REVIEW

Intake of Sugar-Sweetened and Low-Calorie Sweetened Beverages and Risk of Cardiovascular Disease: A Meta-Analysis and Systematic Review

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ABSTRACT

The long-term associations between the consumption of sugar-sweetened beverages (SSBs) and low-calorie sweetened beverages (LCSBs) with cardiovascular diseases (CVDs) remains inconsistent. To synthesize the evidence, we conducted a meta-analysis of prospective cohort studies published up to 1 December, 2019 on the associations between SSB and LCSB intake and the risk of CVD incidence and mortality. Out of 5301 articles retrieved from our literature search, 11 articles evaluating the consumption of SSBs (16,915 incident CVD cases, 18,042 CVD deaths) and 8 articles evaluating the consumption of LCSBs (18,077 incident CVD cases, 14,114 CVD deaths) were included in the meta-analysis. A 1 serving/d increment of SSBs was associated with an 8% (RR: 1.08; 95% CI: 1.02, 1.14, $I^2 = 43.0\%$) and 8% (RR: 1.08; 95% CI: 1.04, 1.13, $I^2 = 40.6\%$) higher risk of CVD incidence and CVD mortality, respectively. A 1 serving/d increment of LCSBs was associated with a 7% (RR: 1.07; 95% CI: 1.05, 1.10, $I^2 = 0.0\%$) higher risk of CVD incidence. The association between LCSBs and CVD mortality appeared to be nonlinear ($P = 0.003$ for nonlinearity) with significant associations observed at high intake levels (>2 servings/d). Under an assumption of causality, the consumption of SSBs may be linked to 9.3% (95% CI: 6.6%, 11.9%) of predicted CVD incidence in the USA from 2015 to 2025, among men and nonpregnant women, who were aged 40–79 y in 2015–2016. The habitual consumption of SSBs was associated with a higher risk of CVD morbidity and mortality in a dose-response manner. LCSBs were also associated with a higher risk of these outcomes, however, the interpretation of these findings may be complicated by reverse causation and residual confounding. *Adv Nutr* 2021;12:89–101.

Keywords: sugar-sweetened beverages, low-calorie sweetened beverages, cardiovascular disease, meta-analysis, systematic review, dose-response analysis, population attributable fraction

Introduction

Sugar-sweetened beverages (SSBs) include the full spectrum of carbonated and noncarbonated soft drinks such as soda, fruit-flavored drinks, and sports/energy drinks that contain caloric sweeteners such as high-fructose corn syrup and sucrose. SSBs are a major contributor to added sugar and the daily SSB intake contains few nutrients and is low in nutritional quality (1). The health effects of SSBs have received considerable attention from scientific and public health communities as the habitual intake of SSBs has been associated with a higher risk of obesity (2), type 2 diabetes (3), and metabolic syndrome (4). As recommended in the 2015–2020 Dietary Guidelines for Americans, the consumption of added sugars should be reduced to <10% of total daily energy intake (5). Similarly, the WHO suggests that the consumption of free sugars (which also includes sugars in fruit juices) should be reduced to <10% of total energy intake (6). Low-calorie sweetened beverages (LCSBs), which are sweetened with low-energy sweeteners such as acesulfame-K, aspartame, and sucralose, have been selected by some consumers as alternatives to SSBs due to their comparable sweet flavor but lack of calories. However, evidence on the health effects of LCSBs continues to be debated (7).

Inconsistent findings between SSBs and LCSBs and risk of cardiovascular disease have been observed (8–11). A previous meta-analysis, including 7 prospective studies, summarized the evidence on SSBs/LCSBs and cardiovascular disease (CVD) risk (12). However, the meta-analysis

omitted several key studies (13, 14) that were eligible and included 1 study that combined SSBs and LCSBs (15). Moreover, since that publication, additional prospective studies have been published in recent years (8–10, 16). Thus, we conducted a systematic review and meta-analysis of prospective studies to update the evidence linking SSBs and LCSBs to CVD risk including CVD incidence and CVD mortality. We also aimed to quantify the potential dose-response relation and population attributable risk.

Methods

We followed the Meta-Analysis of Observational Studies in Epidemiology protocol (17) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (18) for performing the present meta-analysis. This systematic review and meta-analysis was registered in PROSPERO (CRD42019137454). The changes to the original protocol registered along with the reasons for the changes are shown in **Supplemental Table 1**.

Search strategy

We performed a literature search (from the earliest available online indexing year up to 1 December, 2019) in PubMed and Embase databases for prospective cohort studies examining the association between either SSBs or LCSBs and risk of selected cardiovascular outcomes. We used various combinations of the following keywords "beverage," "cardiovascular disease," "coronary heart disease," "stroke," "mortality," "myocardial infarction," "ischemic heart disease," "sudden cardiac arrest," and "acute coronary syndrome." The full details on the search strategy are presented in the Online Supplemental Material (**Supplemental Methods**). We also performed additional manual searches through the reference lists of original publications and review articles to identify further pertinent studies. The searches were restricted to studies in humans that were published in English.

Selection criteria

Studies were considered for inclusion in the systematic review if they met the following criteria: *1*) the authors reported data from an original, peer-reviewed study (not reviews, conferences, and letters); *2*) the study had a prospective design; *3*) the authors reported RRs, HRs, or ORs with 95% CIs for ≥3 quantitative categories of SSB or LCSB consumption; *4*) the investigators reported ≥1 of the outcomes of CVD risk, including incidence of total CVD, coronary heart disease, stroke, or CVD mortality. We included only prospective cohort, case-cohort, and nested case-control studies to minimize recall and selection bias that are common in case-control studies and confounding in cross-sectional studies. Multiple reports from the same cohort study were reviewed, and only reports with the most detailed estimates or the largest number of participants for identical outcomes were included.

Two investigators (JWY and YLZ) conducted a 2-stage selection process to identify eligible studies: an initial screening of titles and abstracts, followed by an evaluation of all potentially relevant articles based on full-length articles. Any discrepancy was resolved by discussions with another investigator (ZLS). Studies were excluded if they failed to meet the criteria detailed above.

Data extraction and quality assessment

Two investigators (JWY and YLZ) independently reviewed each eligible study and the following data were extracted: first author's name, publication year, cohort name, geographical location, age of participants at baseline, duration of follow-up, the number of CVD events, the number of participants/person-years of follow-up, method of assessment of beverage consumption, categories of beverage consumption, outcome ascertainment, and adjusted covariates. For studies with data on both coronary heart disease and stroke as the outcome, we included both in the meta-analysis. To evaluate potential dose-response relations, we further extracted the number of participants/person-years of follow-up, the number of cases, and risk estimates with 95% CIs for all categories of beverage consumption. If the numbers of participants/person-years and cases were not provided, the corresponding author(s) were contacted for the data. The primary aim of our analysis was to quantify the risk of CVD incidence and CVD mortality associated with different beverage consumption levels independently of other cardiovascular risk factors. Therefore, we used the results of the original studies from multivariable-adjusted models with the maximum extent of adjustment for relevant confounders, including BMI, physical activity, smoking, total energy intake, and diet quality.

Study quality assessment was performed according to the Newcastle-Ottawa Quality Assessment Scale (19). Scores ranged from 0 to 9 points, with higher scores indicating higher study quality.

Data synthesis and analysis

In this meta-analysis, SSBs and LCSBs were considered the main exposures of interest, respectively. We defined SSBs as any carbonated or noncarbonated beverage that was sweetened with added sugar, such as sucrose or high-fructose corn syrup (e.g. colas and other soft drinks, fruit-flavored drinks), not including 100% fruit juice. LCSBs included low-calorie sweetened soft drinks, such as low-calorie cola, and other low-calorie fruit-flavored beverages as reported

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Supplemental Methods, Supplemental Tables 1–9, and Supplemental Figures 1–9 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: CVD, cardiovascular disease; LCSB, low-calorie sweetened beverage; SSB, sugar-sweetened beverage.

in each study. RRs were used as the common measure of association across studies, which were deemed equivalent to HRs (20). Studies conducted in 2 independent cohorts were treated as separate reports. Multiple reports from the same cohort study were reviewed, and only articles with the longest follow-up for identical outcomes were included (16). The study by Eshak et al. (21) reported estimates for men and women, separately. We pooled the sex-specific estimates with a fixed-effects model to generate an overall estimate before combining with other studies, but sex-specific results were used in subgroup analyses by sex.

We used both semiparametric and parametric methods to analyze associations between the consumption of SSBs and LCSBs and risk of CVD. For the semiparametric method, the lowest and the highest consumption categories corresponded to the lowest groups and highest groups, respectively. Forest plots were used to evaluate RRs and 95% CIs of outcomes for the highest group of beverage consumption versus the lowest group. For the parametric method, the included studies with detailed data on the number of cases, person-years, RRs, and CIs for $\geq$3 categories of quantified beverage consumption were included in a dose-response analysis to calculate pooled risk estimates for each serving/day increment of beverage consumption (22). For 3 studies, because the number of cases/person-years in each category was not available and the authors did not respond to our query (10, 16, 23), we used the method by Bekkering et al. to provide approximate data (24). We used generalized least squares models to estimate the RR of CVD per 1 serving/d increment of beverage consumption. The RRs from all of the studies were pooled together. We standardized measures of associations to RR per 1 serving/d of beverage consumption after we confirmed that this unit was the most frequently used in the included studies. The studies by Eshak et al. (21) and Mullee et al. (8), which used cups and glasses as the metric, respectively, were standardized by conversion into servings (1 cup/1 glass = 1 serving). For studies reporting data in g/day (13), 250 g/d was regarded as 1 serving/d. As volume per serving varied across populations, ranging from 200 mL (1 glass) to 355 mL (12 oz) (median across publications = 250 mL), we repeated the meta-analysis to estimate the RR for each 250 mL/d increment in a sensitivity analysis. For studies that did not specify the volume for each serving (10, 23), 1 serving was assigned a value of 250 mL. We assigned the mean (13) or median (11, 25) servings of beverage consumption in each category to the corresponding RR for each study. If the mean or median serving per category was not reported, the midpoint of the upper and lower boundaries in each category was assigned. If the highest category was open-ended, the midpoint of the category was assigned 50% higher than the lower boundary. If the lower boundary for the lowest category was not provided, the assigned median value was half of the upper boundary of that category.

All pooled outcome measures were estimated using the random-effects model to provide more conservative results (DerSimonian and Laird method) (26), which accounted for variation both within and between studies. In addition, because a random-effects model may be less precise if the number of studies is small (especially <5) (27), we further included a fixed-effects model (Mantel-Haenszel method) (28) in sensitivity analysis.

We also plotted a dose-response relation between beverage consumption and the outcomes using restricted cubic spline models with knots fixed at percentiles 10%, 50%, and 90% of the distribution (29, 30). A test for potential nonlinearity in the association between beverage consumption and CVD risk was calculated by setting the coefficient of the second spline to zero (30).

The heterogeneity among studies was estimated by Cochran's Q test ($P < 0.10$ to be indicative of statistically significant heterogeneity) and I^2 statistic (I^2 values of 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity, respectively) (31). We regarded the duration of follow-up in each included study as a continuous variable and performed metaregression analyses for the association between SSBs/LCSBs and CVD incidence. Prespecified subgroup and metaregression analyses were performed for the association between SSBs/LCSBs and CVD incidence stratified by sex (male, female, or both), location (USA or others), method of dietary assessment (self-report, interview), exposure assessment (single measurement at baseline, repeated measures), questionnaire validity (high validation coefficients, low validation coefficients, without validation), study quality (Newcastle-Ottawa Quality Assessment Scale score <7 or score $\geq$7) and whether the study adjusted for relevant confounders (age, BMI, education, smoking, alcohol intake, physical activity, total energy intake, dietary quality, and mutually adjusted for SSBs/LCSBs) to assess the influence of these factors on the associations between SSB/LCSB consumption and CVD. We also conducted subgroup analyses on studies with fully adjusted models including all lifestyle factors (including smoking, alcohol intake, physical activity, diet quality, and BMI) and total energy intake to assess the influence of lifestyle and diet on the association. Consistent with the recommendations of Thompson and Higgins, each subgroup was based on a minimum of 8 studies (32). There were relatively few studies on SSBs/LCSBs and CVD mortality to conduct meaningful subgroup analyses, thus, no further stratified analyses were conducted and we could not investigate potential sources of heterogeneity between subgroups by metaregression for SSBs/LCSBs and CVD mortality. Additional sensitivity analyses were preplanned and performed by systematically omitting each study 1 at a time and recalculating the summary association to test the robustness of the results and the influence of individual studies on heterogeneity (33). Potential publication bias was assessed for SSBs/LCSBs and CVD incidence with enough studies by the Egger regression symmetry test (34). The Duval and Tweedie (35) nonparametric trim-and-fill method was used to further assess potential publication bias.

Under an assumption of causality, we conducted an exploratory analysis based on the initial results to estimate the

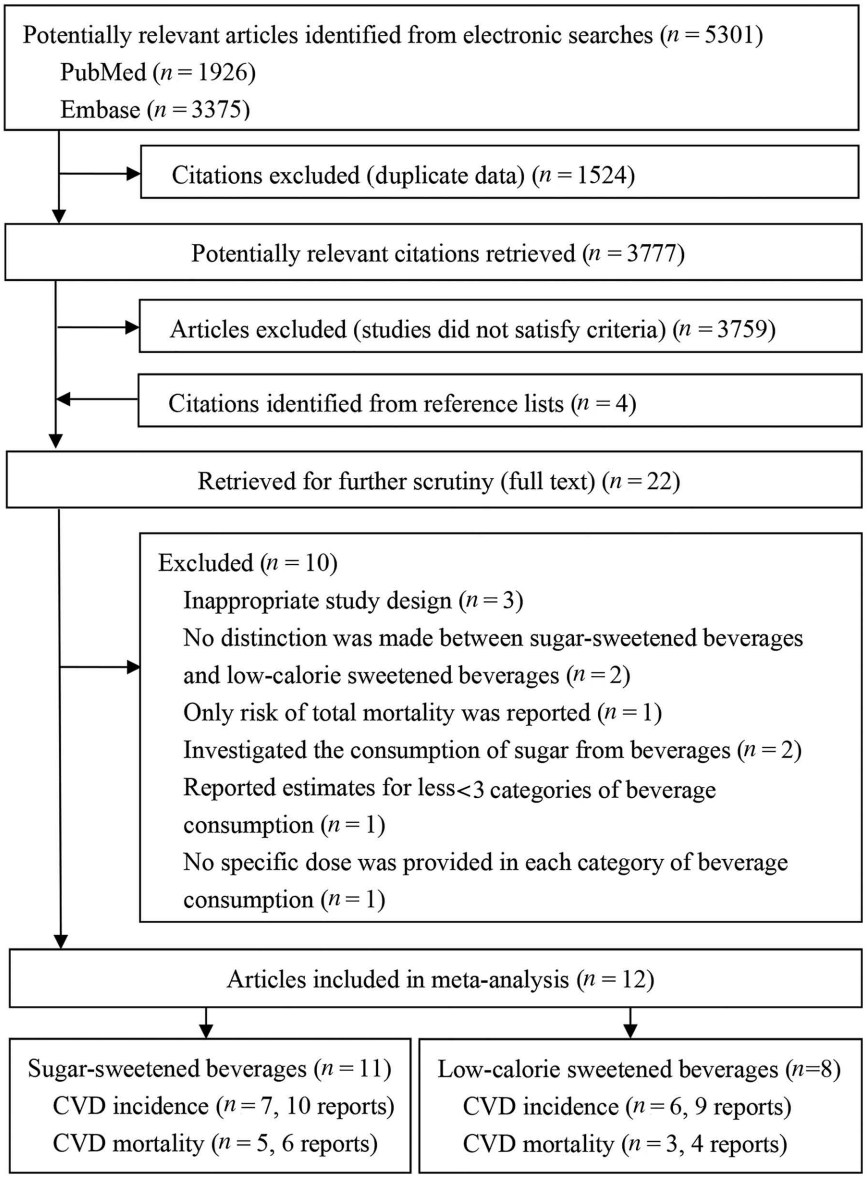

FIGURE 1 Flow chart of article selection. CVD, cardiovascular disease.

proportion of CVD events attributable to the consumption of SSBs in the USA. As there is still limited evidence implying causality between LCSBs and CVD risk, we did not include this analysis for LCSBs. The data on consumption of SSBs and risk factors for CVD were obtained from NHANES (36). The habitual consumption of SSBs was estimated based on 24-h recalls (2 d) from the 2015–2016 cycle. The Pooled Cohort Equations method (37) was used to calculate the predicted 10-y cardiovascular risk for each person (R_p) and we limited the analysis to men and nonpregnant women who were aged 40–79 y and free of self-reported CVD. The altered predicted 10-y risk for each person (R_q), by eliminating the consumption of SSBs, was also calculated and the value of (R_p–R_q) represented the risk attributable to SSBs. The predicted CVD events over 10 y, CVD events attributable to SSBs, and the population attributable fraction from SSBs for CVD risk were further derived (38). Details of the analysis are provided in the Supplemental Methods.

All statistical analyses were performed with Stata version 12 (StataCorp LP) and SAS version 9.4 (SAS Institute), and all tests were 2-sided with a significance level of 0.05 unless otherwise noted.

Results

Literature search

The results from the literature search and study selection process are shown in **Figure 1**. We identified 5301 articles from PubMed and Embase databases by 1 December, 2019.

Several articles examined the consumption of SSBs and LCSBs within the context of dietary patterns only and therefore could not be included. After 2 rounds of reviews and searching citations of retained articles, 22 potentially relevant studies were initially selected. After evaluating the full texts, we further excluded 10 studies: 3 articles (39–41) did not have a prospective design. Two articles (15, 42) made no distinction between SSBs and LCSBs. One article (43) lacked data for CVD incidence or CVD mortality. Two articles (44, 45) investigated total sugar or added sugar from beverages instead of SSBs or LCSBs. One article (46) did not provide RRs for >3 quantitative categories. One article (47) did not provide the specific dose in each category of beverage consumption. The final meta-analysis included 7 articles (10, 11, 13, 21, 23, 25, 48) with 10 reports providing information on SSBs and CVD incidence, 5 articles (8, 9, 14, 23, 49) with 6 reports providing information on SSBs and CVD mortality, 6 articles (10, 11, 16, 23, 25, 48) with 9 reports providing information on LCSBs and CVD incidence. Three articles (8, 9, 23) with 4 reports provided information on LCSBs and CVD mortality.

Study characteristics

The characteristics of identified studies are shown in **Supplemental Table 2**. The included studies for SSBs comprised 16,937,316 person-years of follow-up, 16,915 incident CVD cases (7396 coronary heart disease cases, 6598 stroke cases), and 18,042 CVD deaths. The included studies for LCSBs comprised 16,281,005 person-years of follow-up, 18,077 incident CVD cases (9782 coronary heart disease cases, 8295 stroke cases), and 14,114 CVD deaths. The mean follow-up periods ranged from 9.8 to 28 y. Among the 12 articles included in the total, 8 were conducted in the USA (9–11, 14, 16, 23, 25, 48), 2 in Europe (8, 13), and 2 in Asia (21, 49). Beverage consumption was assessed with FFQs in all studies and by trained interviewers in 2 studies (13, 49) and self-administered FFQ in all others.

All studies adjusted for age, smoking, and physical activity (8–11, 13, 14, 16, 21, 23, 25, 48, 49). Most studies controlled for other RR factors, including BMI (8, 9, 11, 13, 14, 21, 23, 48, 49) (N = 9), education (8, 13, 14, 16, 23, 49) (N = 7), alcohol consumption (8, 9, 11, 13, 14, 16, 21, 23, 25, 48) (N = 10), total energy intake (8–11, 13, 14, 21, 23, 48, 49) (N = 10), and dietary quality (8–11, 14, 16, 21, 25, 48, 49) (N = 10). SSBs and LCSBs were mutually adjusted in 4 studies (8, 9, 23, 48).

The methods used to assess beverage consumption validity from FFQs varied across cohort studies (**Supplemental Table 3**). For SSBs, most studies provided the correlation coefficients between estimates (ranging from 0.30 to 0.84) based on FFQ and a reference assessment such as diet records. However, few correlation coefficients were provided for LCSBs. Four cohorts had repeated measurements of beverage consumption during the follow-up period, whereas the others used a single measurement at baseline (Supplemental Table 3).

The majority of the included studies were rated as high quality as indicated by the Newcastle-Ottawa Quality Assessment Scale score, and the mean study quality scores were 7.3 and 7.0 for SSBs and LCSBs, respectively, out of a maximum of 9 points (**Supplemental Tables 4** and **5**).

SSBs and risk of CVD incidence

Seven articles with 10 reports were included in the analysis of SSBs and risk of CVD incidence. The pooled RR of CVD incidence for the highest compared with the lowest category of SSBs was 1.09 (1.01 to 1.18), with low to moderate heterogeneity (I^2 = 28.8%, P = 0.18) (**Supplemental Figure 1**).

Ten reports with ≥3 quantitative categories of SSBs were included in the dose-response analysis. The pooled RR per 1 serving/d increment of SSBs for CVD incidence was 1.08 (1.02 to 1.14) and low to moderate heterogeneity was observed (I^2 = 43.0%, P = 0.07) (**Figure 2**). In restricted cubic spline models, a linear association (P = 0.81 for nonlinearity; **Figure 3**A) was observed between SSBs and CVD incidence.

In stratified analyses by outcome (coronary heart disease or stroke), each serving/day increment of SSBs was associated with a 15% higher risk of coronary heart disease (1.15, 1.09 to 1.22). The pooled RR per 1 serving/d increment of SSBs for stroke was (1.05, 0.95 to 1.16) (Figure 2).

SSBs and risk of CVD mortality

Five articles with 6 reports were included in the analysis of SSBs and risk of CVD mortality. The pooled RR of CVD mortality for the highest compared with the lowest categories of SSBs was 1.20 (1.10 to 1.31), with low heterogeneity (I^2 = 11.7%, P = 0.34) (**Supplemental Figure 2**).

Six reports were included in the dose-response analysis, and the pooled RR per 1 serving/d increment of SSBs for CVD mortality was 1.08 (1.04 to 1.13). Low to moderate heterogeneity was observed (I^2 = 40.6%, P = 0.13) (**Figure 4**). In restricted cubic spline models, the association between SSBs and risk of CVD mortality appeared to be linear (P = 0.68 for nonlinearity; Figure 3B).

LCSBs and risk of CVD incidence

Six articles with 9 reports were included in the analysis of LCSBs and risk of CVD incidence. The pooled RR of CVD incidence for the highest compared with the lowest categories of LCSBs was 1.17 (1.06 to 1.28), with moderate to high heterogeneity (I^2 = 55.1%, P = 0.02) (**Supplemental Figure 3**). The heterogeneity was generated by 1 report (11), and when this report was excluded, the association remained (1.20, 1.12 to 1.28) with no significant heterogeneity (I^2 = 0.0%, P = 0.49).

Nine reports were included in the dose-response analysis, and the pooled RR per 1 serving/d increment of LCSBs for CVD incidence was 1.07 (1.05 to 1.10). No significant heterogeneity was observed (I^2 = 0.0%, P = 0.61) (**Figure 5**). In restricted cubic spline models, a linear association

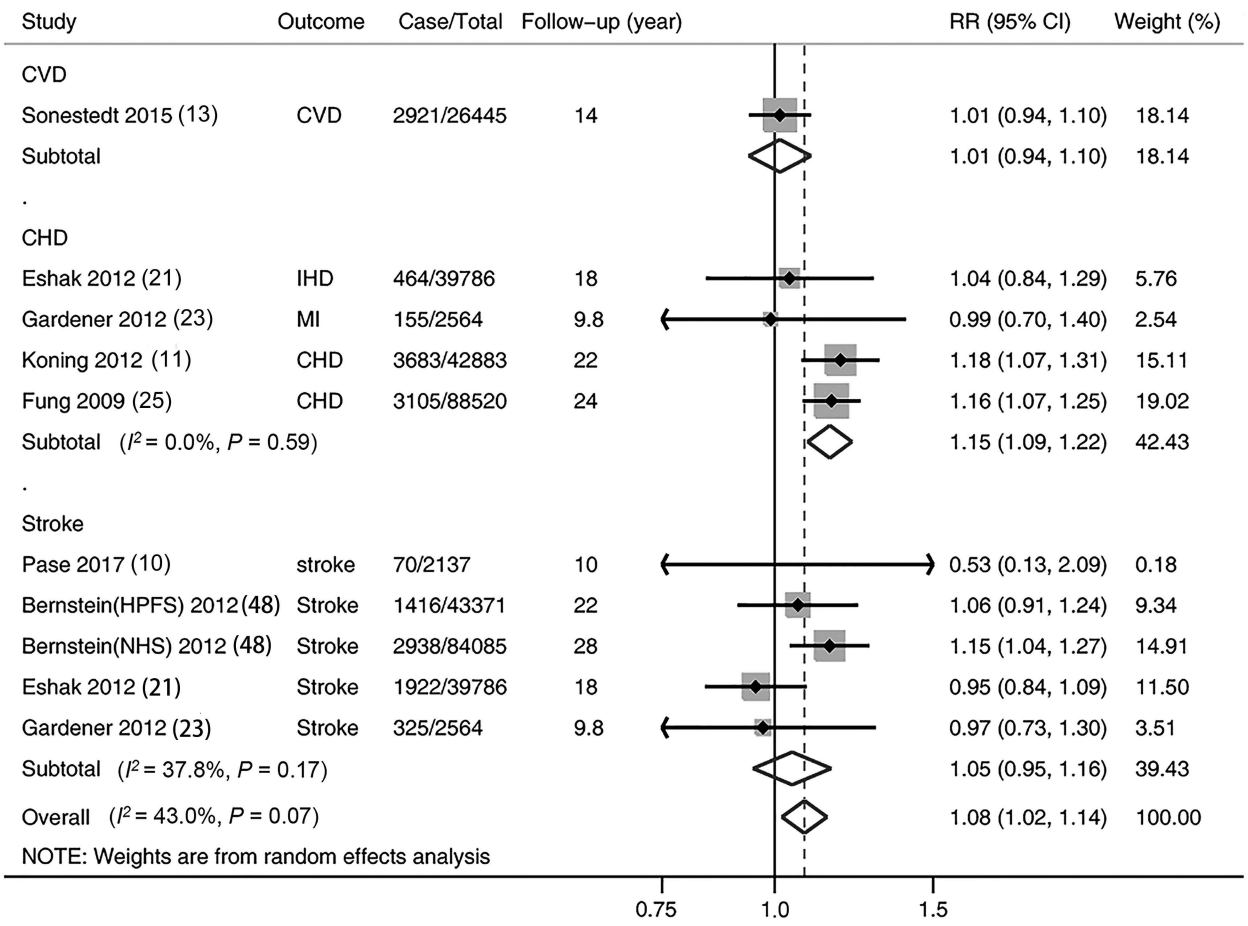

FIGURE 2 Forest plot showing the study-specific estimates and meta-analysis results of SSB intake (per 1 serving/d) and risk of CVD incidence in a random-effects model. CHD, coronary heart disease; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; IHD, ischemic heart disease; MI, myocardial infarction; NHS, Nurses' Health Study; SSB, sugar-sweetened beverage.

($P = 0.09$ for nonlinearity; Figure 3C) was observed between LCSBs and risk of CVD incidence.

In stratified analyses by outcome (coronary heart disease and stroke), the higher consumption of LCSBs was similarly associated with a higher risk of coronary heart disease and stroke (Figure 5). Each serving/day increment of LCSBs was associated with 6% higher risk of coronary heart disease (1.06, 1.02 to 1.11) and 9% higher risk of stroke (1.09, 1.04 to 1.13).

LCSBs and risk of CVD mortality

Three articles with 4 reports were included in the analysis of LCSBs and risk of CVD mortality. The pooled RR of CVD mortality for the highest compared with the lowest categories of LCSBs was 1.25 (1.05 to 1.48), with moderate to high heterogeneity ($I^2 = 72.7\%$, $P = 0.01$) (**Supplemental Figure 4**). The heterogeneity was mainly generated by 1 report (8), and when this report was excluded, the association was not substantially altered (1.15, 1.04 to 1.27) with low heterogeneity ($I^2 = 8.6\%$, $P = 0.33$).

Four reports were included in the dose-response analysis, and the pooled RR per 1 serving/d increment of LCSBs for CVD mortality was 1.07 (1.01 to 1.14), with moderate to high heterogeneity ($I^2 = 72.3\%$, $P = 0.01$) (**Figure 6**). The heterogeneity was generated by 1 report (8), and the association remained when this report was excluded (1.04, 1.01 to 1.07) with no heterogeneity ($I^2 = 0.0\%$, $P = 0.72$). In restricted cubic spline models, the association between LCSBs and risk of CVD mortality appeared to be nonlinear ($P = 0.003$ for nonlinearity; Figure 3D) with a higher risk observed only at high intake levels (>2 servings/d).

Subgroup analyses, metaregression, and sensitivity analyses

For SSBs/LCSBs and CVD incidence, we conducted subgroup analyses defined by sex (male, female, both), study location (USA, others), method of FFQ (self-administered, interview), exposure assessment (single measurement at baseline, repeated measures), questionnaire validity (high validation coefficients, low validation coefficients, no validation), study quality (Newcastle-Ottawa Quality Assessment Scale score <7 or score ≥7), and whether the study adjusted for confounders (age, BMI, education, smoking,

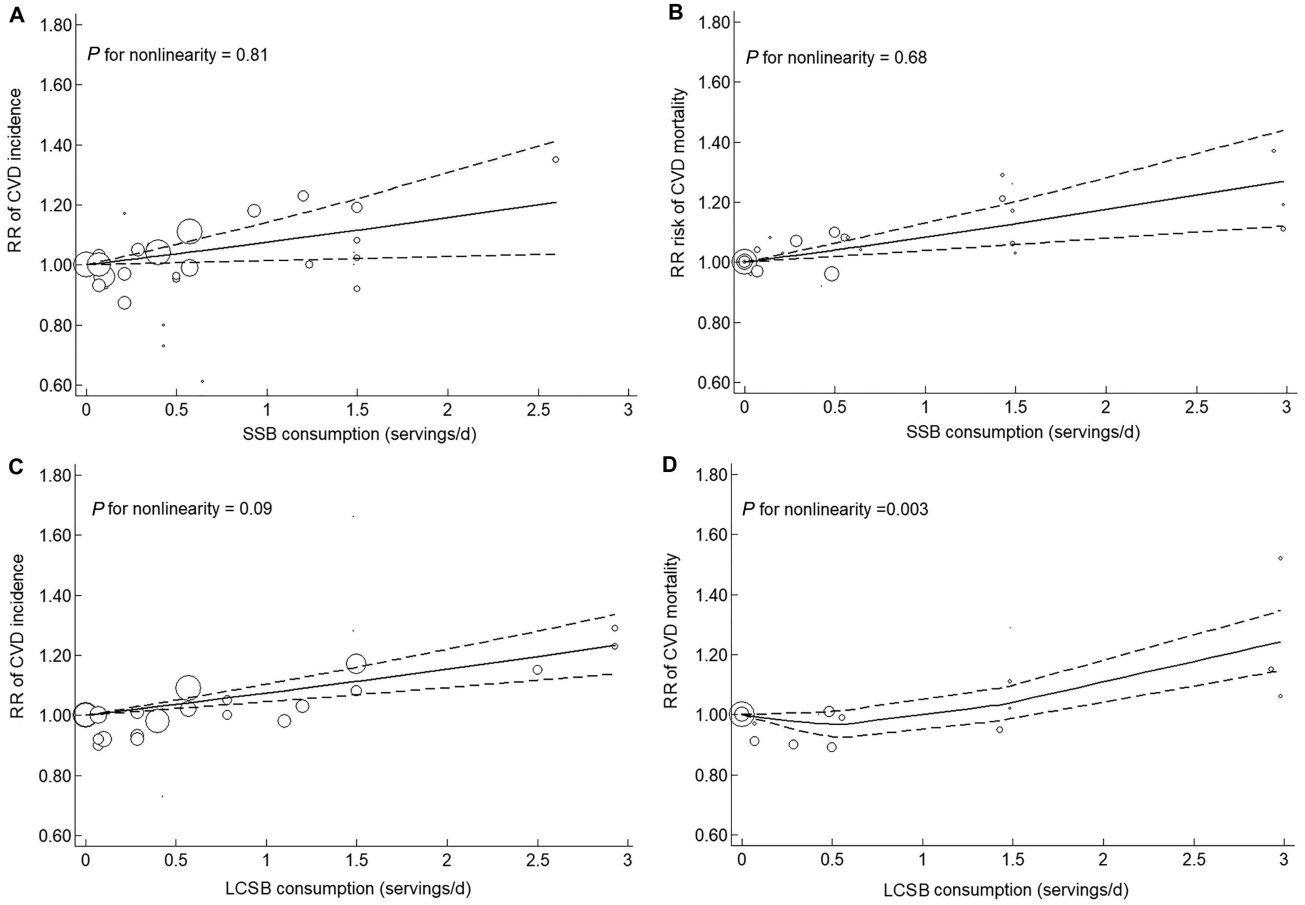

FIGURE 3 Dose-response relations of SSB (A, B) and LCSB (C, D) intake with CVD incidence (A, C) and mortality (B, D) in random-effects models. Modeling was performed using restricted cubic splines with knots fixed at the 10th, 50th, and 90th percentiles of the distribution. The solid line represents point estimates of the association between beverage intake and RRs; dashed lines are 95% CIs. Circles are RRs corresponding to the comparison categories. Sizes of circles are in proportion to the follow-up person-years for each comparison group. CVD, cardiovascular disease; LCSB, low-calorie sweetened beverage; SSB, sugar-sweetened beverage.

alcohol intake, physical activity, total energy intake, dietary quality, mutually adjusted for SSBs/LCSBs and fully adjusted for all lifestyle/diet factors). We did not observe a significant difference in magnitude or direction of the association between SSBs/LCSBs and risk of CVD incidence in most subgroups, with no evidence of heterogeneity observed between subgroups by metaregression (**Supplemental Tables 6** and **7**). However, significant heterogeneity was found in the subgroup of location for SSBs and CVD incidence, and the association was significantly stronger in the USA than in other regions ($P = 0.01$) (Supplemental Table 6). In addition, metaregression analyses showed a significant interaction between duration of follow-up (continuous variable) and the association between SSBs and CVD incidence. The log(RR) was estimated to increase by 0.01 per increment of 1 y of follow-up: exp(b) = 1.01 (1.00 to 1.02) ($P = 0.01$), which meant the association between SSBs and CVD incidence was stronger in those studies with a longer follow-up duration. The estimated variance between studies (I^2) was reduced from 43.0% to 0.0%. In contrast, we found no interaction between duration of follow-up and RR of CVD incidence for LCSBs.

We repeated the dose-response analysis using a fixed-effects model in a sensitivity analysis and the pooled estimates were similar. The pooled estimates for the per 1 serving/d increment of SSBs for CVD incidence and CVD mortality were 1.09 (1.05 to 1.13) and 1.08 (1.05 to 1.11), respectively, in the fixed-effects model. The pooled estimates for per 1 serving/d increment of LCSBs for CVD incidence and CVD mortality were 1.08 (1.05 to 1.11) and 1.06 (1.04 to 1.09), respectively, in the fixed-effects model (**Supplemental Table 8**). When we repeated the meta-analysis to quantify the risk estimates of a 250 mL/d increment rather than a 1 serving/d increment, the results remained consistent (Supplemental Table 8). The pooled estimates per 250 mL/d increment of SSBs for CVD incidence and CVD mortality were 1.08 (1.03 to 1.12) and 1.07 (1.04 to 1.09), respectively. The pooled estimates per 250 mL/d increment of LCSBs for CVD incidence and CVD mortality were 1.06 (1.03 to 1.09) and 1.06 (1.01 to 1.12),

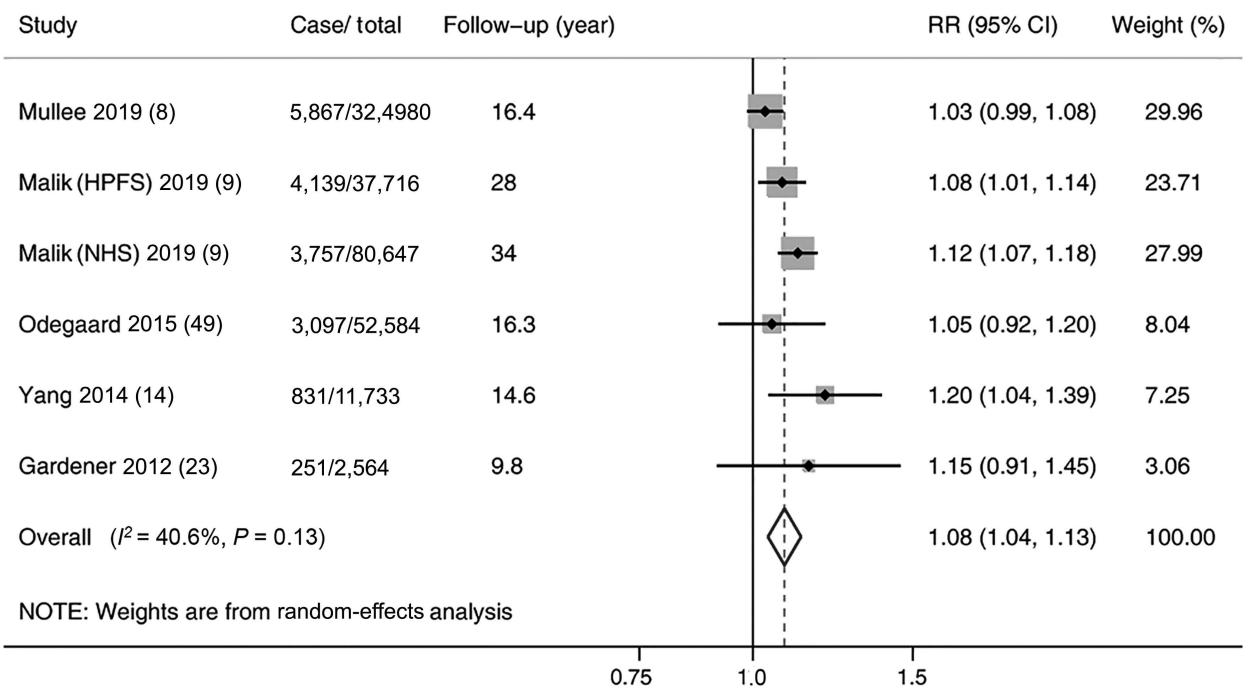

FIGURE 4 Forest plot showing the study-specific estimates and meta-analysis results of SSB intake (per 1 serving/d) and risk of CVD mortality in a random-effects model. CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; SSB, sugar-sweetened beverage.

respectively (Supplemental Table 8). In addition, sensitivity analyses by omitting 1 study at a time did not substantially alter the pooled results of SSBs and LCSBs (**Supplemental Figures 5–8**).

Publication bias

For the categorical analysis, we found evidence for potential publication bias for the association between LCSBs and CVD incidence using Egger's linear regression test ($P = 0.04$). The trim-and-fill method was performed to recalculate our pooled risk estimate and 4 missing studies were imputed to produce a symmetrical funnel plot (**Supplemental Figure 9**). The analysis suggested that the imputed risk estimate was 1.10 (1.00 to 1.21), which was attenuated compared with the original risk estimate. For the dose-response analysis, no significant publication bias was found between SSBs/LCSBs and CVD incidence/mortality.

CVD risk attributable to SSBs

We analyzed 2450 men and nonpregnant women, who were aged 40–79 y and free of self-reported CVD in the NHANES, 2015–2016 cycle. Approximately 117.5 million adults were represented after accounting for the sample weight. Absolute event rates over 10 y from 2015 to 2025 were estimated to be 9.1% (10.8 million CVD events) in the USA. Assuming a causal effect, we estimated that 1.0 million CVD events over 10 y (population attributable fraction 9.3%, 6.6% to 11.9%) were attributable to the consumption of SSBs in the USA (**Supplemental Table 9**). Younger adults (40–59 y), men, and non-Hispanic blacks would have a greater proportion of CVD events related to consumption of SSBs than older adults (60–79 y), women, and other races, given the higher levels of SSB consumption in these groups (Supplemental Table 9).

Discussion

In this systematic review and meta-analysis, we provided summary evidence that the habitual consumption of SSBs was associated with a higher risk of CVD incidence and mortality. The positive associations persisted in stratified analyses and several sensitivity analyses. Moreover, under a causal assumption of causality, 1.0 million CVD events would be attributable to the consumption of SSBs among 10.8 million CVD events predicted to occur from 2015 to 2025 in the USA. The intake of LCSBs was also associated with a higher risk of CVD incidence, and the association between LCSBs and risk of CVD mortality appeared to be nonlinear with a higher risk observed only at high intake levels. However, potential reverse causation and residual confounding complicate interpretation of findings related to LCSBs.

Comparison with other studies

To our knowledge, the present study represents the largest and most comprehensive evaluation of the dose-response association between SSBs/LCSBs and CVD risk in the

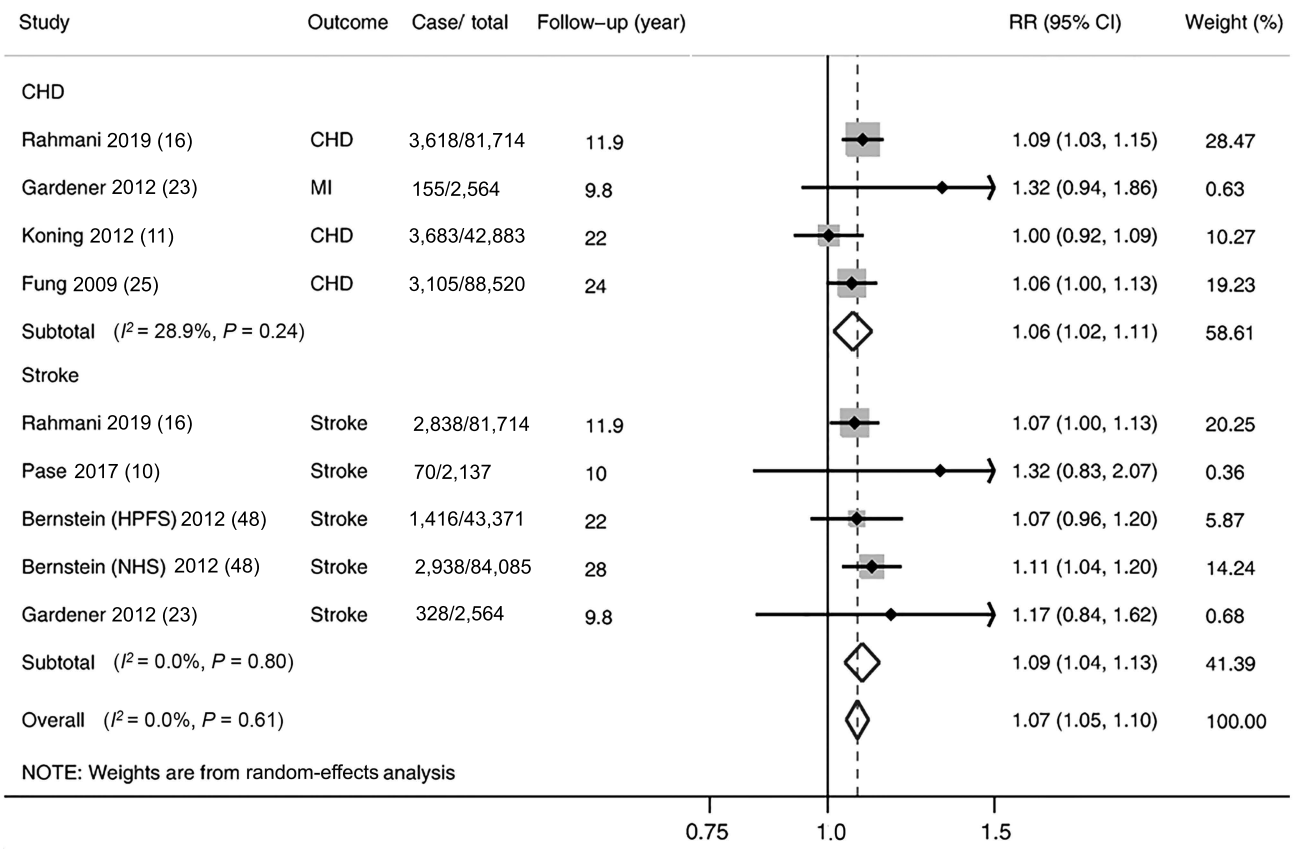

FIGURE 5 Forest plot showing the study-specific estimates and meta-analysis results of LCSB intake (per 1 serving/d) and risk of CVD incidence in a random-effects model. CHD, coronary heart disease; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; LCSB, low-calorie sweetened beverage; MI, myocardial infarction; NHS, Nurses' Health Study.

general population. A previous meta-analysis summarized the relation between SSBs/LCSBs and CVD risk (12), however, that study omitted certain studies and since then additional articles have been published, which warrants an updated synthesis of the evidence. In our study, we included additional key studies (8–10, 13, 14, 16) and assessed the graded dose-response association between SSBs/LCSBs and CVD risk. Another recent meta-analysis conducted by Toews et al. assessed the effect of low-calorie sweetener intake on a broad range of health outcomes in adults and children (50). However, this study did not consider the evidence from prospective cohort studies due to inclusion criteria that resulted in the exclusion of studies that did not specify the specific type of nonsugar sweetener. Most cohort studies use FFQs to evaluate the diet type of low calorie sweetener contained in foods/beverages, which would reflect the predominant type of sweeteners in the food supply at that time. Our study significantly adds to the existing body of literature on this topic by providing an up-to-date summary and drawing conclusions based on precise evaluation of the dose-response relation between SSBs/LCSBs and risk of CVD.

In the current study, the per 1 serving/d increment of SSBs was significantly associated with a 9% higher risk of CVD incidence and 8% higher risk of CVD mortality, which is generally consistent with previous findings from several well-conducted cohort studies. With repeated measurements of SSB intake and long follow-up duration, the Nurses' Health Study and Health Professionals Follow-up Study reported that per 1 serving/d increment of SSBs was associated with an 11% and 7% higher risk of CVD mortality, respectively (9). The magnitude of the pooled estimates for coronary heart disease and stroke in our results were largely comparable to that for total *trans* fat intake, a well-evaluated dietary risk factor for CVD (51). In our study, each serving/day increment of SSBs was associated with a 15% higher risk of coronary heart disease (1.15, 1.09 to 1.22), which is consistent with previous meta-analyses (52, 53). Moreover, each serving/day increment of SSBs was associated with a marginally higher risk of stroke (1.05, 0.95 to 1.16) in our pooled results. In previous studies, a greater consumption of SSBs was observed to be associated with a significantly higher risk of ischemic stroke in women (21, 48). More studies are warranted to evaluate the association between the intake of SSBs and stroke with full consideration given to the subtypes of stroke and potential gender difference. The associations between SSBs and CVD risk were consistent in multiple subgroup and sensitivity analyses, which indicate

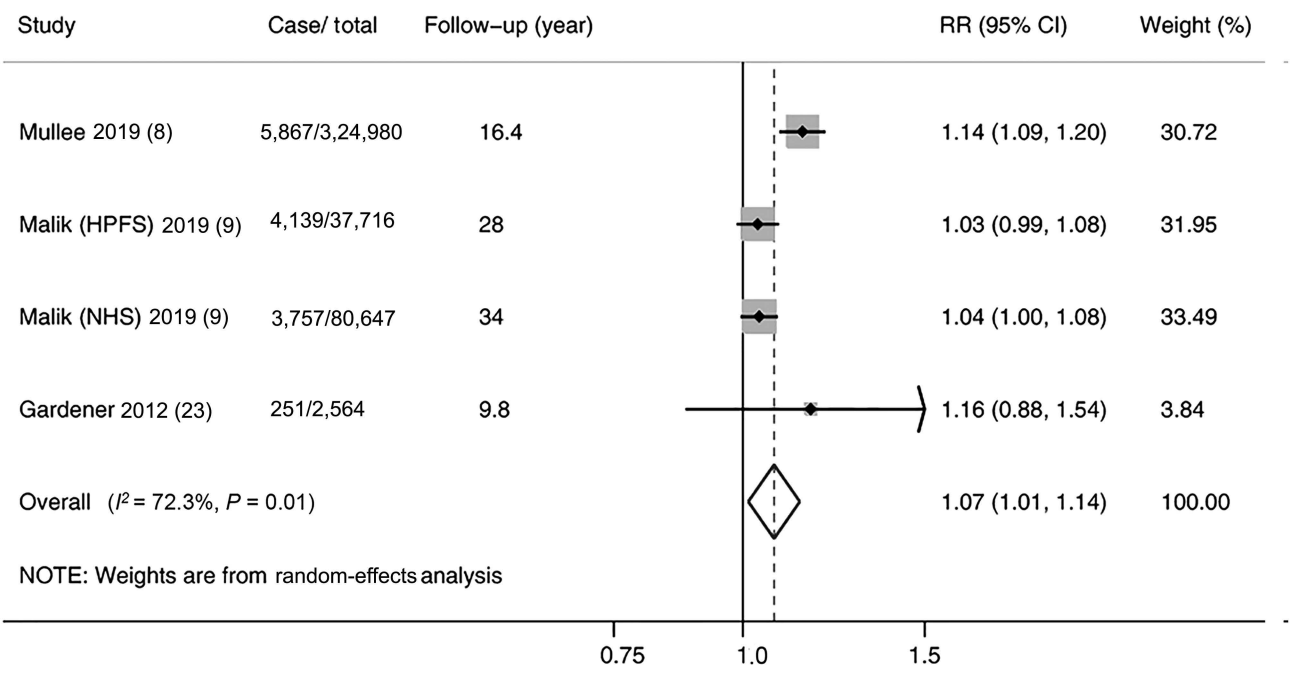

FIGURE 6 Forest plot showing the study-specific estimates and meta-analysis results of LCSB intake (per 1 serving/d) and risk of CVD mortality in a random-effects model. CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; LCSB, low-calorie sweetened beverage.

the robustness of our findings. In contrast to SSBs, few studies have evaluated intake of LCSBs and CVD risk, and associations between LCSBs and CVD risk are not as robust as those for SSBs. This may be due in part to reverse causation and residual confounding. We further found evidence for publication bias for the association between LCSBs and CVD incidence and the pooled estimate was attenuated when the trim-and-fill method was applied. The Women's Health Initiative Observational Study reported that the higher intake of LCSBs (≥2 servings/d) was significantly associated with a higher risk of ischemic stroke as well as coronary heart disease, however, this study did not include repeated measurements of intake, which can help reduce the potential for reverse causation in statistical analysis. The Health Professionals Follow-up Study with repeated measurements reported that LCSB consumption was not significantly associated with stroke (48) or coronary heart disease (11). In the study of coronary heart disease, it was shown that participants appeared to be consuming LCSBs as part of a weight-loss strategy or in response to the diagnosis of a chronic condition supporting the potential for reverse causation (11).

Observational evidence from cohort studies linking the intake of SSBs to CVD risk has been strengthened by consistent positive associations between the intake of SSBs and vascular risk factors, such as weight gain (2), hyperuricemia (54), and type 2 diabetes (3). Additionally, several important trials have elucidated that reducing the consumption of SSBs had favorable effects on body weight (55–57), blood pressure, and vascular function among adults (58, 59). These consistent findings from well-designed cohort studies and high-quality trials provide strong evidence for a potential role of SSBs in the etiology of cardiometabolic diseases. However, the associations between low-calorie sweeteners and CVD risk factors, including obesity, from randomized controlled trials and observational studies have been conflicting (60). A recent meta-analysis of randomized controlled trials indicated that replacing sugar with nonnutritive sweeteners leads to weight reduction (61), which tended to show cardiovascular benefits for low-calorie sweeteners when compared with caloric sweeteners. Although some observational studies have suggested that LCSBs may be associated with a higher risk of obesity and cardiometabolic diseases, biological mechanisms explaining these pathways remain unclear (62). The intake of low-energy sweeteners has been suggested to habituate towards a preference for sweets, which may lead to a positive energy balance (63) or lead to adverse changes in intestinal microbiota that may promote glucose intolerance (64), however, the relevant evidence has been systematically reviewed and found to be equivocal (65, 66).

Under an assumption of causality and using the pooled estimates from the current meta-analysis, we estimated that 1.0 million predicted CVD events would be attributable to the consumption of SSBs in the USA from 2015 to 2025. A recent study also estimated that >50,000 cardiometabolic deaths in US adults in 2012 could be attributed to the high consumption of SSBs (67). These results emphasize

SSBs as an important modifiable risk factor associated with adverse cardiometabolic health. As such, several population-based strategies have been proposed to target SSBs, including taxation (68) and health warning labels (69) among others, which have been further assessed and showed significant health gains and societal cost savings (70). This evidence has provided further support for recommendations to limit intake of SSBs.

Strengths and limitations of study

Our meta-analysis has several strengths. First, the large sample size allowed us to quantitatively assess the association between SSB/LCSB consumption and risk of CVD, thus making it more powerful than any individual study. Second, only prospective cohort studies were included to minimize recall and selection biases from case-control studies and confounding from cross-sectional studies. Third, SSBs/LCSBs are mainly commercially manufactured and consumed in discrete units (bottles/cans), which is simple for subjects to recall and report, unlike most other dietary exposures derived from multiple and complex food sources. Fourth, to confirm the robustness of our study findings, we performed several sensitivity analyses and observed consistent results. Fifth, by using participant data to calculate the population attributable fraction, our estimates are not affected by the exposure distribution of SSBs.

This study has limitations typical of observational studies and meta-analysis. First, residual confounding may still persist in our meta-analysis, though the estimates with the maximum extent of adjustment for confounders from each study were used in our analyses to reduce the potential of confounding. Second, dietary habits and beverage consumption could change over time. The time-varying characteristics might not be random and could result in bias. However, no significant heterogeneity was observed between subgroups of exposure assessment (1 measurement at baseline compared with repeated measures) for both SSBs and LCSBs. Third, volume per serving was specific to a given study, which led to uncertainties and assumptions around quantification of "a serving." Nevertheless, we repeated the meta-analysis to estimate the RR for each 250 mL/d increment in a sensitivity analysis and the results were consistent with our primary analysis. Fourth, reverse causality could also exist because of unmeasured comorbid conditions that might alter the associations between the consumption of beverages and CVD risk, particularly LCSBs. Fifth, we were unable to stratify studies by race/ethnicity due to limited data from the original studies. Sixth, no other beverage consumption was included in analyses, such as 100% fruit juice (an important source of free sugar), tea, and coffee. Therefore, it is unclear whether any other beverage alternatives might fare any differently. Finally, we estimated the population attributable fraction of SSBs under the assumption of causality, and we hypothesized that removing the exposure would not affect other risk factors, which may not be true in practice.

Conclusion

This meta-analysis and systematic review found that the habitual consumption of SSBs was associated with a higher risk of CVD incidence and CVD mortality in a dose-response manner. Intake of LCSBs was also positively associated with the risk of CVD incidence and CVD mortality at high levels (>2 servings/d), but the interpretation of these findings are complicated by potential reverse causation and residual confounding.

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