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Original Research Article

Non-Nutritive Sweeteners and Weight Regulation in Healthy Adults: Current Evidence and Public Health Implications

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Abstract

The use of non-nutritive sweeteners (NNS) as sugar replacements has become widespread as a strategy to reduce caloric intake, thereby supporting weight management, and reduce sugar consumption in modern diets. However, their effectiveness in preventing weight gain in healthy adults remains controversial.

This review aims to evaluate the current evidence regarding the impact of NNS consumption on body weight regulation and metabolic health in healthy adults.

This narrative review synthesizes findings from randomized controlled trials, prospective cohort studies and mechanistic studies identified through a structured search of electronic databases. Emphasis was placed on studies assessing body weight, energy intake, metabolic responses, appetite regulation and gut microbiota.

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Evidence from randomized controlled trials indicates that replacing sugars with NNS may reduce energy intake, body weight and body mass index in the short term. In contrast, long-term observational studies report associations between habitual NNS consumption and higher body weight, waist circumference and risk of cardiometabolic disorders, although causality remains uncertain. Mechanistic studies suggest that these effects may be mediated by context-dependent physiological responses, including variable incretin secretion, changes in reward-related responses and potential changes in gut microbiota composition.

NNS may be effective as a short-term strategy for reducing caloric intake; however, their long-term role in preventing weight gain in healthy individuals remains unclear. Further well-designed long-term studies are needed to clarify these relationships.

Introduction

Obesity is a complex multifactorial disease. The global prevalence of overweight and obesity has increased dramatically since 1980, to the extent that nearly one-third of the global population is now classified as overweight or obese (Li et al. 2026). Leading authorities and researchers concur that despite sugars remaining a staple of the human diet, their excessive consumption has been associated with the increasing prevalence of obesity and associated metabolic dysfunctions (Rogers, Appleton 2020; Walbolt, Koh 2020).

Nonetheless, the prevalence of high sugar intake is not unexpected, as evolutionary mechanisms link sweetness with nutrient-dense food sources essential for survival (Pearlman et al. 2017). To address this preference for sweetness, considerable research efforts have focused on identifying non-nutritive sweeteners (NNS) that provide the desired sensory profile without the associated caloric load. Consequently, their market presence and consumption have grown consistently over recent decades, and they are widely promoted as a weight-management tool, despite the ongoing scientific debate regarding their long-term efficacy (Chia et al. 2016).

Although some studies suggest that NNS may support short-term weight management, their long-term effects in healthy individuals remain uncertain.

This review aims to integrate clinical, neurobiological and microbiome-related evidence to provide a comprehensive perspective on the role of NNS in weight regulation.

Material and methods

This narrative review was conducted to synthesize current evidence on the effects of NNS on body weight regulation and metabolic health in healthy adults. A structured literature search was performed using electronic databases including PubMed and Scopus. Reference lists of relevant reviews and eligible articles were also screened to identify additional studies that met the inclusion criteria.

The search strategy combined keywords related to NNS and metabolic outcomes, including: "non-nutritive sweeteners", "artificial sweeteners", "low-calorie sweeteners", "body weight", "BMI", "obesity", "gut microbiota", "appetite" and "metabolism". Boolean operators (AND, OR) were applied to refine the search.

Studies published in English between 2000 and 2025 were considered. Priority was given to randomized controlled trials (RCTs), systematic reviews and meta-analyses, while relevant prospective cohort studies and mechanistic studies were also included to provide a broader physiological context.

Inclusion criteria included studies published in English between 2000 and 2025, conducted in human populations, particularly healthy adults, studies evaluating body weight, body mass index (BMI), metabolic biomarkers appetite regulation, or gut microbiota, as well as both interventional and observational designs.

Exclusion criteria included studies conducted exclusively in paediatric or diseased populations (unless mechanistically relevant) and articles lacking full text or methodological transparency.

Given the narrative nature of this review, no formal meta-analysis or risk-of-bias assessment was performed. However, priority was given to RCTs, systemic reviews, meta-analyses and large prospective cohort studies. Additionally, studies published in high-impact peer-reviewed journals and those frequently cited within the field were preferentially included to ensure a balanced and comprehensive overview of the available evidence.

Impact of NNS on Weight and BMI in Clinical Contexts

The metabolic impact of NNS is increasingly recognized as context-dependent, with effects significantly modulated by both the duration of NNS intake and the individual's baseline BMI. Importantly, RCTs provide the highest level of evidence for causal inference regarding body weight outcomes, whereas findings from observational studies should be interpreted cautiously due to potential confounding and reverse causality. These findings are most evident in RCT and prospective cohort studies, and these differences are likely driven by distinct underlying physiological mechanisms.

Extensive data from RCTs indicate that substituting NNS for dietary sugar can support modest short-term reductions in body weight, particularly in individuals with obesity. A comprehensive systematic review and meta-analysis conducted in accordance with PRISMA guidelines, including trials with a duration of ≥4 weeks, concluded that this substitution promotes weight loss in both normal-weight and obese populations (Li et al. 2026). Furthermore, systematic reviews and meta-analyses of interventional studies lasting one week or

longer demonstrate that substituting sugar with low-calorie sweeteners (LCS) significantly reduces body weight, BMI and total energy intake. These findings remain consistent across both parallel-group and crossover trials, supporting the intended use of LCS (Rogers, Appleton 2020). Another meta-analysis investigating short-term RCTs consistently demonstrated significant body weight reduction associated with NNS interventions (Walbolt, Koh 2020).

However, evidence from multiple large longitudinal studies indicates a positive association between higher intake of synthetic sweeteners and increased BMI, although these findings do not establish causality and are likely influenced by residual confounding, baseline adiposity, dieting behaviour and reverse causality, whereby individuals at higher risk of obesity may preferentially consume NNS (Pearlman et al. 2017). Notably, the Baltimore Longitudinal Study of Aging, a large-scale cohort study involving 1,454 healthy adults with a median follow-up of 10 years (range: 0–28 years), demonstrated that participants without obesity at baseline who consumed LCS had a higher risk of developing obesity compared to LCS-non-users (Chia et al. 2016).

Moreover, a systematic review and meta-analysis of 30 prospective cohort studies including 405,907 non-obese healthy participants with a median follow-up of 10 years indicated that the consumption of NNS is associated with increased body weight and waist circumference, as well as a heightened risk of cardiometabolic pathologies such as hypertension, metabolic syndrome and type 2 diabetes (T2DM) (Azad et al. 2017). These findings are further corroborated by a World Health Organization (WHO) report, which confirms an increased risk of weight gain based on data from 13 prospective cohort studies (Rios-Leyvraz, Montez 2022). Correspondingly, evidence from several other cohorts suggests that the intake of NNS correlates with elevated levels of visceral adipose tissue over a decade of observation (Sylvetsky, Rother 2018). Importantly, these observational findings should not be interpreted as evidence that NNS directly cause weight gain, as they contrast with the results of (RCTs), which consistently demonstrate neutral or modestly beneficial effects on body weight when NNS replace caloric sugars.

Nevertheless, research shows that short-term LCS consumption in healthy normal-weight adults does not result in significant body weight changes or other metabolic parameters, such as insulin, glucose and leptin levels, compared to the baseline values (Ahmad et al. 2020; Bayındır Gümüş et al. 2022; Sylvetsky et al. 2016). However, as these trials are often limited by small sample sizes, further investigation is needed to address this question definitively.

Taken together, the available evidence suggests that the efficacy of NNS on body weight is strongly context-dependent. The highest-quality evidence from RCTs supports the conclusion that replacing dietary sugars with NNS may reduce energy intake and promote modest short-term weight loss. In contrast, evidence suggesting adverse long-term outcomes originates primarily from observational

studies, where residual confounding and reverse causality limit causal interpretation. Specifically, sugar substitutes appear most effective as a short-term strategy, whereas their long-term effectiveness for preventing weight gain in healthy populations remains uncertain rather than demonstrably harmful.

These discrepancies between interventional and observational evidence highlight the importance of considering study design when interpreting the effects of NNS on body weight and metabolic health.

A simplified overview of the current evidence across different study designs, reflecting differences in the strength of evidence and causal inference, is presented in table 1.

Table 1. A simplified overview of the current evidence across different study designs

Evidence type	Main finding
RCTs	Replacement of dietary sugars with NNS is associated with short-term reductions in energy intake and modest weight loss
Observational studies	Positive associations with weight gain have been reported; however, these findings are likely influenced by confounding factors and reverse causality, and causal relationship remain unconfirmed
Mechanistic studies	Context-dependent metabolic effects that generate biological hypotheses but do not establish clinical causality
Neurobiological studies	Differences in reward-related responses
Microbiota studies	Potential alterations; human evidence remains limited and heterogeneous

Notes: RCTs – randomized controlled trials; NNS – non-nutritive sweeteners

Source: own work.

Potential Neurobiological Mechanisms of NNS

NNS are widely used as sugar substitutes with the aim of reducing caloric intake and preventing weight gain. However, their efficacy in healthy adults remains a subject of ongoing debate (Hedrick et al. 2023). Understanding the neurobiological mechanisms underlying appetite regulation is crucial for assessing whether these compounds promote or counteract long-term energy balance (Yunker et al. 2020). In particular, the interaction between sweet-taste perception, metabolic signalling and central reward pathways may play a critical role in determining the effects of NNS on eating behaviours and body weight regulation (Yeung, Wong 2020).

Sweet-taste perception is mediated primarily by T1R2 and T1R3 receptors, which form a receptor complex (T1R2/T1R3) activated by sugars, artificial sweeteners, and sweet proteins (Lee, Owyang 2017). These receptors are not

confined to the oral cavity but are also expressed in the gastrointestinal tract, pancreas, and central nervous system, indicating their broader role in systemic metabolic regulation (von Molitor et al. 2021). In the intestine, activation of these receptors contributes to the regulation of glucose transporters and stimulates the release of incretin hormones such as glucagon-like peptide-1 (GLP-1), thereby preparing the organism for incoming nutrients (Kreuch et al. 2018). GLP-1 plays a key role in appetite regulation by promoting satiety, slowing gastric emptying, and linking peripheral nutrient sensing with central pathways involved in energy homeostasis (Holst 2007).

Evidence from controlled human studies indicates that NNS do not consistently stimulate incretin secretion when consumed in isolation. Erythritol ingestion did not alter GLP-1 release in lean or obese individuals in a randomized crossover study (Overduin et al. 2016). Acute administration of sucralose in water had no effect on GLP-1 responses in healthy adults. However, when NNS are consumed in combination with, or prior to, a glucose load, an augmentation of glucose-stimulated GLP-1 secretion has been observed, particularly with diet beverages containing mixed sweeteners (Sylvetsky et al. 2016; Temizkan et al. 2015). Given the role of GLP-1 in appetite regulation, these findings suggest that incretin responses to NNS are context-dependent rather than inherent to sweet-taste receptor activation alone. This may indicate a variable rather than consistent role of NNS in appetite regulation. As GLP-1 contributes to satiety and reduced energy intake (Müller et al. 2019), its inconsistent stimulation by NNS may suggests that these compounds may have limited efficacy in supporting appetite control and long-term weight maintenance in healthy individuals.

Sweet taste may function not only as a sensory stimulus, but also as a predictive signal of caloric intake (Han et al. 2019). Despite activating the same receptors as sugars, NNS provide little or no metabolic energy. This creates a physiological scenario in which sensory input does not match post-ingestive outcomes, potentially disrupting established regulatory pathways (Suez et al. 2022). One proposed mechanism linking sweet-taste perception to metabolic responses is the early insulin response triggered by sensory stimulation. It is defined as an early release of insulin triggered by sensory stimuli prior to nutrient absorption (Pullicin et al. 2021). Recent studies from 2021 to 2026 have demonstrated that exposure to sweet stimuli can induce measurable increases in insulin and C-peptide levels shortly after oral stimulation (Pullicin, Lim 2026). However, the magnitude of this response is generally small, and current evidence suggests it does not play a major role in the regulation of appetite in healthy humans (Lasschuijt et al. 2020).

A more speculative explanation for the effects of NNS lies in sensory-metabolic uncoupling. Under physiological conditions, sweet taste serves as a predictive signal of caloric intake, reinforcing neural pathways involved in feeding behaviour (Swithers 2013). However, repeated exposure to NNS may introduce

a mismatch between sensory perception and actual energy delivery, potentially weakening the predictive value of sweetness (Sylvetsky, Rother 2018). This mismatch may disrupt the learnt association between sweet taste and post-ingestive metabolic signals, potentially engaging neural circuits involved in reward and compensatory feeding behaviour (Coccurello 2025). However, current evidence in healthy adults remains mixed, and it is not yet clear to what extent these neurobiological effects translate into real-world weight or obesity outcomes.

Neuroimaging evidence provides further insight into these mechanisms. Studies show that caloric sugars and NNS can elicit distinct patterns of brain activation. Functional Magnetic Resonance Imaging (fMRI) studies indicate that while both types of stimuli engage primary taste regions such as the insula, differences in activation across reward-related areas, including the striatum and anterior cingulate cortex, have been observed, although findings are not entirely consistent across studies (Smeets et al. 2025; Yeung, Wong 2020). Systematic analyses further suggest that neural responses to sweet stimuli vary depending on caloric content and experimental context, reflecting differences in how the brain encodes sweetness and energy value (Budzinska et al. 2025).

Taken together, these findings suggest that neurobiological responses to NNS are complex and context-dependent, and their impact on appetite regulation in healthy individuals remains uncertain.

Impact of NNS on Human Gut Microbiota and Metabolic Responses

The human gut microbiota is a complex community of microorganisms living in the digestive system, which are essential for maintaining normal gut physiology and general health (Thursby, Juge 2017). Historically considered metabolically inert, the physiological role of low/no-calorie sweeteners (LNCS) has been reassessed following the findings of Suez et al. (2014). This study suggested that LNCS intake may alter the composition and function of the gut microbiota, prompting a broader investigation into their metabolic implications (Lobach et al. 2019). There are several hypotheses on the pathophysiological mechanisms that are associated with the influence of the use of NNSs and gut microbiota on obesity development (Kossiva et al. 2024).

Persistent consumption of some NNS, such as saccharin, aspartame, sucralose, and acesulfame K has been suggested to modulate the intestinal microbiota architecture. This shift not only favours the proliferation of pro-inflammatory taxa but also interferes with the biosynthesis of microbial signalling molecules implicated in systemic homeostatic pathways by reductions in Short-Chain Fatty Acids (SCFA)-producing bacteria like *Lactobacillus*, *Faecalibacterium* and *Roseburia* (Coccurello 2025). SCFAs play a key role in lipid and glucose metabolism, and their reduced production may be associated with metabolic disturbances such as

glucose intolerance, dyslipidaemia, increased triglycerides and increased inflammation, although causal pathways remain to be fully established. Such changes may contribute to an increased risk of obesity, insulin resistance, T2DM, metabolic syndrome and cardiovascular conditions, including hypertension (M, Vellapandian 2024).

Beyond their effects on the gut microbiome, certain NNS, including sucralose, neotame and acesulfame K, have been shown to elicit a pro-inflammatory response within hepatic tissues. Mechanistically, these substances modulate redox-sensitive signalling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa B) and mitogen-activated protein kinase (MAPK). The activation of these cascades subsequently triggers the upregulation of downstream inflammatory effectors, including matrix metalloproteinase 2 (MMP-2) and inducible nitric-oxide synthase (iNOS), thereby exacerbating hepatic oxidative damage (Atalay et al. 2025; Feng et al. 2024). However, much of this evidence derives from preclinical models, and its direct relevance to human health remains uncertain.

Additionally, the alteration of microbiota composition promotes systemic oxidative stress by disrupting intestinal epithelial integrity and enabling lipopolysaccharide (LPS) translocation. The resulting endotoxemia aggravates hepatic inflammation and renal damage through the gut-liver and gut-kidney axes. This may further predispose the host to different inflammatory bowel diseases (Atalay et al. 2025; Hosseini et al. 2023).

Furthermore, another mechanism involves the modulation of gut microbial metabolic activity leading to host metabolic dysregulation. Functional pathway analysis conducted via Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2 (PICRUSt2), a bioinformatics tool used to predict the functional potential of microbial communities from sequencing data, and MetaCyc, a curated database of experimentally validated metabolic pathways, revealed a significant upregulation of methanogenesis within the NNS cohort (EASO Secretariat 2025). Intestinal methanogenesis is strongly implicated in the pathophysiology of gastrointestinal dysmotility, particularly chronic constipation and constipation-predominant irritable bowel syndrome, and has been increasingly linked to metabolic disorders, such as obesity (Triantafyllou et al. 2014).

Finally, some studies suggest that artificial sweeteners may be associated with an increased risk of glucose intolerance and metabolic dysregulation, although findings remain heterogenous (del Pozo et al. 2022). In animal models, aspartame intake has been linked to fasting hyperglycaemia and impaired insulin tolerance, a phenomenon observed independently of dietary fat consumption (Feng et al. 2024). Furthermore, evidence suggests that even short-term (one-week) exposure to sucralose and saccharin at doses below the acceptable daily intake can affect glycaemic responses in healthy individuals (Suez et al. 2022). While notable inter-individual variability exists, the ingestion of saccharin and sucralose

appears to impair glucose tolerance, whereas the effects of aspartame and stevia remain neutral during glucose challenge tests (Le Roy, Clément 2022). Ultimately, these disruptions in glucose tolerance and insulin sensitivity may serve as one of the factors potentially involved in obesity and T2DM development (Kahn, Flier 2000).

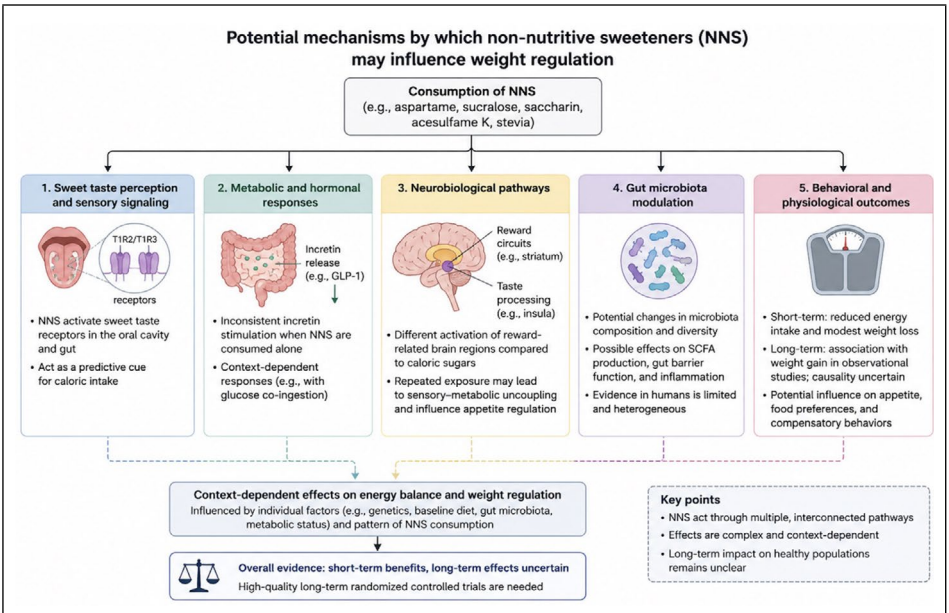

Figure 1. Potential Mechanisms by which NNS may Influence Weight Regulation

Alt-text: Schematic overview of the potential mechanisms by which non-nutritive sweeteners may influence body weight regulation, including appetite regulation, reward-related responses, incretin signalling and gut microbiota alterations.

Source: own work.

Recent findings highlight the need for further investigation into the long-term metabolic effects of NNS, highlighting a gap in our understanding of how they interface with the host microbiome (Conz et al. 2023). As evidenced above, NNS may directly modulate gut microbiota composition, thereby impairing host defence mechanisms and provoking inflammatory pathways. These alterations contribute to metabolic dysregulation and a shift toward an obesogenic microbiota profile, both of which are significant factors in the pathogenesis of obesity. However, each sweetener exerted unique influences on the composition and functional profiles of both oral and faecal microbiomes, suggesting that their biological impact is substance-specific (Le Roy, Clément 2022). Therefore, clarifying these pathways and more studies on humans are essential for a comprehensive risk assessment (Plaza-Diaz et al. 2020).

Importantly, a substantial proportion of the available evidence is derived from animal models or small-scale human studies, which may limit the generalizability of these findings to human populations.

The potential mechanisms underlying the effects of NNS on weight regulation are summarized in figure 1.

Practical Implications

NNS may be useful as a short-term strategy for reducing caloric intake and supporting weight management. However, their long-term use in healthy individuals should be approached with caution.

Public health recommendations should consider the context-dependent nature of NNS effects, including both behavioural and physiological responses. Additionally, increased awareness is needed regarding differences between specific types of sweeteners and their potential metabolic consequences. Healthcare professionals should emphasize overall dietary quality and lifestyle factors rather than relying solely on sugar substitution strategies.

Limitations

Several limitations should be considered when interpreting the available evidence. Many RCTs are short in duration and involve relatively small sample sizes. Observational studies are subject to confounding factors and reverse causality. Furthermore, heterogeneity in study design and types of sweeteners limits direct comparability across studies. Additionally, many mechanistic findings are derived from animal models, which may not fully translate to human physiology. Conversely, although (RCTs) provide the highest level of evidence for causal inference, many are limited by relatively short intervention periods, highlighting the need for well-designed long-term trials.

Conclusions

Evidence from RCTs indicates that replacing dietary sugars with NNS may reduce energy intake and support modest short-term weight loss. Evidence suggests that the relationship between NNS and weight management is complex and context-dependent, extending beyond simple caloric reduction. While short-term interventions often demonstrate modest benefits for weight loss, long-term observational studies have reported associations between NNS consumption and adverse metabolic outcomes; however, these associations do not establish causality and may be explained, at least in part, by residual confounding and reverse causality.

This discrepancy may partially reflect a combination of physiological and neurobiological mechanisms, including sensory-metabolic uncoupling and variable incretin responses. However, the extent to which these mechanisms translate into long-term clinical outcomes remains uncertain.

Importantly, current evidence does not allow for definitive conclusions regarding causality, and observed associations may be influenced by behavioural factors, including dietary patterns and reverse causality.

Furthermore, the impact of NNS on the gut microbiota represents one of the potential pathways linking their consumption to metabolic outcomes, although evidence in humans remains limited and heterogeneous.

In summary, the highest-quality evidence from RCTs supports the use of NNS as a short-term strategy for replacing dietary sugars, reducing caloric intake, and achieving modest weight loss. However, their role in the long-term prevention of weight gain in healthy populations remains uncertain, as current evidence is derived largely from observational studies that are susceptible to confounding and reverse causality. Therefore, further long-term randomized studies are required to clarify their sustained effects on body weight and metabolic health.

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Declaration of Generative AI Use

During the preparation of this manuscript, the authors used ChatGPT-5 powered by OpenAI solely to improve language clarity and assist in the preparation of Figure 1 based on concepts and mechanisms identified by the authors from the reviewed literature. The tool was not used to generate original scientific content, interpret study findings, or draw conclusions. All generated material was reviewed and edited by the authors, who take full responsibility for the content of this publication.

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