Umbrella Review

Non–Sugar-Sweetened Beverages and Risk of Chronic Diseases: An Umbrella Review of Meta-analyses of Prospective Cohort Studies

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Context: *Several effects of non–sugar-sweetened beverage (NSSBs) intake on health outcomes have been reported; however, the evidence on the association between NSSBs intake and chronic diseases and mortality risk is still inconclusive.* ***Objective:*** *This umbrella review aimed to summarize the evidence on the association between NSSBs intake and the risk of chronic diseases and mortality.* ***Data Sources:*** *Embase, ISI Web of Science, Cochrane Central, and PubMed were searched up to September 2023 for relevant meta-analyses of observational prospective cohort studies.* ***Data Extraction:*** *Two groups of researchers independently extracted study data and assessed the risk of bias for meta-analyses and primary studies.* ***Data Analysis:*** *Six meta-analyses, reporting 74 summary hazard ratios (HRs) for different outcomes obtained from 50 primary studies, were included. The summary HRs, 95% CIs, and certainty of evidence on the association of NSSBs intake with risk of chronic diseases and mortality were as follows: all-cause mortality (per 355 mL/d: 1.06 [1.01 to 1.10]; moderate certainty); stroke (per 250 mL/d: 1.09 [1.04 to 1.13]; high certainty); coronary heart disease (CHD) (per 250 mL/d: 1.06 [1.02 to 1.11]; high certainty); hypertension (HTN) (high vs low intake: 1.14 [1.09 to 1.18]; moderate certainty); type 2 diabetes (T2D) (high vs low intake: 1.16 [1.08 to 1.26]; low certainty); metabolic syndrome (MetS) (high vs low intake: 1.32 [1.22 to 1.43]; low certainty); colorectal cancer (high vs low intake: 0.78 [0.62 to 0.99]; moderate certainty); and leukemia (high vs low intake: 1.35 [1.03 to 1.77]; moderate certainty). For other outcomes, including the risk of cardiovascular and cancer mortality, chronic kidney diseases, breast cancer, prostate cancer,*

https://doi.org/10.1093/nutrit/nuae135

endometrial cancer, pancreatic cancer, multiple myeloma, and non-Hodgkin lymphoma, no association was found. ***Conclusion:*** *This study provides further evidence that NSSBs are associated with increased risk of all-cause mortality, stroke, CHD, HTN, T2D, MetS, and leukemia. Moreover, a higher intake of NSSBs was associated with a lower risk of colorectal cancer. However, it should be noted that the magnitudes of the associations are not large. Further studies are needed to clarify the long-term effects of different NSSBs intakes on health.*
Systematic Review Registration: *PROSPERO no. CRD42023429981.*

Key words: *artificially sweetened beverages, low-calorie sweeteners, no-calorie sweeteners, chronic disease, mortality, cardiovascular disease, type 2 diabetes, cancer, umbrella review.*

INTRODUCTION

Non–sugar-sweetened beverages (NSSBs) have been used widely as a replacement to reduce sugar-sweetened beverages (SSBs) given that substituting SSBs with NSSBs might reduce energy intake.[1] Non–sugar-sweetened beverages contain low- or no-calorie sweeteners, artificially produced (eg, aspartame and saccharin) or naturally present in plants (eg, steviol glycoside).[2]

A large number of meta-analyses have investigated the association of NSSBs with the risk of chronic diseases, including cardiovascular diseases (CVDs),[3] hypertension (HTN),[4] chronic kidney disease (CKD),[5] type 2 diabetes (T2D),[6] cancers,[7] and all-cause and cause-specific mortality.[8] Despite a large body of literature on the health aspects of NSSBs, there is still a need for a comprehensive overview. While NSSBs intake has been associated with the increased risk of all-cause mortality,[8] CVD incidence,[3] and metabolic syndrome, (MetS),[9] other studies have found no association between NSSBs intake and cancer mortality[8] or even a lower risk of specific cancers with higher NSSBs intake.[7] In addition, the strength of evidence presented by the published meta-analyses has not been addressed and some of the studies have methodological issues—for instance, including case-control studies,[5,10] which are more prone to biases; pooling results of studies with different health characteristics; and including studies on both adolescents and adults[11] or studies performed on both the general population and patients with chronic conditions may limit the interpretations of the findings.[6,8] While a 2023 umbrella review has been published on the association of NSSBs and health outcomes, there is still a need for a comprehensive appraisal of uncertainty and risk of biases in the observed associations[12] since the recent review followed the same approach as previous meta-analyses and did not account for the previously mentioned methodological issues, mainly including inappropriate primary studies and ignoring some important health outcomes, such as MetS, and site-specific cancer outcomes.

Umbrella reviews have been used to understand the epidemiological credibility of health aspects and summarize the evidence presented by published meta-analyses.[13,14] Using this approach, the methodological quality of published meta-analyses, the certainty of evidence, and the strengths of the claimed associations can be assessed, resulting in a comprehensive overview on a specific topic. Thus, we aimed to perform an umbrella review of the published meta-analyses of prospective cohort studies evaluating the association of NSSBs and risk of chronic diseases with at least 1 published meta-analysis on the topic, and to evaluate the strength and certainty of evidence.

METHODS

The systematic literature search was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] The protocol for the study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023429981).

Literature search

The systematic search was performed in Embase.com, Web of Science Core Collection, Cochrane Central, and PubMed until September 4, 2023, for potential relevant meta-analyses of prospective cohort studies evaluating the association of NSSBs with the risk of any chronic diseases and mortality. A combination set of key words was used to find potentially relevant meta-analyses: [("Sweeteners" OR "sugar free" OR "artificially") AND ("review" OR "systematic review" OR "meta-analysis")]. The literature search was supplemented by screening the reference lists of all relevant reviews and meta-analyses. No language, publication date, or other restrictions were applied. With the help of librarians, the literature search was performed by 2 authors (S.B. and H.R.-D.). The complete search strategy is provided in Table S1.

Table 1. PICOS Criteria for Inclusion of Studies

Parameter	Criterion
Population	General population aged 18 years and older
Interventions/ exposure	Dietary intake of NSSBs
Comparator	Highest versus lowest intake of NSSBs, per serving or dose–response relation between NSSBs intake and outcomes
Outcome	Incidence of chronic diseases and all-cause or specific cause of mortality
Study design	Meta-analyses of observational prospective cohort studies (cohort, case-cohort, nested case-control)

Abbreviation: NSSBs, non–sugar-sweetened beverages.

Selection of meta-analyses

Studies with the following criteria, according to the PICOS (Population, Intervention, Comparison, Outcome, Study design) criteria (Table 1), were included in the present umbrella review: meta-analyses of observational prospective cohort studies (also nested case-control and case-cohort studies) that (1) assessed dietary intakes by a standard dietary assessment tool (eg, food-frequency questionnaires [FFQs], diet history, 24-hour dietary recalls, and dietary records); (2) reported NSSBs as the exposure; (3) assessed the association of NSSBs with risk of chronic diseases (incidence of CVD [stroke and coronary heart disease (CHD)], T2D, HTN, MetS, CKD, site-specific cancers, and all-cause or specific cause of mortality as the outcome) in the general population aged 18 years and older; (4) provided the effect estimates (hazard ratio [HR], risk ratio [RR], and odds ratio [OR]) for the highest versus lowest intake of NSSBs, per serving or dose–response relation between exposure and outcomes; and (5) reported multivariable adjusted summary risk estimates and corresponding 95% CIs.

Primary studies and studies with no summary risk estimate (eg, systematic reviews without meta-analysis or narrative reviews) were excluded. Studies that did not specifically include NSSBs as an independent exposure and provided a combination of NSSBs and SSBs were also excluded. If more than 1 published meta-analysis was available per each specific outcome, the one with the largest number of primary prospective studies was selected to avoid the inclusion of duplicate studies. If effect estimates were available for both the highest versus lowest approach and per linear term, the linear effect estimates were checked for accurate calculation, with priority given to those that were correctly calculated.

Data extraction. Two researchers (S.B. and H.R.-D.) independently screened and cross-checked the titles and abstracts, as well as a final full-text screening to find the relevant studies based on the inclusion and exclusion criteria. Two groups of researchers independently extracted the following information from eligible meta-analyses: first author's name, publication year, outcome (s) of interest, exposure (dose of exposure), study design of the primary studies, number of primary prospective cohort studies, number of participants/cases, type of comparison (high vs low meta-analysis, or dose–response meta-analysis), publication bias, type of outcome metric (hazard ratio [HR], risk ratio [RR], odds ratio [OR]), and effect size and its 95% CI.

For each primary study included in the meta-analysis, the following information was also extracted: first author's name, study name, publication year, number of participants/cases, follow-up duration, covariates adjusted in the models, and maximally adjusted HRs, RRs, and ORs and their 95% CIs. Extracted data were double-checked by 2 independent researchers.

Assessment of methodological quality

The risk of bias was assessed with the A MeaSurement Tool to Assess Systematic Reviews, version 2 (AMSTAR-2), tool.[16] It includes 16 items about the conduct of the meta-analysis, including components of PICOS, protocol registry, literature search, study selection, data extraction, reporting of included and excluded studies, risk-of-bias assessment in the primary studies, statistical methods for the analysis, heterogeneity, publication bias, and conflict of interest. Each question can be answered as "no," "not applicable," "partially yes," and "yes."

Risk-of-bias assessment of individual studies and certainty of evidence

The risk-of-bias assessment of the cohort studies was done with the recent version of the Risk Of Bias In Non-randomized Studies–of Exposures (ROBINS-E) tool.[17] Certainty of evidence was assessed for all associations with the updated Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.[18] Quality assessment of individual studies and certainty of evidence was done by 2 investigators independently.

Statistical analysis

For each outcome, the effect estimates were recalculated from selected meta-analyses using multivariable-adjusted HRs of the primary studies included in the published meta-analysis. The adjusted summary HRs and their 95% CIs were recalculated using the DerSimonian and Laird random-effects model, which takes the between-study heterogeneity into account.[19]

Relative risks were treated equally as HRs. When the published meta-analysis presented HRs from the

same cohort separately (eg, categorized by sex), first a fixed-effects model was performed to combine the HRs and the combined effect size was used for the analysis. If the published meta-analysis included case-control, retrospective cohort, and cross-sectional studies in addition to the prospective cohort studies, only the results of prospective studies were included. If the published meta-analysis included primary studies on patients with chronic diseases (eg, patients with stage 3 cancer) together with studies on the general population, only primary studies conducted in the general population were included. Also, if the published meta-analysis included primary studies that reported combined results for children with adults, only the primary studies on adults were included. If the published meta-analysis included primary studies with unadjusted effect estimates, this study was excluded from the reanalysis. For meta-analysis that reported a dose–response meta-analysis as a summary effect estimate, we recalculated the dose–response meta-analyses if the dose–response estimates for individual primary studies were provided separately. For each meta-analysis, between-study heterogeneity was evaluated using the I^2 statistic. The I^2 statistic may vary from 0% to 100% and represents the percentage of overall variation across studies that is explained by heterogeneity.[20] However, as I^2 is dependent on the sample size, we also calculated τ^2, which is independent of study size and describes variation between studies in relation to the effect estimates.[21] In addition, we calculated 95% prediction intervals, which account for heterogeneity and show the range in which the underlying true effect size of future studies will lie with 95% certainty.[21]

Publication bias was assessed by graphical (funnel plots) and statistical tests (Egger's test) for each meta-analysis with at least 10 primary studies.[21,22] Sensitivity analyses were also performed to explore if the results were robust using a leave-one-out analysis, excluding each study at a time from the analysis. Statistical analyses were performed in R (version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria) using meta, dmetar packages. $P < .05$ was considered significant.

RESULTS

Figure 1 shows the flowchart of the literature search and screening procedure. A total of 4206 articles were initially identified by searching the databases. Based on the title and abstract screening, 46 publications were selected for full-text screening. After the application of the inclusion criteria, 6 meta-analyses were included in the final analysis. Table S2 provides a list of excluded studies.

Characteristics of included meta-analyses

For most outcomes, we identified more than 1 meta-analysis in our search and excluded 29 duplicate meta-analyses. Of those, the meta-analyses with the largest number of primary prospective cohort studies were selected for this umbrella review. All included meta-analyses were published between 2020 and 2022. In addition, we identified meta-analyses for specific outcomes, including obesity,[6] gastric cancer,[7] liver and biliary cancer,[23] thyroid cancer,[7] obesity-related/not-related cancers,[7] and glioma,[7] which had only 1 eligible prospective cohort study based on our eligibility criteria; thus, they were not included in this review (Table S2).

Of the 6 identified meta-analyses of prospective cohort studies, we included 74 summary HRs/RRs obtained from 50 primary prospective cohort studies on all-cause mortality,[8] cardiovascular mortality,[8] cancer mortality,[8] T2D,[6] stroke,[3] CHD,[3] MetS,[9] HTN,[6] CKD,[5] breast cancer,[7] prostate cancer,[7] pancreatic cancer,[7] colorectal cancer,[7] endometrial cancer,[7] multiple myeloma,[7] non-Hodgkin lymphoma,[7] and leukemia.[7]

Fifty included primary studies performed multivariable adjustment using Cox proportional hazard regression models, while 2 primary studies only reported unadjusted effect estimates and were therefore excluded from the meta-analyses on T2D[24] and all-cause mortality.[25] Two primary studies with a cross-sectional design were excluded from the meta-analysis on MetS.[26] Similarly, we excluded a primary case-control study from the meta-analysis on CKD.[27] We found duplicate primary publications of the same population with longer follow-up periods for obesity-related cancer outcome; thus, the study with the smaller sample size was excluded[28]; finally, 1 primary cohort study remained.[29] One primary cohort study considered composite CVD outcomes; therefore, we could not include this study in the meta-analyses on either stroke or CHD.[30] We excluded 5 primary cohort studies for meta-analysis on T2D because of the following reasons: were conducted on women with gestational diabetes mellitus (GDM)[31]; considered only 1 MetS component, high fasting glucose levels as T2D incidence[32]; considered prediabetes as the outcome of interest instead of T2D[33]; and were duplicate studies within the same population with a shorter follow-up period.[34,35] In addition, 3 primary studies provided data for 1 of the components of MetS (high blood pressure) as HTN incidence and were included in the published meta-analyses[32,36,37]; therefore, these 3 studies were excluded from our meta-analysis. One primary cohort study reported a linear effect estimate for breast cancer and endometrial cancer, so we could not include this study in our meta-analyses.[38] In addition, we could not perform the

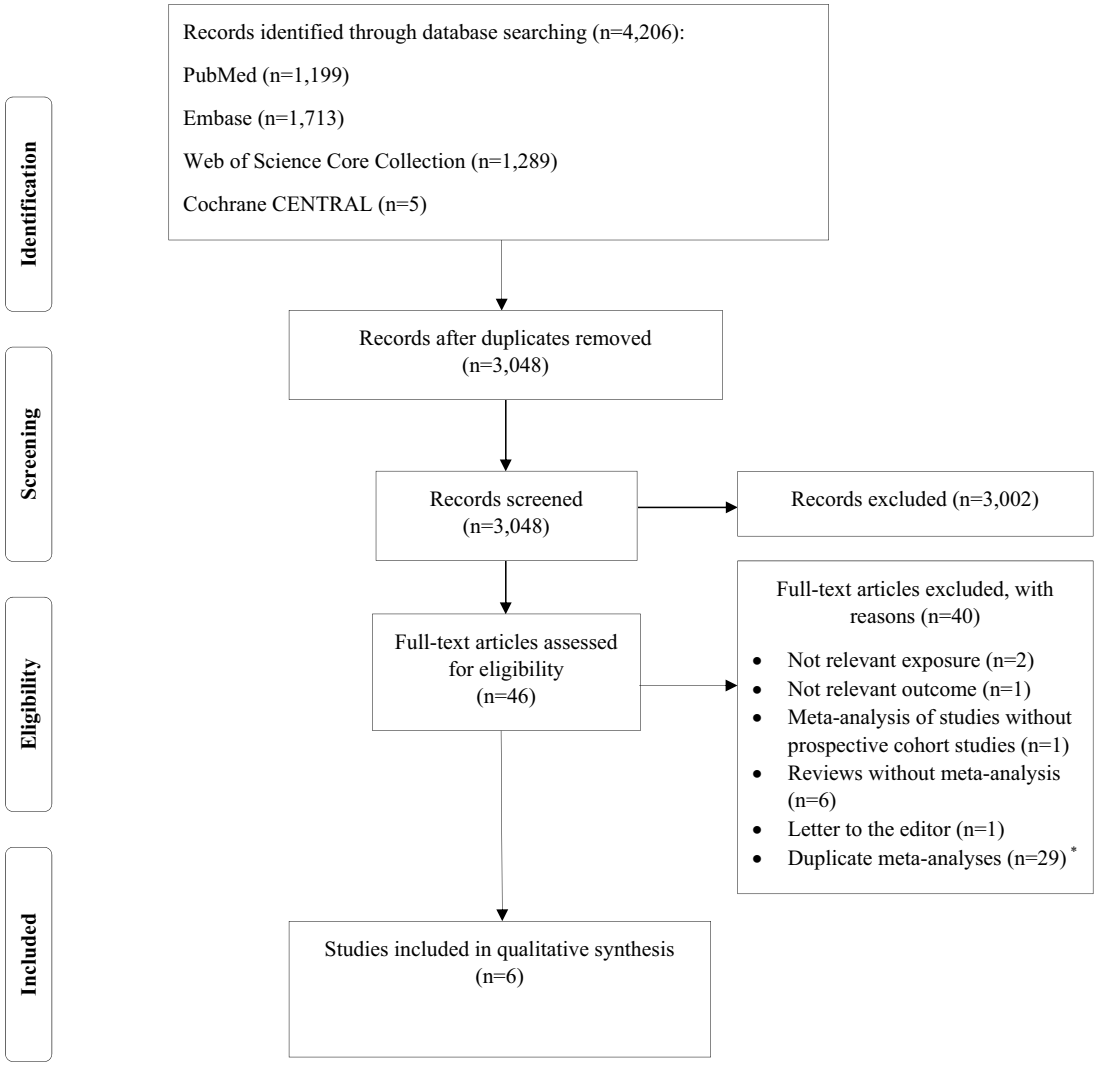

Figure 1. Flowchart of Systematic Search and Selection Process. *When more than 1 published meta-analysis was available per each specific outcome, we included the study with the higher number of primary prospective studies to prevent duplicates

meta-analysis for 2 study outcomes (kidney cancer and ovarian cancer) because 1 of the included studies reported linear effect estimates[38,39] and another reported effect estimates for high versus low values of exposure levels.[28]

Of the 50 primary studies, 98% ($n = 49$) were adjusted for age, 52% ($n = 26$) for sex, 40% ($n = 20$) for total energy intake, 82% ($n = 41$) for body mass index (BMI), 82% ($n = 41$) for physical activity, 90% ($n = 45$) for smoking status, and 76% ($n = 38$) for alcohol intake.

Methodological quality of evidence

The overall and item-specific AMSTAR-2 ratings for each included systematic review and meta-analysis are presented in Table S3. Of the 6 included systematic reviews and meta-analyses, the methodological quality was high in 1 study[8] and critically low in the remaining 5 meta-analyses.[3,5–7,9] The most common critical weaknesses not addressed in the meta-analyses were the absence of protocol registered before the commencement of the meta-analysis (item 2),[3,6,7,9] the lack of a comprehensive literature search strategy (item 4),[5] the missing justification for exclusion of studies (item 7),[5,6,9] the inappropriate meta-analytic methods (item 11),[5] the mostly inadequate assessment of the risk of bias in interpreting/discussing the findings (item 13),[3,7,9] and the lack of assessment of the presence and likely effect of publication bias (item 15).[5]

Associations and quality of evidence between NSSBs and mortality

For a meta-analysis on all-cause mortality, each 355 mL per day increase of NSSBs was associated with a higher

risk of all-cause mortality (HR: 1.06; 95% CI: 1.01 to 1.10; I^2: 87.25%) and the quality of the evidence was rated as high. However, we observed high quality of evidence for a nonsignificant association between NSSBs intake and cardiovascular mortality risk (HR for each 355-mL/d increment: 1.07; 95% CI: 1.00 to 1.15; I^2: 79.28%). In addition, NSSBs consumption was not associated with the risk of cancer mortality (HR for each 355-mL/d increment: 1.01; 95% CI: 0.98 to 1.03; I^2 :0.00%; GRADE: high) (Table 2, Figure S1).

Associations and quality of evidence between NSSBs and stroke, CHD, and HTN

Each 250-mL/d increase of NSSBs was associated with an increased risk of stroke (HR: 1.09; 95% CI: 1.04 to 1.13; I^2: 0.00%; GRADE: high). Moreover, there was high quality of evidence for a linear association between NSSBs intake and CHD risk (HR for each 250-mL/d increment: 1.06; 95% CI: 1.02 to 1.11; I^2: 31.12%). A higher intake of NSSBs was also associated with a higher HTN risk (HR: 1.14; 95% CI: 1.09 to 1.18; I^2: 72.88%; GRADE: moderate) (Table 2, Figure S2).

Associations and quality of evidence between NSSBs and T2D, MetS, and CKD

We found that higher intakes of NSSBs were associated with a higher risk of T2D (HR: 1.16; 95% CI: 1.08 to 1.26; I^2: 52.3%; GRADE: low). Evidence from our analysis showed a linear association between NSSBs consumption and the risk of MetS (HR: 1.32; 95% CI: 1.22 to 1.43; I^2: 12.3%; GRADE: moderate). However, no significant association was observed for the highest versus lowest intake of NSSBs and the risk of CKD (HR: 1.25; 95% CI: 0.51 to 3.10; I^2: 93.74%; GRADE: low) (Table 2, Figure S3).

Associations and quality of evidence between NSSBs and site-specific cancers

There was a moderate quality of evidence that individuals with a higher intake of NSSBs had a higher risk of leukemia (HR: 1.35; 95% CI: 1.03 to 1.77; I^2: 0.00%). However, a higher versus lower intake of NSSBs was associated with a reduced risk of colorectal cancer, with a moderate quality of evidence (HR: 0.78; 95% CI: 0.62 to 0.99; I^2: 0.00%). A nonsignificant association was found between NSSBs intake and risk of breast cancer (HR: 0.99; 95% CI: 0.90–1.08; I^2: 50.26%; GRADE: moderate), prostate cancer (HR: 1.06; 95% CI: 0.70–1.62; I^2: 55.5%; GRADE: very low), endometrial cancer (HR: 0.82; 95% CI: 0.59–1.15; I^2: 0.00%; GRADE: low), pancreatic cancer (HR: 1.05; 95% CI: 0.89–1.25; I^2: 0.00%; GRADE: high), multiple myeloma (HR: 1.04; 95% CI: 0.66–1.64; I^2: 68.4%; GRADE: very low), and non-Hodgkin lymphoma (HR: 1.05; 95% CI: 0.91–1.22; I^2: 16.4%; GRADE: moderate) (Table 3, Figure S4).

Sensitivity analysis and publication bias

Findings of leave-one-out analyses are shown in Figure S5. The association between NSSBs and the risk of cardiovascular mortality was not robust in the leave-one-out analysis.[40,41] However, the link between NSSBs and risk of all-cause mortality, stroke, T2D, and MetS was robust in the leave-one-out analysis (Figure S5).

Type 2 diabetes was the only outcome with 10 or more prospective cohort comparisons available, for which Egger's tests were significant (Egger's test, $P = .002$) using statistical asymmetry tests (Figure S6).

DISCUSSION

The present umbrella review provides a comprehensive overview and appraisal of the currently available meta-analyses evaluating the associations between NSSBs and multiple health outcomes. We provided meta-analyses of prospective cohort studies and assessed the methodological quality of the included meta-analyses and the quality of evidence for all these associations. Our umbrella review notably included health outcomes that have never been meta-analyzed before, such as MetS and site-specific cancer outcomes, including breast cancer, prostate cancer, endometrial cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia. Our findings showed that higher consumption of NSSBs is associated with increased risk of T2D, stroke, CHD, HTN, MetS, leukemia, and all-cause mortality. However, there was an inverse association between NSSBs consumption and colorectal cancer risk. No association was found between NSSBs and incidence of cardiovascular mortality, cancer mortality, CKD, and site-specific cancers, including breast cancer, prostate cancer, pancreatic cancer, endometrial cancer, non-Hodgkin lymphoma, and multiple myeloma.

Comparison with other studies

This umbrella review supports the findings of the recent comprehensive review by the World Health Organization (WHO) on the health aspects of NSSBs (published in 2023).[42] According to the WHO report, high NSSBs intake was associated with an increased risk of all-cause mortality, stroke, HTN, and T2D. The null associations of NSSBs intake and risk of CKD, cancer

Table 2. Characteristics of the Conducted Meta-analyses and Results of the Recalculation, the Methodological Assessment (AMSTAR-2), and the Assessment of Quality of Evidence (GRADE) by Outcome

Outcome	Study, year (ref)	Primary studies, *n*	Participants/cases, *n*/*n*	Comparison	Hazard ratio (95% CI)	*P*	I^2, %	τ^2	95% PI	Egger's *P*	AMSTAR-2	GRADE
All-cause mortality	Zhang et al, 2021[8]	7	848 473/108 953	Per 355 mL NSSBs/d	1.06 (1.01, 1.10)	.011	87.25	0.00	0.92, 1.21		High	High
Cardiovascular mortality	Zhang et al, 2021[8]	5	673 434/18 620	Per 355 mL NSSBs/d	1.07 (1.00, 1.15)	.051	79.28	0.00	0.84, 1.37		High	High
Cancer mortality	Zhang et al, 2021[8]	4	601 508/31 266	Per 355 mL NSSBs/d	1.01 (0.98, 1.03)	.551	0.00	0.00	0.96, 1.06		High	High
Stroke	Yin et al, 2021[3]	5	213 871/7590	Per 250 mL NSSBs/d	1.09 (1.04, 1.13)	<.001	0.00	0.00	1.02, 1.16		Critically low	High
CHD	Yin et al, 2021[3]	4	215 681/10 561	Per 250 mL NSSBs/d	1.06 (1.02, 1.11)	.005	31.12	0.00	0.92, 1.22		Critically low	High
HTN	Qin et al, 2020[6]	3	289 659/77 334	High vs low	1.14 (1.09, 1.18)	<.001	72.88	0.00	0.71, 1.82		Critically low	Moderate
T2D	Qin et al, 2020[6]	11	383 510/22 503	High vs low	1.16 (1.08, 1.26)	.020	52.30	0.00	0.95, 1.42	.002	Critically low	Low
MetS	Zhang et al, 2021[9]	6	33 184/7183	High vs low	1.32 (1.22, 1.43)	<.001	12.30	0.001	_		Critically low	Moderate
CKD	Lo et al, 2021[5]	2	17 320/1241	High vs low	1.25 (0.51, 3.10)	.627	93.74	0.40	_		Critically low	Low

Abbreviations: AMSTAR, A MeaSurement Tool to Assess systematic Reviews; CHD, coronary heart disease; CKD, chronic kidney disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HTN, hypertension; MetS, metabolic syndrome; PI, prediction interval; ref, reference; T2D, type 2 diabetes; NSSBs, non–sugar-sweetened beverages.

Table 3. Characteristics of the Conducted Meta-analyses and Results of the Recalculation, the Methodological Assessment (AMSTAR-2), and the Assessment of Quality of Evidence (GRADE) by Site-Specific Cancers

Outcome	Study, year (ref)	Primary studies, *n*	Participants/cases, *n*/*n*	Comparison	Hazard ratio (95% CI)	*P*	I^2, %	τ^2	95% PI	AMSTAR-2	GRADE
Breast cancer	Yin et al, 2022[7]	4	314 256/13 304	High vs low	0.99 (0.90, 1.08)	.746	50.26	0.00	0.71, 1.38	Critically low	Moderate
Prostate cancer	Yin et al, 2022[7]	2	138 458/836	High vs low	1.06 (0.70, 1.62)	.785	55.52	0.05	_	Critically low	Very low
Endometrial cancer	Yin et al, 2022[7]	3	58 632/673	High vs low	0.82 (0.59, 1.15)	.250	0.00	0.00	0.09, 7.31	Critically low	Low
Pancreatic cancer	Yin et al, 2022[7]	4	1 103 279/2502	High vs low	1.05 (0.89, 1.25)	.562	0.00	0.00	0.72, 0.53	Critically low	High
Colorectal cancer	Yin et al, 2022[7]	3	232 314/1330	High vs low	0.78 (0.62, 0.99)	.037	0.00	0.00	0.17, 3.54	Critically low	Moderate
Leukemia	Yin et al, 2022[7]	3	599 012/618	High vs low	1.35 (1.03, 1.77)	.030	0.00	0.00	0.23, 7.77	Critically low	Moderate
Multiple myeloma	Yin et al, 2022[7]	4	699 434/756	High vs low	1.04 (0.66, 1.64)	.875	68.39	0.15	0.15, 7.23	Critically low	Very low
Non-Hodgkin lymphoma	Yin et al, 2022[7]	4	699 434/2563	High vs low	1.05 (0.91, 1.22)	.504	16.41	0.00	0.69, 1.60	Critically low	Moderate

Abbreviations: AMSTAR, A MeaSurement Tool to Assess systematic Reviews; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PI, prediction interval; ref, reference.

mortality, and a large number of cancer-specific outcomes found by WHO were also consistent with our findings.[42] A network meta-analysis by Yang et al[43] showed that consuming 1 or more serving of NSSBs per day is associated with a higher risk of stroke and cardiovascular mortality; however, no significant association was observed with CHD risk. In line with our findings, a previous meta-analysis revealed that long-term consumption of NSSBs increased the risk of CVD including stroke and CHD.[44] The results of another meta-analysis found that 1 serving per day of NSSBs was associated with a 25% higher risk of T2D, which was attenuated to 8% after adjustment for adiposity.[45] Findings of 2 meta-analyses indicated a higher risk of MetS and HTN with a higher intake of NSSBs, which is consistent with our observations.[9,44] Previous studies mostly agree with our findings on the risk of mortality. The results of a meta-analysis of prospective cohort studies indicated that each additional serving per day of NSSBs is associated with a 7% increased risk for all-cause mortality.[46] In addition, Zhang et al[8] found a J-shaped association between NSSBs and risk of all-cause and cardiovascular mortality, while no association was found for cancer mortality. The controversies between our findings and those of Zhang et al[8] might arise from 2 points. First, we excluded 1 of the included studies in the mentioned meta-analysis that was performed on patients with stage III colon cancer, as they are not representative of the general population and are at higher risk of mortality.[25] Second, by reviewing the reference lists of other meta-analyses, we found and included another relevant study from the National Health and Nutrition Examination Survey with a relatively high sample size ($n = 31\,402$).[41]

With regard to site-specific cancers, we found a moderate quality of evidence that higher consumption of NSSBs was related to a lower risk of colorectal cancer. By contrast, there was a direct association between NSSBs and leukemia with a moderate quality of the evidence. For cancers at the other sites, we did not observe significant associations, and the quality of the evidence was rated from high to very low. A meta-analysis on the association of NSSBs and overall cancer incidence failed to find a relationship between NSSBs and the risk of overall cancer, whereas in Europe, NSSB consumption might increase cancer incidence.[23] Evidence regarding the association between NSSBs and site-specific cancer risk is limited. For breast cancer incidence, our findings are completely in agreement with the most recent meta-analysis by Ye et al.[47] This study on 5 case-control and cohort studies revealed no significant association between NSSBs and breast cancer. Moreover, the results of the subgroup analysis showed no link between the NSSBs dose and the risk of breast cancer. In addition, Tepler et al[48] in a meta-analysis of 8 case-control and cohort studies showed that the consumption of NSSBs was associated with modestly lower odds of luminal gastrointestinal (GI) tract cancer; however, no association was found for pancreatic cancer, as a non-luminal GI cancer.[48] Moreover, in the meta-analysis of observational studies by Jatho et al,[49] the consumption of NSSBs was not significantly related to the risk of overall GI cancer.

In the present umbrella review, we found that some meta-analyses had some flaws in the selection of eligible primary studies. For example, Qin et al[6] performed a meta-analysis on the association of NSSBs and the risk of obesity based on 5 cohort studies; however, none of these primary studies were eligible to be included in our meta-analysis. For instance, 1 of the cohort studies was performed on women with GDM at enrollment, which is not representative of the general population.[31] Another included study provided the risk of obesity for the substitution analysis of water with NSSBs, but not for NSSBs and risk of obesity.[50] Moreover, the 3 remaining cohort studies investigated the association between NSSBs and the risk of MetS and also presented the HRs per specific components of MetS.[32,36,51] Qin et al[6] considered the HRs provided in these 3 studies for high waist circumference (WC) as the incidence of obesity, which is an erroneous approach, since WC shows abdominal obesity, while the incidence of obesity is defined based on BMI. As explained in the Results section, our meta-analyses of the risk of T2D, MetS, and HTN were corrected for the methodological issues.

In a recent umbrella review published in 2023, Diaz and colleagues[12] summarized findings from systematic reviews and meta-analyses on NSSBs and health outcomes. However, our study has several strengths compared with the previous umbrella review. The present study not only summarized the recently published meta-analyses but also conducted the most updated meta-analyses with primary studies. The study by Diaz et al[12] included prospective cohort and case-control studies, whereas our review was conducted only on prospective cohort studies. Diaz et al[12] searched for systematic reviews published up to May 25, 2022, although they missed a systematic review and meta-analysis (conducted in 2021) on all-cause and cause-specific mortality (cardiovascular and cancer mortality), which had the largest number of primary studies and was selected as a reference study in our umbrella review. In addition, Diaz et al[12] did not correct all of the methodological issues for the meta-analysis on the risk of obesity, as explained in details above.

Possible explanations

Beyond the present findings, associations between the consumption of NSSBs, chronic diseases, and mortality

might be attributed to reverse causality. For example, individuals with obesity, T2D, or HTN might choose NSSBs to reduce their weight or blood pressure.[45] Certain studies suggest that the relationship between weight gain and NSSBs consumption precedes the metabolic dysregulation induced by NSSBs, and individuals with obesity tend to consume a higher quantity of NSSBs to manage their weight.[52] Mechanisms that might explain the association between NSSBs and the risk of chronic diseases are less well identified. There have been several plausible mechanisms explaining the potential role of NSSBs in appetite dysregulation and regulation of hormones.[53,54] Non–sugar-sweetened beverages are generally consumed alone, causing a dissociation between calorie intake and sweet taste. It has been hypothesized that the dissociation of these physiological events may disrupt the neurobehavioral and hormonal pathways regulating satiety and hunger.[53] Moreover, increased NSSBs consumption can enhance sweet preference and appetite, which leads to increased calorie intake.[55] The caramel content of diet beverages produces advanced glycation end-products, which can enhance insulin resistance and act as a proinflammatory factor.[56] In addition, previous evidence showed that the consumption of NSSBs in both mice and humans increases the risk of glucose intolerance; they suggest that these adverse metabolic effects of artificial sweeteners are mediated by modulation of the gut microbiota composition and also its function.[57] It is proposed that artificial sweetener consumption can lead to adverse gut immunologic responses through increasing lipopolysaccharide (LPS) levels.[58] LPS is known as an endotoxin that can enhance intestinal permeability and also stimulate monocyte and macrophage production of inflammatory mediators.[58]

Strengths and limitations

To our knowledge, this is the most comprehensive umbrella review summarizing and evaluating the certainty of evidence on NSSBs consumption and its association with chronic diseases and mortality outcomes. Retrospective cohort, case-control, and cross-sectional studies conducted specifically in patients with chronic diseases, and also studies with unadjusted risk estimates, were excluded. We recalculated risk estimates using a random-effects model to find comparable results across different health outcomes. In addition, we graded the quality of the evidence presented in meta-analyses to make a more realistic judgment about the link between NSSBs and health outcomes.

However, several limitations to this study should be considered. We were not able to study the associations in different subgroups of relevant factors for the incidence of chronic diseases and mortality—for instance, in each gender group or BMI category. Except for 2 primary studies, all of the included prospective cohort studies had been conducted in the United States or Europe; thus, potential regional differences related to NSSBs intake and the risk of chronic diseases and mortality could not be assessed. Of the 17 risk estimates presented in the current umbrella review, 5.9% of the associations ($n = 1$) were found with more than 10 primary prospective cohort studies; therefore, the interpretation of these findings should be made with caution. The quality of the evidence was rated as low or very low for 17.6% ($n = 3$) and 11.7% ($n = 2$) of the associations, respectively. Hence, further high-quality research is needed for outcomes with low- or very-low-quality evidence, including endometrial cancer, multiple myeloma, and prostate cancer. Only 1 prospective cohort study was found for some outcomes, including obesity, liver diseases and ovarian, kidney, liver, and obesity-related cancers. Therefore, further prospective cohort studies are needed to assess the association between NSSBs consumption and these health outcomes. Primary studies included in our analyses used different food-intake assessment methods, including FFQs, food records, and 24-hour dietary recall, which are associated with measurement bias (underestimated or overestimated effect sizes). In addition, despite the inclusion of several high-quality cohort studies with large sample sizes, the inability to rule out residual confounding is known to be an inherent limitation of these observational studies. It is worth mentioning that almost all of the included primary studies evaluated the overall intake of NSSBs and none of them specified the types of the NSSBs, although findings of randomized controlled trials have shown that health effects of different NSSBs may vary.[57,59]

We also evaluated the quality of the evidence using GRADE. The results indicated that the evidence for prostate cancer and multiple myeloma was rated as very low. For T2D, CKD, and endometrial cancer, the evidence was rated as low. The evidence for MetS, HTN, breast cancer, colorectal cancer, leukemia, and non-Hodgkin lymphoma was rated as moderate certainty. Moreover, the certainty of the evidence was high for all-cause mortality, cardiovascular mortality, cancer mortality, stroke, and CHD.

Clinical and public health implications

Currently, there is a lack of consensus among health authorities regarding recommendations for the consumption of NSSBs. For example, the recent guideline released by the WHO advises against using NSSBs for controlling weight and reducing the risk of

cardiometabolic diseases.[42] However, this guideline has faced criticism and calls for re-evaluation.[60,61] Conversely, the advisory paper by the American Heart Association suggests that NSSBs intake could be a viable alternative to reducing sugar consumption for adults with high intake levels and may aid individuals with diabetes in managing blood glucose levels.[1] To gain a clearer understanding of the clinical recommendations regarding NSSBs intake, further research is necessary, particularly focusing on the toxicological assessment and safety of each specific type of NSSBs while noting that the safety of all types of sweeteners is currently under re-evaluation by some safety authorities such as the European Food Safety Authority.[62] This approach will help to have fewer contradictory recommendations by health authorities. For instance, the Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives has reaffirmed the safety of aspartame within the Acceptable Daily Intake of 40 mg/kg body weight.

Future research should also focus on outcomes for which the quality of the evidence was rated low or very low, especially site-specific cancers. It is worth mentioning that, in the current study, the baseline exposure levels of NSSBs intake were considered although multiple dietary assessments can provide more information on NSSBs intake, thereby more robust results on the long-term effect of NSSBs intake can be achieved. Additionally, interactions between NSSBs and dietary factors and the impact of mediating/confounding factors such as BMI, gene variations, geographical regions, ethnicity, and various lifestyles/environments were also missing in the current evidence. Thus, daily consumption of NSSBs should be considered with caution until further sound research is established. To achieve a more accurate assessment of NSSBs intake, future research could focus on measuring the urinary excretion of metabolites such as saccharin, acesulfame-K, sucralose, cyclamate, and steviol glycosides, which can serve as potential biomarkers for these specific NSSBs[63]; however, these novel metabolites need validation and further investigation.

CONCLUSION

While the methodological quality of most meta-analyses was critically low, the quality of evidence was only high for associations for the risk of all-cause, cardiovascular, and cancer mortality, stroke, and CHD. Given the growing increase in NSSBs consumption worldwide,[64] the current study has provided substantial information for developing strategies and recommendations for public health policies. We also recommend future epidemiological research to investigate the association of NSSBs consumption by considering the potential influence of possible reverse causation.

To provide clear insight into the possible mechanisms of the effects of NSSBs and health-related outcomes, more well-designed clinical trials with longer follow-up times focusing on particular types of NSSBs are needed. Furthermore, the sex-specific associations of various NSSBs intakes with health outcomes are still unclear.

Author Contributions

S.B. and H.R.-D. designed the research and conducted the literature search and literature screening. S.B., H.R.-D., J.A.H.V., M.A., and V.A.A. extracted the data. S.B., H.R.-D., and M.A. analyzed the data. S.B. and H.R.-D. wrote the first draft of the paper. All authors interpreted the data, read the manuscript, and approved the final version. O.F. is the guarantor. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. S.B., H.R.-D., A.C., and O.H.F. contributed equally to this work.

Supplementary Material

Supplementary material is available at *Nutrition Reviews* online.

Funding

S.B. received funding for her postdoctoral research studies by the Swiss National Science Foundation (SNSF IZSTZ0_190277). H.R.-D. received funding for his PhD studies by the Swiss National Science Foundation (SNSF IZSTZ0_190277). The funding agency had no role in the study (conceptualization, design, data collection, analysis, and writing).

Conflicts of Interest

None declared.

Data Availability

The list of all included and excluded meta-analyses is presented in the article.

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