism and gut microbiota in mice. Chemosphere 2022;287(Pt 4):132414.
[53] Coutzac C, Jouniaux JM, Paci A, Schmidt J, Mallardo D, Seck A, et al. Systemic short chain fatty acids limit antitumor effect of CTLA-4 blockade in hosts with cancer. Nat Commun 2020;11(1):2168.
[54] Wang R, Yang X, Liu J, Zhong F, Zhang C, Chen Y, et al. Gut microbiota regulates acute myeloid leukaemia via alteration of intestinal barrier function mediated by butyrate. Nat Commun 2022;13(1):2522.
[55] Hays KE, Pfaffinger JM, Ryznar R. The interplay between gut microbiota, short-chain fatty acids, and implications for host health and disease. Gut Microbes 2024;16(1):2393270.
[56] Guo M, Liu X, Tan Y, Kang F, Zhu X, Fan X, et al. Sucralose enhances the susceptibility to dextran sulfate sodium (DSS) induced colitis in mice with changes in gut microbiota. Food Funct 2021;12(19):9380–90.
[57] Bishop RE. Structure of a lipopolysaccharide regulator reveals a road to new antibiotics. Nature 2020;584(7821):348–9.
[58] Park BS, Lee JO. Recognition of lipopolysaccharide pattern by TLR4 complexes. Exp Mol Med 2013;45(12):e66.
[59] Gu C, Wang F, Zhang YT, Wei SZ, Liu JY, Sun HY, et al. Microglial MT1 activation inhibits LPS-induced neuroinflammation via regulation of metabolic reprogramming. Aging Cell 2021;20(6):e13375. Corrected in: Aging Cell 2024;23(2):e14068.
[60] Valadez-Cosmes P, Raftopoulou S, Mihalic ZN, Marsche G, Kargl J. Myeloperoxidase: growing importance in cancer pathogenesis and potential drug target. Pharmacol Ther 2022;236:108052.
[61] Arnold S, Kitching AR, Witko-Sarsat V, Wiech T, Specks U, Klapa S, et al. Myeloperoxidase-specific antineutrophil cytoplasmic antibody-associated vasculitis. Lancet Rheumatol 2024;6(5):e300–e313.
[62] Dai X, Wang C, Guo Z, Li Y, Liu T, Jin G, et al. Maternal sucralose exposure induces Paneth cell defects and exacerbates gut dysbiosis of progeny mice. Food Funct 2021;12(24):12634–46.
[63] Yu S, Balasubramanian I, Laubitz D, Tong K, Bandyopadhyay S, Lin X, et al. Paneth cell-derived lysozyme defines the composition of mucolytic microbiota and the inflammatory tone of the intestine. Immunity 2020;53(2):398–416.e8.
[64] Olivier-Van Stichelen S, Rother KI, Hanover JA. Maternal exposure to non-nutritive sweeteners impacts progeny's metabolism and microbiome. Front Microbiol 2019;10:1360.
[65] Zani F, Blagih J, Gruber T, Buck MD, Jones N, Hennequart M, et al. The dietary sweetener sucralose is a negative modulator of T cell-mediated responses. Nature 2023;615(7953):705–11.
[66] Fong W, Li Q, Ji F, Liang W, Lau HCH, Kang X, et al. Lactobacillus gallinarum-derived metabolites boost anti-PD1 efficacy in colorectal cancer by inhibiting regulatory T cells through modulating IDO1/Kyn/AHR axis. Gut 2023;72(12):2272–85.
[67] Martínez-Carrillo BE, Rosales-Gómez CA, Ramírez-Durán N, Reséndiz-Albor AA, Escoto-Herrera JA, Mondragón-Velásquez T, et al. Effect of chronic consumption of sweeteners on microbiota and immunity in the small intestine of young mice. Int J Food Sci 2019;2019:9619020.
[68] Ishihara Y, Kado SY, Hoeper C, Harel S, Vogel CFA. Role of NF-κB RelB in aryl hydrocarbon receptor-mediated ligand specific effects. Int J Mol Sci 2019;20(11):2652.
[69] Mercer EM, Ramay HR, Moossavi S, Laforest-Lapointe I, Reyna ME, Becker AB, et al. Divergent maturational patterns of the infant bacterial and fungal gut microbiome in the first year of life are associated with inter-kingdom community dynamics and infant nutrition. Microbiome 2024;12(1):22.
[70] Tapia-González A, Vélez-Ixta JM, Bueno-Hernández N, Piña-Escobedo A, Briones-Garduño JC, de la Rosa-Ruiz L, et al. Maternal consumption of non-nutritive sweeteners during pregnancy is associated with alterations in the Colostrum microbiota. Nutrients 2023;15(23):4928.
[71] Govrins M, Lass-Flörl C. Candida parapsilosis complex in the clinical setting. Nat Rev Microbiol 2024;22(1):46–59.
[72] Nagpal R, Mainali R, Ahmadi S, Wang S, Singh R, Kavanagh K, et al. Gut microbiome and aging: physiological and mechanistic insights. Nutr Healthy Aging 2018;4(4):267–85.
[73] Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduct Target Ther 2022;7(1):391.
[74] Martino C, Dilmore AH, Burcham ZM, Metcalf JL, Jeste D, Knight R. Microbiota succession throughout life from the cradle to the grave. Nat Rev Microbiol 2022;20(12):707–20.
[75] Siddiqui I, Majid H, Abid S. Update on clinical and research application of fecal biomarkers for gastrointestinal diseases. World J Gastrointest Pharmacol Ther 2017;8(1):39–46.
[76] Struijk EA, Fung TT, Rodriguez-Artalejo F, Bischoff-Ferrari HA, Willett WC, Lopez-Garcia E. Specific dairy foods and risk of frailty in older women: a prospective cohort study. BMC Med 2024;22(1):89.
[77] Guo X, Park Y, Freedman ND, Sinha R, Hollenbeck AR, Blair A, et al. Sweetened beverages, coffee, and tea and depression risk among older US adults. PLoS One 2014;9(4):e94715.
[78] Morder KM, Nguyen M, Wilfahrt DN, Dahmani ZL, Burr ABP, Xie B, et al. Sucralose consumption ablates cancer immunotherapy response through microbiome disruption. Cancer Discov 2025;15(11):2278–97.
[79] Levine A, Rhodes JM, Lindsay JO, Abreu MT, Kamm MA, Gibson PR, et al. Dietary guidance from the International Organization for the study of inflammatory bowel diseases. Clin Gastroenterol Hepatol 2020;18(6):1381–92.
[80] Rodriguez-Palacios A, Basson AR, Cominelli F. Artificial sweeteners and whole-food science: could mice help clinicians make diet recommendations for IBD patients? Gastroenterology 2021;161(1):8–14.
[81] Li X, Liu Y, Wang Y, Li X, Liu X, Guo M, et al. Sucralose promotes colitis-associated colorectal cancer risk in a murine model along with changes in microbiota. Front Oncol 2020;10:710.
[82] Lee JY, Tiffany CR, Mahan SP, Kellom M, Rogers AWL, Nguyen H, et al. High fat intake sustains sorbitol intolerance after antibiotic-mediated Clostridia depletion from the gut microbiota. Cell 2024;187(5):1191–1205.e15.
[83] Collins J, Robinson C, Danhof H, Knetsch CW, van Leeuwen HC, Lawley TD, et al. Dietary trehalose enhances virulence of epidemic Clostridium difficile. Nature 2018;553(7688):291–4.

[84] Witkowski M, Nemet I, Alamri H, Wilcox J, Gupta N, Nimer N, et al. The artificial sweetener erythritol and cardiovascular event risk. Nat Med 2023;29(3):710–8.
[85] Yu Z, Henderson IR, Guo J. Non-caloric artificial sweeteners modulate conjugative transfer of multi-drug resistance plasmid in the gut microbiota. Gut Microbes 2023;15(1):2157698.
[86] Yu Z, Wang Y, Henderson IR, Guo J. Artificial sweeteners stimulate horizontal transfer of extracellular antibiotic resistance genes through natural transformation. ISME J 2022;16(2):543–54.
[87] Yu Z, Wang Y, Lu J, Bond PL, Guo J. Nonnutritive sweeteners can promote the dissemination of antibiotic resistance through conjugative gene transfer. ISME J 2021;15(7):2117–30.
[88] Maslowska KH, Makiela-Dzbenska K, Fijalkowska IJ. The SOS system: a complex and tightly regulated response to DNA damage. Environ Mol Mutagen 2019;60(4):368–84.
[89] Pei Z, Liu Y, Chen Y, Pan T, Sun X, Wang H, et al. A universe of human gut-derived bacterial prophages: unveiling the hidden viral players in intestinal microecology. Gut Microbes 2024;16(1):2309684.
[90] Dahlman S, Avellaneda-Franco L, Rutten EL, Gulliver EL, Solari S, Chonwerawong M, et al. Isolation, engineering and ecology of temperate phages from the human gut. Nature 2025;647(8090):698–705.
[91] Boling L, Cuevas DA, Grasis JA, Kang HS, Knowles B, Levi K, et al. Dietary prophage inducers and antimicrobials: toward landscaping the human gut microbiome. Gut Microbes 2020;11(4):721–34.
[92] Kerr JA, Patton GC, Cini KI, Abate YH, Abbas N, Abd Al Magied AHA, et al.. Global, regional, and national prevalence of child and adolescent overweight and obesity, 1990–2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. Lancet 2025;405(10481):785–812.
[93] Lara-Castor L, Micha R, Cudhea F, Miller V, Shi P, Zhang J, et al.. Intake of sugar sweetened beverages among children and adolescents in 185 countries between 1990 and 2018: population based study. BMJ 2024;386:e079234.
[94] Baker-Smith CM, de Ferranti SD, Cochran WJ, Abrams SA, Fuchs GJ III, Kim JH, et al. The use of nonnutritive sweeteners in children. Pediatrics 2019;144(5):e20192765.
[95] Espinosa A, Mendoza K, Laviada-Molina H, Rangel-Méndez JA, Molina-Segui F, Sun Q, et al. Effects of non-nutritive sweeteners on the BMI of children and adolescents: a systematic review and meta-analysis of randomised controlled trials and prospective cohort studies. Lancet Glob Health 2023;11Suppl 1:S8.
[96] Espinosa A, Mendoza K, Laviada-Molina H, Rangel-Méndez JA, Molina-Segui F, Sun Q, et al. Effects of non-nutritive sweeteners on the BMI of children and adolescents: a systematic review and Meta-analysis of randomized controlled trials and prospective cohort studies. Adv Nutr 2024;15(12):100292.
[97] Chakravartti SP, Jann K, Veit R, Liu H, Yunker AG, Angelo B, et al. Non-caloric sweetener effects on brain appetite regulation in individuals across varying body weights. Nat Metab 2025;7(3):574–85.
[98] Jian C, Carpén N, Helve O, de Vos WM, Korpela K, Salonen A. Early-life gut microbiota and its connection to metabolic health in children: perspective on ecological drivers and need for quantitative approach. EBioMedicine 2021;69:103475.
[99] Derrien M, Alvarez AS, de Vos WM. The gut microbiota in the first decade of life. Trends Microbiol 2019;27(12):997–1010.
[100] Daoust L. Artificial sweeteners and type 2 diabetes. Nat Food 2023;4(9):739.
[101] Thomson P, Santibañez R, Aguirre C, Galgani JE, Garrido D. Short-term impact of sucralose consumption on the metabolic response and gut microbiome of healthy adults. Br J Nutr 2019;122(8):856–62.
[102] Sun L, Xie C, Wang G, Wu Y, Wu Q, Wang X, et al. Gut microbiota and intestinal FXR mediate the clinical benefits of metformin. Nat Med 2018;24(12):1919–29.
[103] Laforest-Lapointe I, Becker AB, Mandhane PJ, Turvey SE, Moraes TJ, Sears MR, et al. Maternal consumption of artificially sweetened beverages during pregnancy is associated with infant gut microbiota and metabolic modifications and increased infant body mass index. Gut Microbes 2021;13(1):e1857513.
[104] Azad MB, Sharma AK, de Souza RJ, Dolinsky VW, Becker AB, Mandhane PJ, et al. Association between artificially sweetened beverage consumption during pregnancy and infant body mass index. JAMA Pediatr 2016;170(7):662–70.
[105] Bridge-Comer PE, Vickers MH, Ferraro S, Pagnon A, Reynolds CM, Sigaudo-Roussel D. Maternal intake of either fructose or the artificial sweetener acesulfame-K results in differential and sex-specific alterations in markers of skin inflammation and wound healing responsiveness in mouse offspring: a pilot study. Nutrients 2023;15(11):2534.
[106] Park S, Belfoul AM, Rastelli M, Jang A, Monnoye M, Bae H, et al. Maternal low-calorie sweetener consumption rewires hypothalamic melanocortin circuits via a gut microbial co-metabolite pathway. JCI Insight 2023;8(10):e156397.
[107] Stockinger B, Shah K, Wincent E. AHR in the intestinal microenvironment: safeguarding barrier function. Nat Rev Gastroenterol Hepatol 2021;18(8):559–70.
[108] Feng J, Peng J, Hsiao YC, Liu CW, Yang Y, Zhao H, et al. Non/low-caloric artificial sweeteners and gut microbiome: from perturbed species to mechanisms. Metabolites 2024;14(10):544.
[109] Hetta HF, Sirag N, Elfadil H, Salama A, Aljadrawi SF, Alfaifi AJ, et al. Artificial sweeteners: a double-edged sword for gut microbiome. Diseases 2025;13(4):115.

Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: