# Relation of Change or Substitution of Low- and No-Calorie Sweetened Beverages With Cardiometabolic Outcomes: A Systematic Review and Meta-analysis of Prospective Cohort Studies

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## BACKGROUND

**Adverse associations of low- and no-calorie sweetened beverages (LNCSB) with cardiometabolic outcomes in observational studies may be explained by reverse causality and residual confounding.**

## PURPOSE

**To address these limitations we used change analyses of repeated measures of intake and substitution analyses to synthesize the association of LNCSB with cardiometabolic outcomes.**

## DATA SOURCES

**MEDLINE, Embase, and the Cochrane Library were searched up to 10 June 2021 for prospective cohort studies with ≥1 year of follow-up duration in adults.**

## STUDY SELECTION

**Outcomes included changes in clinical measures of adiposity, risk of overweight/obesity, metabolic syndrome, type 2 diabetes (T2D), cardiovascular disease, and total mortality.**

## DATA EXTRACTION

**Two independent reviewers extracted data, assessed study quality, and assessed certainty of evidence using GRADE. Data were pooled with a random-effects model and expressed as mean difference (MD) or risk ratio (RR) and 95% CI.**

## DATA SYNTHESIS

**A total of 14 cohorts (416,830 participants) met the eligibility criteria. Increase in LNCSB intake was associated with lower weight (5 cohorts, 130,020 participants; MD −0.008 kg/year [95% CI −0.014, −0.002]). Substitution of LNCSB for sugar-sweetened beverages (SSB) was associated with lower weight (three cohorts, 165,579 participants; MD, −0.12 [−0.14, −0.10,] kg/y) and lower incidence of obesity (OB) (one cohort, 15,765 participants; RR 0.88 [95% CI 0.88, 0.89]), coronary heart disease (six cohorts, 233,676 participants; 0.89 [0.81, 0.98]), cardiovascular disease mortality (one cohort, 118,363 participants; 0.95 [0.90, 0.99]), and**

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total mortality (one cohort, 118,363 participants; 0.96 [0.94, 0.98]) with no adverse associations across other outcomes. Substitution of water for SSB showed lower weight (three cohorts, 165,579 participants; MD −0.10 kg/year [−0.13, −0.06]), lower waist circumference (one cohort, 173 participants; −2.71 cm/year [−4.27, −1.15]) and percent body fat (one cohort, 173 participants; −1.51% per year [−2.61, −0.42]), and lower incidence of OB (one cohort, 15,765 participants; RR 0.85 [0.75, 0.97]) and T2D (three cohorts, 281,855 participants; 0.96 [0.94, 0.98]). Substitution of LNCSB for water showed no adverse associations.

## LIMITATIONS

The evidence was low to very low certainty owing to downgrades for imprecision, indirectness, and/or inconsistency.

## CONCLUSIONS

LNCSB were not associated with cardiometabolic harm in analyses that model the exposure as change or substitutions. The available evidence provides some indication that LNCSB in their intended substitution for SSB may be associated with cardiometabolic benefit, comparable with the standard of care, water.

Sugars have been implicated in the epidemics of obesity (OB) and type 2 diabetes (T2D) and their downstream cardiometabolic complications (1,2). Major health agencies as well as T2D and heart associations have recommended that added/ free sugars be reduced to <5–10% of calories (3,4). Sugar-sweetened beverages (SSB), as the single most important food source of added/free sugars in North America (5–7) and many European countries (8), have become the dominant public health target of these recommendations. Despite safety approvals by the major international health and regulatory bodies (9–12), low- and no-calorie sweetened beverages (LNCSB) are generally not recommended as an effective replacement strategy for SSB. Although major OB and TD2 associations have supported a narrow indication for the use of LNCSB to displace calories from SSB (13–16), water remains the preferred replacement strategy for SSB, and various countries have either explicitly recommended against their use in national dietary guidelines (4,17) or imposed excise taxes on both SSB and LNCSB (18).

Much of the concern regarding LNCSB has been focused on their failure to show established benefits in large prospective cohort studies. Several highly influential systematic reviews and meta-analyses of prospective cohort studies have shown LNCSB to be associated with higher risk of weight gain (19), T2D (20), cardiovascular disease (CVD) events (19,21,22), and all-cause mortality (23). It is well recognized by prospective cohort study investigators, content experts, and guidelines committees (24–26) that these observations come at high risk of reverse causality (i.e., being high risk for OB, T2D, and CVD causes one to increase LNCSB intake as a risk reduction strategy, as opposed to the other way around) and residual confounding from an incomplete adjustment of confounders and behavior clustering (4,15,24–30). The assessment of changes in exposure rather than baseline or prevalent exposure and further modeling of the intended substitution of LNCSB for SSB appear to provide more consistent, robust, and biologically plausible associations (26,28,29,31). Whether LNCSB as a replacement strategy for SSB have the intended benefits remains an important clinical and public health question.

To address the sources of bias in the epidemiology and strengthen causal inferences for the update of the European Association for the Study of Diabetes (EASD) clinical practice guidelines for nutrition therapy (32), the Diabetes and Nutrition Study Group (DNSG) of the EASD commissioned a systematic review and meta-analysis of the available evidence from prospective cohort studies of the relation of LNCSB to cardiometabolic outcomes, restricting the analyses to cohort comparisons where investigators adjusted for initial adiposity and modeled the exposure as either change in intake or substitution of LNCSB for SSB ("intended substitution"), LNCSB for the standard of care, water ("reference substitution"), or water for SSB ("standard of care substitution").

## METHODS

### Data Sources and Searches

The present systematic review and meta-analysis were conducted in accord with the Cochrane Handbook for Systematic Reviews of Interventions (33), and results are reported in accord with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (34) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (35) guidelines.

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from inception to 10 June 2021 for identification of studies that examined the change in LNCSB intake and substitution of LNCSB and cardiometabolic health, supplemented by hand searching of referenced studies of included studies. Abstracts from conferences were included, and no language restrictions were applied. An additional search of MEDLINE, Embase, and CENTRAL databases from inception to 10 June 2021 was conducted to identify studies that examined the substitution of water for

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SSB and cardiometabolic health. Details of search strategies can be found in Supplementary Tables 1 and 2.

## Study Selection

We included prospective cohort studies of adults (age >19 years) of ≥1 year in duration assessing the association of LNCSB intake, defined as "diet" or "low- and no-calorie" beverages where dietary sugars are replaced with no-calorie (e.g., aspartame, sucralose) and/or low-calorie (e.g., stevia) sweeteners to lower the total caloric content. To mitigate residual confounding and reverse causality, we prespecified the inclusion of cohort comparisons where investigators adjusted for initial adiposity and used one of two analytical approaches: 1) change models of repeated measures capturing change in LNCSB intake over time or 2) substitution models. The substitution models were limited to the substitution of LNCSB for SSB, water for SSB, and LNCSB for water. Supplementary Text elaborates on the change and substitution models included in the study.

Outcomes included change in clinical measures of adiposity (body weight, body mass index [BMI], percent body fat [%BF], waist circumference [WC]) and incidence of overweight (OW) or OB, metabolic syndrome, T2D, CVD events and mortality (coronary heart disease [CHD], stroke, and total CVD), and total mortality. Studies were selected with subjects from all health backgrounds including people who did not have the binary outcome of interest at inception.

After the removal of duplicates by a reviewer, two independent reviewers (J.J.L. and T.A.K.) screened and assessed records for eligibility.

## Data Extraction and Quality Assessment

Two independent reviewers (J.J.L. and T.A.K.) extracted relevant data of the largest covariate- adjusted models of primary results, including author information, study design, country of origin, cohort descriptions, follow-up duration, frequency of data collection, confounding variables, type of low- or no-calorie sweetener, statistical analyses, outcome and assessment method, and funding source. Change in means of body weight, %BF, and WC per year were expressed as mean difference (MD) with 95% CIs. Risk of OW/OB, T2D, metabolic

syndrome, CVD events, and total mortality were expressed as risk ratios (RR) with 95% CIs. The authors were contacted for missing outcome data. If required, values were extracted from figures with use of WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/).

When data were only available for the substitution of SSB or water for LNCSB, published data were inverted for estimation of the association of substitution of LNCSB for SSB or water with outcomes. When the beverage substitution was presented in relative terms (i.e., percentage of beverage substitution) (36), 100% substitution was assumed for analyses. If the results were given as a categorical analysis only, the RR change per unit serving for the study was estimated with use of the drmeta routine in Stata 16.1 (37). If several cohort comparisons provided results on the same outcome with inclusion of overlapping groups of individuals, results from studies with the longest follow-up were used to avoid double counting.

Study quality of each of the included cohort comparisons was assessed with the Newcastle-Ottawa Scale (NOS) (38) by the same two independent reviewers (J.J.L., T.A.K.). Up to 9 points were awarded based on cohort selection, ascertainment of the outcome, and comparability of outcomes. (Adjustments for confounding variables were prespecified based on the outcomes, as outlined in Supplementary Table 3.) Cohort comparisons were adjudged for high (score ≥7), moderate (score = 6), or low (score ≤5) study quality (39).

## Data Synthesis and Analysis

Data were analyzed with Stata (version 16.1; StataCorp). Pooled summary estimates were calculated for each outcome by pooling of MD or log-RRs with 95% CIs with use of the generic inverse variance method with DerSimonian-Laird random-effects models (40). When ≤5 cohort comparisons were available for analysis, a fixed-effects model was used to calculate the pooled summary estimates (41). For studies with hazard ratios or odds ratios reported, values were converted to RRs (42,43). We performed separate analyses based on the prespecified study designs. For the change analysis, the associations of

increasing one serving size per day (serving size = 330 mL, the standard manufacturers' portion sizes in the U.K., as previously reported [44]) with outcomes per year were assessed. When change in outcomes was not reported per year (e.g., with reporting per 2 years or per 4 years), we assumed a linear relationship over the given time period to estimate the change per year. For the substitution analysis, the association of substituting LNCSB for SSB or water, matched by volume (1 mL:1 mL), with outcomes was assessed.

For comparison of summary estimates among outcomes on the same scale, the effect estimates of MD and RR were converted into standardized MD (SMD) (also known as Cohen d) and 95% CIs with the formula described in the Cochrane Handbook for Systematic Reviews of Interventions (33).

Heterogeneity was assessed with the Cochran $Q$ ($\chi^2$) statistic with a significance set at $P_Q < 0.10$ and quantified with the $I^2$ statistic. Sources of heterogeneity were investigated by sensitivity through systematic removal of each cohort comparison and recalculation of summary estimates to assess the influence of each cohort comparison. A cohort comparison was considered influential if it changed the direction, significance of the pooled estimates, or the evidence of heterogeneity. If >10 cohort comparisons were available, then we also performed a priori subgroup analyses by follow-up duration, sex, study quality, and funding source with subgroup differences assessed with meta-regression. Results of both the change (cardiometabolic outcome assessed against the increasing beverage [1 serving] intake over time) and substitution (difference between regression coefficients of the two beverages included as continuous terms of dose-intake) analyses were assumed to represent linear dose-response associations. If enough data points were available, the shape of the dose-response association was also assessed with a one-stage mixed model using restricted cubic splines with three knots according to Harrell's recommended percentiles (10%, 50%, and 90%) (37,45). If >10 cohort comparisons were available, we assessed publication bias through visual inspection of funnel plots for asymmetry and formal testing with the Begg and Egger tests with adjustment for

funnel plot asymmetry using the Duval and Tweedie trim-and-fill method (46).

## Quality Assessment

Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence, with certainty of evidence ranging from "very low" to "high" (47,48). GRADE was completed by two independent reviewers (J.J.L., T.A.K.), with any disagreement resolved by a third reviewer (J.L.S.). Observational studies start at a rating of "low" certainty of evidence. Downgrades or upgrades based on established criteria are then applied. Criteria to downgrade include risk of bias (weight of studies show low study quality by NOS), inconsistency (substantial unexplained heterogeneity, $I^2 > 50\%$, $P_Q < 0.10$), indirectness (presence or absence of factors that limit generalizability based on populations, exposures, and outcomes), imprecision (95% CIs cross minimally important difference of 5%), and publication bias (evidence of small study effects). Criteria to upgrade included a large magnitude of effect (RR $<0.5$ or $>2$ in the absence of plausible confounders), a dose-response gradient, and attenuation by plausible confounders.

At the request of the referees, certainty of evidence was also assessed with NutriGrade (49). We performed a sensitivity analysis comparing the results from the two methods.

The predefined protocol for this systematic review and meta-analysis was registered at ClinicalTrials.gov (clinical trial reg. no. NCT04245826).

## Data and Resource Availability

Full data sets can be obtained from the corresponding author at john.sievenpiper@utoronto.ca.

## RESULTS

Figure 1 shows the flow of the literature with examination of the association of LNCSB using change and substitution analyses. Of 486, 14 studies (14 unique cohort comparisons, $n = 416{,}830$) met the eligibility criteria. In six studies (six unique cohort comparisons, $n = 204{,}380$), the change in LNCSB intake was assessed. In 10 (12 unique cohort comparisons, $n = 409{,}683$), 8 (6 unique cohort comparisons, $n = 297{,}793$), and 4 (5 unique cohort comparisons, $n = 272{,}967$) studies,

investigators assessed the substitution of LNCSB for SSB, water for SSB, and LNCSB for water, respectively. We identified at least one cohort comparison with assessment of one or more of the prespecified cardiometabolic outcomes, not including metabolic syndrome. Three authors provided additional information (50–52). Supplementary Fig. 1 shows the flow of the literature examining the effect of substituting water for SSB and cardiometabolic health.

Tables 1 and 2 show the characteristics of the included studies. Most of the cohort comparisons were from the U.S. (eight cohort comparisons) with one cohort comparison each from the U.K., Spain, Finland, and Mexico. The participants were predominantly middle-aged (baseline median age 50 years [range 25–75]) and female (79.3% female and 20.7% male) with varying cardiometabolic risk profiles inclusive of T2D (except for the analyses of T2D, with exclusion of people with T2D). Median follow-up was 17.5 years (range 1–34). Ascertainment of incident cases and mortality was by medical record linkage (CHD events, CHD mortality, CVD mortality, and total mortality) (20% of cohort comparisons for T2D incidence), calculated with self-reported values (OB incidence) by self-report (20% of cohort comparisons for T2D incidence), and on the basis of confirmed diagnosis according to the National Diabetes Data Group criteria (53) (60% of cohort comparisons for T2D incidence). Mean intakes of LNCSB and SSB were 0.57 and 0.40 servings/day, respectively, while mean water intake was 3.73 servings/day ($n = 6$). Dietary intake was assessed through semiquantitative food-frequency questionnaires (sFFQ) (78.6%), food diaries (7.1%), or 24-h recalls (14.3%). All studies reported funding from agency alone.

Supplementary Table 4 shows the statistical adjustments in the included studies. The largest covariate-adjusted models included 10 to 27 covariates. All studies included adjustment for the prespecified primary covariate (age) and at least three of seven prespecified secondary covariates (sex; markers of adiposity; smoking; energy intake; family history of metabolic syndrome, T2D, or CVD; physical activity; and alcohol intake).

Supplementary Table 5 shows the study quality assessments by NOS. The quality of all cohort comparisons was

rated as high (score 7–9) to moderate (score 6), with no studies assessed to be of low quality ($<6$ NOS score). Sources of low quality included indirect exposure assessment, indirect outcome assessment, and no adjustment for prespecified key confounding variables.

Figure 2 and Supplementary Fig. 2A–C show the association of change in LNCSB intake with cardiometabolic outcomes. A 1 serving/day increase of LNCSB was associated with lower weight (MD −0.008 kg/year [95% CI −0.014, −0.002]; evidence of interstudy heterogeneity, $I^2 = 66\%$, $P_Q = 0.02$; $n = 5$) and lower WC (−1.15 cm/year [−2.34, −0.045]; $n = 1$), but there was no association with risk of T2D (RR 1.02 [95% CI 0.99, 1.06]; evidence of interstudy heterogeneity, $I^2 = 84\%$, $P_Q < 0.01$; $n = 3$).

Figure 3 (top panel) and Supplementary Fig. 3A–J show the association of the substitution of LNCSB for SSB with cardiometabolic outcomes. Substitution of LNCSB for SSB was associated with lower weight (MD −0.12 kg/year [95% CI −0.14, −0.10]; no evidence of heterogeneity, $I^2 = 46\%$, $P_Q = 0.16$; $n = 3$) and lower risk of OB (RR 0.88 [95% CI 0.88, 0.89]; $n = 1$), CHD (0.89 [0.81, 0.98]; no evidence of heterogeneity, $I^2 = 28\%$, $P_Q = 0.22$; $n = 6$), total CVD mortality (0.95 [0.90, 0.99]; $n = 1$), and total mortality (0.96 [0.94, 0.98]; $n = 1$). No other associations were significant.

Figure 3 (middle panel) and Supplementary Fig. 4A–F show the substitution analysis association of the substitution of water for SSB with cardiometabolic outcomes. Substitution of water for SSB was associated with lower weight (MD −0.10 kg/year [95% CI −0.13, −0.06]; evidence of interstudy heterogeneity, $I^2 = 82\%$, $P_Q < 0.01$; $n = 3$), lower WC (−2.71 cm/year [−4.27, −1.15]; $n = 1$) and %BF (−1.51% per year [−2.61, −0.42]; $n = 1$), and lower risk of OB (RR 0.85 [95% CI 0.75, 0.97]; $n = 1$) and T2D (0.96 [0.94, 0.98]; evidence of interstudy heterogeneity, $I^2 = 79\%$, $P_Q < 0.01$; $n = 3$).

Figure 3 (bottom panel) and Supplementary Fig. 5A–D show the substitution analysis of the association of the substitution of LNCSB for water with cardiometabolic outcomes. Substitution of LNCSB for water was not associated with changes in any outcomes.

Supplementary Fig. 6A and B show the influence analyses for the change in LNCSB and cardiometabolic outcomes.
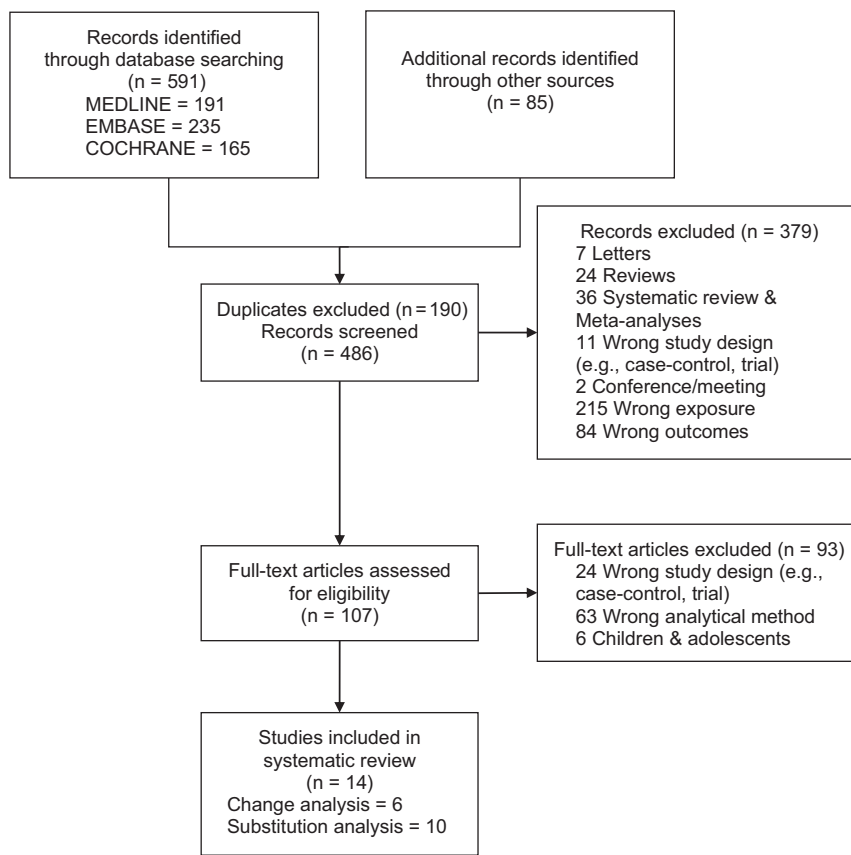
Figure 1—CONSORT diagram outlining the summary of the evidence search and selection for LNCSB and cardiometabolic outcomes. Of the 486 studies screened, 379 were excluded based on title and abstract review. The remaining 107 studies were reviewed in full. A total of 14 studies met the inclusion criteria and qualified for further analysis.

Removal of several cohort comparisons explained the heterogeneity (Health Professionals Follow-Up Study [HPFS] [31] and Nurses' Health Study [NHS] II [31] for body weight and NHS [52] for T2D) or altered the significance of the association (HPFS [31] and NHS II [31] for body weight and NHS [52] for T2D). None of the other cohort comparisons influenced the significance, direction, or magnitude of the associations or the evidence for heterogeneity.

Supplementary Figs. 7A–D, 8A and B, and 9 show the influence analysis for the substitution of LNCSB for SSB, LNCSB for water, and water for SSB and cardiometabolic outcomes. Removal of several cohort comparisons explained the heterogeneity (HPFS/NHS/NHS II [52] for both the substitution of water for SSB and substitution of LNCSB for water and T2D) and altered the significance (pooled HPFS/NHS/NHS II [54] for the substitution of LNCSB for SSB and body weight; Atherosclerosis Risk in Communities [ARIC]

study [females] [51], HPFS [51], NHS80 [51], or Women's Health Study [WHS] [51] for the substitution of LNCSB for SSB and CHD incidence; pooled HPFS/NHS/ NHS II [54] for the substitution of water for SSB and body weight; Women's Health Initiative [WHI] [55] for the substitution of water for SSB and T2D; and NHS [52] for the substitution of LNCSB for water and T2D) or direction (NHS II [52] for the substitution of LNCSB for SSB and T2D and NHS80 [51] for the substitution of LNCSB for SSB and CHD mortality) of the association. None of the other cohort comparisons influenced the significance, direction, or magnitude of the associations or the evidence for heterogeneity.

Supplementary Fig. 10 shows the shape of the dose response for the change in LNCSB intake and T2D incidence across the whole range of intake. Neither linear nor nonlinear dose-response relationship was significant for the change in LNCSB intake with change in T2D incidence.

Prespecified subgroup analyses and publication bias could not be assessed, as <10 cohort comparisons were available for analyses.

Supplementary Table 6 shows the GRADE assessments. In the change analyses, the evidence was assessed as "low" for the association with lower body weight and WC and "very low" for the lack of association with T2D, owing to downgrades for inconsistency, indirectness, or imprecision with an upgrade for dose-response association for body weight and WC. In the substitution analyses for the LNCSB for SSB the evidence was assessed as "moderate" for lower body weight with no downgrades, "low" for incident OB and CHD and for CVD and total mortality with downgrades for indirectness, imprecision, or inconsistency and upgrade for dose-response association for all the above outcomes. The evidence was "low" for substitution of water for SSB for all outcomes except stroke incidence owing to downgrades for indirectness, imprecision, or inconsistency and upgrade for dose-response association. For all other associations the evidence was rated as "very low" owing to downgrades with no upgrades.

We performed a post hoc sensitivity analysis comparing the ratings for the certainty of evidence using GRADE against NutriGrade (Supplementary Table 6). For the three outcomes for change analysis with NutriGrade, one had the same rating as GRADE, while one was rated higher and another was rated lower compared with GRADE. In the substitution analysis with NutriGrade, 13 of 20 (65%) outcomes had the same rating as GRADE, while 7 of 20 (35%) were rated higher compared with GRADE.

## CONCLUSIONS

We conducted a systematic review and meta-analysis of 14 prospective cohort studies (14 cohort comparisons) of the relation of LNCSB and cardiometabolic outcomes in 416,830 adults with varying cardiometabolic risk profiles inclusive of T2D. To mitigate the influence of reverse causality and residual confounding, we restricted our analyses to cohort comparisons with adjustment for initial adiposity and modeled the exposure as change in intake or the substitution of LNCSB for SSB (intended substitution),

**Table 1—Characteristics of prospective cohort comparisons in examining the relationship between increasing LNCSB intake and cardiometabolic outcomes**

| Cohort comparison (first author, year) | Country | Total follow-up duration (years) | Sex | N | Baseline age (years) | Baseline LNCSB intake (servings/day) | Baseline SSB intake (servings/day) | Dietary assessment | Outcome(s) | Incidence | Outcome assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HPFS (Drouin-Chartier, 2019 [52]) | U.S. | 26 | M | 34,224 | 40–75 | 0.52 | 0.39 | sFFQ | T2D incidence | 5,993 | Confirmed diagnosis |
| HPFS (Mozaffarian, 2011 [85])‡ | U.S. | 20 | M | 22,557 | 50.8 (7.5) | 0.54 | 0.33 | sFFQ | Body weight | | Self-report |
| HPFS (Pan, 2013 [54])‡ | U.S. | 20 | M | 21,988 | 50.6 | 0.56 | 0.40 | sFFQ | Body weight | | Self-report |
| HPFS (Smith, 2015 [31]) | U.S. | 24 | M | 21,472 | 41–63 | 0.55 | 0.33 | sFFQ | Body Weight | | Self-report |
| NHS (Drouin-Chartier, 2019 [52]) | U.S. | 26 | F | 76,531 | 30–55 | 0.58 | 0.26 | sFFQ | T2D incidence | 3,613 | Confirmed diagnosis |
| NHS (Mozaffarian, 2011 [85])‡ | U.S. | 20 | F | 50,422 | 52.2 (7.2) | 0.55 | 0.22 | sFFQ | Body weight | | Self-report |
| NHS (Pan, 2013 [54])‡ | U.S. | 20 | F | 50,013 | 51.8 | 0.56 | 0.26 | sFFQ | Body weight | | Self-report |
| NHS (Smith, 2015 [31]) | U.S. | 24 | F | 48,449 | 30–44 | 0.55 | 0.22 | sFFQ | Body weight | | Self-report |
| NHS II (Drouin-Chartier, 2019 [52]) | U.S. | 22 | F | 81,597 | 25–42 | 1.08 | 0.50 | sFFQ | T2D incidence | 2,300 | Confirmed diagnosis |
| NHS II (Mozaffarian, 2011 [85])‡ | U.S. | 12 | F | 47,898 | 37.5 (4.1) | 1.09 | 0.33 | sFFQ | Body weight | | Self-report |
| NHS II (Pan, 2013 [54])‡ | U.S. | 16 | F | 52,987 | 37.7 | 1.16 | 0.50 | sFFQ | Body weight | | Self-report |
| NHS II (Smith, 2015 [31]) | U.S. | 16 | F | 48,071 | 40–63 | 1.09 | 0.33 | sFFQ | Body weight | | Self-report |
| Mexican Teachers' Cohort (Stern, 2017 [50]) | Mexico | 2 | F | 11,218 | 43.3 (5.2) | 0.11 | 0.44 | sFFQ | Body weight and WC | | Self-report |
| PREMIER (Chen, 2009 [86]) | U.S. | 1.5 | Both | 810 (500 female, 310 male) | 50.0 (8.9) | 1 | 0.94 | 24-h dietary recalls | Body weight | | Measured |

Baseline age is represented as mean, mean (SD), or range as presented in the original article. For baseline LNCSB intake and SSB intake, data are means; serving size of LNCSB and SSB was defined as 330 mL, the standard manufacturers' portion sizes in the U.K., as previously reported (44). F, female; M, male. †Baseline characteristics were only reported as combined values from both cohort comparisons. ‡Cohort comparisons that were not included in the meta-analyses for avoidance of double counting of results.

**Table 2—Characteristics of prospective cohort comparisons with examination of the relationship between substituting LNCSB, SSB, and water and cardiometabolic outcomes**

| Cohort comparison (first author, year) | Country | Follow-up duration (years) | Sex | N | Baseline age (years) | Baseline LNCSB intake (servings/day) | Baseline SSB intake (servings/day) | Baseline water intake (servings/day) | Dietary assessment | Substituted beverage(s) | Outcome(s) | Incidence | Outcome assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stanford A TO Z (Stookey, 2008 [36]) | U.S. | 1 | F | 173 | 25–50 | 1.35 | 1.25 | 2.52 | 24-h dietary recalls | SSB, water | Body weight, WC, %BF | | Measured |
| ARIC, females (Keller, 2020 [51]) | U.S. | 9.2‡ | F | 5,238 | 53.9 | 0.52| | 0.42| | NR | sFFQ | SSB | CHD incidence | 123 | Verified by records |
| ARIC, males (Keller, 2020 [51]) | U.S. | 9.2‡ | M | 6,481 | 54.6 | 0.40| | 0.35| | NR | sFFQ | SSB | CHD incidence, CHD mortality | Events, 269; deaths, 52 | Verified by records |
| ATBC (Keller, 2020 [51]) | Finland | 6* | M | 21,141 | 57.3 | 0.40| | 0.35| | NR | sFFQ | SSB | CHD incidence, CHD mortality | Events, 1,339; deaths, 534 | Verified by records |
| EPIC-Norfolk (O'Connor, 2015 [44]) | UK | 10 | Both | 24,653 (F 13,485 and M 11,168) | 58.7 (9.3) | 0.52 | 0.25 | NR | 7-day food diary | SSB, water | T2D incidence | 847 | Verified by records |
| HPFS (Drouin-Chartier, 2019 [52]) | U.S. | 26 | M | 34,224 | 40–75 | 0.52 | 0.39 | NR | sFFQ | SSB, water | T2D incidence | 2,300 | Confirmed diagnosis |
| HPFS (Keller, 2020 [51]) | U.S. | 9.7‡ | M | 41,684 | 53.4 | 0.52| | 0.35| | NR | sFFQ | SSB | CHD incidence, CHD mortality | Events, 1,272; deaths, 420 | Verified by records |
| HPFS, NHS (Bernstein, 2012 [87]) | U.S. | HPFS, 22; NHS, 28 | HPFS, M; NHS, F | 127,456 (F 84,085 and M 43,371) | HPFS, 40–75; NHS, 30–55 | NR | NR | NR | sFFQ | SSB, water | Stroke incidence | 4,354 (F 2,938, M 1,416) | Verified by records |
| HPFS, NHS (Malik, 2019 [77]) | U.S. | HPFS, 28; NHS, 34 | HPFS, M; NHS, F | 118,363 (F 80,647 and M 37,716) | 40–75 | NR | NR | NR | sFFQ | SSB | Total CVD mortality, total mortality | CVD, 7,896 (F 4,139 and M 3,757); total, 36,436 (F 23,432 and M 13,004) | Verified by records |
| HPFS, NHS, NHS II (Pan, 2013 [54]) | U.S. | HPFS, 20; NHS, 20; NHS, 16 | HPFS, M; NHS, F; NHS II, F | 124,988 (F 51,500 and M 21,988) | HPFS, 50.6; NHS, 51.8; NHS II, 37.7 | HPFS, 0.51; NHS, 0.5; NHS II, 1.16 | HPFS, 0.41; NHS, 0.26; NHS II, 0.50 | HPFS, 3.00; NHS, 3.20; NHS II, 3.23 | sFFQ | SSB | Body weight | | Self-report |
| IWHS (Keller, 2020 [51]) | U.S. | 10.0‡ | F | 29,528 | 61.4 | 0.40| | 0.42| | NR | sFFQ | SSB | CHD mortality | 291 | Verified by records |
| NHS (Drouin-Chartier, 2019 [52]) | U.S. | 26 | F | 76,531 | 30–55 | 0.58 | 0.26 | NR | sFFQ | SSB | T2D incidence | 5,993 | Confirmed diagnosis |

**Table 2—Continued**

| Cohort comparison (first author, year) | Follow-up duration (years) | Country | Sex | N | Baseline age (years) | Baseline LNCSB intake (servings/day) | Baseline SSB intake (servings/day) | Baseline water intake (servings/day) | Dietary assessment | Substituted beverage(s) | Outcome(s) | Incidence | Outcome assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NHS80 (Keller, 2020 [51]) | 6.5‡ | U.S. | F | 81,412 | 46.9 | 0.52‖ | 0.42‖ | NR | sFFQ | SSB | CHD incidence, CHD mortality | Events, 397; deaths, 97 | Verified by records |
| NHS86 (Keller, 2020 [51]) | 10.0‡ | U.S. | F | 61,700 | 52.6 | 0.52‖ | 0.42‖ | NR | sFFQ | SSB | CHD incidence, CHD mortality | Events, 696; deaths, 208 | Verified by records |
| NHS II (Drouin-Chartier, 2019 [52]) | 22 | U.S. | F | 81,597 | 25–42 | 1.08 | 0.52 | NR | sFFQ | SSB, water | T2D incidence | 3,613 | Confirmed diagnosis |
| NHS II (Pan, 2012 [88])† | 18 | U.S. | F | 82,902 | 36.0 (4.7) | 1.11 | 0.50 | 3.0 | sFFQ | SSB | T2D incidence | 2,718 | Confirmed diagnosis |
| SUN (Fresán, 2016 [89]) | 2 | Spain | Both | 15,765¶ (F 9,431 and M 6,334) | 37.9 (11.7) | 0.12 | 0.20 | 4.22 | sFFQ | SSB, water | Body weight, OB incidence | 873 | Self-report |
| WHI (Huang, 2017 [55]) | 8.4 | U.S. | F | 64,850 | 50–79 | 0.36 | 0.46 | NR | sFFQ | SSB, water | T2D incidence | 4,675 | Self-report |
| WHS (Keller, 2020 [51]) | 5.3‡ | U.S. | F | 37,161 | 53.9 | 0.52‖ | 0.42‖ | NR | sFFQ | SSB | CHD incidence | Events, 152 | Verified by records |

Follow-up duration is presented as means unless otherwise indicated. Baseline age is represented as means, means (SD), or range. Baseline LNCSB, SSB, and water intake are means. Serving size of LNCSB and SSB was defined as 330 mL (44), and serving size of water was defined as 200 mL (89). ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; IWHS, Iowa Women's Health Study; M, male; NR, not reported; SUN, Seguimiento Universidad de Navarra. †Cohort comparisons that were not included in the meta-analyses for avoidance of double counting of results. ‡Median follow-up duration in years. ‖Baseline beverage intake was reported as means pooled by sex as reported in the original study (51). ¶Number of female and male participants included in the analysis was estimated from the proportion of all female and male participants in the cohort (89).

## CHANGE ANALYSIS



| Outcome | Cohort Comparisons | N | Estimate | Pooled Estimate [95% CI] | P-value | SMD [95% CI] | I² | P_Q | GRADE Downgrade/Upgrade | Certainty of Evidence |
|---|---|---|---|---|---|---|---|---|---|---|
| Body Weight (kg/y) | 5 | 130,020 | MD | -0.008 [-0.014, -0.002] | 0.01 | -0.01 [-0.02, -0.004] | 66% | 0.02 | | ⊕⊕◯◯ Low |
| Waist Circumference (cm/y) | 1 | 9,294 | MD | -1.15 [-2.34, -0.045] | <0.05 | -0.02 [-0.04, -0.002] | N/A | N/A | | ⊕⊕◯◯ Low |
| T2D Incidence | 3 | 192,352 | RR | 1.02 [0.99, 1.06] | 0.23 | 0.01 [-0.01, 0.03] | 84% | <0.01 | | ⊕◯◯◯ Very Low |

Figure 2—Summary plot of the association between increasing intake of LNCSB by one serving (330 mL) per day and cardiometabolic outcomes (change analysis). For comparison of summary estimates among outcomes on the same scale, the effect estimates of MD and RR were converted into SMD and 95% CIs. SMD, ●; 95% CI, horizontal lines. Values of $I^2 \geq 50\%$ ($P_Q < 0.10$) indicate substantial interstudy heterogeneity. Values >0 indicate an adverse association. With GRADE for prospective cohort studies, studies were by default rated to have low certainty of the evidence, with the rating downgraded by five domains and upgraded by three domains. ■, downgrades or upgrades for each outcome. N/A, not applicable; y, year.

water for SSB (standard of care substitution), and LNCSB for water (reference substitution). An increase in LNCSB intake was associated with lower weight and borderline lower WC without any adverse association with T2D. The intended substitution of LNCSB for SSB was associated with lower weight and lower risk of incident OB, CHD, CVD morality, and total mortality without an adverse association with any other cardiometabolic outcomes including T2D. Substitution of water for SSB showed lower weight, lower WC and %BF, and lower incidence of OB and T2D. Substitution of LNCSB for water as the standard of care showed no associations with any cardiometabolic outcomes.

Although our findings are not consistent with those of other systematic reviews and meta-analyses of prospective cohort studies that have relied largely on baseline or prevalent intakes of LNCSB (19,20,23,56,57), importantly they are in agreement with those of studies with modeling that specifically accounts for the displacement of calories from SSB by LNCSB or other sugar reduction strategies in beverages (58–63). Findings of systematic reviews and meta-analyses of prospective cohort studies have shown that SSB are associated with greater energy intake and risk of weight gain, OB, T2D, metabolic syndrome, hypertension, and CVD (23,56,64–66). In an analysis of

data from the Netherlands it was predicted that the displacement of SSB through the substitution of LNCSB for SSB would result in ~80 kcal/day lower total energy intake and in turn lower BMI and prevalent OB (58). Other modeling studies from the U.K. (59), Portugal (60), Australia (61), Mexico (62), and Argentina (63) have shown that a reduction in SSB with or without low- and no-calorie sweeteners would reduce body weight and prevalent OW, OB, T2D, and/or CVD.

Our findings are also in agreement with the evidence from systematic reviews and meta-analyses of randomized controlled trials of intermediate cardiometabolic risk factors that account for the



| Outcome | Cohort Comparisons | N | Estimate | Pooled Estimate [95% CI] | P-value | SMD [95% CI] | I² | P_Q | Certainty of Evidence |
|---|---|---|---|---|---|---|---|---|---|
| **Substituted Beverages: LNCSB for SSB (Intended Substitution)** | | | | | | | | | |
| Body Weight (kg/y) | 3 | 165,579 | MD | -0.12 [-0.14, -0.10] | <0.01 | -0.03 [-0.05, -0.004] | 46% | 0.16 | ⊕⊕⊕◯ Moderate |
| Waist Circumference* (cm/y) | 1 | 173 | MD | -1.83 [-3.70, 0.05] | 0.06 | -0.05 [-0.10, 0.001] | N/A | N/A | ⊕◯◯◯ Very Low |
| % Body Fat* (%/y) | 1 | 173 | MD | -0.96 [-2.32, 0.41] | 0.17 | -0.03 [-0.08, 0.01] | N/A | N/A | ⊕◯◯◯ Very Low |
| OB Incidence | 1 | 15,765 | RR | 0.88 [0.88, 0.89] | <0.01 | -0.07 [-0.07, -0.07] | N/A | N/A | ⊕⊕◯◯ Low |
| T2D Incidence | 5 | 281,855 | RR | 0.99 [0.96, 1.01] | 0.23 | -0.01 [-0.04, 0.02] | 69% | 0.01 | ⊕◯◯◯ Very Low |
| CHD Incidence | 6 | 233,676 | RR | 0.89 [0.81, 0.98] | 0.02 | -0.06 [-0.11, -0.02] | 28% | 0.22 | ⊕⊕◯◯ Low |
| Stroke Incidence | 1 | 127,456 | RR | 1.03 [0.93, 1.14] | 0.57 | 0.02 [-0.04, 0.07] | N/A | N/A | ⊕◯◯◯ Very Low |
| CHD Mortality | 5 | 220,805 | RR | 0.94 [0.81, 1.09] | 0.52 | -0.03 [-0.12, 0.06] | 36% | 0.18 | ⊕◯◯◯ Very Low |
| CVD Mortality | 1 | 118,363 | RR | 0.95 [0.90, 0.99] | 0.02 | -0.03 [-0.05, -0.002] | N/A | N/A | ⊕⊕◯◯ Low |
| Total Mortality | 1 | 118,363 | RR | 0.96 [0.94, 0.98] | <0.01 | -0.02 [-0.03, -0.01] | N/A | N/A | ⊕⊕◯◯ Low |
| **Substituted Beverages: Water for SSB (Standard of Care Substitution)** | | | | | | | | | |
| Body Weight (kg/y) | 3 | 165,579 | MD | -0.10 [-0.13, -0.06] | <0.01 | -0.02 [-0.02, -0.01] | 82% | <0.01 | ⊕⊕◯◯ Low |
| Waist Circumference* (cm/y) | 1 | 173 | MD | -2.71 [-4.27, -1.15] | <0.01 | -0.09 [-0.14, -0.04] | N/A | N/A | ⊕⊕◯◯ Low |
| % Body Fat* (%/y) | 1 | 173 | MD | -1.51 [-2.61, -0.42] | 0.01 | -0.07 [-0.12, -0.02] | N/A | N/A | ⊕⊕◯◯ Low |
| OB Incidence | 1 | 15,765 | RR | 0.85 [0.75, 0.97] | 0.01 | -0.09 [-0.16, -0.02] | N/A | N/A | ⊕⊕◯◯ Low |
| T2D Incidence | 3 | 281,855 | RR | 0.96 [0.94, 0.98] | <0.01 | -0.02 [-0.03, -0.01] | 79% | 0.01 | ⊕⊕◯◯ Low |
| Stroke Incidence | 1 | 127,456 | RR | 1.00 [0.94, 1.06] | 1.00 | 0.00 [-0.05, 0.05] | N/A | N/A | ⊕◯◯◯ Very Low |
| **Substituted Beverages: LNCSB for Water (Reference Substitution)** | | | | | | | | | |
| Body Weight (kg/y) | 1 | 173 | MD | 0.08 [-0.11, 0.27] | 0.43 | 0.01 [-0.01, 0.02] | N/A | N/A | ⊕◯◯◯ Very Low |
| OB Incidence | 1 | 15,765 | RR | 1.19 [0.94, 1.50] | 0.16 | 0.09 [-0.03, 0.22] | N/A | N/A | ⊕◯◯◯ Very Low |
| T2D Incidence | 4 | 257,202 | RR | 1.00 [0.98, 1.02] | 0.87 | 0.00 [-0.02, 0.02] | 83% | <0.01 | ⊕◯◯◯ Very Low |
| Stroke Incidence | 1 | 127,456 | RR | 1.03 [0.98, 1.09] | 0.26 | 0.02 [-0.01, 0.05] | N/A | N/A | ⊕◯◯◯ Very Low |

Figure 3—Summary plot of the association between substituting LNCSB, SSB, and water (matched by volume) and cardiometabolic outcomes. For comparison of summary estimates among outcomes on the same scale, the effect estimates of MD and RR were converted into SMD and 95% CIs. SMD and 95% CIs are represented by ● and horizontal lines, respectively. Values of $I^2 \geq 50\%$ ($P_Q < 0.10$) indicate substantial interstudy heterogeneity. Values >0 indicate an adverse association. With GRADE for prospective cohort studies, studies were by default rated to have low certainty of the evidence, with the rating downgraded by five domains and upgraded by three domains. ■, downgrades or upgrades for each outcome. *We divided SMD and 95% CIs by 3 to allow the outcomes to be plotted within the available graph space. N/A, not applicable; y, year.

displacement of calories from SSB. Fructose-containing sugars providing excess calories especially in beverage form have been shown to lead to weight gain (67) and increase in triglycerides (68), glycemia (69), insulinemia (69), uric acid (70,71), and nonalcoholic fatty liver disease markers (72). The substitution of low- and no-calorie sweeteners for these sugars in food/beverages has resulted in the expected reductions in adiposity markers including body weight, BMI, WC, and fat mass as shown by several systematic reviews and meta-analyses in predominantly OW/OB participants (73–76). Small reductions in BMI and blood pressure were also seen with the substitution of low- and no-calorie sweeteners for sucrose in food/beverages in predominantly healthy participants (21). On the other hand, in analyses restricted to the effect of LNCSB in substitution for water or matched noncaloric comparators that did not allow for the displacement of calories from SSB (placebo, no intervention, water, or weight loss diet) (27,73–75), no differences were found in body weight in participants predominantly with OW/OB.

Interpreted together with the modeling studies and randomized controlled trials, the findings from our prespecified change and substitution analyses are consistent with the mechanism that LNCSB lead to lower weight insofar as they contribute to a reduction in net energy intake. Although both models were associated with reductions in adiposity outcomes with LNCSB, these associations did not translate into the expected reductions in T2D risk, but reductions were seen in the substitution of water for SSB. One reason may be an inability to mitigate reverse causality through incomplete adjustment for adiposity and other risk factors for T2D more so than CHD. Those with high intake of LNCSB in the available cohorts were at higher risk of T2D (44,52). Another reason may be surveillance bias owing to the increased risk of T2D for those with high intake. The three largest prospective cohort studies in the analysis showed a greater prevalence of fasting glucose screening among individuals who increased their LNCSB intake compared with those who maintained stable intake (52). A third reason could be the unexplained large heterogeneity among studies examining the substitution of SSB for LNCSB and water and

change in LNCSB intake in relation to T2D risk. Post hoc analysis with alternative modeling (random effects if fixed effects were used because of only five or fewer studies) only changed the result for the substitution of SSB for water, but the direction of association still indicated benefit. This highlights the need for further high-quality cohort studies assessing substitution of water or LNCSB for SSB with T2D to increase the precision, direction, and certainty of this association.

There are several strengths of our synthesis. First, we included statistical models of exposure that minimize reverse causality and residual confounding from incomplete adjustment of confounders and behavior clustering, providing evidence that is more robust, biologically plausible, and consistent with the evidence from randomized controlled trials. Prevalent or baseline analyses of LNCSB cannot capture the intended replacement strategy of the substitution of LNCSB for SSB and are susceptible to reverse causation, resulting in an underestimation of the intended cardiometabolic benefits (13,24,28,29,31,52,77,78). Second, we used a systematic approach to identify all available prospective cohort studies including the systematic search strategy, quantitative synthesis, and assessment of the certainty of the evidence with GRADE. While GRADE has been recommended as the standard for assessing certainty of evidence for dietary recommendations from nutrition synthesis (79); our sensitivity analysis with the alternative NutriGrade showed, on average, a higher degree of confidence in the results. Third, the available prospective cohort studies provided large sample sizes, long durations of follow-up, and adjustment for multiple dietary and lifestyle factors. Finally, both the change and substitution analyses were considered as dose-response analyses where the association was significant, which strengthened the certainty of the evidence.

There were several limitations of our synthesis. First, the certainty of evidence started at low owing to the observational nature of the prospective cohort studies and the inability to exclude both unmeasured and measured residual confounding (80), make any causal relationships, or completely eliminate the effects of reverse causality. Second, there was serious inconsistency in the estimates for changes in LNCSB

and body weight, the substitution of LNCSB for water and T2D, and the substitution of water for SSB and body weight. Third, there were sources of serious indirectness owing to the limited number of available cohorts with use of the two prespecified statistical models. Only single-sex cohort comparisons were available to assess the evidence of change in LNCSB intake and WC (50) and substitution of LNCSB or water for SSB in relation to adiposity measures (36), and no studies included assessment of metabolic syndrome. Finally, the small number of available prospective cohort studies resulted in serious imprecision in the pooled estimates for many outcomes. The pooled estimates and 95% CIs contained clinically important benefits and harms, and there was instability in the estimates in sensitivity analyses for several outcomes. Balancing the limitations and strengths of this analysis, the available evidence was rated as low or very low across the outcomes.

Our findings are relevant for informing guidance on the role of LNCSB as part of sugar reduction strategies. Whereas there is a universal call to reduce SSB (3,4), support for LNCSB as a replacement strategy for SSB has been mixed owing to concerns that LNCSB may increase the risk of OB, T2D, and CVD (19–23). Our prespecified models show that LNCSB were not associated with higher risk; rather, they were associated with a lower risk in important cardiometabolic outcomes in the intended substitution for SSB and may provide some benefits as the standard of care in substitution for water across cardiometabolic outcomes. We suggest that, in updates of clinical practice guidelines (32), national dietary guidelines (17,81), and the resulting food, nutrition, and public health policies and programs that target a reduction in SSB (18,82–84), recommending LNCSB be considered as an alternative replacement strategy to the standard of care water along with other currently recommend alternatives.

In conclusion, LNCSB are not associated with weight gain or an increase in adverse cardiometabolic outcomes and may be associated with some advantages in analyses that model the change in intake of LNCSB or the substitutions of LNCSBS for SSB in people with varying cardiometabolic risk profiles inclusive of T2D. The available evidence provides some indication that increased intake of LNCSB is associated with lower adiposity

and LNCSB in their intended substitution for SSB are modestly associated with lower adiposity, lower risk of OB and CHD, and reductions in total mortality; these associations are comparable with those of the standard of care, water. Our confidence in the pooled estimates was reduced largely by the few available prospective cohort studies, which contributed to imprecision and indirectness. More prospective cohort studies with robust analytical approaches will be important for addressing these uncertainties and strengthening causal inferences, but there is also a need for large high-quality randomized trials of clinical outcomes. In the meantime, given the importance of targeting reductions in SSB, the evidence supports the use of LNCSB as an alternative to water as part of clinical and public health strategies to reduce SSB consumption.

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