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Review Article

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Low- and no-calorie sweeteners and beverages and their associated health outcomes: an umbrella review of systematic reviews and meta-analyses

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ABSTRACT

BACKGROUND: Long-term health effects of low- and no-calorie sweeteners (LNCSs) have not been established.
OBJECTIVE: This review aimed to evaluate the associations between different types of LNCSs and a wide range of health outcomes from observational studies and randomized controlled trials (RCTs).
METHODS: We systematically searched PubMed/MEDLINE, Embase, CINAHL, and Google Scholar from inception to December 2024 for meta-analyses. LNCSs were categorized into artificial sweeteners and other non-sugar sweeteners (NSSs), including non-nutritive sweeteners and sugar alcohols, along with their corresponding beverages. The A Measurement Tool Assessment Systematic Reviews 2 (AMSTAR 2) tool was used in this study. The credibility of observational evidence was evaluated using a classification system. The certainty of evidence from RCTs was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Eligible meta-analyses were reanalyzed using random-effects models and presented as estimated odds ratios (eOR) or standard mean differences (SMDs) with 95% confidence intervals (CIs).
RESULTS: A total of 29 meta-analyses (AMSTAR 2: high, 22; moderate, 2; low, 3; and critically low, 2) with 24 observational studies and 6 RCTs, covering 50,034,327 participants, were

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Trial Registration

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Conflict of Interest

The authors declare no potential conflicts of interests.

Author Contributions

Conceptualization: Jeong J, Cho J, Jo Y, Yon DK; Data curation: Jeong J, Cho J, Jo Y, Yon DK; Formal analysis: Jeong J, Cho J, Jo Y, Yon DK; Investigation: Jeong J, Cho J, Jo Y, Yon DK; Supervision: Yon DK; Writing - original draft: Jeong J, Cho J, Jo Y, Yon DK; Writing - review & editing: Jeong J, Cho J, Jo Y, Yeo D, Hwang J, Son Y, Hong S, Woo S, Rahmati M, Smith L, Hajek A, Yon DK.

included. Among the 135 associations, observational studies indicated that higher intake of NSSs was associated with increased risk of being overweight (eOR, 1.84; 95% CI, 1.30 to 2.61; credibility of evidence [CE], IV), having metabolic syndrome (eOR, 1.31; 95% CI, 1.21 to 1.42; CE, I), type 2 diabetes (eOR, 1.14; 95% CI, 1.02 to 1.29; CE, IV), and hypertension (eOR, 1.13; 95% CI, 1.07 to 1.19; CE, II). In contrast, RCTs showed that NSS consumption significantly decreased body weight in populations with overweight or obesity (SMD, −0.50; 95% CI, −0.70 to −0.30; GRADE, high).

CONCLUSIONS: Our findings indicate that the use of LNCSs and their corresponding beverages is associated with potential health risks and modest benefits.

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Keywords: Beverages; health; sweetening agents; systematic review

INTRODUCTION

Increasing global rates of obesity, diabetes, and cardiovascular diseases (CVDs) have intensified efforts to reduce excessive sugar consumption [1]. Low- and no-calorie sweeteners (LNCSs) have emerged as widely promoted alternatives with dramatic increases in their use across diverse populations [2]. LNCSs include artificial sweeteners (ASs) and non-sugar sweeteners (NSSs) that comprise non-nutritive sweeteners (NNSs) and sugar alcohols. These sweeteners are commonly consumed in artificially sweetened beverages (ASBs) and low- and no-calorie sweetened beverages (LNCSBs). However, the long-term health effects of these substitutes remain controversial.

Growing concerns regarding LNCSBs have centered on their limited ability to provide clear health benefits in large-scale prospective cohort studies. Multiple influential systematic reviews and meta-analyses have reported that LNCSB consumption is associated with an increased risk of weight gain [3], type 2 diabetes [4], CVDs [5], and all-cause mortality [6]. However, the findings remain subject to uncertainty owing to the study designs, differences in LNCSB types, dose-response relationships, and population characteristics across studies. Analyses examining changes in LNCSB consumption over time and modeling their substitution for sugar-sweetened beverages (SSBs) have suggested more consistent and biologically plausible associations, although these approaches remain relatively underexplored [2,3,7]. Whether substituting LNCSBs for SSBs yields meaningful clinical or public health benefits remains an important but unresolved question.

To address the inherent biases in existing epidemiological evidence and to strengthen causal inferences, the present study aimed to conduct an umbrella review of meta-analyses of both observational studies and randomized controlled trials (RCTs). Thus, this review systematically evaluated the associations between different types of LNCSs and LNCSBs and a wide range of health outcomes, integrating the magnitude, consistency, and credibility of evidence (CE) to better inform clinical decision-making and public health policies.

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METHODS

Search strategy and selection criteria

This umbrella reviews synthesized evidence from meta-analyses of observational studies (including cohort and case-control designs) and RCTs that assessed the clinical health outcomes associated with LNCSs and LNCSBs. This systematic review article does not require Institutional Review Board approval. The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines [8] and was prospectively registered in PROSPERO (registration number: CRD420251006761) [9].

Two independent reviewers (JC and JJ) systematically searched PubMed/MEDLINE, Embase, CINAHL, and Google Scholar from inception to December 20, 2024, without applying any restrictions. The search targeted studies evaluating the clinical outcomes associated with LNCS or LNCSB intake using the terms ((non-sugar sweetener) OR (non-nutritive sweetener) OR (non-caloric) OR (low-caloric)) AND (meta), along with relevant variations. The clinical outcomes were defined as those reported in the original meta-analyses. In this review, LNCSs were categorized into ASs and other NSSs, with NSSs further including NNSs) (e.g., stevia and monk fruit) and sugar alcohols (e.g., xylitol and sorbitol). LNCSBs were classified as ASBs, LNCBs, or NNSBs.

Duplicate studies, systematic reviews without meta-analyses, reviews of meta-analyses lacking pooled estimates, non-English publications, studies with non-extractable data, and studies in which the exposure or outcomes did not align with the objectives of this review were excluded. When multiple meta-analyses examined the same association, the version that included the largest number of primary studies was selected for the analysis. Exposure levels (e.g., highest vs. lowest intake) were defined according to the original meta-analysis. In cases where standardized thresholds (e.g., ≥ 1 serving/day) were not reported, we adhered to the original authors' definitions and categorized comparisons accordingly.

The study selection process involved a manual review of the reference lists of eligible articles, with screening conducted at the levels of the title, abstract, and full text. An initial pool of 432 studies underwent title and abstract screening to assess relevance. Consequently, 35 studies met the predefined inclusion criteria (**Fig. 1**). A recursive search of the reference lists of the included studies was performed to identify additional eligible articles. Two reviewers (JC and JJ) independently evaluated the eligibility of each study. Discrepancies were resolved through discussion, and final decisions were confirmed in consultation with the corresponding author (DKY).

Data extraction and analysis

Two authors (JC and JJ) independently extracted data. For each included study, we extracted the following information: first author, year of publication, study design (RCT or observational), clinical outcomes, country, total sample size, number of included primary studies, characteristics of the study population (e.g., general population, children, or individuals with different weight statuses), type of LNCS or LNCSB exposure, analytical metrics (e.g., standardized mean difference [SMD], odds ratio [OR], relative risk [RR]), effect model used (random- or fixed-effects), and the corresponding 95% confidence interval (CI). To ensure comparability across studies, pooled effect sizes were recalculated where necessary, and effect measures were standardized by converting values (e.g., mean differences [MDs] and weighted mean differences [WMDs] to SMDs; RRs, hazard ratios

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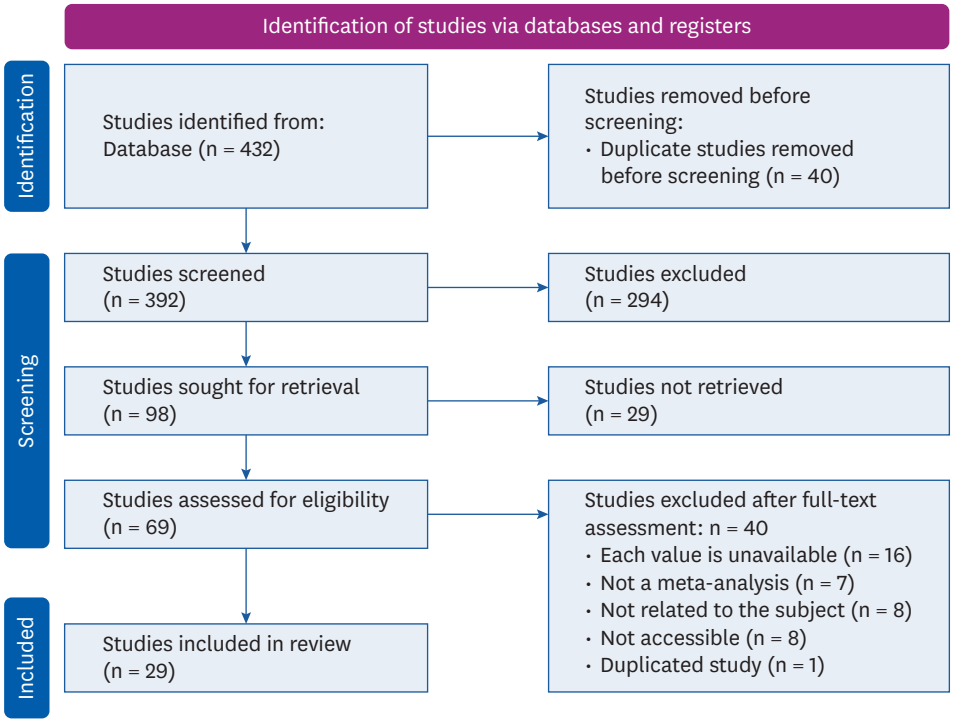

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram.

[HRs], and correlation coefficients to equivalent odds ratios [eORs]). Two independent reviewers (JC and JJ) evaluated the methodological quality of each included meta-analysis using the "A Measurement Tool Assessment Systematic Reviews 2" (AMSTAR 2) tool [10].

All included meta-analyses were reanalyzed using a random-effects model. For meta-analyses that included ≥ 10 primary studies, the DerSimonian and Laird method was used. In cases with < 10 studies, the Hartung–Knapp–Sidik–Jonkman method was used to reduce the likelihood of type I error [11]. Dose–response meta-analyses were not performed when relevant data were unavailable. To further examine the methodological robustness, additional analyses were conducted. Between-study heterogeneity was assessed using both I^2 and τ^2 statistics [12]. I^2 quantifies the percentage of total variation attributable to heterogeneity rather than chance, with values of ≥ 50% interpreted as substantial. τ^2 represents the estimated variance of true effect sizes across studies.

We used a *P*-curve analysis to examine the risk of *P*-hacking [13]. Additionally, we adopted 95% prediction intervals to evaluate the uncertainty surrounding the pooled estimates, and Bayesian methods were applied to estimate the distribution of potential future effects [14]. Egger's test was used to investigate publication bias, with a *P*-value of ≤ 0.10 considered indicative of bias [12]. Evidence of small-study effects was deemed present when both of the following conditions were met: 1) Egger's test suggested the presence of potential publication bias ($P < 0.10$) and 2) the pooled estimate from the random-effects model exceeded the effect size reported by the largest single study in the meta-analysis [15]. All statistical analyses were conducted using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria), with 2-sided *P*-values < 0.05 considered statistically significant.

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Assessment of the quality of the study and evidence

In this review, we evaluated the class and CE for each outcome using predefined criteria adopted from previous umbrella reviews [11,12,15]. Associations derived from observational studies were graded into 5 categories based on the strength of evidence for potential environmental risks or protective factors: class I (convincing), class II (highly suggestive), class III (suggestive), class IV (weak), and not significant. Credibility was evaluated using several methodological criteria such as the number of events, *P*-value significance, evidence of small-study effects, excess significance bias, prediction interval estimates, statistical significance of the largest study, and the degree of heterogeneity across studies. Sensitivity analyses were performed for associations classified as class I or II when sufficient data were available to examine the robustness of the evidence by excluding the selected component studies.

For meta-analyses of RCTs, the certainty of evidence was assessed using a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [16]. Certainty ratings were categorized as high, moderate, low, or very low, based on the following 5 domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias [17].

Patient and public involvement

The research question, outcome selection, and overall study design and implementation were conducted without patient involvement. They were also not consulted for the interpretation of the findings or the preparation of the manuscript. The results of this study will be made available to participants and relevant communities upon request.

RESULTS

Literature search

Initially, 432 articles were identified, and 40 duplicates were excluded. After screening, we selected 29 meta-analyses that met the inclusion criteria (**Fig. 1**). Characteristics of included studies are provided in **Table 1**. A list of excluded studies and the detailed reasons for exclusion are provided in **Supplementary Table 1**. Included studies were published between 1980 and 2024. Among the 29 articles included in this study, 22 were high, two were moderate, three were low, and two were critically low in quality assessment (**Supplementary Table 2**). Of the 135 associations, 110 were observational studies, and 25 were RCTs. Effect sizes are presented as mean correlations, SMDs, RRs, HRs, MDs, WMDs, effect estimates, correlation coefficients, and ORs. The mean correlations, WMDs, and MDs were transformed into SMDs, and RRs and HRs were transformed into eORs.

Thirty-five of the 136 associations were statistically significant in the random effects model. Among these, 30 associations were observational studies, and five associations were RCTs. Among 30 associations, which were observational studies, 76.67% (23/30) were based on studies with > 20,000 participants, and 53.33% (16/30) showed large heterogeneity (I^2 > 50). Egger's test suggested no evidence of small-study effects or publication bias in 70.00% (21/30) of reported associations. According to the evaluation of the CE for each association, 10.00% (3/30) were classified as having strong evidence (class I), and 3.33% (1/30) as having substantial evidence (class II), 20.00% (6/30) as showing moderate evidence (class III), and 66.67% (20/30) as having limited evidence (class IV). More details of CE for each association are shown in **Supplementary Table 3**. According to the evaluation of the GRADE framework,

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Table 1. Characteristics of included studies in the meta-analysis on maternal age and its association with maternal and neonatal health outcomes

Type of sweetener	Outcomes	Author	Included countries	AMSTAR 2
1. Sweeteners				
1.1 AS only				
AS	All-cause mortality	Shoumeng *et al.* (2022)	10 European countries, UK, and USA	Critical Low
AS	All cancer	Shoumeng *et al.* (2022)	10 European countries, UK, and USA	Critical Low
AS	Non-luminal gastrointestinal cancer	Adam *et al.* (2021)	10 European countries, Italy, Sweden, and USA	High
AS	Breast cancer	Xia *et al.* (2023)	Australia, Denmark, France, Italy, and USA	High
AS	Cancer mortality	Shoumeng *et al.* (2022)	Europe and USA	Critical Low
AS	All gastrointestinal cancers	Adam *et al.* (2021)	Australia, Europe, Italy, Sweden, and USA	High
AS	Luminal gastrointestinal cancer	Adam *et al.* (2021)	Australia and Italy	High
1.2 AS intake comparison				
AS vs. control	Breast cancer	Cheonglou *et al.* (2024)	Australia, Egypt, France, Italy, Spain, and USA	High
High-dose AS	Colorectal cancer	Cheonglou *et al.* (2024)	Australia, France, Italy, Spain, and USA	High
AS vs. control	Genitourinary cancer	Liping *et al.* (2021)	Argentina, Canada, Cophenhagen, France, Italy, Japan, Na, UK, and USA	High
AS vs. control	Breast cancer mortality	Cheonglou *et al.* (2024)	Europe and USA	High
AS vs. control	All cancer	Liping *et al.* (2021)	Argentina, Canada, Cophenhagen, France, Italy, Japan, Na, UK, and USA	High
AS vs. control	Digestive system cancer	Liping *et al.* (2021)	Italy	High
AS vs. control	Gynecological	Liping *et al.* (2021)	Italy	High
AS (male) vs. control	All cancer	Liping *et al.* (2021)	Argentina, Cophenhagen, Japan, Na, UK, and USA	High
AS (female) vs. control	All cancer	Liping *et al.* (2021)	Argentina, Cophenhagen, Japan, Na, UK, and USA	High
High-dose AS	Colorectal cancer mortality	Cheonglou *et al.* (2024)	Europe and USA	High
Middle-dose AS	Colorectal cancer	Cheonglou *et al.* (2024)	Australia, France, and USA	High
Middle-dose AS	Colorectal cancer mortality	Cheonglou *et al.* (2024)	Europe and USA	High
Low-dose AS	Colorectal cancer mortality	Cheonglou *et al.* (2024)	Europe and USA	High
Low-dose AS	Colorectal cancer	Cheonglou *et al.* (2024)	Australia, France, Italy, Spain, and USA	High
1.3 NSS only				
NSS	Weight change	Meghan *et al.* (2017)	USA	High
NSS	Type 2 diabetes	Meghan *et al.* (2017)	UK and USA	High
NSS	Daily sugar intake (g)	Ingrid *et al.* (2019)	Canada	High
NSS	BMI change	Meghan *et al.* (2017)	Australia and USA	High
NSS	BMI increase (children/adolescents)	Maira *et al.* (2018)	UK and USA	High
NSS	Fat mass accumulation (children/adolescents)	Maira *et al.* (2018)	UK and USA	High
NSS	Bladder cancer	Ingrid *et al.* (2019)	NA	High
NSS	Normal weight	Ingrid *et al.* (2019)	USA	High
NSS	Overweight and obese	Ingrid *et al.* (2019)	Canada and Denmark	High
NSS	Daily energy intake (kJ)	Ingrid *et al.* (2019)	Canada	High
NSS	Weight difference (overweight/obesity population)	Hugo *et al.* (2020)	NA	Low
NSS	Gamma-glutamyl transferase	Amirhossein *et al.* (2023)	Brazil, Paraguay, and USA	High
NSS	Alanine aminotransferase	Amirhossein *et al.* (2023)	Brazil, China, Paraguay, Switzerland, UK, and USA	High
NSS	Weight difference (unrestricted diet)	Hugo *et al.* (2020)	NA	Low
NSS	Weight difference (normal weight population)	Hugo *et al.* (2020)	NA	Low
NSS	Weight difference (weight-reduction diet)	Hugo *et al.* (2020)	NA	Low
NSS	Aspartate aminotransferase	Amirhossein *et al.* (2023)	Brazil, China, Paraguay, Switzerland, UK, and USA	High
NSS	Creatinine changes	Ingrid *et al.* (2019)	NA	High
NSS	Haematocrti changes	Ingrid *et al.* (2019)	NA	High
NSS	BMI z-score change (children)	Ingrid *et al.* (2019)	NA	High
NSS	Serum Hb (children)	Ingrid *et al.* (2019)	NA	High

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Table 1. (Continued) Characteristics of included studies in the meta-analysis on maternal age and its association with maternal and neonatal health outcomes

Type of sweetener	Outcomes	Author	Included countries	AMSTAR 2
1.4 NSS intake comparison				
NSS (highest vs. lowest)	Overweight	Meghan *et al.* (2017)	Spain and USA	High
NSS (highest vs. lowest)	Metabolic syndrome	Meghan *et al.* (2017)	Spain and USA	High
NSS (highest vs. lowest)	Type 2 diabetes	Meghan *et al.* (2017)	France, Japan, UK, and USA	High
NSS (highest vs. lowest)	Hypertension	Meghan *et al.* (2017)	USA	High
NSS (highest vs. lowest)	Cardiovascular diseases	Meghan *et al.* (2017)	USA	High
NSS (highest vs. lowest)	Stroke	Meghan *et al.* (2017)	USA	High
NSS (highest vs. lowest)	Coronary heart disease	Meghan *et al.* (2017)	USA	High
NSS vs. control	Weight difference	Hugo *et al.* (2020)	NA	Low
NSS vs. control	BMI changes	Meghan *et al.* (2017)	Brazil, China, Denmark, Iran, and USA	High
NSS vs. control	Waist circumference changes	Meghan *et al.* (2017)	Iran and USA	High
NSS vs. control	BMI changes (children/adolescents)	Alan *et al.* (2024)	UK and USA	High
NSS vs. control	Insulin resistance	Meghan *et al.* (2017)	Brazil, Denmark, and Iran	High
1.5 LNC intake comparison				
LCS vs. water/nothing	Weight change	Peter *et al.* (2021)	Denmark, Iran, Mexico, UK, and USA	High
LCS vs. water/nothing	Energy intake (kJ)	Peter *et al.* (2021)	Denmark, France, Iran, Mexico, and USA	High
2. Beverages				
2.1 ASB only				
ASB	Metabolic syndrome	Xiao *et al.* (2020)	America and Spain	High
ASB	Cardiovascular diseases	Yantong *et al.* (2021)	USA	Low
ASB	All-cause mortality	Zhangling *et al.* (2024)	10 European countries, Netherlands, UK, and USA	High
ASB	Chronic kidney disease	Wei-Cheng *et al.* (2021)	USA	Low
ASB	Liver cancer	Alfred *et al.* (2021)	Europe and USA	High
ASB	Type 2 diabetes	Greenwood *et al.* (2014)	Europe and USA	High
ASB	Pancreatic cancer	Alfred *et al.* (2021)	Europe, Italy, Japan, Sweden, and USA	High
ASB	Cardiovascular diseases mortality	Zhangling *et al.* (2024)	10 European countries, UK, and USA	High
ASB	Gastrointestinal cancer	Alfred *et al.* (2021)	Australia, Egypt, Euopre, Europe, France, Italy, Sweden, and USA	High
ASB	Gastric cancer	Alfred *et al.* (2021)	Australia, Italy, Japan, Sweden, and USA	High
ASB	Cancer mortality	Zhangling *et al.* (2024)	10 European countries, UK, and USA	High
ASB	Colorectal cancer	Alfred *et al.* (2021)	Australia, Egypt, Europe, France, Italy, Japan, and USA	High
ASB	Oesophageal cancer	Alfred *et al.* (2021)	Australia, Italy, Sweden, and USA	High
2.2 ASB intake comparison				
ASB vs. control	Chronic kidney disease	Wisit *et al.* (2015)	USA	High
ASB vs. control	Hypertension	Wisit *et al.* (2015)	USA	High
ASB (≥ 1 daily doses vs. minimum intake)	Cardiovascular disease mortality	Ivo *et al.* (2025)	10 European countries and USA	High
ASB (highest vs. lowest)	Leukemia	Tongxin *et al.* (2022)	USA	High
ASB (highest vs. lowest)	Cardiovascular disease mortality	Zhangling *et al.* (2024)	10 European countries, Netherlands, UK, and USA	High
ASB (highest vs. lowest)	Type 2 diabetes	Pei *et al.* (2020)	China, Denmark, France, Spain, UK, and USA	Low
ASB (highest vs. lowest)	Hypertension	Pei *et al.* (2020)	Spain and USA	Low
ASB (highest vs. lowest)	All-cause mortality	Zhangling *et al.* (2024)	10 European countries, UK, and USA	High
ASB (highest vs. lowest)	Endometrial cancer	Tongxin *et al.* (2022)	Australia and USA	High
ASB (highest vs. lowest)	Colorectal cancer	Tongxin *et al.* (2022)	Australia, Europe, and USA	High
ASB (highest vs. lowest)	Cardiovascular diseases	Yantong *et al.* (2021)	USA	Low
ASB vs. control	Overweight and obesity	Ruanpeng *et al.* (2017)	Australia and USA	High
ASB (≥ 1 daily doses vs. minimum intake)	Stroke	Ivo *et al.* (2025)	USA	High
ASB (≥ 1 daily doses vs. minimum intake)	All-cause mortality	Ivo *et al.* (2025)	10 European countries, Europe, UK, and USA	High
ASB (≥ 1 daily doses vs. minimum intake)	Coronary heart disease	Ivo *et al.* (2025)	USA	High
ASB (≥ 2 daily doses vs. minimum intake)	Cardiovascular disease mortality	Ivo *et al.* (2025)	10 European countries, and USA	High
ASB (2 × 2 daily doses vs. minimum intake)	All-cause mortality	Ivo *et al.* (2025)	10 European countries, UK, and USA	High
ASB (2 × 2 daily doses vs. minimum intake)	Stroke	Ivo *et al.* (2025)	USA	High
ASB (highest vs. lowest)	Obesity	Pei *et al.* (2020)	Denmark, Spain, and USA	Low
ASB (highest vs. lowest)	Multiple myeloma	Tongxin *et al.* (2022)	USA	High

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Table 1. (Continued) Characteristics of included studies in the meta-analysis on maternal age and its association with maternal and neonatal health outcomes

Type of sweetener	Outcomes	Author	Included countries	AMSTAR 2
ASB (highest vs. lowest)	Pancreatic cancer	Tongxin *et al.* (2022)	Europe and USA	High
ASB (highest vs. lowest)	Non-obesity-related cancers	Tongxin *et al.* (2022)	Australia, Europe and USA	High
ASB (highest vs. lowest)	Hematopoietic cancers	Tongxin *et al.* (2022)	USA	High
ASB (highest vs. lowest)	Non-Hodgkin lymphoma	Tongxin *et al.* (2022)	USA	High
ASB (highest vs. lowest)	Male hormone-related cancers	Tongxin *et al.* (2022)	Australia and Europe	High
ASB (highest vs. lowest)	Prostate cancer	Tongxin *et al.* (2022)	Australia and Europe	High
ASB (highest vs. lowest)	Obesity-related cancers	Tongxin *et al.* (2022)	Australia, Europe and USA	High
ASB (highest vs. lowest)	Cancer mortality	Zhangling *et al.* (2024)	10 European countries, UK, and USA	High
ASB (highest vs. lowest)	Breast cancer	Tongxin *et al.* (2022)	Australia, Europe and USA	High
ASB (highest vs. lowest)	Female hormone-related cancers	Tongxin *et al.* (2022)	Australia, Europe and USA	High
ASB (highest vs. lowest)	Digestive system cancers	Tongxin *et al.* (2022)	Australia, Europe and USA	High
ASB (moderate vs. minimum)	Stroke	Ivo *et al.* (2025)	USA	High
ASB (moderate vs. minimum)	All-cause mortality	Ivo *et al.* (2025)	10 European countries, Europe, UK, and USA	High
ASB (moderate vs. minimum)	Coronary heart disease	Ivo *et al.* (2025)	USA	High
ASB (moderate vs. minimum)	Cardiovascular disease mortality	Ivo *et al.* (2025)	10 European countries and USA	High
Low-dose ASB (1–3/mon)	Breast cancer	Xia *et al.* (2023)	Australia and USA	High
Middle-dose ASB (> 1 time/week)	Breast cancer	Xia *et al.* (2023)	Australia and USA	High
High-dose ASB (≥ 1 time/week)	Breast cancer	Xia *et al.* (2023)	Australia, Italy, and USA	High
ASB (per 250 mL/day increase)	Metabolic syndrome	Xiao *et al.* (2020)	America and Spain	High
2.3 NSS beverage intake				
NSS beverage	BMI changes (adolescents)	Alan *et al.* (2024)	USA	High
NSS beverage	BMI changes (children)	Alan *et al.* (2024)	Netherlands and South Africa	High
2.4. LNCB only				
LNCB	CVD mortality	Jiawei *et al.* (2021)	USA	High
LNCB	Coronary heart disease	Jiawei *et al.* (2021)	USA	High
LNCB	Stroke	Jiawei *et al.* (2021)	USA	High
3. Prenatal and maternal				
Prenatal AS consumption	Preterm delivery	Chenxi *et al.* (2021)	Denmark, Norway, and UK	High
Prenatal AS consumption	Overweight of a 1-yr-old	Chenxi *et al.* (2021)	Canada and Denmark	High
Prenatal AS consumption	BMI-z score of 1-yr-old children	Chenxi *et al.* (2021)	Canada, Denmark, and USA	High
Maternal NNS during pregnancy	BMI z-score of offspring at 1 yr of age	Guowei *et al.* (2022)	Canada and Denmark	High
Maternal NNS during pregnancy vs control	BMI z-score of offspring at birth	Guowei *et al.* (2022)	Denmark and USA	High
Maternal NNS during pregnancy vs control	BMI z-score of offspring in early childhood	Guowei *et al.* (2022)	Canada and USA	High
Maternal NNS during pregnancy vs control	BMI z-score of offspring at mid-childhood	Guowei *et al.* (2022)	Denmark and USA	High
Prenatal AS consumption	Gestational age	Chenxi *et al.* (2021)	Canada and Denmark	High
Prenatal AS consumption	Birth weight	Chenxi *et al.* (2021)	Canada and Denmark	High

AMSTAR 2, A Measurement Tool Assessment Systematic Reviews 2; AS, artificial sweetener; NSS, non-sugar sweetener; BMI, body mass index; LNC, low/no calorie sweetener; LCS, low-calorie sweetener; ASB, artificially sweetened beverage; LNCB, low/no calorie sweetened beverage; CVD, cardiovascular disease; NNS, non-nutritive sweetener.

40.00% (2/5) were graded as high quality, and 60.00% (3/5) as moderate quality. Additional details are presented in **Supplementary Table 4**.

Associations between sweetener types and health outcomes in observational studies

NSS increased the risk of weight gain (eOR, 1.21; 95% CI, 1.14 to 1.30; CE, IV) and type 2 diabetes (eOR, 1.03; 95% CI, 1.02 to 1.04; CE, IV), while slightly reducing daily sugar intake (SMD, −0.09; 95% CI, −0.17 to −0.01; CE, IV). Additionally, compared with the lowest intake, the highest intake of NSS was associated with increased risks of overweight (eOR, 1.84; CI, 1.30 to 2.61; CE, IV), metabolic syndrome (eOR, 1.31; 95% CI, 1.21 to 1.42; CE, I), type 2 diabetes (eOR, 1.14; 95% CI, 1.02 to 1.29; CE, IV), and hypertension (eOR, 1.13; 95% CI, 1.07 to 1.19; CE, II). Maternal NSS intake during pregnancy was associated with increased body mass index (BMI) z-scores of offspring during early childhood (SMD, 0.20; 95% CI, 0.02

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to 0.38; CE, IV) and at 1 yr of age (SMD, 0.19; 95% CI, 0.07 to 0.31; CE, IV). Furthermore, AS consumption was associated with a reduced risk of breast cancer (eOR, 0.91; 95% CI, 0.83 to 1.00; CE, I), and high-dose AS intake was associated with a reduced risk of colorectal cancer (eOR, 0.89; 95% CI, 0.81 to 0.99; CE, III). Prenatal AS consumption was associated with an increased risk of preterm delivery (eOR, 1.18; 95% CI, 1.03 to 1.36; CE, IV) and decreased gestational age (SMD, −0.11; 95% CI, −0.21 to −0.01; CE, IV). Compared with water or placebo, LCS slightly increased energy intake (SMD, 0.24; 95% CI, 0.08 to 0.40; CE, IV) (**Fig. 2**).

ASB consumption was associated with increased risks of metabolic syndrome (eOR, 1.44; 95% CI, 1.02 to 2.03; CE, IV), CVDs (eOR, 1.17; 95% CI, 1.04 to 1.31; CE, IV), all-cause mortality (eOR, 1.06; 95% CI, 1.02 to 1.09; CE, III), chronic kidney disease (CKD) (eOR, 1.20; 95% CI, 1.17 to 1.23; CE, I), and hypertension (eOR, 1.15; 95% CI, 1.09 to 1.21; CE, IV). Compared with the lowest dose, the highest intake of ASBs was associated with increased risk of leukemia (eOR, 1.35; 95% CI, 1.09 to 1.67; CE, III), CVD mortality (eOR, 1.26; 95% CI, 1.08 to 1.47; CE, III), type 2 diabetes (eOR, 1.20; 95% CI, 1.05 to 1.38; CE, IV), hypertension (eOR, 1.13; 95% CI, 1.08 to 1.19; CE, IV), and all-cause mortality (eOR, 1.13; 95% CI, 1.06 to 1.21; CE, III). However, the highest intake of ASB was associated with decreased risks of endometrial cancer (eOR, 0.81; 95% CI, 0.81 to 0.81; CE, III), colorectal cancer (eOR, 0.78; 95% CI, 0.71–0.86; CE, IV), and CVDs (eOR, 0.14; 95% CI, 0.03 to 0.25; CE, IV). Whereas LNCB consumption was associated with an increased risk of strokes (eOR, 1.07; 95% CI, 1.05 to 1.15; CE, IV) (**Fig. 2**). Other results that were not statistically significant are presented in **Supplementary Fig. 1**. The results of the sensitivity analyses for all class II outcomes remained consistent, with no changes in the strength or direction of the association. Other results showing no significant associations are presented in **Supplementary Table 5**.

Associations between sweetener types and health outcomes in RCTs

NSS intake slightly reduced BMI z-score changes in children (SMD, −0.08; 95% CI, −0.14 to −0.03; GRADE, moderate) and reduced weight under unrestricted diet (SMD, −0.45; 95% CI, −0.64 to −0.27; GRADE, high) and in populations with overweight or obesity (SMD, −0.50; 95% CI, −0.70 to −0.30; GRADE, high). Compared with controls, NSS intake also reduced body weight (SMD, −0.39; 95% CI, −0.54 to −0.24; CE, moderate). Among specific sweeteners, compared with no treatment, sorbitol reduced decayed, missing, and filled dental surfaces (SMD, −0.13; 95% CI, −0.24 to −0.02; GRADE, moderate), whereas stevia decreased blood glucose levels (SMD, −2.24; 95% CI, −4.12 to −0.36; GRADE, moderate) (**Fig. 3** and **Supplementary Fig. 2**). Other results showing no significant associations are presented in **Supplementary Table 6**. The forest plot, Funnel plot, and *P*-curve for each health outcome are presented in **Supplementary Data 1**.

DISCUSSION

This umbrella review is the first to comprehensively evaluate the associations between different types of LNCSs or LNCSBs and a wide range of health outcomes. A comprehensive literature review identified 432 articles published between 1980 and 2025, of which 35 were ultimately included, encompassing 50,034,327 participants. Overall, the findings suggest a complex and inconsistent pattern, with observational studies indicating potential adverse cardiometabolic associations, including type 2 diabetes, overweight, metabolic syndrome, CVD mortality, CKD, and hypertension. However, some evidence suggests modest benefits, particularly in reducing daily sugar intake.

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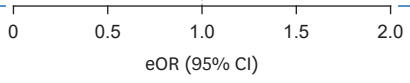
Sugar type	Outcome	No. of study	eOR (95% CI)	Evidence class
1. Sweeteners				
1.1 AS intake comparison				
AS vs. control	Breast cancer	18	0.91 (0.83 to 0.99)	I
High-dose AS	Colorectal cancer	5	0.89 (0.81 to 0.99)	III
1.2 NSS only				
NSS	Weight change	4	1.21 (1.14 to 1.30)	IV
NSS	Type 2 diabetes	4	1.03 (1.02 to 1.04)	IV
1.3 NSS intake comparison				
NSS (highest vs. lowest)	Overweight	3	1.84 (1.30 to 2.61)	IV
NSS (highest vs. lowest)	Metabolic syndrome	5	1.31 (1.21 to 1.42)	I
NSS (highest vs. lowest)	Type 2 diabetes	9	1.14 (1.02 to 1.29)	IV
NSS (highest vs. lowest)	Hypertension	5	1.13 (1.07 to 1.19)	II
1.4 Prenatal and maternal				
Prenatal AS consumption	Preterm delivery	4	1.18 (1.03 to 1.36)	IV
2. Beverages				
2.1 ASB only				
ASB	Metabolic syndrome	5	1.44 (1.02 to 2.03)	IV
ASB	Cardiovascular diseases	8	1.17 (1.04 to 1.31)	IV
ASB	All-cause mortality	10	1.06 (1.02 to 1.09)	III
2.2 ASB intake comparison				
ASB (highest vs. lowest)	Leukemia	3	1.35 (1.09 to 1.67)	III
ASB (≥ 1 daily doses vs. minimum intake)	Cardiovascular disease mortality	5	1.30 (1.07 to 1.57)	IV
ASB (highest vs. lowest)	Cardiovascular disease mortality	7	1.26 (1.08 to 1.47)	III
ASB vs. control	Chronic kidney disease	4	1.20 (1.17 to 1.23)	I
ASB (highest vs. lowest)	Type 2 diabetes	13	1.20 (1.05 to 1.38)	IV
ASB vs. control	Hypertension	4	1.15 (1.09 to 1.21)	IV
ASB (highest vs. lowest)	Hypertension	6	1.13 (1.08 to 1.19)	IV
ASB (highest vs. lowest)	All-cause mortality	12	1.13 (1.06 to 1.21)	III
ASB (highest vs. lowest)	Endometrial cancer	2	0.81 (0.81 to 0.81)	III
ASB (highest vs. lowest)	Colorectal cancer	3	0.78 (0.71 to 0.86)	IV
ASB (highest vs. lowest)	Cardiovascular diseases	8	0.14 (0.03 to 0.25)	IV
3. LNCB only				
LNCB	Stroke	5	1.07 (1.05 to 1.15)	IV



Sugar type	Outcome	No. of study	SMD (95% CI)	Evidence class
1. Sweeteners				
1.1 NSS only				
NSS	Daily sugar intake (kg)	3	−0.09 (−0.17 to −0.01)	IV
1.2 Prenatal and maternal				
Maternal NSS during pregnancy vs. control	BMI z-score of offspring at early childhood	2	0.20 (0.02 to 0.38)	IV
Maternal NSS during pregnancy	BMI z-score of offspring at 1 yr of age	3	0.19 (0.07 to 0.31)	IV
Maternal AS consumption	Gestational age	3	−0.11 (−0.21 to −0.01)	IV
2. Beverages				
2.1 LNCB intake comparison				
LCS vs. water/nothing	Energy intake (kJ)	10	0.24 (0.08 to 0.40)	IV

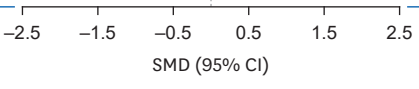


Fig. 2. Health outcomes associated with various sweeteners: evidence from observational studies.
eOR, equivalent odds ratio; CI, confidence interval; AS, artificial sweetener; NSS, non-sugar sweetener; ASB, artificially sweetened beverage; LNCB, low/no calorie sweetened beverage; SMD, standardized mean difference; BMI, body mass index; LCS, low-calorie sweetener.

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Sugar type	Outcome	No. of study	SMD (95% CI)	GRADE
1. Sweeteners				
1.1 NSS only				
NSS	Aspartate aminotransferase	13	0.00 (−0.75 to 0.75)	Very low
NSS	Serum Hb (children)	2	0.04 (−0.77 to 0.84)	Very low
Stevia	HbA1C	6	0.06 (−0.05 to 0.17)	Moderate
NSS	BMI z-score change (children)	2	−0.08 (−0.14 to −0.03)	Moderate
NSS	Weight difference (weight-reduction diet)	7	−0.16 (−0.59 to 0.27)	Very low
NSS	Haematocrti changes	2	0.22 (−0.57 to 1.01)	Low
NSS	Weight difference (normal weight population)	9	−0.22 (−0.65 to 0.21)	Low
Stevia	Insulin concentration	15	0.28 (−0.36 to 0.92)	Moderate
NSS	Weight difference (unrestricted diet)	24	−0.45 (−0.64 to −0.27)	High
NSS	Alanine aminotransferase	13	−0.45 (−1.23 to 0.33)	Very low
NSS	Gamma-glutamyl transferase	8	−0.48 (−2.87 to 1.91)	Very low
NSS	Weight difference (overweight/obesity population)	20	−0.50 (−0.70 to −0.30)	High
NSS	Creatinine changes	2	−1.46 (−18.30 to 15.37)	Moderate
Stevia	Blood glucose levels	31	−2.24 (−4.12 to −0.36)	Moderate
1.2 NNS intake comparison				
Sorbitol vs. placebo	DMFS	2	0.11 (−0.39 to 0.62)	Moderate
NNS vs. control	Insulin resistance	3	0.02 (−0.73 to 0.77)	Low
NNS vs. control	BMI changes (children/adolescents)	11	0.03 (−0.01 to 0.07)	Low
NNS vs. control	Waist circumference changes	3	−0.13 (−1.06 to 0.81)	Low
Sorbitol vs. no treatment	DMFS	6	−0.13 (−0.24 to −0.02)	Moderate
NNS vs. control	BMI changes	5	−0.14 (−0.71 to 0.43)	Low
Xylitol vs. placebo	DMFS	3	−0.26 (−0.81 to 0.28)	Low
NNS vs. control	Weight difference	31	−0.39 (−0.54 to −0.24)	Moderate
Xylitol vs. no treatment	DMFS	6	−0.63 (−1.27 to 0.01)	Low
2. Beverages				
2.1 NSS only				
NNS beverage	BMI changes (children)	3	−0.05 (−0.24 to 0.14)	Low
NNS beverage	BMI changes (adolescents)	2	−0.21 (−1.23 to 0.81)	Very low

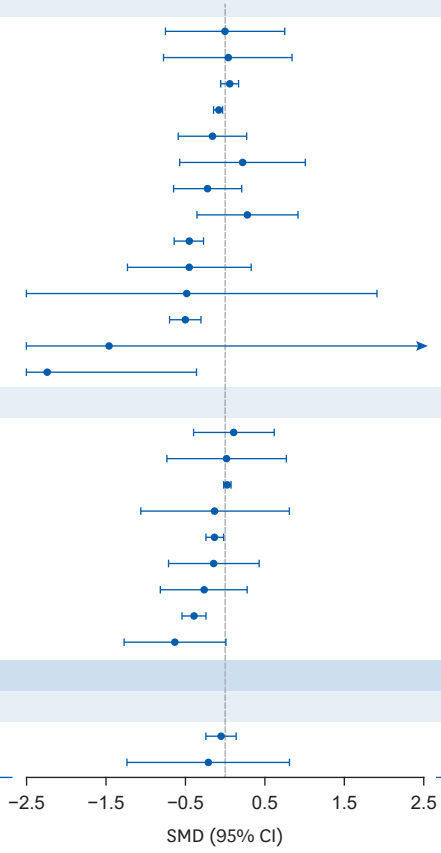

Fig. 3. Health outcomes associated with various sweeteners: evidence from randomized controlled trials.
SMD, standardized mean difference; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNS, non-nutritive sweetener; Hb, hemoglobin; HbA1C, hemoglobin A1c; BMI, body mass index; DMFS, decayed, missing, and filled surfaces.

Although NSS intake is associated with reduced sugar consumption, it has also been associated with an increased risk of obesity and weight gain. This apparent paradox may be explained by the dissociation between the perception of sweetness and the lack of corresponding caloric signals, which is a key feature of NSSs [18]. By providing sweetness without energy, NSSs may fail to elicit the appropriate metabolic responses, potentially limiting their effectiveness in appetite regulation. Neurobiological evidence suggests that this mismatch may enhance the functional connectivity between the hypothalamus and brain regions involved in motivation and somatosensory processing, which could promote increased appetite [19]. Consistently, although NSS consumption reduces sugar intake, it does not necessarily lead to a reduction in overall caloric intake [20].

Additionally, the highest NSS consumption increased the risk of type 2 diabetes, hypertension, and metabolic diseases. This may be attributed to several mechanisms, including dysbiosis characterized by a reduction in beneficial gut bacteria such as *Clostridiales*, overgrowth of *Bacteroides* species, impaired learning of the sweet taste-energy association, disrupted insulin responses due to dysbiosis, and compensatory overeating [21,22]. Furthermore, the consumption of NSSs and ASs during pregnancy was associated

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with a higher risk of reduced gestational age and elevated BMI z-scores in offspring. These consequences may be mediated by alterations in the maternal gut microbiota induced by sweetener intake, which can activate pro-inflammatory pathways. These pathways may contribute to placental vascular dysfunction, ultimately increasing the risk of preterm delivery [23].

Although AS consumption showed little association with health outcomes, ASB intake increased the risk of metabolic diseases, CVDs, all-cause mortality, and leukemia. Compared with the consumption of solid sweeteners, the intake of sweeteners in beverage form allows for more frequent, rapid, and high-dose consumption, resulting in faster absorption [24]. This may impose greater metabolic stress and cause more pronounced disruptions in gut metabolic pathways and insulin sensitivity. In addition, consuming AS in liquid form rather than in solid form may fail to induce satiety, potentially leading to increased subsequent food intake and contributing to the observed effects [25].

As LNCSs have been increasingly used as substitutes for caloric sweeteners, the number of studies examining their health effects has grown [26-28]. However, these studies primarily focused on the influence of a single sweetener type on a specific health outcome, limiting their ability to comprehensively assess or comparatively analyze the overall health effects of sweetener intake.

Several studies have also synthesized these studies to compare and analyze the effects of LNCSs on health outcomes [29-31]. Similar to the present study, these reviews found that, while LNCS intake was associated with reduced sugar consumption, it did not confer health benefits and, in some cases, was associated with adverse health outcomes. However, these studies had several limitations. First, they focused only on specific types of sweeteners [29,30] or examined a limited range of health outcomes [31], making it difficult to comprehensively assess overall health outcomes. Additionally, they often did not consider the form of consumption, making it challenging to compare outcomes based on product types [29-31]. Second, vulnerable populations such as individuals who are overweight or pregnant women were not adequately represented, limiting the generalizability of the findings [30,31]. Finally, differences in dosage were not addressed, making it difficult to evaluate dose-dependent effects [29-31]. Therefore, this study addressed these limitations by being the first to comprehensively examine the influence of LNCSs and LNCSBs, including ASs, NSSs, and LCSs, on comprehensive health outcomes, while also conducting a comparative analysis of dose-dependent responses.

With the increasing prevalence of obesity and non-communicable diseases (NCDs) in modern society, LNCSs have been utilized as a potential solution to address these health challenges [32]. However, the World Health Organization (WHO) does not recommend the use of NSSs for weight loss or the prevention of NCDs and instead advises that their use be limited or discontinued [33]. Similarly, numerous studies have emphasized the need for caution regarding the long-term consumption of such sweeteners, owing to their potential health risks [26,27]. Nevertheless, the actual consumption of these sweeteners continues to increase [2], and international policy efforts to regulate their use remain insufficient [33,34].

Therefore, effective policy responses must be developed. First, strengthening the clinical evidence based on the consumption of LNCS and establishing national and international guidelines are urgently needed. In particular, global health organizations such as the

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WHO and the Food and Agriculture Organization should educate healthcare professionals that improving dietary habits by reducing the overall preference for sweetness is key and that simply replacing sugar with LNCSs does not guarantee long-term health benefits. Special recommendations are also warranted for pregnant individuals, as excessive intake of ASs or NSSs during pregnancy may alter the fetal gut microbiome and increase the risk of metabolic disorders later in life.

Furthermore, current evidence suggests that the effectiveness of LNCS consumption in weight reduction and NCD prevention is limited. Nevertheless, long-term use may be associated with increased risks of type 2 diabetes, CVDs, and other chronic conditions. Public health campaigns and consumer education efforts are essential for promoting appropriate intake levels and encouraging alternative strategies that support healthier dietary behaviors. Ultimately, the establishment of international governance is essential to ensure the appropriate management of sweetener consumption and promote health equity [35]. This can be achieved through the development of harmonized regulatory standards and unified guidelines on the use of LNCSs across countries.

To our knowledge, this is the first umbrella review to analyze the associations between LNCSs, LNCSBs, and overall health outcomes. However, this study had several limitations. First, as with all umbrella reviews, our findings were inherently dependent on the quality of the included meta-analyses. Although we applied rigorous criteria to include the most comprehensive and recent meta-analyses for each association, the reliability of our results was constrained by the methodological rigor of the original studies. Second, most associations included in this umbrella review were derived from observational studies, which are inherently prone to residual confounding and reverse causality. Despite statistical adjustments, observational data cannot fully eliminate the effects of unmeasured or inadequately measured confounders, such as dietary patterns, physical activity, socioeconomic status, or health-seeking behaviors. Furthermore, individuals with a higher risk of obesity, diabetes, or CVDs may be more likely to consume LNCSs as a compensatory strategy, rather than sweeteners being the causal agent of the health outcomes, an issue of reverse causation acknowledged across multiple studies. Third, the harmonization of effect sizes across studies, including the transformation of various statistical measures (e.g., MD, HR, and RR) into standardized metrics such as SMD or eOR, may introduce additional assumptions and potential biases. Particularly for continuous outcome measures, the influence of extreme values and variations in measurement scales could have affected the pooled effect estimates, particularly in smaller meta-analyses. These limitations should be carefully considered to avoid potential misinterpretation or overgeneralization of the results. Fourth, contrasting results regarding weight were observed between observational studies and RCTs. This discrepancy may be because the observational studies analyzed obesity or weight gain as a discrete variable, whereas the RCTs considered obesity as a continuous variable. The results derived from continuous weight variables may have been influenced by a small number of extreme values [36]; a similar result was observed in the review conducted by the WHO [37]. Therefore, cautious interpretation of these results is necessary, and further studies are required to clarify these findings. Fifth, this study is an umbrella review, and unlike traditional systematic reviews, its procedures and criteria have not yet been fully standardized across research teams. To mitigate this limitation, two authors independently assessed the eligibility of the included studies, and internationally recognized appraisal tools such as GRADE and AMSTAR 2 were used. Nevertheless, variations in the inclusion and exclusion criteria, as well as meta-analytic synthesis procedures, may persist depending on the research team. These

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methodological differences may have influenced the reproducibility and reliability of the findings. Therefore, caution is warranted in their interpretation.

Despite these limitations, this study holds significant value as the first umbrella review to comprehensively compare and evaluate the impact of various types of LNCSs and LNCSBs on overall health outcomes. Notably, it included both observational studies and RCTs, addressed dose-response associations, and examined outcomes in specific populations, such as pregnant females, thereby helping to fill gaps in the existing literature.

In summary, this umbrella review is the first to comprehensively evaluate the associations between various types of sweeteners, sweetened beverages, and a broad spectrum of health outcomes. While NSS consumption was associated with a marked reduction in sugar intake, it was also associated with increased risks of weight gain, metabolic syndrome, type 2 diabetes, and hypertension. Similarly, ASB intake was associated with elevated risks of metabolic syndrome, CVD, all-cause mortality, CKD, hypertension, and leukemia. Additionally, LNCS consumption was associated with a higher risk of stroke. These findings underscore the dire necessity to develop clear, evidence-based guidelines for the use of LNCS, as well as to implement public education campaigns to promote informed and responsible consumption.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Studies excluded, with reason for exclusion

Supplementary Table 2
AMSTAR 2 quality assessment of meta-analyses

Supplementary Table 3
Grading of recommendations assessment, development, and evaluation assessment of each association in observational studies

Supplementary Table 4
Grading of recommendations assessment, development, and evaluation assessment of each association in randomized controlled trials

Supplementary Table 5
Reanalysis of estimated effect using Hartung-Knapp-Sidik-Jonkman (HS) method, and CE on association between low- or no-calorie sweeteners and beverages and their health outcomes from observational studies

Supplementary Table 6
Reanalysis of estimated effect using Hartung-Knapp-Sidik-Jonkman (HS) method, and CE on association between low- or no-calorie sweeteners and beverages and their health outcomes from randomized controlled trials

Supplementary Fig. 1
Health outcomes associated with various sweeteners.

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Supplementary Fig. 2

Health outcomes associated with various sweetened beverages.

Supplementary Data 1

Supplementary Figs. 3-125 and supplementary references

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