Sugar-Sweetened Beverages and Adverse Human Health Outcomes: An Umbrella Review of Meta-Analyses of Observational Studies

Lane, Melissa M; Travica, Nikolaj; Gamage, Elizabeth; Marshall, Skye; Trakman, Gina L; Young, Claire; Teasdale, Scott B; Dissanayaka, Thusharika; Dawson, Samantha L; Orr, Rebecca; Jacka, Felice N; O'Neil, Adrienne; Lawrence, Mark; Baker, Phillip; Rebholz, Casey M; Du, Shutong; Marx, Wolfgang

Published in:
Annual Review of Nutrition

DOI:
10.1146/annurev-nutr-062322-020650

Annual Review of Nutrition

Sugar-Sweetened Beverages and Adverse Human Health Outcomes: An Umbrella Review of Meta-Analyses of Observational Studies

Melissa M. Lane,[1,*] Nikolaj Travica,[1,*] Elizabeth Gamage,[1] Skye Marshall,[2,3,4] Gina L. Trakman,[5] Claire Young,[1] Scott B. Teasdale,[6,7] Thusharika Dissanayaka,[1] Samantha L. Dawson,[1] Rebecca Orr,[1] Felice N. Jacka,[1,8,9] Adrienne O'Neil,[1] Mark Lawrence,[10] Phillip Baker,[11] Casey M. Rebholz,[12,13] Shutong Du,[12,13] and Wolfgang Marx[1]

[1]Institute for Mental and Physical Health and Clinical Translation (IMPACT), Food & Mood Centre, School of Medicine, Deakin University, Barwon Health, Geelong, Victoria, Australia; email: m.lane@deakin.edu.au

[2]Research Institute for Future Health, Gold Coast, Queensland, Australia

[3]Bond University Nutrition and Dietetics Research Group, Faculty of Health Science and Medicine, Bond University, Gold Coast, Queensland, Australia

[4]Centre for Health Services Research, Faculty of Medicine, The University of Queensland, Saint Lucia, Queensland, Australia

[5]Department of Food, Nutrition, and Dietetics, Sport, Performance, and Nutrition Research Group, La Trobe University, Melbourne, Victoria, Australia

[6]Discipline of Psychiatry and Mental Health, School of Clinical Medicine, University of New South Wales, Sydney, New South Wales, Australia

[7]Mindgardens Neuroscience Network, Randwick, New South Wales, Australia

[8]Centre for Adolescent Health, Murdoch Children's Research Institute, Parkville, Victoria, Australia

[9]Department of Immunology, Therapeutics, and Vaccines, James Cook University, Townsville, Queensland, Australia

[10]Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, Victoria, Australia

[11]Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia

[12]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[13]Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, Maryland, USA

Annu. Rev. Nutr. 2024. 44:383–404

The *Annual Review of Nutrition* is online at nutr.annualreviews.org

https://doi.org/10.1146/annurev-nutr-062322-020650

*These authors contributed equally to this article

Keywords

sugar-sweetened beverages, ultraprocessed food, Nova food classification system, noncommunicable disease, umbrella review, meta-analysis

Abstract

Our aim was to conduct an umbrella review of evidence from meta-analyses of observational studies investigating the link between sugar-sweetened beverage consumption and human health outcomes. Using predefined evidence classification criteria, we evaluated evidence from 47 meta-analyses encompassing 22,055,269 individuals. Overall, 79% of these analyses indicated direct associations between greater sugar-sweetened beverage consumption and higher risks of adverse health outcomes. Convincing evidence (class I) supported direct associations between sugar-sweetened beverage consumption and risks of depression, cardiovascular disease, nephrolithiasis, type 2 diabetes mellitus, and higher uric acid concentrations. Highly suggestive evidence (class II) supported associations with risks of nonalcoholic fatty liver disease and dental caries. Out of the remaining 40 meta-analyses, 29 were graded as suggestive or weak in the strength of evidence (classes III and IV), and 11 showed no evidence (class V). These findings inform and provide support for population-based and public health strategies aimed at reducing sugary drink consumption for improved health.

Contents

INTRODUCTION

Sugar-sweetened beverages are characterized as any drink containing added caloric sweeteners, which can include ingredients such as fruit juice concentrates, high-fructose corn syrup, and sucrose (62). These beverages are considered to be ultraprocessed in the Nova food classification system, which aims to categorize consumables based on the extent and purpose of industrial processing (71). Ultraprocessed foods, which include beverages and belong to group four in the Nova system, are defined as industrial formulations made from food extracts, derivatives, or synthesized

compounds, typically lacking whole-food components (71). In many high-income countries, the consumption of sugar-sweetened beverages is approaching or has already surpassed the recommended limit that is set at less than 10% of total daily energy intake from added sugar (97) or free sugar (107). Free sugar is defined as added sugar plus the natural sugars present in fruit juices, honey, and syrup (84). Consumption of sugar-sweetened beverages is also on the rise in many low- and middle-income countries (3, 65). Notably, per capita sales of these beverages are among the highest in the world in countries such as Argentina and Mexico (101). At the national level in the United States, individuals who are younger, male, of Hispanic and non-Hispanic Black decent, current smokers, residents of nonmetropolitan counties, and employed and those with less than a high school education, a high body mass index, and no physical activity tend to exhibit higher intake of sugar-sweetened beverages compared with other sociodemographic groups and behavioral and health-related characteristics (58, 84).

Many individual studies, along with several subsequent meta-analyses, have consistently shown direct associations between sugar-sweetened beverage consumption and adverse health outcomes related to chronic noncommunicable diseases. These outcomes include higher risks of cancers (56), cardiometabolic diseases (111), and depression (37), as well as all-cause and cause-specific mortality (79). One recent umbrella review of meta-analyses emphasized that overall dietary consumption of sugar can be considered detrimental, particularly in terms of cardiometabolic outcomes (38). While examining nutrient intakes such as sugar provides valuable insights, it is essential to prioritize research efforts on major food sources and widely consumed items, such as sugar-sweetened beverages. This approach allows for a more comprehensive assessment of dietary associations with health outcomes. Such an endeavor holds the potential to better inform population-based strategies and public health policies, particularly in the context of improving overall dietary quality. Our aim was to conduct an umbrella review to evaluate the evidence from meta-analyses of observational studies assessing the associations between sugar-sweetened beverage consumption and human health outcomes.

METHODS

Our systematic umbrella review of meta-analyses was conducted and reported in line with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (78).

Literature Search and Selection Criteria

Meta-analyses of data extracted from original research articles using observational designs (e.g., cross-sectional, prospective, and case-control) that examined the association between sugar-sweetened beverage intake and adverse health outcomes were eligible. There were no restrictions on population type or age group. All and any detrimental health outcomes were eligible for inclusion, including chronic physical diseases (e.g., cardiovascular disease), mental disorders (e.g., depression), intermediate risk factors (e.g., hypertension), and mortality (e.g., all-cause).

Three authors (W.M., N.T., and E.G.) independently searched MEDLINE (via PubMed), Epistemonikos, and EMBASE from database inception to January 2023. Key search terms pertaining to sugar-sweetened beverage consumption and the study design of meta-analyses are outlined in the **Supplemental Material**. Two authors (E.G. and W.M.) used the Covidence systematic review software (**https://www.covidence.org**) to undertake independent screening, first based on the title and abstract, and then by examining the full text. Any discrepancies between authors over study eligibility were resolved by consensus. To limit biases caused by the nonidentification of studies (33), and in line with methods used in prior umbrella reviews (67, 102), the most recently updated and/or largest meta-analysis was included where two or more meta-analyses were

Supplemental Material >

available for the same disease outcome. Where meta-analyses modeled the sugar-sweetened beverage consumption continuously (e.g., dose-response) and categorically (e.g., high versus low intake), both pooled analyses were included.

Data Extraction

For the description of review characteristics and evidence synthesis, data from the included meta-analyses (e.g., study design, sample size, outcome types, and effect sizes) were extracted in duplicate using a purpose-designed spreadsheet. In the case of missing information in the meta-analyses, data were retrieved from the original research articles cited by the meta-analyses and/or data reported upon request from the studies' corresponding author(s). When discrepancies arose between the data presented in the original research article and the meta-analysis included in our review, we gave priority to extracting data from the original research article. In cases where a meta-analysis did not provide enough information, such as individual study effect sizes or missing citations necessary for reanalysis, we excluded that particular analysis from our review.

Data Analysis

The characteristics of included meta-analyses were summarized by the approximate number of risk factors, total number of participants, number of cases, and their design. A random effect meta-analysis model was used to reanalyze all extracted effect sizes for each outcome, including risk ratios (RRs), hazard ratios (HRs), odds ratios (ORs), and standardized mean differences or weighted mean differences (WMDs), with 95% confidence intervals (CIs) (33). Additionally, the 95% prediction intervals were calculated for all random effect sizes, which provide the possible range in which the effect sizes of additional future studies are expected to fall (36). In the context of an umbrella review, when 95% prediction intervals do not include the null, it indicates that the range of effect sizes being considered is statistically significant (36). Statistical heterogeneity between studies was evaluated using the I^2 statistic, with a value $\geq$50% indicative of high heterogeneity and values $\geq$75% suggestive of very high heterogeneity. We used Egger's regression asymmetry test to assess whether there was evidence for small-study effects (i.e., whether smaller studies tended to give substantially larger estimates of effect size compared with larger studies) (21). A test for excess significance for all outcomes was conducted (40), which evaluated whether the number of studies with nominally significant results (i.e., $P < 0.05$) within an included meta-analysis exceeded what would be expected based on the statistical power of the meta-analysis. Data analyses were conducted using the online version of the R statistical package metaumbrella (**https://metaumbrella.org**) (33). The terms direct and inverse were used to describe the direction of associations between sugar-sweetened beverage consumption and adverse health outcomes, with direct indicating a higher risk and inverse indicating a lower risk. These terms were chosen to avoid ambiguity compared with so-called positive or negative associations.

Evidence Grading

In agreement with the approach taken in previous umbrella reviews, and for the purpose of consistency and comparison (67, 103), each pooled result within this umbrella review was categorized using evidence classification criteria (39). These categories include convincing, highly suggestive, suggestive, weak, or no evidence, as outlined in **Table 1** (39).

Quality Assessment

The quality of all eligible meta-analyses was assessed using the second edition of the AMSTAR 2 (a measurement tool to assess systematic reviews) quality assessment tool (88). This tool provided

Table 1 Evidence classification criteria

Class	Description
Convincing (class I)	The number of cases is >1,000 (or >20,000 for continuous outcomes), statistically significant using a P of $<1 \times 10^{-6}$, $I^2 < 50\%$, 95% prediction interval excludes the null hypothesis, no small-study effects, and no excess significance bias
Highly suggestive (class II)	The number of cases is >1,000, statistically significant using a P value of $<1 \times 10^{-6}$, the largest included individual study has a statistically significant effect ($P \leq 0.05$), and other class I criteria not met
Suggestive (class III)	The number of cases is >1,000, P of $<1 \times 10^{-3}$, and class I–II criteria not met
Weak (class IV)	Statistically significant ($P \leq 0.05$) and class I–III criteria not met
No evidence (class V)	No statistical significance ($P > 0.05$)

a broad assessment of quality across critical domains that may have affected the validity of a review. These domains included the adequacy of the literature search, justification for excluding individual studies, risk of bias from individual studies being included in the review, appropriateness of meta-analytical methods, and consideration of the risk of bias when interpreting the results of the review (88). A qualitative appraisal was applied, with consideration of the potential impact of an inadequate rating for each item given, particularly the critical domains shown in **Supplemental Table 1** (88).

Supplemental Material >

RESULTS

After removing duplicates, the systematic search yielded 534 unique and nonrepeated studies (**Figure 1**). After applying the eligibility criteria, 25 studies (1, 2, 4, 7, 12, 19, 20, 25, 26, 37, 43, 49, 51, 52, 56, 57, 63, 69, 73, 76, 79, 85, 99, 109, 112) with 47 distinct meta-analyses of an outcome were included.

Study Characteristics

All but one of the included studies (63) were published within the past 5 years. The average number of individual original research articles included in each distinct meta-analysis was 8 and ranged from 3 (85) to 26 (49). The total number of children and adult participants included across the 47 distinct meta-analyses was 22,055,269 and ranged between 7,676 (26) and 9,574,173 (49). The average number of cases (i.e., individuals who developed an outcome of interest) was 17,729 and ranged from 1,090 (26) to 138,641 (79). Close to half of the meta-analyses included prospective designs ($n = 21$), with the remaining meta-analyses including a mix of study designs ($n = 15$) or cross-sectional designs ($n = 11$). **Table 2** shows the range of adverse health parameters reviewed across seven key outcome domains, such as mortality and cancer, as well as cardiometabolic, mental/cognitive, dental, respiratory, and gastrointestinal health.

Sugar-sweetened beverage consumption was modeled in a dose-response manner in 10 meta-analyses, each focusing on different health outcomes. These dose-response meta-analyses related to the associations between an increase of 250 mL per day and all-cause mortality (79), cancer mortality (79), obesity (85), and stroke (7). Additionally, these dose-response meta-analyses related to the associations between an increase in daily servings and body mass index (63), body mass index one-year change in children (63), cardiovascular disease (69), coronary heart disease (109), type 2 diabetes mellitus (69), and weight gain in adults (63).

Most outcomes ($n = 38$) across the 47 distinct meta-analyses were modeled categorically and compared the highest versus lowest sugar-sweetened beverage consumption categories (e.g.,

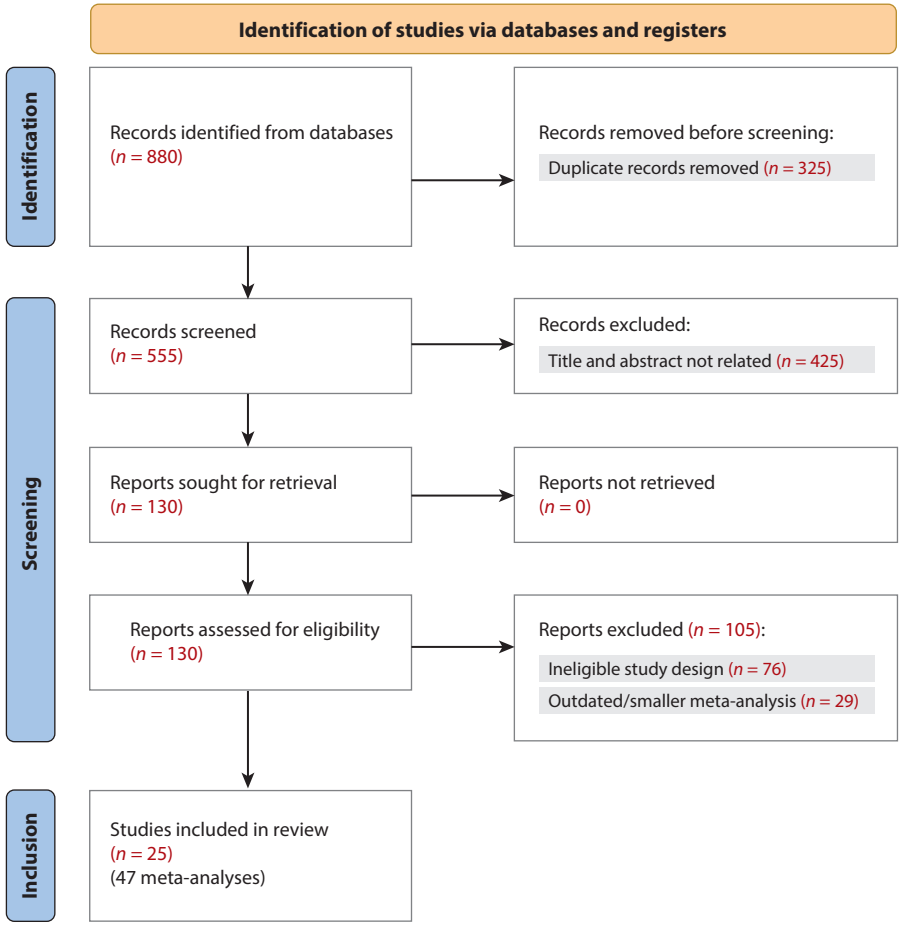

Figure 1

PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines flowchart.

tertiles, quartiles). Nine outcomes were modeled continuously, with the following six in children: body mass index (63), one-year change in body mass index (63), high- and low-density lipoprotein cholesterol (76), total cholesterol (76), and triglyceride concentrations (76). In adults, bone density (1), uric acid concentrations (20), and weight change (63) were modeled continuously.

Overall, and after applying a random effects model, 37 (79%) of the 47 distinct meta-analyses reported statistically significant associations between greater sugar-sweetened beverage consumption and higher risks of adverse health outcomes at $P \leq 0.05$. Additionally, seven of these associations remained statistically significant at a more stringent significance level ($P < 1 \times 10^{-6}$). This was observed for outcomes such as depression (37), dental caries (99), cardiovascular disease (69), nephrolithiasis (51), nonalcoholic fatty liver disease (12), type 2 diabetes mellitus (69), and uric acid concentrations (20).

In 26 (55%) meta-analyses, the largest included study (i.e., with the highest number of participants) was statistically significant (as per $P \leq 0.05$). This included associations of greater sugar-sweetened beverage consumption with higher risks of all-cause mortality (dose-response and high versus low) (79), overall cancer (49), coronary heart disease (dose-response and high

Table 2 Summary of associations between sugar-sweetened beverage consumption and adverse health outcomes

Outcome	Level of exposure comparison (study design)	Studies (*n*)	Participants (*n*)	Cases (*n*)	Effect size metric	Effect size (95% CIs)	*P* value	Largest study significance	Small-study effect	Excess significance bias	I^2	Evidence class
Mortality outcomes												
All-cause mortality (79)	Dose-response, prospective	11	1,088,542	94,962	HR	1.042 (1.019, 1.065)	<0.001	Significant	Not significant	Not significant	88	III
All-cause mortality (79)	High versus low, prospective	12	1,442,293	138,641	HR	1.113 (1.046, 1.185)	0.001	Significant	Significant	Not significant	83	III
Cancer mortality (79)	Dose-response, prospective	6	797,349	28,895	HR	1.022 (0.992, 1.052)	0.148	Not significant	Not significant	Not significant	63	V
Cancer mortality (79)	High versus low, prospective	8	1,154,258	35,465	HR	1.043 (0.974, 1.117)	0.224	Not significant	Not significant	Not significant	40	V
Cardiovascular disease mortality (112)	Dose-response, prospective	13	898,005	24,365	HR	1.082 (1.047, 1.119)	<0.001	Not significant	Not significant	Not significant	5	III
Cancer outcomes												
Overall cancer (49)	High versus low, prospective	26	9,574,173	31,402	RR	1.08 (1.012, 1.153)	0.02	Significant	Not significant	Not significant	59	IV
Breast cancer (56)	High versus low, mixed	7	147,891	4,870	RR	1.132 (0.999, 1.282)	0.052	Not significant	Not significant	Not significant	0	V
Colorectal cancer (56)	High versus low, prospective	4	218,787	2,607	RR	1.192 (1.021, 1.392)	0.027	Not significant	Significant	Not significant	0	IV
Pancreatic cancer (56)	High versus low, mixed	6	1,269,895	4,000	RR	1.008 (0.883, 1.152)	0.901	Not significant	Not significant	Not significant	0	V
Prostate cancer (56)	High versus low, mixed	5	170,882	3,694	RR	1.181 (1.068, 1.306)	0.001	Not significant	Not significant	Not significant	0	IV
Cardiometabolic outcomes												
Body mass index (children) (63)	Dose-response, prospective	20	25,724	NA	WMD	0.066 (0.009, 0.123)	0.023	Not significant	Significant	Not significant	90	III
Body mass index—one-year change (children) (63)	Dose-response, prospective	11	15,928	NA	WMD	0.06 (0.017, 0.103)	0.006	Not significant	Not significant	Not significant	62	IV
Bone density (1)	High versus low, cross-sectional	10	7,861	NA	WMD	−0.652 (−0.998, −0.306)	<0.001	Not significant	Significant	Significant	91	IV
Cardiovascular disease (69)	Dose-response, prospective	11	430,526	26,225	RR	1.093 (1.052, 1.135)	<0.001	Not significant	Not significant	Not significant	42	III

(*Continued*)

Table 2 (*Continued*)

Outcome	Level of exposure comparison (study design)	Studies (*n*)	Participants (*n*)	Cases (*n*)	Effect size metric	Effect size (95% CIs)	*P* value	Largest study significance	Small-study effect	Excess significance bias	I^2	Evidence class
Cardiometabolic outcomes												
Cardiovascular disease (69)	High versus low, prospective	14	560,870	30,676	RR	1.163 (1.1, 1.23)	<0.001	Significant	Not significant	Not significant	14	I
Chronic kidney disease (57)	High versus low, mixed	6	25,455	5,143	RR	1.304 (0.879, 1.935)	<0.001	Not significant	Not significant	Significant	83	V
Coronary heart disease (109)	Dose-response, prospective	4	173,753	7,407	RR	1.152 (1.086, 1.221)	<0.001	Significant	Not significant	Not significant	0	III
Coronary heart disease (109)	High versus low, prospective	4	173,753	7,407	RR	1.187 (1.084, 1.299)	<0.001	Significant	Not significant	Not significant	0	III
Gout (19)	High versus low, prospective	3	141,091	4,821	RR	1.349 (1.176, 1.548)	<0.001	Significant	Not significant	Not significant	38	III
Hyperuricemia (19)	High versus low, cross-sectional	6	32,380	10,104	RR	1.348 (1.193, 1.523)	<0.001	Significant	Not significant	Significant	42	III
Hypertension (children) (25)	High versus low, cross-sectional	5	71,632	5,528.113	OR	1.364 (1.144, 1.625)	0.001	Not significant	Not significant	Not significant	0	III
High-density lipoprotein cholesterol (children) (76)	High versus low, cross-sectional	14	26,846	NA	WMD	−1.413 (−2.234, −0.591)	0.001	Significant	Not significant	Not significant	97	III
Low-density lipoprotein cholesterol (children) (76)	High versus low, cross-sectional	9	17,178	NA	WMD	1.215 (0.223, 2.208)	0.016	Not significant	Not significant	Not significant	97	IV
Metabolic syndrome (73)	High versus low, prospective	7	32,528	10,798	RR	1.205 (1.059, 1.372)	0.005	Significant	Significant	Significant	68	IV
Nonalcoholic fatty liver disease (12)	High versus low, mixed	12	35,300	3,625.13	RR	1.477 (1.29, 1.691)	<0.001	Significant	Not significant	Significant	42	II
Nephrolithiasis (51)	High versus low, mixed	5	219,759	7,018	RR	1.379 (1.258, 1.512)	<0.001	Significant	Not significant	Not significant	36	I
Obesity (85)	High versus low, prospective	3	25,774	7,867	RR	1.20 (1.008, 1.429)	0.040	Significant	Not significant	Significant	23	IV
Obesity (85)	Dose-response, prospective	3	25,774	7,867	RR	1.052 (0.999, 1.107)	0.08	Significant	Not significant	Significant	27	V
Stroke (7)	Dose-response, prospective	6	238,264	10,011	RR	1.068 (1.022, 1.115)	0.003	Not significant	Not significant	Not significant	0	IV

(*Continued*)

Table 2 (*Continued*)

Outcome	Level of exposure comparison (study design)	Studies (*n*)	Participants (*n*)	Cases (*n*)	Effect size metric	Effect size (95% CIs)	*P* value	Largest study significance	Small-study effect	Excess significance bias	I^2	Evidence class
Cardiometabolic outcomes												
Stroke (7)	High versus low, prospective	7	264,709	11,187	RR	1.088 (1.006, 1.176)	0.034	Not significant	Not significant	Not significant	1	IV
Total cholesterol (children) (76)	High versus low, cross-sectional	7	18,413	NA	WMD	−2.49 (−2.887, −2.095)	<0.001	Significant	Not significant	Not significant	74	IV
Triglycerides (children) (76)	High versus low, cross-sectional	13	17,514	NA	WMD	5.286 (−0.351, 10.922)	0.066	Significant	Not significant	Not significant	99	IV
Type 2 diabetes (69)	Dose-response, prospective	16	445,040	15,778	RR	1.271 (1.146, 1.408)	<0.001	Significant	Not significant	Not significant	81	III
Type 2 diabetes (69)	High versus low, prospective	20	645,658	30,904	RR	1.291 (1.216, 1.369)	<0.001	Significant	Not significant	Not significant	30	I
Uric acid (20)	High versus low, cross-sectional	6	26,260	NA	WMD	0.176 (0.106, 0.246)	<0.001	Significant	Not significant	Not significant	0	I
Waist circumference (4)	High versus low, prospective	10	32,999	10,784	RR	1.148 (0.869, 1.516)	0.331	Significant	Not significant	Not significant	90	V
Weight change (63)	Dose-response, prospective	8	170,141	NA	WMD	0.213 (0.089, 0.337)	0.001	Significant	Significant	Significant	70	III
Mental and cognitive outcomes												
Attention-deficit/ hyperactivity disorder (26)	High versus low, mixed	5	7,676	675	OR	1.821 (0.974, 3.405)	0.061	Not significant	Not significant	Significant	54	V
Cognition (52)	High versus low, mixed	18	263,296	15,905	OR	1.165 (1.052, 1.29)	0.003	Not significant	Not significant	Significant	90	IV
Depression (37)	High versus low, mixed	10	620,411	37,131	RR	1.31 (1.212, 1.416)	<0.001	Significant	Not significant	Not significant	29	I
Dental outcomes												
Dental caries (99)	High versus low, cross-sectional	8	13,499	5,574.83	OR	1.948 (1.573, 2.412)	<0.001	Significant	Not significant	Not significant	59	II
Dental erosion (99)	High versus low, cross-sectional	10	13,330	4,845.28	OR	2.902 (1.317, 6.395)	0.008	Significant	Not significant	Not significant	97	IV

(*Continued*)

Table 2 (*Continued*)

Outcome	Level of exposure comparison (study design)	Studies (*n*)	Participants (*n*)	Cases (*n*)	Effect size metric	Effect size (95% CIs)	*P* value	Largest study significance	Small-study effect	Excess significance bias	I^2	Evidence class
Respiratory outcomes												
Asthma (adults) (2)	High versus low, cross-sectional	6	167,688	15,817	OR	1.359 (1.115, 1.656)	0.002	Significant	Not significant	Not significant	60	IV
Asthma (children) (2)	High versus low, mixed	6	48,225	6,088	OR	1.261 (1.073, 1.482)	0.005	Significant	Not significant	Significant	66	IV
Gastrointestinal outcomes												
Crohn's disease (43)	High versus low, mixed	5	86,483	1,987	RR	1.221 (0.904, 1.649)	0.193	Not significant	Not significant	Not significant	75	V
Ulcerative colitis (43)	High versus low, mixed	4	85,728	1,622	RR	1.013 (0.929, 1.106)	0.764	Not significant	Not significant	Not significant	9	V
Inflammatory bowel disease (43)	High versus low, mixed	4	85,728	1,622	RR	1.024 (0.941, 1.115)	0.579	Not significant	Not significant	Not significant	98	V

Abbreviations: CI, confidence interval; HR, hazard ratio; I^2, I-squared statistic; *n*, number; NA, not applicable; OR, odds ratio; *P* value, probability value; RR, risk ratio; WMD, weighted mean difference.

Evidence class criteria—class I: statistical significance at $P < 10^{-6}$, >1,000 cases (or >20,000 participants for continuous outcomes), the 95% prediction interval excluded the null, no large heterogeneity ($I^2 < 50\%$), no evidence of small-study effects, excess significance bias; class II: significance at $P < 10^{-6}$, >1,000 cases (or >20,000 participants for continuous outcomes), the largest component study reported a significant effect ($P < 0.05$); class III: statistical significance at $P < 10^{-3}$, >1,000 cases (or >20,000 participants for continuous outcomes); class IV: remaining significant associations at $P < 0.05$.

versus low) (109), gout (19), hyperuricemia (19), high-density lipoprotein cholesterol (children) (76), metabolic syndrome (73), nonalcoholic fatty liver disease (12), nephrolithiasis (51), obesity (dose-response and high versus low) (85), total cholesterol (children) (76), triglycerides (children) (76), type 2 diabetes mellitus (dose-response and high versus low) (69), uric acid (20), waist circumference (4), weight change (63), depression (37), dental caries (99), dental erosion (99), asthma (adults and children) (2), and inflammatory bowel disease (43).

In seven (15%) meta-analyses, we observed small-study effects, which refer to the evidence from smaller studies showing different, often larger, effect estimates compared with larger studies within the same meta-analysis (92). This small-study effect was found for associations of greater sugar-sweetened beverage consumption with higher risks of dental erosion (99), all-cause mortality (79), metabolic syndrome (73), type 2 diabetes mellitus (dose-response) (69), body mass index one-year change in children (63), weight change in adults (63), and bone density (1). Heterogeneity was generally high with approximately half of the meta-analyses (23, 49%) displaying an I^2 value $\geq$ 50%. For 15 outcomes, the 95% prediction intervals excluded the null value. These outcomes included cardiovascular disease mortality (112), coronary heart disease (109), cardiovascular disease (69), dental carries (99), depression (37), hypertension in children (25), nephrolithiasis (51), overall cancer (105), prostate cancer (56), gout (19), nonalcoholic fatty liver disease (12), stroke (dose-response) (7), type 2 diabetes mellitus (69), uric acid concentrations (20), and total cholesterol in children (76). This suggests that in future studies exploring these associations, there is a greater chance of identifying a statistically significant range of effect estimates.

Evidence Grading

When the credibility assessment criteria were applied, convincing evidence (class I) was found for direct associations of greater sugar-sweetened consumption with higher risks of depression (RR: 1.31, 95% CIs: 1.21, 1.42) (37) and several cardiometabolic parameters, including cardiovascular disease (RR: 1.16, 95% CIs: 1.10, 1.23) (69), nephrolithiasis (RR: 1.38, 95% CIs: 1.26, 1.51) (51), type 2 diabetes mellitus (RR: 1.29, 95% CIs: 1.22, 1.37) (69), and higher uric acid concentrations (WMD: 0.176, 95% CIs: 0.11, 0.25) (20). Highly suggestive (class II) evidence supported direct associations between greater sugar-sweetened beverage consumption and higher risks of nonalcoholic fatty liver disease (RR: 1.48, 95% CIs: 1.29, 1.69) (12) and dental carries (OR: 1.95, 95% CIs: 1.57, 2.41) (99).

Suggestive evidence (class III) was shown for associations of greater sugar-sweetened beverage consumption with higher risks of mortality outcomes [i.e., all-cause mortality (dose-response HR: 1.04, 95% CIs: 1.02, 1.07 and high versus low HR: 1.11, 95% CIs: 1.05, 1.19) (79) and cardiovascular disease mortality (dose-response HR: 1.08, 95% CIs: 1.05, 1.12) (112)]. Suggestive evidence (class III) was also demonstrated for a number of cardiometabolic outcomes [i.e., body mass index in children (dose-response WMD: 0.07, 95% CIs: 0.01, 0.12) (63), cardiovascular disease (dose-response RR: 1.09, 95% CIs: 1.05, 1.14) (69), coronary heart disease (dose-response RR: 1.15, 95% CIs: 1.09, 1.22 and high versus low RR: 1.19, 95% CIs: 1.08, 1.30) (109), gout (RR: 1.35, 95% CIs: 1.18, 1.66) (19), hyperuricemia (RR: 1.35, 95% CIs: 1.19, 1.52) (19), hypertension in children (OR: 1.36, 95% CIs: 1.14, 1.63) (25), high-density lipoprotein cholesterol in children (WMD: −1.41, 95% CIs: −2.23, −0.59) (76), type 2 diabetes mellitus (dose-response OR: 1.63, 95% CIs: 1.24, 2.14) (69), and weight change in adults (dose-response WMD: 0.21, 95% CIs: 0.09, 0.34) (63)].

More than half (27; 57%) of the 47 meta-analyses revealed weak evidence (class IV) or no evidence (class V), including for the associations of sugar-sweetened beverage consumption with higher risks of some cancers [cancer mortality (79), breast cancer (56), and pancreatic cancer (56)];

cardiometabolic outcomes [chronic kidney disease (57), metabolic syndrome (73), obesity (85), stroke (7), triglycerides (76), and low-density lipoprotein (76) and total cholesterol in children (76)]; mental and cognitive outcomes [attention-deficit/hyperactivity disorder (26) and cognition (52)]; gastrointestinal outcomes [Crohn's disease (43), ulcerative colitis (43), and inflammatory bowel disease (43)]; as well as dental erosion (99) and asthma (2). This was most notable in terms of $P > 0.05$ for some outcomes such as cancer [cancer mortality (79) and pancreatic cancer (56)] and gastrointestinal outcomes [Crohn's disease (43), ulcerative colitis (43), and inflammatory bowel disease (43)].

Quality Assessment

Supplemental Material >

Using the AMSTAR 2 tool, the overall quality of the results of most meta-analyses was considered low based largely on the inadequate provision of details pertaining to the justification for excluding individual studies, AMSTAR critical item 7 (**Supplemental Table 1**) (88). This item, which requires authors to present a list of potentially relevant studies with justifications for their exclusion, is essential to prevent the introduction of bias into the review findings. The lack of detailed justifications for exclusions increases the risk of incomplete or skewed assessments (see the supplementary appendix 1: AMSTAR 2 guidance document in 88).

DISCUSSION

This umbrella review provides a high-level overview and evaluates the observational evidence investigating associations between greater sugar-sweetened beverage consumption and the risks of adverse health outcomes. Twenty-five studies comprising 47 discrete meta-analyses and a total population of 22,055,269 participants were included. These meta-analyses covered seven outcome domains related to mortality and cancer, as well as cardiometabolic, mental/cognitive, dental, respiratory, and gastrointestinal health. On average, greater sugar-sweetened beverage consumption was linked to poorer health outcomes (79%), in contrast with lower consumption levels. Of the 10 outcomes for which dose-response data were available, every 250-mL increase in daily sugar-sweetened beverage intake was associated with higher risks of all-cause mortality (79), cancer mortality (79), and stroke (7). In children, every serving increase in daily sugar-sweetened beverages was associated with higher body mass index (63) and one-year changes in body mass index (63). Additionally, in adults, every daily serving increase was associated with higher risks of coronary heart disease (109), cardiovascular disease (69), type 2 diabetes mellitus (69), and greater weight gain (63). Although the overall strength and quality of evidence varied across outcomes, our findings related to changes in body weight are in line with the only meta-analysis of randomized controlled trials (68), which demonstrated dose-dependent increases in weight upon the addition of sugar-sweetened beverages to individuals' diets.

Although most meta-analyses included in our review demonstrated direct associations between greater sugar-sweetened beverage consumption and higher risks of adverse health outcomes (as per the commonly used inference criterion of $P \leq 0.05$), less than a fifth (15%) were graded as convincing (class I) or highly suggestive (class II) evidence. These meta-analyses encompassed a range of effect sizes, from a 29% higher risk for type 2 diabetes mellitus (69) to a considerable 95% higher risk for dental caries (99) when comparing higher sugar-sweetened beverage consumption to lower consumption. The majority of associations (83%) were thus considered as suggestive evidence (class III) or lower. This can largely be attributed to two factors: (*a*) a notable level of statistical heterogeneity (49%, with $I^2 \geq 50\%$), and (*b*) a *P* value greater than 10^{-6} (81%).

The notable level of between-study variance or heterogeneity observed in the current review may have been due to the proportion of meta-analyses that included mixed study designs (15/47,

32%) (104). Compared with prospective study designs, cross-sectional and case-control studies may observe larger effect estimates (67). Indeed, close to half (6/15, 40%) of these mixed study design meta-analyses reported 95% CIs that included the null value such as for breast cancer (56), pancreatic cancer (56), chronic kidney disease (57), Crohn's disease (43), ulcerative colitis (43), and inflammatory bowel disease (43). This suggests heterogeneity of variance in the data around the point estimate (106). The proximity of the lower-bound CIs for these mixed study design meta-analyses was relatively close to the composite null hypothesis of 1.0 (range: 0.73 to 0.99), with the upper-bound CIs showing a possible higher risk of up to three times (range: 1.10 to 2.7). This indicates that based on the available data, there is some uncertainty in the estimated effect sizes, but it does not necessarily indicate that there is no evidence of an association (106). In addition, only 45% of the meta-analyses included in our review pooled results exclusively from prospective cohort studies. Approximately 23% of meta-analyses pooled estimates from cross-sectional studies, encompassing a range of outcomes such as asthma (2), dental caries (99), dental erosion (99), biochemical metabolic outcomes (19, 20, 76), hypertension (25), and bone density (1). It is important to note that while causation cannot be established from any observational data, cross-sectional meta-analyses are more liable to issues that limit causal inferences such as reverse causation and incidence-prevalence bias (i.e., the inclusion of prevalent cases in a study) (41). To address these existing limitations, and given the constraints of randomized controlled trials in nutritional research for evaluating the effects of products that are considered to be potentially harmful to health, including unattainable (and unethical) hard disease end points (e.g., incident cancer and cardiovascular disease), more well-designed prospective cohort studies are needed.

Potential Mechanisms

Any risk of adverse cardiometabolic outcomes associated with greater consumption of sugar-sweetened beverage intakes may occur via a range of mechanisms, for example, the metabolic effects of glucose and other intermediate risk factors that are induced by the liver's metabolism of glucose to fructose (44). The overconsumption of fructose has been implicated in the development of gout and nonalcoholic fatty liver disease through hepatic de novo lipogenesis and uric acid production (61). That is, higher hepatic uric acid production or hyperuricemia typically precipitates gout (13, 14), and both hyperuricemia and gout have been associated with cardiovascular disease, hypertension, and type 2 diabetes mellitus (75, 82). Higher risk for cardiometabolic outcomes may also ensue through the typically moderate-to-high glycemic load of sugar-sweetened beverages (5). Limited evidence exists for an association between high-glycemic-index consumables and weight-related outcomes (30). However, there appears to be evidence for associations with the development of type 2 diabetes mellitus (10, 55) and coronary heart disease (54), as well as elevations in related intermediates including insulin resistance and circulatory concentrations of inflammatory cytokines such as high-sensitivity C-reactive protein (53). In addition, habitual dietary intake of ultraprocessed, high-glycemic-load consumables such as sugar-sweetened beverages has been implicated in the development of some cancers (e.g., colorectal and endometrial) through the induction of insulin-like growth factor axis and hyperinsulinemia (32).

The alterations to the food matrix structure in ultraprocessed formulations offer a plausible, novel explanation for the associations of sugar-sweetened beverage consumption with adverse health outcomes (72). For example, fructose, which is abundant in ultraprocessed sugar-sweetened beverages in some regions, is more bioavailable and metabolized differently than the fructose found in whole foods, such as fruits and dairy products, due to changes in the food matrix structure (24). Indeed, another recent meta-analysis that focused on major dietary sources of fructose, including sugar-sweetened beverages, but that was limited to cardiovascular outcomes, supports this notion (93). It found that the direct associations observed between greater intakes of sugary

drinks and higher risks of cardiovascular diseases, coronary heart disease, and stroke morbidity and mortality did not extend to other dietary sources of fructose, such as fruits, breakfast cereals, and yogurt (93). The authors of that review concluded that the food matrix appeared to alter the relationship between fructose intake and cardiovascular outcomes (93).

Furthermore, weight gain may also partly explain the observed associations of sugar-sweetened beverage consumption with adverse cardiometabolic and mental disorder outcomes. Mendelian randomization studies support high body mass index or adiposity as being causally related to adverse cardiometabolic and mental health outcomes (9, 11, 16, 23, 35, 59, 77, 90, 96, 100, 108). Several behavioral and biological pathways are implicated in the possible adiposity-mediated association between sugar-sweetened beverage consumption and adverse cardiometabolic and mental health. These pathways include the notion that liquid calories sourced from sugar-sweetened beverages may be unsatiating compared with calories obtained from solid food (61). In this instance, energy imbalance might disrupt the satiety mechanisms and absolute intake of calories from foods consumed in subsequent meals [otherwise known as an incomplete compensatory reduction in calorie intake (64)]. Moreover, rapid absorption of glucose from sugar-sweetened beverage consumption and subsequent induction of hyperinsulinemia (5, 94), as well as stimulation of the brain's dopaminergic reward system, may foster overconsumption (6, 18).

Limitations and Strengths

An essential limitation of our umbrella review is its reliance on meta-analyses as the primary source of evidence. While recent individual studies have consistently reported associations between higher sugar-sweetened beverage consumption and higher risks of outcomes such as obesity (110) and dental caries (34), it is worth noting that these studies might not have been incorporated into meta-analyses at this stage, potentially restricting the comprehensiveness of our analysis. Another limitation of this umbrella review is its focus on sugar-sweetened beverages as a single food-and-beverage category in the absence of participants' dietary patterns. People typically consume food combinations rather than isolated or individual items, and foods comprise many components (nonnutritive and nutritive) that are likely to have synergistic effects (87). Thus, focusing only on sugar-sweetened beverages does not account for the composite interactions between consumables and broader dietary patterns (98). However, direct associations have recently been reported between so-called "unhealthy" behavioral patterns including higher intakes of ultraprocessed foods, as a broad food category, and higher odds of sugar-sweetened beverage consumption (83). Although sugar-sweetened beverage consumption appears to be independently associated with adverse physical and mental health, such consumption is likely indicative of a high overall proportion of ultraprocessed food intake. In high-income regions, more than 50% of total energy intake consists of ultraprocessed foods (86), and higher versus lower consumption patterns of these foods are associated with many of the health outcomes included in our review (22, 45–47).

Our review's focus on sugar-sweetened beverages is important and timely. Sugar-sweetened beverages have been estimated to be one of the most commonly consumed subgroups of the broad category of ultraprocessed foods in nationally representative samples from high-income countries (60, 66). In children, adolescents, and adults, two recent studies found that sugar-sweetened beverages were the only category to consistently be a top contributor to overall intakes of "nonessential" or "discretionary" foodstuffs (27, 28). These are unnecessary for meeting nutritional requirements or promoting health and are characterized by their limited nutritional value and high energy, saturated fat, and sugar content, coupled with deficient essential micronutrient content (27, 28).

Another limitation is that although many original research articles included in the meta-analyses of our review adjusted for potential confounders that may cluster with both ultraprocessed foods and sugar-sweetened beverages, including smoking and sedentariness (83), residual

confounding remains possible. The potential for residual confounding may be more pronounced in our review because of variations in how adjustment methods were applied and differences in data quality across the original research articles. However, residual confounding bias is a limitation of epidemiological studies and quantitative reviews of such studies in general (17). It is also important to note that umbrella reviews, by their nature (31), provide a broad overview and may not capture specific nuances including how sugar-sweetened beverage consumption was measured and defined in the original research articles, with divergent and even overlapping quantiles for lowest versus highest consumption categories possibly explaining the observed meta-analysis heterogeneity. A strength of our review is that we used the established frameworks to evaluate both the strength (8, 67, 103) and quality (88) of the available evidence, with the key outputs from these providing guidance for further research.

Implications

This umbrella review generated evidence implicating greater sugar-sweetened beverage consumption with higher risks of adverse health outcomes, particularly depression, dental caries, and cardiometabolic diseases. These findings are consistent with the 2017 Global Burden of Disease Study, which identified compelling evidence of a causal relationship between sugar-sweetened beverage consumption and adverse cardiometabolic outcomes, such as high body mass index, ischemic heart disease, and type 2 diabetes mellitus (91). Collectively, this body of evidence suggests the need for strategies aimed at reducing the health risks associated with sugar-sweetened beverage consumption. These findings support recommendations by the World Health Organization, which advocates for limiting added sugar intake (i.e., to less than 10% of daily energy consumption, or preferably even lower, at less than 5%) (97). Furthermore, the findings from our review can inform and bolster the implementation of other population-based strategies designed to curb or eliminate sugar-sweetened beverage consumption. Such population-based strategies include the incorporation of recommendations to avoid ultraprocessed products such as sugar-sweetened beverages into national dietary guidelines and policies, as observed in Latin American countries (29, 70) as well as France (48), and Israel (95). Similar recommendations to improve cardiovascular health and prevent liver disease were recently made by the American Heart Association (50) and *The Lancet* in conjunction with the European Association for the Study of the Liver, respectively (42). Other population-based strategies include sweetened beverage taxation [as implemented in countries such as Mexico (15) and the United Kingdom (80) and in cities such as Berkeley, California (89)], as well as restrictions on marketing and front-of-package warning labels along with concurrent public health education strategies (74, 81).

CONCLUSIONS

Our umbrella review shows that the strongest evidence against sugar-sweetened beverage consumption pertains to direct associations with higher risks of depression, dental caries, and cardiometabolic diseases. Dose-response evidence was found for each additional milliliter per serving increase in sugar-sweetened beverages and higher risks of all-cause mortality, cancer mortality, cardiovascular disease, coronary heart disease, stroke, and type 2 diabetes mellitus in adults, as well as higher anthropometric measures in children and adults. To address the between-study disparities and noted limitations in the strength and quality of evidence from other meta-analyses, especially in relation to some cancer and gastrointestinal outcomes, further evidence is required from well-designed and well-appraised meta-analyses of prospective cohort studies. Nonetheless, the weight of evidence is such that addressing sugar-sweetened beverage consumption by population-based and public health strategies is a pressing imperative to improve dietary quality and human health.

DISCLOSURE STATEMENT

M.M.L. is secretary for the Melbourne Branch Committee of the Nutrition Society of Australia (unpaid) and has received travel funding support from the International Society for Nutritional Psychiatry Research, the Nutrition Society of Australia, the Australasian Society of Lifestyle Medicine, and the Gut Brain Congress. M.M.L. is an associate investigator for the MicroFit Study, an investigator-led randomized controlled trial exploring the effect of diets with varying levels of industrial processing on gut microbiome composition and partially funded by Be Fit Food (payment received by the Food & Mood Centre, Deakin University). R.O. (Food & Mood Centre) has received grant/research support from the A2 Milk Company, Be Fit Foods, Meat and Livestock Australia, and Woolworths Ltd. and philanthropic support from the Fernwood Foundation, the Wilson Foundation, the JTM Foundation, the Serp Hills Foundation, the Roberts Family Foundation, and the Waterloo Foundation. F.N.J. has received industry support for research from Meat and Livestock Australia, Woolworths Ltd., the A2 Milk Company, Be Fit Foods, and Bega Cheese and has written two books for commercial publication. A.O. has received fellowship funding support from the National Health and Medical Research Council (2009295) and is affiliated with Deakin University, which has received grant funding support from the Medical Research Future Fund, Dasman Diabetes Institute, MTP Connect–Targeted Translation Research Accelerator Program, the National Health and Medical Research Council, Barwon Health, and the Waterloo Foundation. A.O. has received funding support for academic editing and as a grant reviewer from SLACK Incorporated (*Psychiatric Annals*) and the National Health and Medical Research Council, respectively, and travel funding support from the International Society for Nutritional Psychiatry Research. C.M.R. is an associate editor of *Diabetes Care*; immediate past chair of the Nutritional Epidemiology Research Interest Section, American Society for Nutrition; immediate past chair of the Early Career Committee, Council on Lifestyle and Cardiometabolic Health, American Heart Association; a member of the American Diabetes Association; a member of the American Society of Nephrology; and has received funding from the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the Office of Dietary Supplements, and Johns Hopkins Bloomberg American Health Initiative. W.M. is currently funded by a National Health and Medical Research Council Investigator Grant (2008971); has previously received funding from the Cancer Council Queensland and university grants/fellowships from La Trobe University, Deakin University, University of Queensland, and Bond University; has received funding and/or has attended events funded by Cobram Estate Pty. Ltd. and Bega Dairy and Drinks Pty. Ltd.; has received travel funding from the Nutrition Society of Australia; has received consultancy funding from Nutrition Research Australia and ParachuteBH; and has received speakers honoraria from the Cancer Council Queensland and the Princess Alexandra Research Foundation.

AUTHOR CONTRIBUTIONS

M.M.L. and N.T. contributed to the conceptualization; data curation; project administration; writing of the original draft; writing, reviewing, and editing; and as guarantors. E.G., S.M., G.L.T., C.Y., S.B.T., T.D., S.L.D., and R.O. contributed to the conceptualization; data curation; and writing, reviewing, and editing. F.N.J., A.O., M.L., P.B., C.M.R., and S.D. contributed to the conceptualization and writing, reviewing, and editing. W.M. contributed to the conceptualization; data curation; formal analysis; supervision; and writing, reviewing, and editing.

LITERATURE CITED

1. Ahn H, Park YK. 2021. Sugar-sweetened beverage consumption and bone health: a systematic review and meta-analysis. *Nutr. J.* 20:41

2. Al-Zalabani AH, Noor Elahi I, Katib A, Alamri AG, Halawani A, et al. 2019. Association between soft drinks consumption and asthma: a systematic review and meta-analysis. *BMJ Open* 9:e029046
3. Ambikapathi R, Schneider KR, Davis B, Herrero M, Winters P, Fanzo JC. 2022. Global food systems transitions have enabled affordable diets but had less favourable outcomes for nutrition, environmental health, inclusion and equity. *Nat. Food* 3:764–79
4. Ardeshirlarijani E, Jalilpiran Y, Daneshzad E, Larijani B, Namazi N, Azadbakht L. 2021. Association between sugar-sweetened beverages and waist circumference in adult populations: a meta-analysis of prospective cohort studies. *Clin. Nutr. ESPEN* 41:118–25
5. Atkinson FS, Foster-Powell K, Brand-Miller JC. 2008. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* 31:2281–83
6. Avena NM, Rada P, Hoebel BG. 2008. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. *Neurosci. Biobehav. Rev.* 32:20–39
7. Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knüppel S, et al. 2019. Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies. *Crit. Rev. Food Sci. Nutr.* 59:1071–90
8. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. 2016. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. *Parkinsonism Relat. Disord.* 23:1–9
9. Berk M, Köhler-Forsberg O, Turner M, Penninx BWJH, Wrobel A, et al. 2023. Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management. *World Psychiatry* 22(3):366–87
10. Bhupathiraju SN, Tobias DK, Malik VS, Pan A, Hruby A, et al. 2014. Glycemic index, glycemic load, and risk of type 2 diabetes: results from 3 large US cohorts and an updated meta-analysis. *Am. J. Clin. Nutr.* 100:218–32
11. Casanova F, O'Loughlin J, Martin S, Beaumont RN, Wood AR, et al. 2021. Higher adiposity and mental health: causal inference using Mendelian randomization. *Hum. Mol. Genet.* 30:2371–82
12. Chen H, Wang J, Li Z, Lam CWK, Xiao Y, et al. 2019. Consumption of sugar-sweetened beverages has a dose-dependent effect on the risk of non-alcoholic fatty liver disease: an updated systematic review and dose-response meta-analysis. *Int. J. Environ. Res. Public Health* 16(12):2192
13. Choi HK, Curhan G. 2008. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ* 336:309–12
14. Choi HK, Willett W, Curhan G. 2010. Fructose-rich beverages and risk of gout in women. *JAMA* 304:2270–78
15. Colchero MA, Rivera-Dommarco J, Popkin BM, Ng SW. 2017. In Mexico, evidence of sustained consumer response two years after implementing a sugar-sweetened beverage tax. *Health Aff.* 36:564–71
16. Dale CE, Fatemifar G, Palmer TM, White J, Prieto-Merino D, et al. 2017. Causal associations of adiposity and body fat distribution with coronary heart disease, stroke subtypes, and type 2 diabetes mellitus: a Mendelian randomization analysis. *Circulation* 135:2373–88
17. Dekkers OM, Vandenbroucke JP, Cevallos M, Renehan AG, Altman DG, Egger M. 2019. COSMOS-E: guidance on conducting systematic reviews and meta-analyses of observational studies of etiology. *PLOS Med.* 16:e1002742
18. DiNicolantonio JJ, O'Keefe JH, Wilson WL. 2018. Sugar addiction: Is it real? A narrative review. *Br. J. Sports Med.* 52:910–13
19. Ebrahimpour-Koujan S, Saneei P, Larijani B, Esmaillzadeh A. 2020. Consumption of sugar sweetened beverages and dietary fructose in relation to risk of gout and hyperuricemia: a systematic review and meta-analysis. *Crit. Rev. Food Sci. Nutr.* 60:1–10
20. Ebrahimpour-Koujan S, Saneei P, Larijani B, Esmaillzadeh A. 2021. Consumption of sugar-sweetened beverages and serum uric acid concentrations: a systematic review and meta-analysis. *J. Hum. Nutr. Diet.* 34:305–13
21. Egger M, Davey Smith G, Schneider M, Minder C. 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629–34
22. Elizabeth L, Machado P, Zinöcker M, Baker P, Lawrence M. 2020. Ultra-processed foods and health outcomes: a narrative review. *Nutrients* 12(7):1955

23. Emdin CA, Khera AV, Natarajan P, Klarin D, Zekavat SM, et al. 2017. Genetic association of waist-to-hip ratio with cardiometabolic traits, type 2 diabetes, and coronary heart disease. *JAMA* 317:626–34
24. Fardet A, Rock E. 2018. Perspective: Reductionist nutrition research has meaning only within the framework of holistic and ethical thinking. *Adv. Nutr.* 9:655–70
25. Farhangi MA, Nikniaz L, Khodarahmi M. 2020. Sugar-sweetened beverages increases the risk of hypertension among children and adolescence: a systematic review and dose–response meta-analysis. *J. Translational Med.* 18:344
26. Farsad-Naeimi A, Asjodi F, Omidian M, Askari M, Nouri M, et al. 2020. Sugar consumption, sugar sweetened beverages and attention deficit hyperactivity disorder: a systematic review and meta-analysis. *Complement Ther. Med.* 53:102512
27. Fayet-Moore F, McConnell A, Cassettari T, Tuck K, Petocz P, Kim J. 2019. Discretionary intake among Australian adults: prevalence of intake, top food groups, time of consumption and its association with sociodemographic, lifestyle and adiposity measures. *Public Health Nutr.* 22:1576–89
28. Fayet-Moore F, McConnell A, Tuck K, Petocz P, Cassettari T, et al. 2022. Patterns of discretionary food intake among Australian children and their association with socio-demographic, lifestyle, and adiposity measures. *Nutr. Diet.* 79:623–35
29. Food Agric. Organ. U. N. (FAO). 2023. Food-based dietary guidelines. *Food and Agriculture Organization of the United Nations*. **https://www.fao.org/nutrition/education/food-dietary-guidelines/regions/en/**
30. Gaesser GA, Miller Jones J, Angadi SS. 2021. Perspective: Does glycemic index matter for weight loss and obesity prevention? Examination of the evidence on "fast" compared with "slow" carbs. *Adv. Nutr.* 12:2076–84
31. Gianfredi V, Nucci D, Amerio A, Signorelli C, Odone A, Dinu M. 2022. What can we expect from an umbrella review? *Adv. Nutr.* 13:684–85
32. Gnagnarella P, Gandini S, La Vecchia C, Maisonneuve P. 2008. Glycemic index, glycemic load, and cancer risk: a meta-analysis. *Am. J. Clin. Nutr.* 87:1793–801
33. Gosling CJ, Solanes A, Fusar-Poli P, Radua J. 2023. metaumbrella: the first comprehensive suite to perform data analysis in umbrella reviews with stratification of the evidence. *BMJ Ment. Health* 26:e300534
34. Ha DH, Arora A, Harford J, Luzzi L, Chrisopoulos S, Do LG. 2022. Population impact of sugar-sweetened beverages on dental caries and overweight/obesity in Australian children. *JDR Clin. Transl. Res.* 8:224–33
35. Hägg S, Fall T, Ploner A, Mägi R, Fischer K, et al. 2015. Adiposity as a cause of cardiovascular disease: a Mendelian randomization study. *Int. J. Epidemiol.* 44:578–86
36. Higgins JP, Thompson SG, Spiegelhalter DJ. 2009. A re-evaluation of random-effects meta-analysis. *J. R. Stat. Soc. Ser. A Stat. Soc.* 172:137–59
37. Hu D, Cheng L, Jiang W. 2019. Sugar-sweetened beverages consumption and the risk of depression: a meta-analysis of observational studies. *J. Affect. Disord.* 245:348–55
38. Huang Y, Chen Z, Chen B, Li J, Yuan X, et al. 2023. Dietary sugar consumption and health: umbrella review. *BMJ* 381:e071609
39. Ioannidis JP. 2009. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *Cmaj* 181:488–93
40. Ioannidis JP, Trikalinos TA. 2007. An exploratory test for an excess of significant findings. *Clin. Trials* 4:245–53
41. Jager KJ, Tripepi G, Chesnaye NC, Dekker FW, Zoccali C, Stel VS. 2020. Where to look for the most frequent biases? *Nephrology* 25:435–41
42. Karlsen TH, Sheron N, Zelber-Sagi S, Carrieri P, Dusheiko G, et al. 2022. The EASL-*Lancet* Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. *Lancet* 399:61–116
43. Khademi Z, Milajerdi A, Larijani B, Esmaillzadeh A. 2021. Dietary intake of total carbohydrates, sugar and sugar-sweetened beverages, and risk of inflammatory bowel disease: a systematic review and meta-analysis of prospective cohort studies. *Front. Nutr.* 8:707795

44. Lanaspa MA, Ishimoto T, Li N, Cicerchi C, Orlicky DJ, et al. 2013. Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome. *Nat. Commun.* 4:2434
45. Lane MM, Davis JA, Beattie S, Gómez-Donoso C, Loughman A, et al. 2021. Ultraprocessed food and chronic noncommunicable diseases: a systematic review and meta-analysis of 43 observational studies. *Obes. Rev.* 22:e13146
46. Lane MM, Gamage E, Travica N, Dissanayaka T, Ashtree DN, et al. 2022. Ultra-processed food consumption and mental health: a systematic review and meta-analysis of observational studies. *Nutrients* 14:2568
47. Lane MM, Lotfaliany M, Forbes M, Loughman A, Rocks T, et al. 2022. Higher ultra-processed food consumption is associated with greater high-sensitivity C-reactive protein concentration in adults: cross-sectional results from the Melbourne Collaborative Cohort Study. *Nutrients* 14:3309
48. Le Haut Cons. santé publique (High Counc. Public Health). 2023. Avis relatif aux objectifs quantifiés pour la politique nutritionnelle de santé publique (PNNS) 2018–2022. [Opinion relating to the quantified objectives for the public health nutritional policy (PNNS) 2018–2022]. *Le Haut Conseil de la santé publique*. **https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=648**
49. Li Y, Guo L, He K, Huang C, Tang S. 2021. Consumption of sugar-sweetened beverages and fruit juice and human cancer: a systematic review and dose-response meta-analysis of observational studies. *J. Cancer* 12:3077–88
50. Lichtenstein AH, Appel LJ, Vadiveloo M, Hu FB, Kris-Etherton PM, et al. 2021. 2021 dietary guidance to improve cardiovascular health: a scientific statement from the American Heart Association. *Circulation* 144:e472–87
51. Lin B-B, Lin M-E, Huang R-H, Hong Y-K, Lin B-L, He X-J. 2020. Dietary and lifestyle factors for primary prevention of nephrolithiasis: a systematic review and meta-analysis. *BMC Nephrol.* 21:267
52. Liu H, Liu Y, Shi M, Zhou Y, Zhao Y, Xia Y. 2022. Meta-analysis of sugar-sweetened beverage intake and the risk of cognitive disorders. *J. Affect. Disord.* 313:177–85
53. Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. 2002. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am. J. Clin. Nutr.* 75:492–98
54. Livesey G, Livesey H. 2019. Coronary heart disease and dietary carbohydrate, glycemic index, and glycemic load: dose-response meta-analyses of prospective cohort studies. *Mayo Clinic Proc. Innov. Qual. Outcomes* 3:52–69
55. Livesey G, Taylor R, Livesey HF, Buyken AE, Jenkins DJ, et al. 2019. Dietary glycemic index and load and the risk of type 2 diabetes: a systematic review and updated meta-analyses of prospective cohort studies. *Nutrients* 11:1280
56. Llaha F, Gil-Lespinard M, Unal P, de Villasante I, Castañeda J, Zamora-Ros R. 2021. Consumption of sweet beverages and cancer risk. A systematic review and meta-analysis of observational studies. *Nutrients* 13:516
57. Lo WC, Ou SH, Chou CL, Chen JS, Wu MY, Wu MS. 2021. Sugar- and artificially-sweetened beverages and the risks of chronic kidney disease: a systematic review and dose-response meta-analysis. *J. Nephrol.* 34:1791–804
58. Lundeen EA, Park S, Pan L, Blanck HM. 2018. Daily intake of sugar-sweetened beverages among US adults in 9 states, by state and sociodemographic and behavioral characteristics, 2016. *Prev. Chronic Dis.* 15:E154
59. Lyall DM, Celis-Morales C, Ward J, Iliodromiti S, Anderson JJ, et al. 2017. Association of body mass index with cardiometabolic disease in the UK Biobank: a Mendelian randomization study. *JAMA Cardiol.* 2:882–89
60. Machado PP, Steele EM, Levy RB, Sui Z, Rangan A, et al. 2019. Ultra-processed foods and recommended intake levels of nutrients linked to non-communicable diseases in Australia: evidence from a nationally representative cross-sectional study. *BMJ Open* 9:e029544
61. Malik VS, Hu FB. 2019. Sugar-sweetened beverages and cardiometabolic health: an update of the evidence. *Nutrients* 11:1840
62. Malik VS, Hu FB. 2022. The role of sugar-sweetened beverages in the global epidemics of obesity and chronic diseases. *Nat. Rev. Endocrinol.* 18:205–18

63. Malik VS, Pan A, Willett WC, Hu FB. 2013. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. *Am. J. Clin. Nutr.* 98:1084–102
64. Malik VS, Popkin BM, Bray GA, Després J-P, Hu FB. 2010. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation* 121:1356–64
65. Malik VS, Willett WC, Hu FB. 2013. Global obesity: trends, risk factors and policy implications. *Nat. Rev. Endocrinol.* 9:13–27
66. Martini D, Godos J, Bonaccio M, Vitaglione P, Grosso G. 2021. Ultra-processed foods and nutritional dietary profile: a meta-analysis of nationally representative samples. *Nutrients* 13:3390
67. Marx W, Veronese N, Kelly JT, Smith L, Hockey M, et al. 2021. The Dietary Inflammatory Index and human health: an umbrella review of meta-analyses of observational studies. *Adv. Nutr.* 12(5):1681–90
68. Mattes RD, Shikany JM, Kaiser KA, Allison DB. 2011. Nutritively sweetened beverage consumption and body weight: a systematic review and meta-analysis of randomized experiments. *Obes. Rev.* 12:346–65
69. Meng Y, Li S, Khan J, Dai Z, Li C, et al. 2021. Sugar- and artificially sweetened beverages consumption linked to type 2 diabetes, cardiovascular diseases, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Nutrients* 13:2636
70. Minist. Health Brazil. 2014. *Dietary guidelines for the Brazilian population*. Rep., Minist. Health Brazil, Brasília. **https://bvsms.saude.gov.br/bvs/publicacoes/dietary_guidelines_brazilian_population.pdf**
71. Monteiro CA, Cannon G, Levy RB, Moubarac JC, Louzada ML, et al. 2019. Ultra-processed foods: what they are and how to identify them. *Public Health Nutr.* 22:936–41
72. Monteiro CA, Cannon G, Moubarac J-C, Levy RB, Louzada MLC, Jaime PC. 2018. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr.* 21:5–17
73. Muñoz-Cabrejas A, Guallar-Castillón P, Laclaustra M, Sandoval-Insausti H, Moreno-Franco B. 2023. Association between sugar-sweetened beverage consumption and the risk of the metabolic syndrome: a systematic review and meta-analysis. *Nutrients* 15:430
74. Muth ND, Dietz WH, Magge SN, Johnson RK. 2019. Public policies to reduce sugary drink consumption in children and adolescents. *Pediatrics* 143:e20190282
75. Nakagawa T, Tuttle KR, Short RA, Johnson RJ. 2005. Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome. *Nat. Clin. Practice Nephrol.* 1:80–86
76. Nikniaz L, Abbasalizad-Farhangi M, Vajdi M, Nikniaz Z. 2021. The association between sugars sweetened beverages (SSBs) and lipid profile among children and youth: a systematic review and dose-response meta-analysis of cross-sectional studies. *Pediatr. Obes.* 16:e12782
77. Nordestgaard BG, Palmer TM, Benn M, Zacho J, Tybjaerg-Hansen A, et al. 2012. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach. *PLOS Med.* 9:e1001212
78. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, et al. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71
79. Pan B, Ge L, Lai H, Wang Q, Wang Q, et al. 2022. Association of soft drink and 100% fruit juice consumption with all-cause mortality, cardiovascular diseases mortality, and cancer mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Crit. Rev. Food Sci. Nutr.* 62:8908–19
80. Rogers NT, Pell D, Mytton OT, Penney TL, Briggs A, et al. 2023. Changes in soft drinks purchased by British households associated with the UK soft drinks industry levy: a controlled interrupted time series analysis. *BMJ Open* 13(12):e077059
81. Popkin BM, Hawkes C. 2016. Sweetening of the global diet, particularly beverages: patterns, trends, and policy responses. *Lancet Diabetes Endocrinol.* 4:174–86
82. Richette P, Bardin T. 2010. Gout. *Lancet* 375:318–28
83. Rocha LL, Pessoa MC, Gratão LHA, Carmo ASD, Cunha CF, et al. 2021. Health behavior patterns of sugar-sweetened beverage consumption among Brazilian adolescents in a nationally representative school-based study. *PLOS ONE* 16:e0245203
84. Rosinger A, Herrick K, Gahche J, Park S. 2017. Sugar-sweetened beverage consumption among U.S. adults, 2011–2014. *NCHS Data Brief* 270:1–8

85. Schlesinger S, Neuenschwander M, Schwedhelm C, Hoffmann G, Bechthold A, et al. 2019. Food groups and risk of overweight, obesity, and weight gain: a systematic review and dose-response meta-analysis of prospective studies. *Adv. Nutr.* 10:205–18
86. Scrinis G, Monteiro C. 2022. From ultra-processed foods to ultra-processed dietary patterns. *Nat. Food* 3:671–73
87. Sempos CT, Liu K, Ernst ND. 1999. Food and nutrient exposures: what to consider when evaluating epidemiologic evidence. *Am. J. Clin. Nutr.* 69:1330S–38S
88. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, et al. 2017. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 358:j4008
89. Silver LD, Ng SW, Ryan-Ibarra S, Taillie LS, Induni M, et al. 2017. Changes in prices, sales, consumer spending, and beverage consumption one year after a tax on sugar-sweetened beverages in Berkeley, California, US: a before-and-after study. *PLOS Med.* 14:e1002283
90. Speed MS, Jefsen OH, Børglum AD, Speed D, Østergaard SD. 2019. Investigating the association between body fat and depression via Mendelian randomization. *Transl. Psychiatry* 9:184
91. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, et al. 2018. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392:1923–94
92. Sterne JA, Egger M. 2001. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J. Clin. Epidemiol.* 54:1046–55
93. Sun T, Zhang Y, Ding L, Zhang Y, Li T, Li Q. 2023. The relationship between major food sources of fructose and cardiovascular outcomes: a systematic review and dose-response meta-analysis of prospective studies. *Adv. Nutr.* 14:256–69
94. Tey S, Salleh N, Henry J, Forde C. 2017. Effects of aspartame-, monk fruit-, stevia-and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake. *Int. J. Obes.* 41:450–57
95. The Israeli Minist. Health. 2019. *Nutritional recommendations*. Rep., The Israeli Minist. Health, Jerusalem. **https://www.health.gov.il/PublicationsFiles/dietary%20guidelines%20EN.pdf**
96. Tyrrell J, Mulugeta A, Wood AR, Zhou A, Beaumont RN, et al. 2018. Using genetics to understand the causal influence of higher BMI on depression. *Int. J. Epidemiol.* 48:834–48
97. U. S. Dep. Health Human Serv., U. S. Dep. Agric. 2015. *2015–2020 Dietary Guidelines for Americans.* Rep., U. S. Dep. Agric., Washington, DC. **http://health.gov/dietaryguidelines/2015/guidelines/**
98. U. S. Dep. Agric. 2014. *A series of systematic reviews on the relationship between dietary patterns and health outcomes*. Rep., U. S. Dep. Agric., Washington, DC. **https://nesr.usda.gov/sites/default/files/2019-06/DietaryPatternsReport-FullFinal2.pdf**
99. Valenzuela MJ, Waterhouse B, Aggarwal VR, Bloor K, Doran T. 2021. Effect of sugar-sweetened beverages on oral health: a systematic review and meta-analysis. *Eur. J. Public Health* 31:122–29
100. van den Broek N, Treur JL, Larsen JK, Verhagen M, Verweij KJH, Vink JM. 2018. Causal associations between body mass index and mental health: a Mendelian randomisation study. *J. Epidemiol. Commun. Health* 72:708–10
101. Vandevijvere S, Jaacks LM, Monteiro CA, Moubarac J-C, Girling-Butcher M, et al. 2019. Global trends in ultraprocessed food and drink product sales and their association with adult body mass index trajectories. *Obes. Rev.* 20:10–19
102. Veronese N, Demurtas J, Thompson T, Solmi M, Pesolillo G, et al. 2020. Effect of low-dose aspirin on health outcomes: an umbrella review of systematic reviews and meta-analyses. *Br. J. Clin. Pharmacol.* 86:1465–75
103. Veronese N, Solmi M, Caruso MG, Giannelli G, Osella AR, et al. 2018. Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. *Am. J. Clin. Nutr.* 107:436–44
104. von Hippel PT. 2015. The heterogeneity statistic I^2 can be biased in small meta-analyses. *BMC Med. Res. Methodol.* 15:35
105. Wang Y, Zhao R, Wang B, Zhao C, Zhu B, Tian X. 2022. The dose-response associations of sugar-sweetened beverage intake with the risk of stroke, depression, cancer, and cause-specific mortality: a systematic review and meta-analysis of prospective studies. *Nutrients* 14:777

106. Wasserstein RL, Schirm AL, Lazar NA. 2019. Moving to a world beyond "p < 0.05." *Am. Stat*. 73:1–19
107. World Health Organ. (WHO). 2015. *Guideline: sugars intake for adults and children*. Rep., WHO, Geneva. **https://www.who.int/publications/i/item/9789241549028**
108. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, et al. 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* 50:668–81
109. Yin J, Zhu Y, Malik V, Li X, Peng X, et al. 2021. Intake of sugar-sweetened and low-calorie sweetened beverages and risk of cardiovascular disease: a meta-analysis and systematic review. *Adv. Nutr.* 12:89–101
110. Yu J, Huang F, Zhang X, Xue H, Ni X, et al. 2023. Association of sugar-sweetened beverage consumption and moderate-to-vigorous physical activity with childhood and adolescent overweight/obesity: findings from a surveillance project in Jiangsu Province of China. *Nutrients* 15:4164
111. Zhang X, Li X, Liu L, Hong F, Zhao H, et al. 2021. Dose-response association between sugar- and artificially sweetened beverage consumption and the risk of metabolic syndrome: a meta-analysis of population-based epidemiological studies. *Public Health Nutr*. 24:3892–904
112. Zhang YB, Jiang YW, Chen JX, Xia PF, Pan A. 2021. Association of consumption of sugar-sweetened beverages or artificially sweetened beverages with mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Adv. Nutr.* 12:374–83