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Reconciling conflicting evidence on low- and no-calorie sweeteners and cardiometabolic outcomes: an umbrella review using naïve and bias-adjusted methods

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Abstract

Inconsistency among evidence syntheses has led to opposing guidelines and public confusion regarding low- and no-calorie sweeteners (LNCS) in noncommunicable diseases. To understand the role of different analytical approaches in assessing LNCS and cardiometabolic outcomes, we conducted an umbrella review of systematic reviews and meta-analyses. MEDLINE, EMBASE, and Cochrane were searched for systematic reviews and meta-analyses of trials or cohorts that had at least two analytical approaches: naïve (LNCS vs. all-comparators (trials) and prevalent (cohorts)) and bias-adjusted (LNCS vs. intended or reference substitution (trials) and LNCS change or intended or reference substitution (cohorts)). Grading of Recommendations Assessment, Development, and Evaluation assessed certainty of evidence. We included six trial- and five cohort-based analyses. In trials, LNCS reduced energy, body weight, and body fat in both analyses and body mass index and systolic blood pressure in bias-adjusted only, while glycosylated hemoglobin showed smaller reductions than water in bias-adjusted only. In analyses of cohorts, LNCS was associated with higher obesity, diabetes, stroke, and cardiovascular and all-cause mortality in naïve analyses but lower body weight, waist circumference, obesity, coronary heart disease, and cardiovascular and all-cause mortality in bias-adjusted analyses. The certainty of evidence was generally moderate for trials and very low for cohorts. LNCS show benefits across analytical approaches in both analyses of trials. These results agree with bias-adjusted analyses of cohorts, in which LNCS are associated benefits across cardiometabolic outcomes, but not naïve analyses of cohorts. Systematic reviews and meta-analyses using bias-reduction methods support the use of LNCS as a sugar-reduction strategy. Protocol registration: https://doi.org/10.17605/OSF.IO/TSEQM.

Key words: low- and no-calorie sweeteners, sugar-sweetened beverages, randomized controlled trial, prospective cohort studies, cardiometabolic risk factors, cardiometabolic disease

Introduction

Dietary (U.S. Department of Health and Human Services and U.S. Department of Agriculture 2021, 2025) and clinical practice guidelines for obesity and diabetes (Sievenpiper et al. 2018; Twells et al. 2020; DNSG 2023; ElSayed et al. 2024) support low- and no-calorie sweeteners (LNCS) as a strategy to reduce caloric intake and manage weight (Sievenpiper et al. 2018; Twells et al. 2020; U.S. Department of Health and Human Services and U.S. Department of Agriculture 2021, 2025; ElSayed et al. 2024). However, recent World Health Organization (WHO) guidance recommends against their use as a means of achieving weight control or reducing the risk of noncommunicable disease (World Health Organization 2023*a*). This guidance has raised concerns within the scientific community, as it conflicts with evidence of benefit from randomized controlled trials (henceforth referred to as trials) and robustly analyzed prospective cohort studies employing bias-adjusted methods (Hedrick et al. 2023; Khan et al. 2023). Trials consistently demonstrate benefit of using LNCS when displacing calories, with comparable effects to water on intermediate cardiometabolic outcomes (Toews et al. 2019; Laviada-Molina et al. 2020; Rogers and Appleton 2021; McGlynn et al. 2022; Rios-Leyvraz et al. 2022). Similarly, prospective cohort studies using bias-adjusted methodologies—modeling changes in LNCS consumption and substitution for sugars to better-define LNCS exposures in the hopes of mitigating reverse causality and confounding—also reveal benefits for cardiometabolic outcomes, directly aligning with trial findings (Lee et al. 2022), indicating a potential role for LNCS in calorie reduction

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and weight management. The WHO guideline prioritized prospective cohort studies using "naïve", i.e., prevalent exposure assessment, known to be susceptible to bias, while disregarding the more informative cohort studies employing bias-adjusted methodologies like change and substitution analyses. This approach not only undermines the established hierarchy of evidence (Brighton et al. 2003) and best practices in nutritional research, but also conflicts with other WHO guidelines that emphasize methodological alignment across study designs (Reynolds et al. 2022). It remains unclear whether systematic reviews and meta-analyses (SRMAs) of LNCS adequately differentiate findings based on naïve versus bias-adjusted methodological approaches.

In light of ongoing calls for rigorous LNCS research (Sievenpiper et al. 2017; Khan et al. 2019, 2023; Malik 2019; Mela et al. 2020; Hedrick et al. 2023; Higgins et al. 2024), this umbrella review aims to synthesize existing SRMAs examining the association between LNCS and cardiometabolic outcomes, encompassing disease risk, intermediate outcomes, and energy intake. We will compare findings from reviews utilizing at least two distinct methodological approaches—naïve and bias-adjusted—and assess the certainty of evidence using Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Methods

Design

This umbrella review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2022) and reported according to the PRISMA guidelines (Page et al. 2021). The study protocol was registered on the Open Science Framework (https://doi.org/10.17605/OSF.IO/TSEQM).

Search strategy

Supplementary Table 1 shows the systematic search strategy, based on the participants, intervention, comparator, outcome, time, study design framework (Supplementary Table 2) (Moher et al. 2009). Medline, Embase, and the Cochrane Database of Systematic Reviews were searched from inception through 9 December 2024, using search terms of exposure (e.g., "low- and no-calorie sweeteners" or "non-nutritive sweeteners") and study design (e.g., "systematic review" or "meta-analysis"). Manual searches using references lists of included articles and other relevant reviews on the topic complemented the systematic search.

Study selection

SRMAs of trials and prospective cohort studies were included if they report data on adults (≥18 years) of all health backgrounds, if they had an intervention period of ≥7 days (for trials) or a follow-up duration of ≥1 year (for cohort studies), and if they investigated the role of orally consumed LNCS from any sources including beverages, table-top sweeteners and low- or no-calorie foods on cardiometabolic disease and intermediate cardiometabolic disease outcomes and/or energy intake (described below) employing both naïve and bias-adjusted analytical approaches. These analytical approaches were defined as LNCS versus all comparators lumped (naïve) and LNCS versus intended or reference substitution (bias-adjusted) for SRMAs of trials, and prevalent LNCS analyses (naïve) or LNCS intended or reference substitution analyses with additional adjustment for baseline adiposity (as defined by each SRMA author; bias-adjusted) for SRMAs of cohorts.

LNCS were defined as high-intensity sweeteners (e.g., aspartame, sucralose, stevia glycosides, acesulfame-K, saccharin, etc.) whose caloric contribution was considered negligible due to high sweetness intensity and minimal food quantities, excluding sugar alcohols (e.g., xylitol, erythritol), which have lower sweetness intensity and non-negligible caloric contribution (Magnuson et al. 2016). For each outcome, we prioritized the most recent SRMA to ensure up-to-date synthesized evidence from both naïve and bias-adjusted methods.

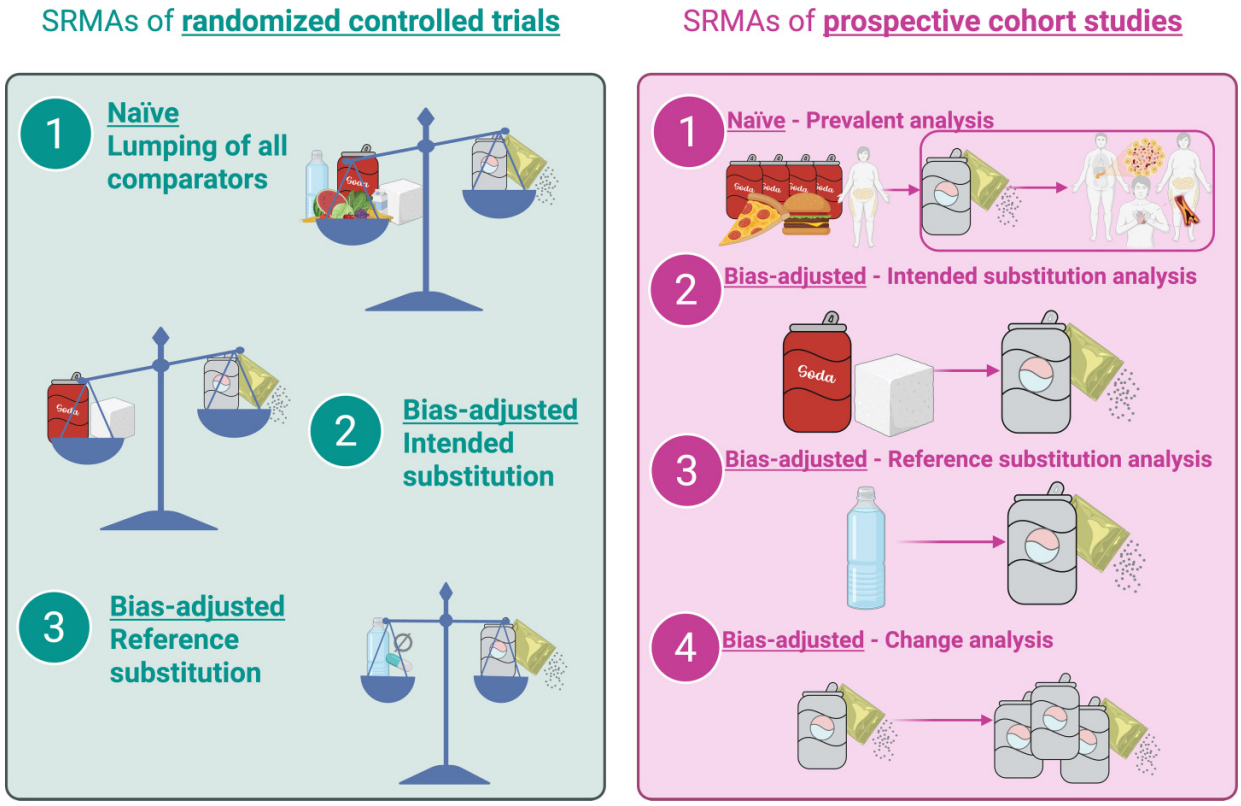
Data extraction and methodological quality assessment

Two independent reviewers extracted data from each included SRMA. Extracted data for all reviews included publication details, participant characteristics, and study setting. For trial-based SRMAs, data extraction encompassed intervention details (LNCS type, dose, comparator type, feeding control level (intended substitution or reference substitution)) and outcome information (participant numbers, pooled effect estimates as mean differences (MDs) and standard errors). For cohort SRMAs, extracted data included exposure information (LNCS type, dose in highest/lowest quantiles, dose changes over time, substitution model type (intended substitution or reference substitution)) and outcome data (case numbers, pooled effect estimates, and standard errors). Review quality was independently assessed by two reviewers using the assessment of multiple systematic reviews (AMSTAR 2) tool (Shea et al. 2017).

Methodology types

Outcomes were included only if SRMA data originated from at least two different methodology types. Figure 1 depicts methodology types for trials and cohorts. For trials, methodology types were: (1) naïve (lumping all comparators: sugars, water/placebo, usual diet), bias-adjusted: (2) intended substitution (LNCS replacing sugars), or bias-adjusted: (3) reference substitution (LNCS replacing water/placebo). Cohort methodology types were: (1) naïve analyses (baseline or prevalent LNCS exposure only), bias-adjusted: (2) intended substitution analyses (modeling LNCS substitution for sugars) with adjustment for baseline adiposity, bias-adjusted: (3) reference substitution analyses (modeling LNCS substitution for water/placebo) with adjustment for baseline adiposity, or bias-adjusted: (4) change analyses (modeling change in LNCS exposure over time using repeated measures) with adjustment for baseline adiposity and in addition if they employed any advanced g-methods to fully account for time-varying confounding (Mansournia et al. 2017).

Fig. 1. Visual depiction of the different methodology types for SRMAs of trials and cohorts investigating low- and no-calorie sweeteners (LNCS). For trials, methodology types were: (1) naïve (lumping all comparators: sugars, water/placebo, usual diet), bias-adjusted: (2) intended substitution (LNCS replacing sugars), or bias-adjusted: (3) reference substitution (LNCS replacing water, placebo or no intervention). Cohort methodology types were: (1) naïve analyses (baseline or prevalent LNCS exposure only), bias-adjusted: (2) intended substitution analyses (modeling LNCS substitution for sugars) with adjustment for baseline adiposity, bias-adjusted: (3) reference substitution analyses (modeling LNCS substitution for water/placebo) with adjustment for baseline adiposity, or bias-adjusted: (4) change analyses (modeling change in LNCS exposure over time) with adjustment for baseline adiposity. SRMA = systematic review and meta-analysis. Created in BioRender. Ayoub-charette, S. (2025) https://BioRender.com/29wsf08.



Outcomes

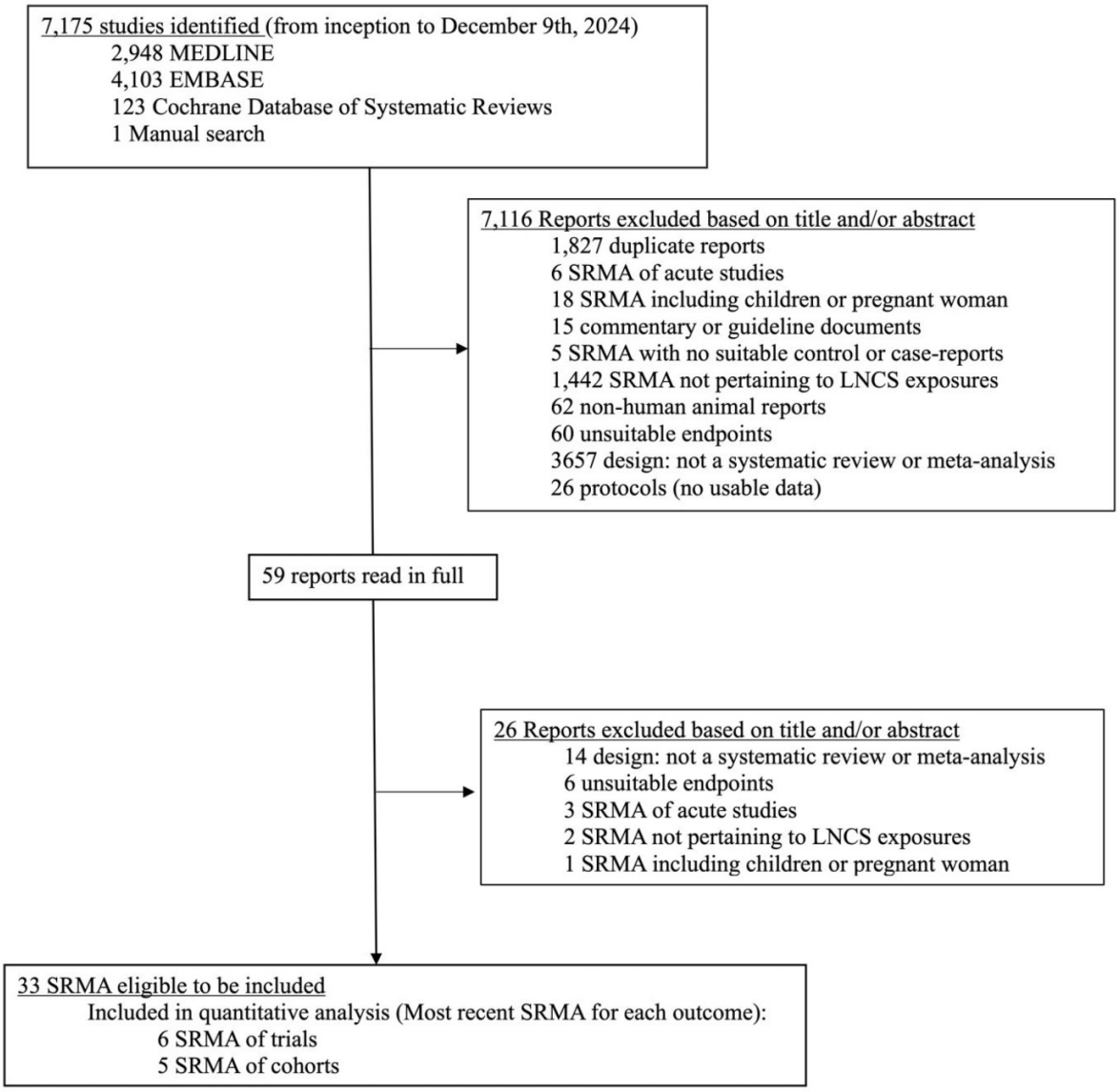
For trial SRMAs, outcomes included changes in energy intake; adiposity measures (body weight, body mass index (BMI), body fat, waist circumference (WC)); glycemic control (fasting blood glucose/insulin, 2 h postprandial glucose, plasma glucose area under the curve, glycosylated hemoglobin (HbA1c)); cardiovascular risk factors (systolic/diastolic blood pressure (SBP/DBP), plasma lipids: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglycerides (TG), apolipoprotein B (apoB)); and metabolic dysfunction-associated steatotic liver disease (MASLD) markers (intrahepatocellular lipid, alanine transaminase, aspartate aminotransferase, fatty liver index). For cohort SRMAs, outcomes included changes in energy intake, body weight, WC, and body fat (continuous); incidence overweight/obesity; metabolic syndrome; type 2 diabetes (T2D); MASLD; cardiovascular disease (CVD) and cardiovascular mortality (coronary heart disease (CHD), stroke, total CVD); and all-cause mortality. For cohort studies, effect measures were extracted as reported in the original SRMA studies (hazard ratios, relative risks, and odds ratios) and treated as comparable estimates of association for reporting purposes, given that outcomes were relatively rare and follow-up periods were comparable across studies and were referred to collectively as measures of disease risk or incidence in our interpretation. We did not assess cancer as an outcome.

Evidence synthesis and certainty of the evidence

Extracted SRMA evidence including pooled estimates was report in tables and as superplots. GRADE certainty assessments were reported as provided by original SRMAs. If no GRADE assessment was available, at least two independent reviewers (SA-C, MEK, and/or TAK) evaluated the certainty of evidence for each SRMA using established GRADE criteria (Schünemann et al. 2013) and published information. GRADE assesses evidence certainty as high, moderate, low, or very low. Randomized controlled trial (RCT) meta-analyses are ini-

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Fig. 2. PRISMA flow. Flow of the literature for the effect/association of LNCS and energy intake, intermediate cardiometabolic outcomes, cardiometabolic disease, and mortality risk. SRMAs = systematic reviews and meta-analyses; LNCS = low- and no-calorie sweeteners.



tially considered high-quality evidence; prospective cohort study meta-analyses are initially low-quality. Evidence downgrade was based upon study limitations (risk of bias weight), inconsistency (substantial unexplained heterogeneity, $I^2 \geq 50\%$ and $P < 0.10$), indirectness (factors limiting generalizability), imprecision (wide 95% confidence intervals (CIs) crossing a minimally important difference (MID)), and publication bias (small-study effects). Evidence upgrade was based upon large association magnitude (risk ratio (RR) or hazard ratio (HR) ≤ 0.5 or ≥ 2), dose-response gradient, and attenuation by plausible confounding. Reviewer discrepancies were resolved by consensus or arbitration by the senior author (JLS). For the interpretation of the magnitude, we used the MIDs to assess the importance of magnitude of our point estimate using the effect size categories according to the new GRADE guidance (Santesso et al. 2020). Then, we used the MIDs to assess the importance of the magnitude of our point estimates using the effect size categories according to the GRADE guidance (Balshem et al. 2011; Schünemann et al. 2013; Santesso et al. 2020) as follows: a large effect ($\geq 5 \times$ MID); moderate effect ($\geq 2 \times$ MID); small important effect ($\geq 1 \times$ MID); and trivial/unimportant effect (<1 MID).

Role of the funder

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and take full responsibility for the integrity and accuracy of the data and analyses.

Results

Search results

Figure 2 illustrates the study selection process. From 7175 reports, we excluded 7116 based on title or abstract. Full-text review of 59 reports yielded 33 meeting eligibility criteria. Applying the criteria of latest review and at least two methodology types per outcome, we included six trial-based SRMAs (N = 24 497 across outcomes and methodology types). These reviews reported on the following outcomes, assessed using reference substitution, intended substitution, and lumping of all comparators methodologies: energy intake (Rios-Leyvraz et al. 2022; Rostampour et al. 2024), body weight (Li et al. 2023*b*; Movahedian et al. 2024), BMI (Rios-Leyvraz et al. 2022; Movahedian et al. 2024), body fat (McGlynn et al. 2022; Movahedian et al. 2024), WC (McGlynn et al. 2022; Movahedian et al. 2024), HbA1c (McGlynn et al. 2022; Rios-Leyvraz et al. 2022), fasting plasma glucose (McGlynn et al. 2022; Rios-Leyvraz et al. 2022), fasting plasma insulin (McGlynn et al. 2022; Rios-Leyvraz et al. 2022), SBP (McGlynn et al. 2022; Rios-Leyvraz et al. 2022), DBP (McGlynn et al. 2022; Rios-Leyvraz et al. 2022), LDL-C, HDL-C (McGlynn et al. 2022; Movahedian et al. 2023), and TG (McGlynn et al. 2022; Movahedian et al. 2023). Although we searched for data on other outcomes (post-prandial glucose, non-HDL-C, apoB, intrahepatocellular lipid, alanine transaminase, aspartate aminotransferase, fatty liver index), we did not identify at least two analyses using the specified methodologies for inclusion.

We also included five SRMAs of cohort studies (N = 2759 806 across outcomes and methodology types). These meta-analyses reported on the associations between replacing free sugars with LNCS and the following outcomes, using prevalent, change, intended substitution, and reference substitution analyses: body weight (Lee et al. 2022; Rios-Leyvraz et al. 2022), WC (Lee et al. 2022; Rios-Leyvraz et al. 2022), obesity incidence (Lee et al. 2022; Rios-Leyvraz et al. 2022), T2D incidence (Lee et al. 2022; Li et al. 2023*a*), CHD incidence (Lee et al. 2022; Queiroz et al. 2024), stroke incidence (Lee et al. 2022; Queiroz et al. 2024), cardiovascular mortality (Chen et al. 2024; Queiroz et al. 2024), and all-cause mortality (Chen et al. 2024; Queiroz et al. 2024). Although we searched for data on other outcomes (BMI, body fat, energy intake, metabolic syndrome, CVD and MASLD incidence, CHD and stroke mortality), we did not identify at least two analyses using the specified methodologies for inclusion. Supplemental Table 3 lists the excluded SRMAs, with reasons for exclusion being either the availability of more recent reviews or an insufficient number of methodology types for a given outcome.

Systematic review and meta-analyses characteristics

Tables 1 and 2 detail the characteristics of included trial-based and cohort-based SRMAs, respectively. In SRMAs of trials, only one SRMA specifically included studies assessing the effect of low- and no-calorie sweetened beverages (McGlynn et al. 2022), while the other five included studies assessing the effect of LNCS in any food form. In SRMAs of cohorts, only one SRMA specifically included studies assessing the effect of LNCS in any food form (Rios-Leyvraz et al. 2022), while the other four included studies assessing the effect of low- and no-calorie sweetened beverages only. Mean LNCS dose reporting was limited in trial SRMAs and LNCS type or dose was nearly absent in cohort SRMAs. Cohort SRMAs using bias-adjusted analyses included only studies adjusted for initial adiposity, whereas those using naïve analyses included a mixture of studies with or without adjustment for adiposity. Supplementary Tables 4a and 4b detail the AMSTAR 2 ratings for SRMAs of trials and cohorts, respectively. AMSTAR 2-assessed risk of bias varied from low to high for trial SRMAs (majority high confidence) and low to moderate for cohort SRMAs (majority moderate confidence).

Outcomes

Figure 3 presents LNCS effects on outcomes from trial-based SRMAs, categorized by methodology type. Naïve analyses (lumping all comparators; red font) showed LNCS use associated with a trivial energy intake reduction (−135.89 kcals [95% CI −205.39, −66.38 kcals], $P < 0.01$, $I^2 = 81\%$, $P_Q < 0.01$, low certainty); a small, important body weight reduction (−1.02 kg [95% CI −1.57, −0.46 kg], $I^2 = 71\%$, $P_Q < 0.0001$, low certainty); and a trivial body fat reduction (−1.09% [95% CI −1.90, −0.29%], $I^2 = 0\%$, $P_Q = 0.803$, low certainty). Bias-adjusted (blue font) intended substitution analyses (LNCS for sugars) showed a trivial energy intake reduction (−175.26 kcals [95% CI −296.47, −54.06 kcals], $P < 0.001$, $I^2 = 61\%$, $P_Q < 0.001$, high certainty); a trivial body weight reduction (−0.71 kg [95% CI −1.19, −0.24 kg], $I^2 = 78\%$, $P_Q < 0.01$, very low certainty); a trivial BMI reduction (−0.21 kg/m^2 [95% CI −0.36, −0.06 kg/m^2], $P < 0.01$, $I^2 = 42\%$, $P_Q = 0.040$, low certainty); and a trivial body fat reduction (−0.60% [95% CI −1.03, −0.18%], $I^2 = 0\%$, $P_Q = 0.998$, moderate certainty). Bias-adjusted reference substitution analyses (LNCS for water/placebo) showed trivial increases in HbA1c that related to smaller reductions in HbA1c than water/placebo (0.21% [95% CI 0.02, 0.40%], $P = 0.034$, $I^2 = 93\%$, $P_Q < 0.001$, low certainty) and a small, important reduction in SBP that related to larger reductions in SBP than water (−2.63 mm Hg [95% CI −4.71, −0.55 mm Hg], $P = 0.013$, $I^2 = 29\%$, $P_Q = 0.275$, low certainty). No differences were observed for other outcomes.

Figures 4 and 5 present associations of LNCS with outcomes from cohort-based SRMAs, categorized by methodology type (Fig. 4 shows MDs; Fig. 5 shows ratios). Naïve prevalent analyses (red font) showed LNCS use positively associated with obesity risk (large magnitude, HR 1.76 [95% CI 1.25, 2.49], $P < 0.01$, $I^2 = 0\%$, $P_Q = 0.620$, low certainty); T2D risk (large magnitude, RR 1.32 [95% CI 1.11, 2.56], $I^2 = 93\%$, $P_Q < 0.001$, high certainty); stroke risk (at 1 dose/day) (moderate magnitude, HR 1.16 [95% CI 1.01, 1.32], $P = 0.036$, $I^2 = 25\%$, $P_Q = 0.260$, very low certainty); cardiovascular mortality risk (1 dose/day: large magnitude, HR 1.30 [95% CI 1.10, 1.53], $P = 0.002$, $I^2 = 63\%$,

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Table 1. Characteristics of the included SRMAs of trials.

Outcome and methodology type	Study (year)	$N_{Studies}$ (direct)	$N_{Studies}$ (indirect)[a]	$N_{Participants}$ (direct)	$N_{Participants}$ (indirect)	Model	GRADE[b]	Eligibility criteria/PICOTS framework				Mean LNCS dose (mg)	Mean LNCSB dose (mL)	LNCS type	SRMA funding
								Participants	Interventions	Control/ comparators	Time				
Energy intake (kcal)															
Lumping of all comparators	Rios-Leyvraz et al. (2022)	25	NA	2208	NA	Random	Low	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	No or lower doses of NSS consumption (i.e., any type of sugar, placebo, plain water or no intervention)	≥1 week	NR	NR	Mixed	A
Intended substitution	Rostampour et al. (2024)	18	NA	944	NA	Random	High	Adults	Direct and indirect consumption of NNS pure or in the context of foods and beverages	Comparison with sugar sweetener beverage, and placebo or control group	≥4 weeks	480–4000	1000–1750	Mixed	A
Reference substitution	Rostampour et al. (2024)	11	NA	655	NA	Random	Low	Adults	Direct and indirect consumption of NNS pure or in the context of foods and beverages	Comparison with water	≥4 weeks	48–284	178–454	Mixed	A
Body weight (kg)															
Lumping of all comparators	Movahedian et al. (2024)	17	NA	1451	NA	Random	Low	Adults with varying health statuses	Artificial and herbal sugar substitute sweeteners	Water, sucrose, or other high-calorie sweeteners	≥1 week	658	NR	Mixed	None
Intended substitution	Li et al. (2023*a*)	6	NA	401	NA	Random	Very low	Adults with BMI ≥ 24 kg/m^2	Any type of NNS, either alone or in combination with another NNS	Sucrose	≥4 weeks	NR	NR	Mixed	NR
Reference substitution (water)	Li et al. (2023*a*)	3	NA	560	NA	Random	Low	Adults with BMI ≥ 24 kg/m^2	Any type of NNS, either alone or in combination with another NNS	Water	≥4 weeks	NR	NR	Mixed	NR
Reference substitution (placebo)	Li et al. (2023*a*)	3	NA	318	NA	Random	Moderate	Adults with BMI ≥ 24 kg/m^2	Any type of NNS, either alone or in combination with another NNS	Placebo	≥4 weeks	NR	NR	Mixed	NR

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Table 1. (*continued*).

Outcome and methodology type	Study (year)	$N_{Studies}$ (direct)	$N_{Studies}$ (indirect)[a]	$N_{Participants}$ (direct)	$N_{Participants}$ (indirect)	Model	GRADE[b]	Eligibility criteria/PICOTS framework				Mean LNCS dose (mg)	Mean LNCSB dose (mL)	LNCS type	SRMA funding
								Participants	Interventions	Control/ comparators	Time				
BMI (kg/m^b)															
Lumping of all comparators	Movahedian et al. (2024)	11	NA	980	NA	Random	Low	Adults with varying health statuses	Artificial and herbal sugar substitute sweeteners	Water, sucrose, or other high-calorie sweeteners	≥1 week	531	NR	Mixed	None
Intended substitution	Rios-Leyvraz et al. (2022)	16	NA	1300	NA	Random	Low	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	No or lower doses of NSS consumption (i.e., any type of sugar, placebo, plain water, or no intervention)	≥1 week	NR	NR	Mixed	A
Reference substitution (water)	Rios-Leyvraz et al. (2022)	6	NA	499	NA	Random	Low	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	No or lower doses of NSS consumption (i.e., any type of sugar, placebo, plain water, or no intervention)	≥1 week	NR	NR	Mixed	A
Reference substitution (nothing)	Rios-Leyvraz et al. (2022)	4	NA	189	NA	Random	Low	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	No or lower doses of NSS consumption (i.e., any type of sugar, placebo, plain water, or no intervention)	≥1 week	NR	NR	Mixed	A
Body fat (%)															
Lumping of all comparators	Movahedian et al. (2024)	7	NA	436	NA	Random	Low	Adults with varying health statuses	Artificial and herbal sugar substitute sweeteners	Water, sucrose, or other high-calorie sweeteners	≥1 week	583	NR	Mixed	None
Intended substitution	McGlynn et al. (2022)	7	14	210	559	Random	Moderate	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	1039	Mixed	A + I

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Table 1. (*continued*).

Outcome and methodology type	Study (year)	$N_{Studies}$ (direct)	$N_{Studies}$ (indirect)[a]	$N_{Participants}$ (direct)	$N_{Participants}$ (indirect)	Model	GRADE[b]	Eligibility criteria/PICOTS framework				Mean LNCS dose (mg)	Mean LNCSB dose (mL)	LNCS type	SRMA funding
								Participants	Interventions	Control/ comparators	Time				
Reference substitution	McGlynn et al. (2022)	4	14	124	559	Random	Moderate	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	618	Mixed	A + I
Waist circumference (cm)															
Lumping of all comparators	Movahedian et al. (2024)	5	NA	680	NA	Random	Very low	Adults with varying health statuses	Artificial and herbal sugar substitute sweeteners	Water, sucrose, or other high-calorie sweeteners	≥1 week	408	NR	Mixed	None
Intended substitution	McGlynn et al. (2022)	0	6	0	868	Random	Low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	NR	Mixed	A + I
Reference substitution	McGlynn et al. (2022)	5	6	628	868	Random	Low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	716	Mixed	A + I

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Table 1. (*continued*).

Outcome and methodology type	Study (year)	$N_{Studies}$ (direct)	$N_{Studies}$ (indirect)[a]	$N_{Participants}$ (direct)	$N_{Participants}$ (indirect)	Model	GRADE[b]	Eligibility criteria/PICOTS framework				Mean LNCS dose (mg)	Mean LNCSB dose (mL)	LNCS type	SRMA funding
								Participants	Interventions	Control/ comparators	Time				
Fasting plasma glucose (mmol/L)															
Lumping of all comparators	Rios-Leyvraz et al. (2022)	16	NA	1494	NA	Random	Moderate	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	No or lower doses of NSS consumption (i.e., any type of sugar, placebo, plain water, or no intervention)	≥1 week	NR	NR	Mixed	A
Intended substitution	McGlynn et al. (2022)	7	19	210	1183	Random	Moderate	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	1039	Mixed	A + I
Reference substitution	McGlynn et al. (2022)	9	19	748	1183	Random	High	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	679	Mixed	A + I
Fasting plasma insulin (pmol/L)															
Lumping of all comparators	Rios-Leyvraz et al. (2022)	10	NA	759	NA	Random	Low	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	No or lower doses of NSS consumption (i.e., any type of sugar, placebo, plain water, or no intervention)	≥1 week	NR	NR	Mixed	A

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Table 1. (*continued*).

Outcome and methodology type	Study (year)	$N_{Studies}$ (direct)	$N_{Studies}$ (indirect)[a]	$N_{Participants}$ (direct)	$N_{Participants}$ (indirect)	Model	GRADE[b]	Eligibility criteria/PICOTS framework				Mean LNCS dose (mg)	Mean LNCSB dose (mL)	LNCS type	SRMA funding
								Participants	Interventions	Control/ comparators	Time				
Intended substitution	McGlynn et al. (2022)	7	16	210	512	Random	Low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	1039	Mixed	A + I
Reference substitution	McGlynn et al. (2022)	7	16	317	512	Random	Low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	503	Mixed	A + I
HbA1c (%)															
Lumping of all comparators	Rios-Leyvraz et al. (2022)	6	NA	411	NA	Random	Moderate	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	No or lower doses of NSS consumption (i.e., any type of sugar, placebo, plain water, or no intervention)	≥1 week	NR	NR	Mixed	A
Intended substitution	McGlynn et al. (2022)	4	9	154	630	Random	Moderate	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	1500	Mixed	A + I

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Table 1. (*continued*).

Outcome and methodology type	Study (year)	$N_{Studies}$ (direct)	$N_{Studies}$ (indirect)[a]	$N_{Participants}$ (direct)	$N_{Participants}$ (indirect)	Model	GRADE[b]	Eligibility criteria/PICOTS framework				Mean LNCS dose (mg)	Mean LNCSB dose (mL)	LNCS type	SRMA funding
								Participants	Interventions	Control/ comparators	Time				
Reference substitution	McGlynn et al. (2022)	4	9	236	630	Random	Low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	250	Mixed	A + I
Systolic blood pressure (mm Hg)															
Lumping of all comparators	Rios-Leyvraz et al. (2022)	14	NA	1440	NA	Random	Moderate	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	No or lower doses of NSS consumption (i.e., any type of sugar, placebo, plain water, or no intervention)	≥1 week	NR	NR	Mixed	A
Intended substitution	McGlynn et al. (2022)	3	10	56	706	Random	Moderate	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	885	Mixed	A + I
Reference substitution	McGlynn et al. (2022)	4	10	425	706	Random	Low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	944	Mixed	A + I

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Table 1. (*continued*).

Outcome and methodology type	Study (year)	$N_{Studies}$ (direct)	$N_{Studies}$ (indirect)[a]	$N_{Participants}$ (direct)	$N_{Participants}$ (indirect)	Model	GRADE[b]	Eligibility criteria/PICOTS framework				Mean LNCS dose (mg)	Mean LNCSB dose (mL)	LNCS type	SRMA funding
								Participants	Interventions	Control/ comparators	Time				
Diastolic blood pressure (mm Hg)															
Lumping of all comparators	Rios-Leyvraz et al. (2022)	13	NA	1137	NA	Random	Moderate	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	No or lower doses of NSS consumption (i.e., any type of sugar, placebo, plain water, or no intervention)	≥1 week	NR	NR	Mixed	A
Intended substitution	McGlynn et al. (2022)	3	9	56	483	Random	Low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	885	Mixed	A + I
Reference substitution	McGlynn et al. (2022)	3	9	202	483	Random	Low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	1022	Mixed	A + I
LDL-C (mmol/L)															
Lumping of all comparators	Movahedian et al. (2023)	11	NA	760	NA	Random	Moderate	Adults	Artificial and herbal sugar substitute sweeteners	NR	≥1 week	642	480	Mixed	None

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Table 1. (*continued*).

Outcome and methodology type	Study (year)	$N_{Studies}$ (direct)	$N_{Studies}$ (indirect)[a]	$N_{Participants}$ (direct)	$N_{Participants}$ (indirect)	Model	GRADE[b]	Eligibility criteria/PICOTS framework				Mean LNCS dose (mg)	Mean LNCSB dose (mL)	LNCS type	SRMA funding
								Participants	Interventions	Control/ comparators	Time				
Intended substitution	McGlynn et al. (2022)	6	16	183	894	Random	Moderate	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	952	Mixed	A + I
Reference substitution	McGlynn et al. (2022)	7	16	486	894	Random	High	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	510	Mixed	A + I
HDL-C (mmol/L)															
Lumping of all comparators	Movahedian et al. (2023)	15	NA	1080	NA	Random	High	Adults	Artificial and herbal sugar substitute sweeteners	NR	≥1 week	730	480	Mixed	None
Intended substitution	McGlynn et al. (2022)	7	17	210	923	Random	Moderate	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	1038	Mixed	A + I

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Table 1. (*concluded*).

Outcome and methodology type	Study (year)	$N_{Studies}$ (direct)	$N_{Studies}$ (indirect)[a]	$N_{Participants}$ (direct)	$N_{Participants}$ (indirect)	Model	GRADE[b]	Eligibility criteria/PICOTS framework				Mean LNCS dose (mg)	Mean LNCSB dose (mL)	LNCS type	SRMA funding
								Participants	Interventions	Control/ comparators	Time				
Reference substitution	McGlynn et al. (2022)	7	17	488	923	Random	Low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	511	Mixed	A + I
Triglycerides (mmol/L)															
Lumping of all comparators	Movahedian et al. (2023)	16	NA	1154	NA	Random	Moderate	Adults	Artificial and herbal sugar substitute sweeteners	NR	≥1 week	770	480	Mixed	None
Intended substitution	McGlynn et al. (2022)	7	17	210	923	Random	Moderate	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	SSB	≥2 weeks	NR	1039	Mixed	A + I
Reference substitution	McGlynn et al. (2022)	7	17	488	923	Random	Very low	Adults, no pregnant or breastfeeding women	LNCSB Studies of LNCSs added to foods, fortified beverages, or nutrient-dense beverages (e.g., milk, juice, etc.) were excluded due to the presence of other macronutrients	Water	≥2 weeks	NR	511	Mixed	A + I

Note: A = agency funding; ADI = acceptable daily intake; BMI = body mass index; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; HbA1c = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; I = industry funding; LDL-C = low-density lipoprotein cholesterol; LNCSB = low- and no-calorie sweetened beverages; LNCS = low- and no-calorie sweeteners; NA = not applicable; NSS = nonsugar-sweeteners; NR = not reported; PICOTS = participants, intervention, comparator, outcome, time, study design; SRMA = systematic reviews and meta-analysis; SSB = sugar-sweetened beverages.

[a]Indirect estimates only apply to network meta-analyses.

[b]If the authors of the SRMA evaluated the certainty of their evidence using GRADE, we report here their evaluation. If they did not evaluate the certainty of their evidence using GRADE, we conducted our own GRADE assessment as shown in Supplemental Table 4.

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Table 2. Characteristics of the included SRMAs of cohorts.

Outcome and methodology type	Study (year)	$N_{studies}$	$N_{participants}$	Model	GRADE[a]	Eligibility criteria			Including studies that adjusted for initial adiposity	Mean LNCS dose (mg) in the lowest quantile	Mean LNCS dose (mg) in the highest quantile	Mean LNCSB dose (mL) in the lowest quantile	Mean LNCSB dose (mL) in the highest quantile	Increment change dose	LNCS type	SRMA funding
						Participants	Exposure	Time								
Body weight (kg)																
Prevalent analysis	Rios-Leyvraz et al. (2022)	4	118 457	Random	Very low	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	≥1 year	Mixed	NR	NR	NR	NR	NA	Mixed	A
Intended substitution analysis	Lee et al. (2022)	3	165 579	Fixed	Moderate	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I
Reference substitution analysis	Lee et al. (2022)	1	173	Fixed	Very low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I
Change analysis	Lee et al. (2022)	5	130 020	Fixed	Low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	1 serving = 330 mL	NR	A + I
Waist circumference (cm)																
Prevalent analysis	Rios-Leyvraz et al. (2022)	3	12 886	Random	Very low	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	≥1 year	Mixed	NR	NR	NR	NR	NA	NR	A
Intended substitution analysis	Lee et al. (2022)	1	173	Fixed	Very low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I
Change analysis	Lee et al. (2022)	1	9294	Fixed	Low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	1 serving = 330 mL	NR	A + I

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Table 2. (*continued*).

Outcome and methodology type	Study (year)	$N_{studies}$	$N_{participants}$	Model	GRADE[a]	Eligibility criteria			Including studies that adjusted for initial adiposity	Mean LNCS dose (mg) in the lowest quantile	Mean LNCS dose (mg) in the highest quantile	Mean LNCSB dose (mL) in the lowest quantile	Mean LNCSB dose (mL) in the highest quantile	Increment change dose	LNCS type	SRMA funding
						Participants	Exposure	Time								
Obesity incidence																
Prevalent analysis	Rios-Leyvraz et al. (2022)	2	1668	Random	Low	Generally healthy adults	Any type of NSS (excluding sugar alcohols and natural caloric sweeteners) within the ADI	≥1 year	Mixed	NR	NR	NR	NR	NA	NR	A
Intended substitution analysis	Lee et al. (2022)	1	15 765	Fixed	Low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I
Reference substitution analysis	Lee et al. (2022)	1	15 765	Fixed	Very low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I
Type 2 diabetes incidence																
Prevalent analysis	Li et al. (2023*a*)	10	367 447	Random	High	Adults	ASBs	≥2 years	Mixed	NR	NR	NR	NR	NA	NR	A
Intended substitution analysis	Lee et al. (2022)	5	281 855	Fixed	Very low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I
Reference substitution analysis	Lee et al. (2022)	4	257 202	Fixed	Very low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I
Change analysis	Lee et al. (2022)	3	192 352	Fixed	Very low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	1 serving = 330 mL	NR	A + I
CHD incidence																
Prevalent analysis (1 dose/day)	Queiroz et al. (2024, 2025)	2	NR	Random	Very low	NR	ASBs, diet soda, diet soft drinks, nonsugar artificially sweetened beverages, low-calorie soft drinks, low-calorie artificially sweetened beverages	NR	Mixed	NR	NR	<355 mL per month	≥355 mL per day	NA	NR	None

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Table 2. (*continued*).

Outcome and methodology type	Study (year)	$N_{studies}$	$N_{participants}$	Model	GRADE[a]	Eligibility criteria			Including studies that adjusted for initial adiposity	Mean LNCS dose (mg) in the lowest quantile	Mean LNCS dose (mg) in the highest quantile	Mean LNCSB dose (mL) in the lowest quantile	Mean LNCSB dose (mL) in the highest quantile	Increment change dose	LNCS type	SRMA funding
						Participants	Exposure	Time								
Intended substitution analysis	Lee et al. (2022)	6	233 676	Random	Low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I
Stroke incidence																
Prevalent analysis (1 dose/day)	Queiroz et al. (2024, 2025)	4	NR	Random	Very low	NR	ASBs, diet soda, diet soft drinks, nonsugar artificially sweetened beverages, low-calorie soft drinks, low-calorie artificially sweetened beverages	NR	Mixed	NR	NR	<355 mL per month	≥355 mL per day	NA	NR	None
Prevalent analysis (2 doses/day)	Queiroz et al. (2024, 2025)	2	NR	Random	Very low	NR	ASBs, diet soda, diet soft drinks, nonsugar artificially sweetened beverages, low-calorie soft drinks, low-calorie artificially sweetened beverages	NR	Mixed	NR	NR	<355 mL per month	≥710 mL per day	NA	NR	None
Intended substitution analysis	Lee et al. (2022)	1	127 456	Fixed	Very low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I
Reference substitution analysis	Lee et al. (2022)	1	127 456	Fixed	Very low	Adults	LNCSB	≥1 year	Only	NR	NR	NR	NR	NA	NR	A + I

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Table 2. (*continued*).

Outcome and methodology type	Study (year)	$N_{studies}$	$N_{participants}$	Model	GRADE[a]	Eligibility criteria			Including studies that adjusted for initial adiposity	Mean LNCS dose (mg) in the lowest quantile	Mean LNCS dose (mg) in the highest quantile	Mean LNCSB dose (mL) in the lowest quantile	Mean LNCSB dose (mL) in the highest quantile	Increment change dose	LNCS type	SRMA funding
						Participants	Exposure	Time								
CVD mortality																
Prevalent analysis (1 dose/day)	Queiroz et al. (2024, 2025)	5	NR	Random	Very low	NR	ASBs, diet soda, diet soft drinks, nonsugar artificially sweetened beverages, low-calorie soft drinks, low-calorie artificially sweetened beverages	NR	Mixed	NR	NR	<355 mL per month	≥355 mL per day	NA	NR	None
Prevalent analysis (2 doses/day)	Queiroz et al. (2024, 2025)	4	NR	Random	Very low	NR	ASBs, diet soda, diet soft drinks, nonsugar artificially sweetened beverages, low-calorie soft drinks, low-calorie artificially sweetened beverages	NR	Mixed	NR	NR	<355 mL per month	≥710 mL per day	NA	NR	None
Intended substitution analysis	Chen et al. (2024)	4	434 110	Random	Low	Generally healthy adults	≥3 levels of ASB consumption	NR	Only	NR	NR	~0 355 mL servings/day	≥2355 mL servings/day	NA	NR	A + I

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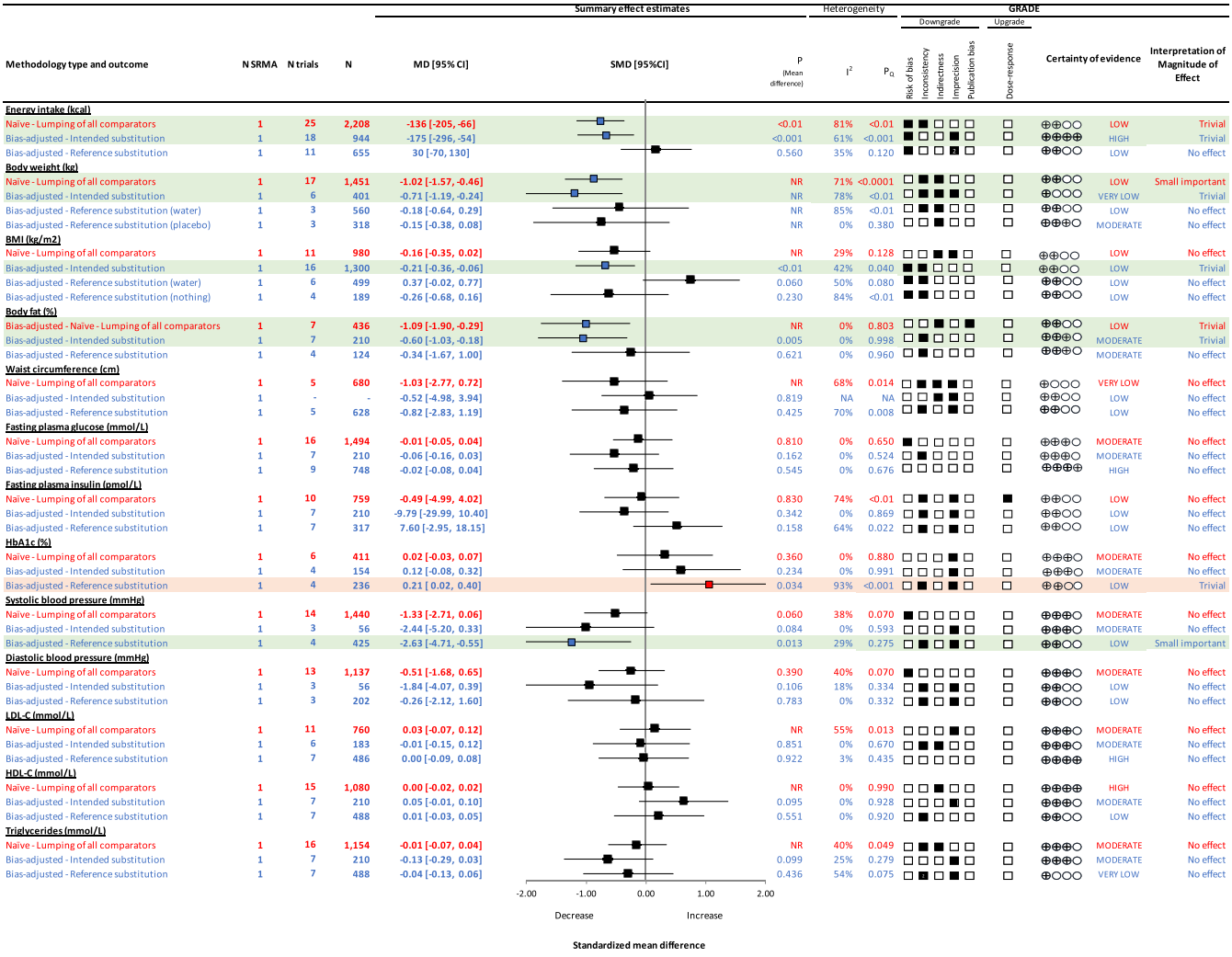
Table 2. (*concluded*).

Outcome and methodology type	Study (year)	$N_{studies}$	$N_{participants}$	Model	GRADE[a]	Eligibility criteria			Including studies that adjusted for initial adiposity	Mean LNCS dose (mg) in the lowest quantile	Mean LNCS dose (mg) in the highest quantile	Mean LNCSB dose (mL) in the lowest quantile	Mean LNCSB dose (mL) in the highest quantile	Increment change dose	LNCS type	SRMA funding
						Participants	Exposure	Time								
All-cause mortality																
Prevalent analysis (1 dose/day)	Queiroz et al. (2024, 2025)	6	NR	Random	Very low	NR	ASBs, diet soda, diet soft drinks, nonsugar artificially sweetened beverages, low-calorie soft drinks, low-calorie artificially sweetened beverages	NR	Mixed	NR	NR	<355 mL per month	≥355 mL per day	NA	NR	None
Prevalent analysis (2 doses/day)	Queiroz et al. (2024, 2025)	5	NR	Random	Very low	NR	ASBs, diet soda, diet soft drinks, nonsugar artificially sweetened beverages, low-calorie soft drinks, low-calorie artificially sweetened beverages	NR	Mixed	NR	NR	<355 mL per month	≥710 mL per day	NA	NR	None
Intended substitution analysis	Chen et al. (2024)	4	268 472	Random	Very low	Generally healthy adults	≥3 levels of ASB consumption	NR	Only	NR	NR	~0 355 mL servings/day	≥2355 mL servings/day	NA	NR	A + I

Note: A = agency funding; ADI = acceptable daily intake; ASB = artificially sweetened beverage; CHD = coronary heart disease; CVD = cardiovascular disease; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; I = industry funding; LNCS = low- and no-calorie sweeteners; LNCSB = low- and no-calorie sweetened beverages; NA = not applicable; NR = not reported; NSS = nonsugar-sweeteners; SRMA = systematic reviews and meta-analysis.

[a]If the authors of the SRMA evaluated the certainty of their evidence using GRADE, we report here their evaluation. If they did not evaluate the certainty of their evidence using GRADE, we conducted our own GRADE assessment as shown in Supplemental Table 4.

Fig. 3. Summary plot for the effect of low- and no-calorie sweeteners on included outcomes by methodology type in SRMAs of trials. Plotted data are SMDs (95% confidence intervals (CIs)) and corresponding MDs (95% CIs) are reported in the column to the left of the plot. Where the authors of each original SRMAs conducted a GRADE evaluation to evaluate the certainty and strength of the evidence, this evaluation was taken and summarized for each outcome. If no GRADE evaluation was conducted, we conducted our own GRADE assessment as shown in Supplemental Table 4. In red font are the naïve (prevalent) analyses, in blue font are the bias-adjusted (intended and reference substitutions and change analyses) analyses. Significant results are highlighted in orange (for harm) and green (for benefit). BMI = body mass index; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; HbA1c = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; NA = not applicable; NR = not reported; SMDs = standardized mean differences; SRMA = systematic reviews and meta-analysis.ī



$P_Q = 0.030$, very low certainty; 2 doses/day: large magnitude, HR 1.30 [95% CI 1.07, 1.57], $P = 0.007$, $I^2 = 72\%$, $P_Q = 0.010$, very low certainty); and all-cause mortality risk (at 1 dose/day) (moderate magnitude, HR 1.14 [95% CI 1.03, 1.26], $P = 0.009$, $I^2 = 79\%$, $P_Q < 0.01$, very low certainty).

Bias-adjusted (blue font) intended substitution analyses (LNCS for SSB substitution) showed associations with lower body weight (trivial magnitude, −0.12 kg [95% CI −0.14, −0.10 kg], $P < 0.01$, $I^2 = 46\%$, $P_Q = 0.160$, moderate certainty); lower obesity risk (large magnitude, RR 0.88 [95% CI 0.88, 0.89], $P < 0.01$, low certainty); lower CHD risk (large magnitude, RR 0.89 [95% CI 0.81, 0.98], $P = 0.020$, $I^2 = 28\%$, $P_Q = 0.220$, low certainty); lower cardiovascular mortality risk (large magnitude, RR 0.94 [95% CI 0.90, 0.99], $I^2 = 0\%$, $P_Q = 0.647$, very low certainty); and lower all-cause mortality risk (large magnitude, HR 0.96 [95% CI 0.94, 0.98], $I^2 = 0\%$, $P_Q = 0.578$, very low certainty). Bias-adjusted (blue font) change analyses showed associations with lower body weight (trivial magnitude, −0.01 kg [95% CI −0.01, 0.00 kg], $P = 0.010$, $I^2 = 66\%$, $P_Q = 0.020$, low certainty) and lower WC (small important magnitude, −1.15 cm [95% CI −2.34, −0.05 cm], $P < 0.05$, $I^2 = 2884$, $P_Q < 0.01$, low certainty). No differences were observed for other outcomes.

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Fig. 4. Summary plot for the effect of low- and no-calorie sweeteners on each included outcomes by methodology type in SRMAs of cohorts reporting MDs. Plotted data are SMDs (95% confidence intervals (CIs)) and corresponding MDs (95% CIs) are reported in the column to the left of the plot. Where the authors of each original SRMA conducted a GRADE evaluation to evaluate the certainty and strength of the evidence, this evaluation was taken and summarized for each outcome. If no GRADE evaluation was conducted, we conducted our own GRADE assessment as shown in Supplemental Table 4. In red font are the naïve (prevalent) analyses, in blue font are the bias-adjusted (intended and reference substitutions and change analyses) analyses. Significant results are highlighted in orange (for harm) and green (for benefit). BMI = body mass index; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MD = mean difference; NA = not applicable; NR = not reported; SMDs = standardized mean differences; SRMA = systematic reviews and meta-analysis.

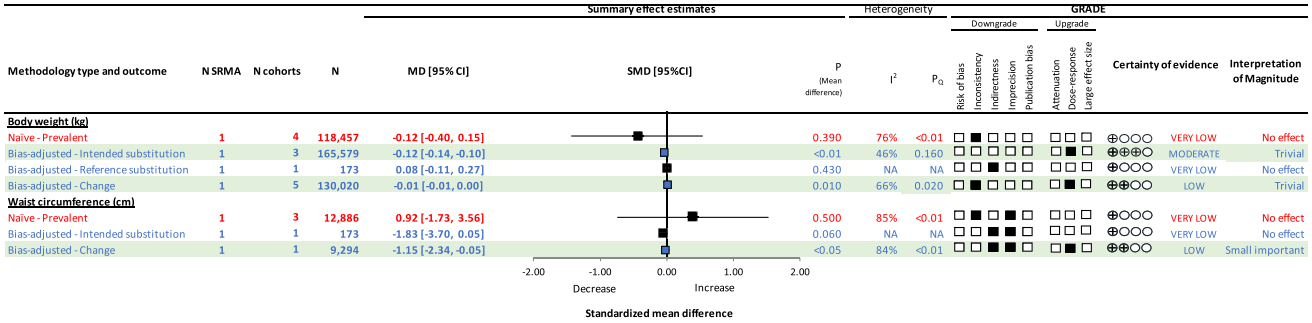
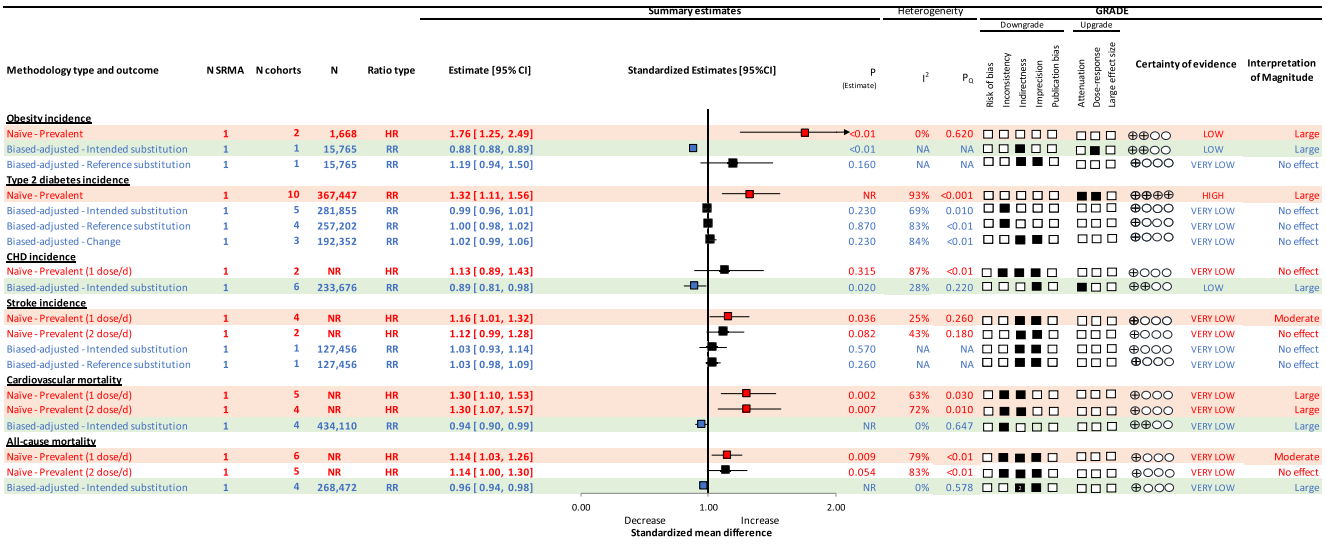


Fig. 5. Summary plot for the effect of low- and no-calorie sweeteners on each included outcomes by methodology type in SRMAs of cohorts reporting ratios. Plotted data are standardized estimates (95% confidence intervals (CIs)) and corresponding estimates (95% CIs) are reported in the column to the left of the plot. Where the authors of each original SRMA conducted a GRADE evaluation to evaluate the certainty and strength of the evidence, this evaluation was taken and summarized for each outcome. If no GRADE evaluation was conducted, we conducted our own GRADE assessment as shown in Supplemental Table 4. In red font are the naïve (prevalent) analyses, in blue font are the bias-adjusted (intended and reference substitutions and change analyses) analyses. Significant results are highlighted in orange (for harm) and green (for benefit). CHD = coronary heart disease; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MD = mean difference; NA = not applicable; NR = not reported; SMDs = standardized mean differences; SRMA = systematic reviews and meta-analysis



Certainty of the evidence

GRADE evaluations were available from the authors of included SRMAs for most outcomes and methodology types. Exceptions were trial-based SRMAs for body weight, intended substitution, reference substitution (water), and reference substitution (placebo) (Li et al. 2023*b*); cohort-based SRMAs for T2D incidence, prevalent analyses (Li et al. 2023*a*), CHD incidence, prevalent analysis (Queiroz et al. 2024); stroke incidence, prevalent analysis (1 and 2 doses/day) (Queiroz et al. 2024); cardiovascular mortality, substitution analysis (Chen et al. 2024), and prevalent analysis (1 and 2 doses/day) (Queiroz et al. 2024); and all-cause mortality, substitution analysis (Chen et al. 2024), and prevalent analysis (1 and 2 doses/day) (Queiroz et al. 2024). Supplementary Table

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4 presents our GRADE evaluations, conducted using published information where original GRADE assessments were lacking.

Across trial-based and cohort-based SRMAs, evidence certainty ranged from very low to high, with downgrades primarily due to risk of bias, inconsistency, indirectness, imprecision, and/or publication bias. Upgrades were applied for dose-response gradients (trials only) and attenuation by confounders (cohorts only).

Discussion

This umbrella review synthesizes evidence from SRMAs of the association between LNCS and cardiometabolic health and energy intake, categorized by study methodology. Our findings reveal a crucial methodological dichotomy—naïve analyses versus bias-adjusted methodologies. In trial-based SRMAs, both naïve (lumping all comparators) and bias-adjusted intended substitution analyses demonstrated LNCS-associated reductions in energy intake, body weight, and body fat. Specifically, while naïve analyses showed benefits, these were largely driven by the intended substitution context–LNCS replacing sugars and displacing calories. This underscores that LNCS's benefit lies in calorie displacement, offering a useful alternative to added sugars, especially in SSBs, which are the largest sources of added sugars (Brisbois et al. 2014; Malik and Hu 2022). Conversely, bias-adjusted reference substitution analyses in trials without calorie displacement (LNCS replacing water/placebo) showed similar results across outcomes with only minimal differences, including a small important reduction in SBP that related to greater reductions than water, and a trivial increase in HbA1c that related to smaller reductions than water. In cohort-based SRMAs, naïve prevalent analyses, susceptible to bias, showed positive associations between LNCS intake and risks of obesity, T2D, stroke, cardiovascular, and all-cause mortality. However, bias-adjusted intended substitution and change analyses in cohorts, designed to mitigate bias, presented a contrasting picture, aligning with trial findings by showing associations between higher LNCS intake and lower risks of obesity, lower body weight, CHD, cardiovascular, and all-cause mortality.

Cohort studies, often analyzed using naïve prevalent methods, are inherently prone to bias like reverse causality (Sievenpiper et al. 2017; Lee et al. 2020). Our review highlights this vulnerability, contrasting prevalent analyses, which suggest harm, with robustly analyzed cohorts employing bias-adjusted intended substitution and change analyses (Sievenpiper et al. 2017; Khan et al. 2019, 2023; Malik 2019; Mela et al. 2020; Hedrick et al. 2023; Higgins et al. 2024). The former naïve analyses method underpinned WHO guidelines advising against LNCS for weight control (World Health Organization 2023*a*) which failed to capture the benefit revealed by bias-adjusted approach we report here. Intended substitution modeling, mirroring real-world sugar replacement, aligns with trial findings, demonstrating LNCS's potential benefits when used to displace sugars. Reference substitution modeling, in contrast, shows negligible effects, further emphasizing the importance of calorie displacement in mediating LNCS benefits. Change analyses, though less common, reinforce these beneficial findings, indicating associations between changes in LNCS exposure and favorable adiposity outcomes, consistent with trial evidence.

Findings in the context of the literature

Our findings diverge from other umbrella reviews of relying solely on biased prevalent analyses of cohort SRMAs, which report inconsistent evidence on LNCS (Lohner et al. 2017; Abbasi 2019; Green and Syn 2019; Kim et al. 2019; Andrade et al. 2021; Diaz et al. 2023). This perceived inconsistency has fueled controversy (Khan et al. 2023, 2024; Hedrick et al. 2023). The recent WHO guideline, prioritizing biased/naïve cohort evidence, amplified this controversy. This, coupled with events like International Agency for Research on Cancer's aspartame classification (World Health Organization 2023*b*, 2023*c*), has negatively influenced public perception of LNCS. Our review demonstrates that the apparent trial-cohort disagreement disappears when considering bias-reducing methodologies in cohorts. Trial-based SRMA results, already largely consistent, become even more translatable to real-world scenarios when the comparator context is considered.

Strengths and limitations

Our analysis has several strengths. First, we included recent SRMAs, with publication dates from 2022 to 2025. Second, we are the first to incorporate the WHO-commissioned SRMA that informed recent WHO guidelines on LNCS (Rios-Leyvraz et al. 2022; World Health Organization 2023*a*). Third, we effectively disentangled effects/associations by methodology type, enhancing result translatability. Fourth, we rigorously assessed overall evidence certainty using GRADE. Fifth, dose-response gradients were evident in trial-based SRMAs (naïve analysis, fasting insulin, as assessed by Rios-Leyvraz et al. (2022)) and in cohort-based SRMAs (bias-adjusted analysis of body weight, as assessed by Lee et al. (2022)), WC, as assessed by Lee et al. (2022), obesity, as assessed by Lee et al. (2022), naïve analysis of T2D incidence (positive relationship)). Sixth, attenuation by key confounders was observed in cohort analyses (bias-adjusted analysis of CHD incidence, as assessed by Lee et al. (2022) and naïve analysis of T2D incidence, where results were attenuated by most of the included cohorts adjusting for BMI (as observed in Supplementary Table 18)).

Limitations include: first, study limitations (risk of bias) in 9 of 41 trial-based analyses (energy intake, BMI, fasting glucose, SBP/DBP) due to some studies with high risk of bias. Second, inconsistency in 23 of 41 trial-based analyses (all outcomes) and 11 of 17 cohort-based analyses (body weight, WC, T2D/CHD incidence, cardiovascular/all-cause mortality) due to substantial unexplained heterogeneity. Third, indirectness in 11 of 41 trial-based analyses (adiposity, lipids) and 16 of 17 cohort-based analyses (all outcomes) due to generalizability limitations. Fourth, imprecision in 21 of 41 trial-based analyses (energy intake, adiposity, insulin, HbA1c, SBP/DBP, lipids) and 14 of 17 cohort-based analyses (WC, obesity, T2D, CHD/stroke incidence, all-cause mortality) due to wide 95%

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CIs. Finally, publication bias was detected in 1 of 41 trial-based analyses (naïve analysis of body fat, as assessed by Movahedian et al. (2024)). Balancing strengths and limitations, GRADE certainty for LNCS effects/associations on cardiometabolic outcomes ranged from very low to high.

Implications

Recent WHO guidelines, prioritizing cohort evidence from naïve analyses, made a conditional recommendation against use of LNCS for weight control and disease risk reduction, citing perceived lack of long-term benefit and potential harms (World Health Organization 2023*a*). However, WHO cohort analyses relied on naïve but biased prevalent analyses, which, as we show, do indicate higher cardiometabolic disease risk. Robust analytical methods (Sievenpiper et al. 2017; Khan et al. 2019, 2023; Malik 2019; Mela et al. 2020; Hedrick et al. 2023; Higgins et al. 2024) that are bias-adjusted reconcile trial and cohort evidence, suggesting a need to reconsider the WHO's conditional recommendation. These reconciled findings, warrant dissemination to scientists and the public. LNCS, when used as sugar/calorie replacements, show potential benefits, particularly for adiposity management and possibly for long-term T2D/CVD risk improvement. Clinical practice, public health and nutrition guidelines would benefit from considering and reporting on the context of LNCS use—substitution versus addition—and the methodological limitations of naïve analyses. Future primary research and SRMAs employing bias-adjusted methodologies are needed, especially for underexamined outcomes like postprandial glucose, non-HDL-C, apoB, MASLD outcomes, metabolic syndrome, and MASLD incidence, to further refine our understanding of LNCS and cardiometabolic health. Additionally, as there was limited reporting of LNCS doses across SRMAs, future primary research studies, especially of cohorts, reporting should prioritize reporting the type of LNCS used in their population as well as estimated average intake doses.

Finally, while bias-adjusted change and substitution analyses represent a significant methodological improvement over naïve prevalent analyses by mitigating reverse causality, the certainty of evidence could be strengthened through advanced causal inference techniques. The bias-adjusted cohort analyses do not use g-methods, which are specifically designed to handle time-varying confounders affected by past exposures (Mansournia et al. 2017). Future research using these more sophisticated methods could provide more robust estimates by better accounting for the dynamic relationship between LNCS consumption and cardiometabolic outcome over time.

Conclusions

Evidence from trial-based SRMAs consistently supports LNCS use, especially in substitution for sugars, to reduce energy intake and improve adiposity outcomes, without harm to other intermediate cardiometabolic outcomes. Cohort-based SRMA evidence appears inconsistent when considering only naïve prevalent associations, as is often the case. However, bias-adjusted intended substitution and change analyses reconcile trial-cohort discrepancies. Intended substitution modeling, utilizing bias-reducing methods, demonstrates LNCS's potential to lower adiposity, obesity incidence, cardiovascular, and all-cause mortality, with no harm observed in reference substitution modeling. Based on our findings, and when considering bias-adjusted evidence, LNCS are a useful strategy to reduce calories from sugars and should be promoted to reduce adiposity and disease risk, when used as substitutes for caloric sweeteners.

Take home message

The evidence on low- and no-calorie sweeteners has often been cited to be discordant between trials and cohorts. We show that when cohorts employ bias-adjusted methodologies, the evidence consistently supports the use of sweeteners for sugar-reduction.

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Data availability

All data used herein are publicly available.

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Competing interests

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Supplementary material

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