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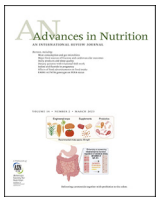

Review

The Relationship Between Major Food Sources of Fructose and Cardiovascular Outcomes: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies

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A B S T R A C T

There is emerging evidence of associations between intake of sugar-sweetened beverages (SSBs), those that include various forms of added sugar, and increased risk of cardiovascular disease (CVD) but whether consumption of other dietary sources of fructose affects CVD is unclear. In this study, we conducted a meta-analysis to examine potential dose-response relationships between such foods and CVD, coronary heart disease (CHD), and stroke morbidity and mortality. We systematically searched the literature indexed in PubMed, Embase, and the Cochrane Library from the inception of each database to February 10, 2022. We included prospective cohort studies analyzing the association between at least 1 dietary source of fructose and CVD, CHD, and stroke. Based on data from 64 included studies, summary HRs and 95% CIs were calculated for the highest intake category compared with the lowest, and dose-response analyses were performed. Of all fructose sources examined, only SSB intakes showed positive associations with CVD, giving summary HRs per 250 mL/d increase of 1.10 (95% CI: 1.02, 1.17) for CVD, 1.11 (95% CI: 1.05, 1.17) for CHD, 1.08 (95% CI: 1.02, 1.13) for stroke morbidity, and 1.06 (95% CI: 1.02, 1.10) for CVD mortality. Conversely, 3 dietary sources showed protective associations: between fruits and CVD morbidity (HR: 0.97; 95% CI: 0.96, 0.98), fruits and CVD mortality (HR: 0.94; 95% CI: 0.92, 0.97), yogurt and CVD mortality (HR: 0.96; 95% CI: 0.93, 0.99), and breakfast cereals and CVD mortality (HR: 0.80; 95% CI: 0.70, 0.90). All these relationships were linear except for fruit, which was J-shaped: CVD morbidity was the lowest at 200 g/d and there was no protective association above 400 g/d. These findings indicate that the adverse associations between SSBs and CVD, CHD, and stroke morbidity and mortality do not extend to other dietary sources of fructose. The food matrix seemed to modify the association between fructose and cardiovascular outcomes.

Keywords: fructose, diets, cardiovascular disease, meta-analysis, dose response

Statement of Significance

This meta-analysis updates the evidence about fructose and CVD risk by quantifying the dose-response associations between major dietary sources of fructose and CVD morbidity and mortality. The adverse association between SSBs and CVD does not extend to other dietary sources of fructose and the potential health benefits of fruit may not be infinite.

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; NOS, Newcastle-Ottawa Assessment Scale; SSB, sugar-sweetened beverage.

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Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide and accounted for 17.8 million deaths in 2017, in which ischemic heart disease represents ~50% of these CVD deaths and stroke accounts for ~35% of the death provided by the Global Burden of Disease study [1]. In 2019, ischemic heart disease and stroke were the top-ranked causes for disability-adjusted life-years in both population aged 50–74 years and population aged 75 years and older [2]. The increasing risk of CVD incidence and mortality is associated with a poor diet quality and can be prevented by addressing the unhealthy diet [3–5].

The increasing risk of CVD incidence and mortality is associated with a poor diet quality and can be prevented by addressing the unhealthy diet [3–5]. A major dietary factor associated with this risk seems to be consumption of fructose [6–8]. High-fructose corn syrup is added to many processed foods and drinks as the major sweetener [9]. There is mounting evidence suggesting that fructose potentially correlates with the increase of the diet-related disease prevalence. Several intervention studies suggest that overconsumption of fructose is linked to cardiovascular risk [6–8]. In particular, sugar-sweetened beverages (SSBs), an important dietary source of fructose in the United States and Canada, are associated with the increased risk of overall CVD and its specific subtypes [10–13]. These studies helped lead to recommendations for limiting dietary intake of fructose, particularly foods and drinks containing added sugars [14] For example, the "2021 Dietary Guidance to Improve Cardiovascular Health" from the American Heart Association recommends to minimize the intake of beverages and foods with added sugars [15].

However, SSBs are not the only source of fructose. There are many other common food sources of fructose, such as fruit, fruit drinks, ready-to-eat breakfast cereals, dairy desserts, yogurt, cakes, cookies, and confectionary [9, 16, 17]. A meta-analysis of 155 studies showed that food sources of fructose seemed to mediate the effect of fructose-containing sugars on glycemic control [18]. Two animal studies have suggested that sugar provided in liquid form may be more deleterious than those in solid form [19, 20]. Recently, dietary guidelines have addressed the importance of foods and dietary patterns instead of individual nutrients. These considerations highlight the need for research into the associations between specific dietary sources of fructose and CVD risk.

A meta-analysis has linked consumption of major dietary sources of fructose to increased long-term risk of death due to CVD [21], but how different dietary sources influence short-term risk of CVD is uncertain.

To address these questions and provide a more comprehensive assessment of the association between fructose and CVD, we conducted a systematic review and dose-response meta-analysis of prospective cohort studies examining major dietary sources of fructose and risk of CVD, coronary heart disease (CHD), stroke or associated mortality.

Methods

We conducted this systematic review and meta-analysis following the Cochrane Handbook for Systematic Reviews and Interventions. All results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [22] and the Meta-Analysis of Observational Studies in Epidemiology guidelines [23]. The study protocol was registered at the International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO, identifier CRD42022325507).

Search strategy

We searched for relevant prospective studies in PubMed, Embase, and the Cochrane Library database (Cochrane Central Register of Controlled Trials) from their respective inceptions to February 10, 2022. Search terms included major dietary sources of fructose, such as "sugar-sweetened beverages," "fruit," and "fructose"; outcomes of interest, such as "cardiovascular disease," "coronary disease," and "stroke"; and study design, which had to be "prospective study." Details of search terms are listed in Supplemental Table 1. In addition, the references lists of potentially eligible studies were manually searched to identify additional studies.

Study selection

Two authors independently assessed the eligibility of the literatures at 2 stages: *1*) titles and abstract reviewing and *2*) full-text article reviewing. Studies were eligible for inclusion if they met the following criteria: *1*) a prospective cohort study; *2*) with a minimum follow-up duration of 1 year; *3*) providing data on the association between major food sources of fructose and incidence or mortality from CVD, CHD, and stroke; *4*) participants free of outcome of interest at baseline; *5*) reporting HRs, RRs, or ORs with associated 95% CIs. The exclusion criteria were as the following: *1*) the study was conducted in patients with specific disease such as diabetes mellitus and chronic kidney disease, *2*) only abstract available, and *3*) non-English publications. For those duplicate publications from the same cohort, the one with the longest duration of follow-up were included.

Data extraction

Two reviewers independently extracted relevant data from included studies using standardized forms. Disagreements between the 2 reviewers were resolved through discussions with a third reviewer. If necessary, the authors of the original study were contacted to obtain missing data. The following data were extracted from each study: name of first author, publication year, name of the cohort, country, follow-up duration, sample size, sex, age at baseline, method of dietary assessment, food source of fructose, amount or frequency of intake, type of outcome, total number of cases or deaths, distribution of cases or person-years, adjusted risk estimates (HRs, RRs, or ORs) and associated 95% CIs, and variables that were adjusted in the most-adjusted model.

Study quality assessment

We assessed the quality of each study using the Newcastle-Ottawa Assessment Scale (NOS) for cohort studies [24]. NOS points were awarded based on selection of the study groups, comparability of the groups, and assessment of the outcome of interest. The maximum points that could be awarded was 9, and studies that received $\geq$7 points were considered high quality.

Statistical methods

Stata version 16 was used for the primary pairwise meta-analysis, dose-response meta-analysis, meta-regression analysis, subgroup analysis, sensitivity analysis, and analysis of publication bias. HRs and 95% CIs from the most-adjusted model were used as the effect size in all analyses. Reported RRs were treated as approximate HRs, and ORs were converted to RRs as described [25]. To produce summarized estimate, we used natural log-transformed HRs and 95% CIs and reported results as HRs and 95% CIs.

In pairwise meta-analysis, we calculated summary HRs and 95% CIs for the highest intake category versus the lowest intake categories using the DerSimonian and Laird random-effects model [26]. Heterogeneity among studies was assessed using the Cochran Q (χ^2) test and I^2 statistic, where $I^2 \geq 50\%$ and $P < 0.10$ were considered evidence of substantial heterogeneity [27]. If the highest category was considered to be the reference, we made the lowest category as the reference and recalculated the HRs and 95% CIs. If studies conducted in 2 independent cohorts or reported results were stratified by sex, we treated them as separate reports.

In linear dose-response analysis, we estimated summary HRs and 95% CIs per 1-unit increment using the method in the study published by Greenland et al. [28, 29]. The method consists of 2 stages where study-specific slopes and 95% CIs are estimated using generalized least-squares trend estimation and then pooled using a random-effects meta-analysis [26, 28]. For this analysis, we extracted data on doses, distribution of cases and participants or person-years, and the corresponding HRs and their 95% CIs across categories. Doses were defined as median or mean consumption in each category. If the food intake was reported as a range, we assumed the midpoint of that range to be the median. When intake categories were open ended, for the lowest category, we assumed the lowest category to be zero; otherwise, we assumed the widths of these open-ended categories to be the same as the adjunct category. If the numbers of individuals in each category were not reported and intake was categorized into quantiles, we assumed that the sample size was the same for all categories and was equal to the total number of participants divided by the number of categories [30]. For studies that reported the effect size per specific increase in the amount of exposure, we exponentiated the log effect size by multiplying the study-specific intake of exposure to obtain the effect size for 1 additional serving of exposure [31].

Moreover, we tested the potential nonlinear dose-response association using the recently developed a 1-stage mixed-effects meta-analysis described by Crippa et al. [32] and Orsini et al. [33]. This method pools the aggregated data before a trend analysis, which is more flexible and precise than the traditional 2-stage method and avoids excluding studies reporting less than 3 exposure categories [32, 34]. For this analysis, restricted cubic splines with 3 knots at 10%, 50%, and 90% percentiles of the distribution were used according to the Harrell method [35]. We performed the Wald test to assess departure from linearity and reported a nonlinear association with risk of CVD if Wald test for departure from linearity was significant at $P < 0.10$.

If at least 10 pairwise comparisons were available in a given meta-analysis, a priori meta-regression and subgroup analysis were performed with data stratified by sex (male, female, or both), duration of follow-up (<10 and ≥10 years), study quality (NOS < 7 and NOS ≥7), use of a validated dietary assessment (yes/no), and geographic location (Europe, America, and Asia). In the meta-regression based on sex and geographic location, 1 of the 3 categories was defined as the reference. Moreover, we did the subgroup analysis with data stratified by whether for some potential confounding factors (age, socioeconomic status, education level, body mass index, physical activity, hypertension, dyslipidemia, smoking, alcohol intake, energy intake, red meat, fish, vegetables, and a family history of CVD). A sensitivity analysis was performed by systematically removing 1 study at a time from the meta-analysis and recalculating the summary estimates. We considered a study as an influential study if its removal changed the significance of the pooled effect, changed the effect size by >20%, or was able to account for the observed heterogeneity. For meta-analyses involving at least 10 comparisons, publication bias was analyzed using Egger test and visual inspection funnel plots, with $P < 0.05$ considered significant. We assessed the certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) scheme [36].

Results

Search results

A total of 6885 reports were identified in the databases, of which 1459 were duplicates and 5185 were excluded based on review of titles and abstracts (Figure 1). We reviewed the full text of the remaining reports, leading to the exclusion of another 177. In the end, we included 64 publications [37–100] that prospectively analyzed 45 unique cohorts. There were 19 publications [37–55] for SSBs (16 cohorts), 31 publications [48, 56–85] for fruit (28 cohorts), 7 publications [45, 51, 68, 81, 86–88] for 100% fruit juice (7 cohorts), 10 publications [89–98] for yogurt (11 cohorts), 2 publications [99, 100] for breakfast cereals (2 cohorts), 2 publications [43, 86] for cakes and cookies (2 cohorts), and 2 publications [43, 86] for confectionary (2 cohorts).

Study characteristics

Supplemental Tables 2 and 3 list a summary of the study characteristics. Sixteen studies were from Europe, 13 from the United States, 13 from Asia, 2 from Australia, and 1 from 7 geographical regions: North America and Europe, South America, the Middle East, South Asia, China, Southeast Asia, and Africa [84, 90]. Follow-up ranged from 5 to 34 years, and sample size ranged from 1529 to 462,342. The majority of the studies ($n = 31$) included both sexes, 4 of which reported results stratified by sex, which were considered as separate reports. Six studies included only men, whereas 8 included only women. Most studies assessed dietary intake using food frequency questionnaires. The remaining studies used a modified diet history method in the case of the Swedish Malmö Diet and Cancer cohort [43, 46, 87, 89], dietary history interview in the case of the Finnish Mobile Clinic Health Examination Survey [61], 3-day weighted dietary records in the case of the NIPPON DATA80 study [85], 24-hour dietary records in the case of the NutriNet-Santé study [93], or a dietary questionnaire combined with a 7-day record in the case of the United Kingdom and Malmö cohorts [53, 77].

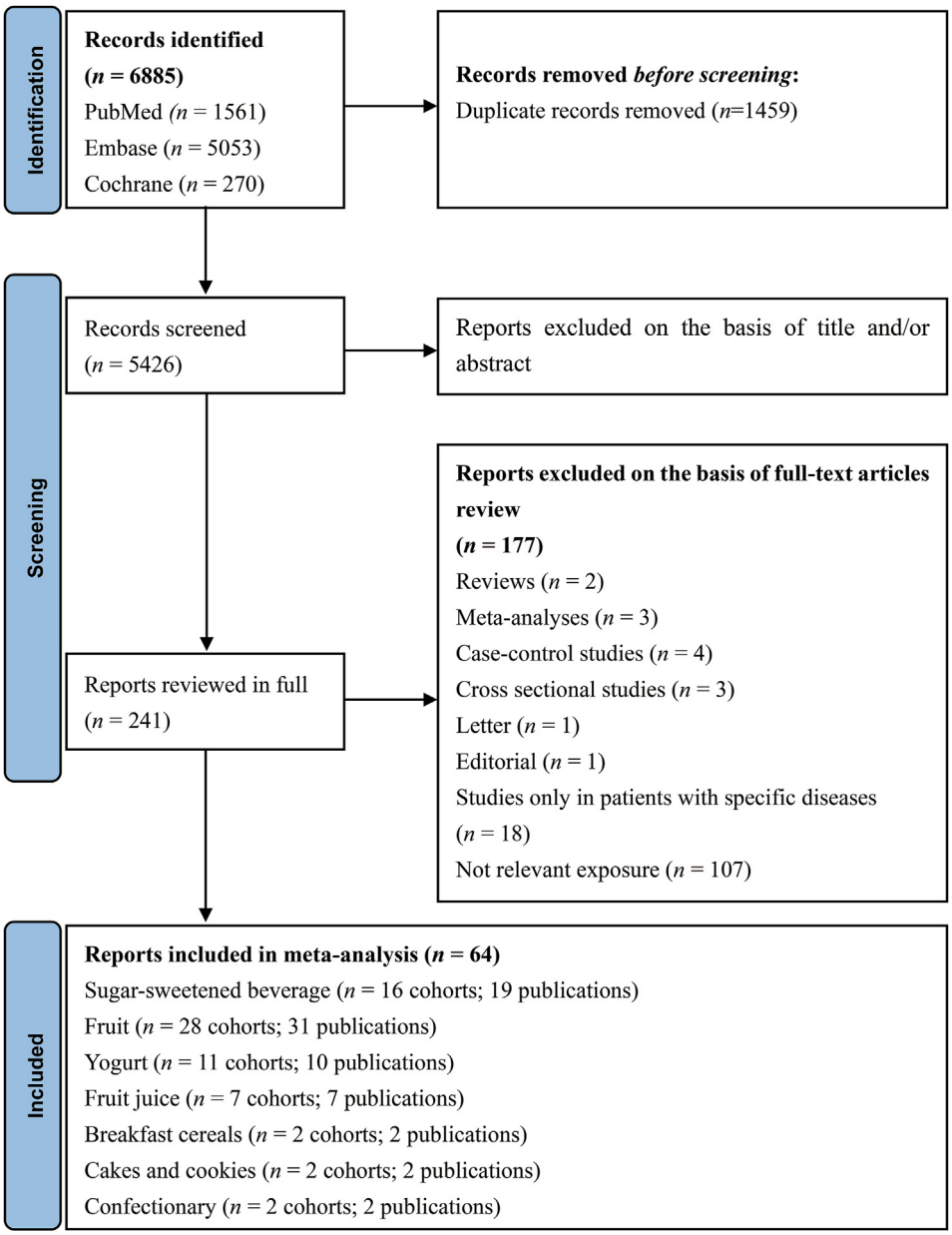

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart.

Supplemental Table 4 summarizes the percentage of studies that have adjusted for some potential confounding factors. Most studies adjusted for age, body mass index, physical activity, smoking, and alcohol and energy intake, whereas a few studies adjusted for socioeconomic status, dyslipidemia, fish, and a family history of CVD.

Study quality

Of the 64 included studies, 58 were of high quality (Supplemental Table 5). The remaining 6 studies scored no more than 6 points.

SSBs and CVD incidence

Two studies investigated the association between SSB intakes and risk of CVD, comprising 118,586 participants, of whom 9594 developed CVD. SSB intakes ranged from 0 to 462 mL/d. The summary HR for the highest intake versus the lowest intake was 1.20 (95% CI: 1.07, 1.34; I^2 = 0%, *P*-heterogeneity = 0.73) (Supplemental Figure 1, Table 1). The summary HR per 250 mL/d increment was 1.10 (95% CI: 1.02, 1.17; I^2 = 0%, *P*-heterogeneity = 0.60) (Table 1, Supplemental Figure 21). There was a positive linear relationship between SSB intakes and risk of CVD (*P*-nonlinearity = 0.21) (Figure 2A).

SSBs and CHD incidence

Four studies investigated the association between SSB intake and risk of CHD, comprising 160,899 participants, of whom 9694 developed CHD. SSB intakes ranged from 0 to 948 mL/d. The summary HR for the highest level compared with the lowest level was 1.21 (95% CI: 1.05, 1.39; I^2 = 50%, *P*-heterogeneity = 0.11) (Table 1, Supplemental Figure 2). This result did not change substantially when each of the 4 studies was omitted from the meta-analysis (Supplemental Table 7).

TABLE 1
Associations between consumption of SSBs and food sources of fructose and CVD, CHD, and stroke incidence and CVD-associated mortality[1]

Outcome	Highest vs. lowest analysis				Linear dose-response analysis			
	Cohorts, *n*	HR (95% CI)	I^2 (%)	*P*-heterogeneity	*n*	HR (95% CI)	I^2 (%)	*P*-heterogeneity
SSBs								
CVD incidence	2	1.20 (1.07, 1.34)	0.0	0.730	2	1.10 (1.02, 1.17)	0.0	0.600
CHD incidence	4	1.21 (1.05, 1.39)	50.1	0.111	4	1.11 (1.05, 1.17)	30.6	0.228
Stroke incidence	10	1.14 (1.04, 1.24)	27.2	0.194	10	1.08 (1.02, 1.13)	24.1	0.221
CVD mortality	8	1.16 (1.06, 1.27)	43.4	0.089	8	1.06 (1.02, 1.10)	59.3	0.016
Fruit								
CVD incidence	9	0.89 (0.85, 0.93)	24.3	0.227	9	0.97 (0.96, 0.98)	59.9	0.010
CHD incidence	8	0.89 (0.83, 0.96)	0.0	0.950	8	0.96 (0.94, 0.98)	0.0	0.689
Stroke incidence	11	0.86 (0.80, 0.92)	19.7	0.256	11	0.97 (0.95, 0.99)	37.1	0.102
CVD mortality	13	0.78 (0.70, 0.88)	76.1	0.000	13	0.94 (0.92, 0.97)	68.1	0.000
Stroke mortality	7	0.77 (0.67, 0.90)	62.8	0.013	7	0.83 (0.74, 0.93)	87.6	0.000
Fruit juice								
CVD incidence	2	0.98 (0.89, 1.08)	0.0	0.619	2	0.99 (0.96, 1.02)	0.0	0.821
CHD incidence	3	0.88 (0.74, 1.04)	28.4	0.247	3	0.97 (0.94, 1.01)	0.0	0.421
CVD mortality	1	0.81 (0.52, 1.27)	NC	NC	1	0.99 (0.93, 1.06)	NC	NC
CHD mortality	2	1.07 (0.83, 1.40)	64.3	0.094	1	1.07 (0.99, 1.17)	NC	NC
Yogurt								
CVD incidence	5	0.92 (0.84, 1.02)	59.8	0.041	5	0.98 (0.94, 1.02)	54.0	0.069
CVD mortality	7	0.90 (0.83, 0.98)	0.0	0.893	7	0.96 (0.93, 0.99)	0.0	0.839
Breakfast cereals								
Stroke incidence	1	0.88 (0.80, 0.96)	NC	NC	0	NC	NC	NC
CVD mortality	2	0.80 (0.70, 0.90)	54.8	0.137	1	0.63 (0.53, 0.71)	NC	NC
Cakes and cookies								
CVD incidence	2	0.91 (0.80, 1.05)	23.1	0.254	2	0.93 (0.86, 1.01)	0.0	0.433
Confectionary								
CVD incidence	2	1.08 (0.95, 1.23)	0.0	0.802	2	1.06 (0.96, 1.16)	0.0	0.916

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; NC, not calculable; SSBs, sugar-sweetened beverages.
[1] Highest and lowest intake categories were compared and linear dose-response analyses conducted.

In the dose-response analysis, the summary HR per 250 mL/d increment was 1.11 (95% CI: 1.05, 1.17; I^2 = 31%, *P*-heterogeneity = 0.23) (Table 1, Supplemental Figure 22). In addition, a positive linear relationship was observed between SSB intakes and the risk of CHD incidence (*P*-nonlinearity = 0.49) (Figure 2B).

SSBs and stroke incidence

Ten studies (7 publications) investigated the association between SSB intakes and risk of stroke, comprising 372,918 participants, of whom 21,524 experienced stroke. SSB intakes ranged from 0 to 479 mL/d. The summary HR for the highest level compared with the lowest level was 1.14 (95% CI: 1.04, 1.24; I^2 = 27%, *P*-heterogeneity = 0.19) (Table 1, Supplemental Figure 3). The summarized HR was not substantially altered when each study was systematically removed from the main analysis (Supplemental Table 7).

In the subgroup analyses, the observed association was stronger in studies involving only women (HR: 1.19; 95% CI: 1.08, 1.31; I^2 = 0%, *P*-heterogeneity = 0.98, *n* = 4) (Table 2), and studies involving participants in Europe (HR: 1.20; 95% CI: 1.08, 1.33; I^2 = 0%, *P*-heterogeneity = 0.86, *n* = 3) (Table 2). Conversely, the association was no longer significant in the following subsets of studies: studies involving only men (HR:1.06; 95% CI: 0.93, 1.21; I^2 = 76%, *P*-heterogeneity = 0.02, *n* = 3) (Table 2), studies of low NOS quality (HR: 0.92; 95% CI: 0.75, 1.13; I^2 = 79%, *P*-heterogeneity = 0.03, *n* = 2), studies involving participants in Asia (HR: 0.92; 95% CI: 0.75, 1.13; I^2 = 79%, *P*-heterogeneity = 0.03, *n* = 2), a study that was not based on a validated dietary assessment (HR: 1.00; 95% CI: 0.65, 1.54; *n* = 1), and a study in which follow-up was shorter than 10 years (HR: 1.00; 95% CI: 0.65, 1.54; *n* = 1).

There was no significant evidence in the meta-regression analysis. No serious publication bias was detected with the Egger test (*P* = 0.073) (Supplemental Figure 4).

In the dose-response analysis, each additional 250 mL/d in SSB intakes was positively correlated with the risk of stroke (HR: 1.08; 95% CI: 1.02, 1.13; I^2 = 24%, *P*-heterogeneity = 0.22) (Table 1, Supplemental Figure 23). A positive linear relationship was observed between SSB intakes and the risk of stroke incidence (*P*-nonlinearity = 0.24) (Figure 2C).

SSBs and CVD mortality

Eight studies (6 publications) with 25,076 deaths from CVD among 742,173 participants were eligible for the analysis of correlation between SSBs and the risk of CVD mortality. SSB intakes ranged from 0 to 971 mL/d. the summary HR for the highest category compared with the lowest category was 1.16 (95% CI: 1.06, 1.27; I^2 = 43%, *P*-heterogeneity = 0.09) (Table 1, Supplemental Figure 5). This result did not change substantially when each of the studies was omitted from the meta-analysis (Supplemental Table 7).

In the dose-response analysis, the summary HR per 250 mL/d increment in SSB intakes was 1.06 (95% CI: 1.02, 1.10; I^2 = 59%, *P*-heterogeneity = 0.02) (Table 1, Supplemental Figure 24). There was a positive linear relationship between SSB intakes and the risk of CVD mortality (*P*-nonlinearity = 0.56) (Figure 2D).

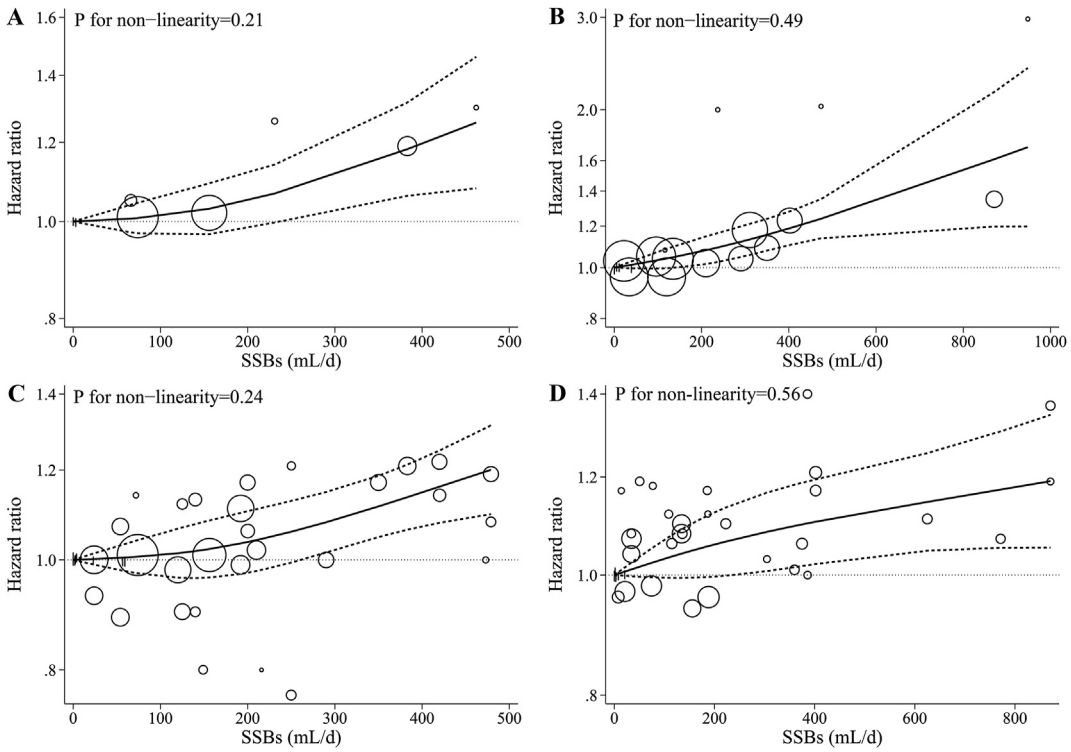

FIGURE 2. Nonlinear dose-response relationships between daily intake of sugar-sweetened beverages (SSBs) and cardiovascular disease incidence (A), coronary heart disease incidence (B), stroke incidence (C), and cardiovascular disease mortality (D). Solid line represents the nonlinear dose response, and dotted lines demarcate the 95% confidence interval. Circles represent hazard ratio point estimates for fruit intake categories from each study, with circle sizes proportional to the inverses of standard errors. Small vertical lines represent baseline SSB intake categories for each study.

Fruit intake and CVD incidence

Nine studies involving 922,094 participants, of whom 63,534 experienced CVD, were meta-analyzed. Fruit intake ranged from 0 to 653 g/d. The summary HR comparing the highest and lowest categories linked fruit intake to a lower risk of CVD (HR 0.89; 95% CI: 0.85, 0.93; $I^2 = 24\%$, *P*-heterogeneity = 0.23) (Table 1, Supplemental Figure 6). The summarized HR was not substantially altered when each study was systematically removed from the primary analysis (Supplemental Table 7).

In the linear dose-response analysis, each increase of 80 g/d in fruit intake led to a lower risk (HR 0.97; 95% CI: 0.96, 0.98; $I^2 = 60\%$, *P*-heterogeneity = 0.01) (Table 1, Supplemental Figure 25). The analysis of a nonlinear dose-response based on 8 studies that reported sufficient data suggested a J-shaped association: risk of CVD was the lowest at fruit intake of 200 g/d ($HR_{200g/d}$: 0.86; 95% CI: 0.81, 0.91), after which it slowly increased in a linear manner (*P*-nonlinearity = 0.03) (Figure 3A). However, no longer protection from CVD incidence by fruit intake was detected any more when the fruit intake was above 400 g/d.

Fruit intake and CHD incidence

Eight studies (6 publications) investigated the association between fruit intake and risk of CHD, comprising 409,025 participants, of whom 9907 experienced CHD. Fruit intake ranged from 7 to 449 g/d. The pooled analysis comparing the highest and lowest categories indicated that fruit intake was associated with lower risk of CHD (HR: 0.89; 95% CI: 0.83, 0.96; $I^2 = 0\%$, *P*-heterogeneity = 0.95) (Table 1, Supplemental Figure 7). This result did not change substantially when each of the studies was omitted from the meta-analysis (Supplemental Table 7).

In the linear dose-response analysis, the summary HR per 80 g/d increment was 0.96 (95% CI: 0.94, 0.98; $I^2 = 0\%$, *P*-heterogeneity = 0.69) (Table 1, Supplemental Figure 26). There was evidence of a nonlinear association: risk decreased slightly when fruit intake increased from 0 to 200 g/d, above which risk remained relatively constant (*P*-nonlinearity = 0.04) (Figure 3B).

Fruit intake and stroke incidence

Eleven studies (9 publications) investigated the association between fruit intake and risk of stroke, comprising 625,547 participants, of whom 16,143 experienced stroke. Fruit intake ranged from 7 to 608 g/d. The summary HR comparing the highest and lowest categories indicated that fruit intake was associated with a lower risk of stroke (HR: 0.86; 95% CI: 0.80, 0.92; $I^2 = 20\%$, *P*-heterogeneity = 0.26) (Table 1, Supplemental Figure 8). This result did not change substantially when each of the studies was omitted from the meta-analysis (Supplemental Table 7).

The association was stronger in studies where follow-up was shorter than 10 years than in studies where follow-up was at least 10 years (HR: 0.81 and 0.88, respectively) (Table 2). The association remained significant regardless of whether studies relied on a validated dietary assessment. The association between fruit intake and stroke incidence was inconsistent among subgroups of European, American, or Asian cohorts, which may reflect substantial heterogeneity across the subgroups (*P*-heterogeneity = 0.063)

TABLE 2
Subgroup analyses of studies investigating associations between consumption of SSBs and food sources of fructose and risk of stroke incidence and CVD mortality

Subgroup factor	Subgroup	*n*	HR (95% CI)	I^2 (%)	P_h[1]	P_h[2]	P[3]
SSBs and stroke incidence							
All included		10	1.14 (1.04, 1.24)	27	0.190		
Sex	Male	3	1.06 (0.93, 1.21)	76	0.015	0.374	0.497/0.256
	Female	4	1.19 (1.08, 1.31)	0	0.976		
	Both	3	1.17 (1.02, 1.36)	0	0.407		
Follow-up duration (y)	<10	1	1.00 (0.65, 1.54)	NC	NC	0.521	0.616
	≥10	9	1.15 (1.08, 1.24)	33	0.153		
Study quality	NOS <7	2	0.92 (0.75, 1.13)	79	0.030	0.024	0.054
	NOS ≥7	8	1.18 (1.10, 1.27)	0	0.922		
Validated dietary assessment	Yes	9	1.15 (1.08, 1.24)	33	0.153	0.521	0.526
	No	1	1.00 (0.65, 1.54)	NC	NC		
Geographic location	Europe	3	1.20 (1.08, 1.33)	0	0.861	0.071	0.057/0.086
	America	5	1.16 (1.05, 1.29)	0	0.724		
	Asia	2	0.92 (0.75, 1.13)	79	0.030		
Fruit and stroke incidence							
All included		11	0.86 (0.80, 0.92)	20	0.260		
Sex	Male	2	0.93 (0.80, 1.08)	44	0.182	0.513	0.417/0.575
	Female	2	0.86 (0.73, 1.01)	48	0.165		
	Both	7	0.84 (0.79, 0.90)	19	0.285		
Follow-up duration (y)	<10	4	0.81 (0.74, 0.90)	39	0.178	0.179	0.248
	≥10	7	0.88 (0.82, 0.95)	0	0.453		
Study quality	NOS <7	1	1.01 (0.68, 1.50)	NC	NC	0.414	0.471
	NOS ≥7	10	0.85 (0.79, 0.92)	24	0.226		
Validated dietary assessment	Yes	10	0.87 (0.82, 0.92)	19	0.270	0.243	0.251
	No	1	0.75 (0.59, 0.95)	NC	NC		
Geographic location[4]	Europe	5	0.85 (0.78, 0.93)	16	0.314	0.063	0.248/0.051
	America	3	0.77 (0.69, 0.86)	0	0.666		
	Asia	2	0.94 (0.83, 1.06)	0	0.660		
Fruit and CVD mortality							
All included		13	0.78 (0.70, 0.88)	76	0.000		
Sex	Male	2	0.84 (0.46, 1.52)	83	0.016	0.973	0.999/0.920
	Female	3	0.79 (0.62, 1.00)	27	0.257		
	Both	8	0.78 (0.68, 0.90)	83	0.000		
Follow-up duration (y)	<10	8	0.76 (0.66, 0.86)	57	0.024	0.288	0.290
	≥10	5	0.83 (0.73, 0.94)	63	0.028		
Validated dietary assessment	Yes	12	0.78 (0.68, 0.88)	77	0.000	0.353	0.858
	No	1	0.85 (0.73, 0.98)	NC	NC		
Geographic location[4]	Europe	8	0.77 (0.69, 0.86)	65	0.006	0.817	0.773
	Asia	4	0.74 (0.55, 1.00)	68	0.024		

CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; NC, not calculable; NOS, Newcastle-Ottawa Assessment Scale; SSBs, sugar-sweetened beverages.
[1] *P*-heterogeneity within each subgroup.
[2] *P*-heterogeneity between the subgroups.
[3] *P* for the meta-regression analysis. For sex and geographic location, 1 of the 3 categories was defined as the reference.
[4] One study with individuals from America, Europe, Asia, and Africa was excluded (84).

(Table 2). The association lost significance in studies involving only 1 sex and in studies with Asian cohorts (Table 2).

There was no significant evidence in the meta-regression analysis. No publication bias was found by the Egger test ($P = 0.414$) (Supplemental Figure 9).

In the linear dose-response analysis, the summary HR per 80 g/d increment was 0.97 (95% CI: 0.95, 0.99; $I^2 = 37\%$, *P*-heterogeneity = 0.10) (Table 1, Supplemental Figure 27). There was evidence of a nonlinear association: risk fell strongly and linearly as fruit intake increased to 200 g/d, it continued to fall slightly until intake of 300 g/d, above which it remained relatively constant (*P*-nonlinearity = 0.008) (Figure 3C).

Fruit intake and CVD mortality

Thirteen studies investigated the association between fruit intake and risk of CVD mortality, comprising 1,438,968 participants, of whom 20,605 died of CVD. Fruit intake ranged from 0 to 1033 g/d. The summary HR for the highest category compared with the lowest category of intake was 0.78 (95% CI: 0.70, 0.88; $I^2 = 76\%$, *P*-heterogeneity < 0.00001) (Table 1, Supplemental Figure 10). This result did not change substantially when each of the studies was omitted from the meta-analysis (Supplemental Table 7).

In the subgroup analysis, the association was stronger in studies where follow-up was shorter than 10 years than in studies where follow-up was at least 10 years (HR: 0.76 and 0.83, respectively) (Table 2). The association lost significance in studies involving only 1 sex and in studies with Asian cohorts (Table 2).

We did not find the factors in the subgroups accounting for the heterogeneity (Table 2). There was not significant evidence in the meta-regression analysis. No evidence was found for publication bias with the Egger test ($P = 0.854$) (Supplemental Figure 11).

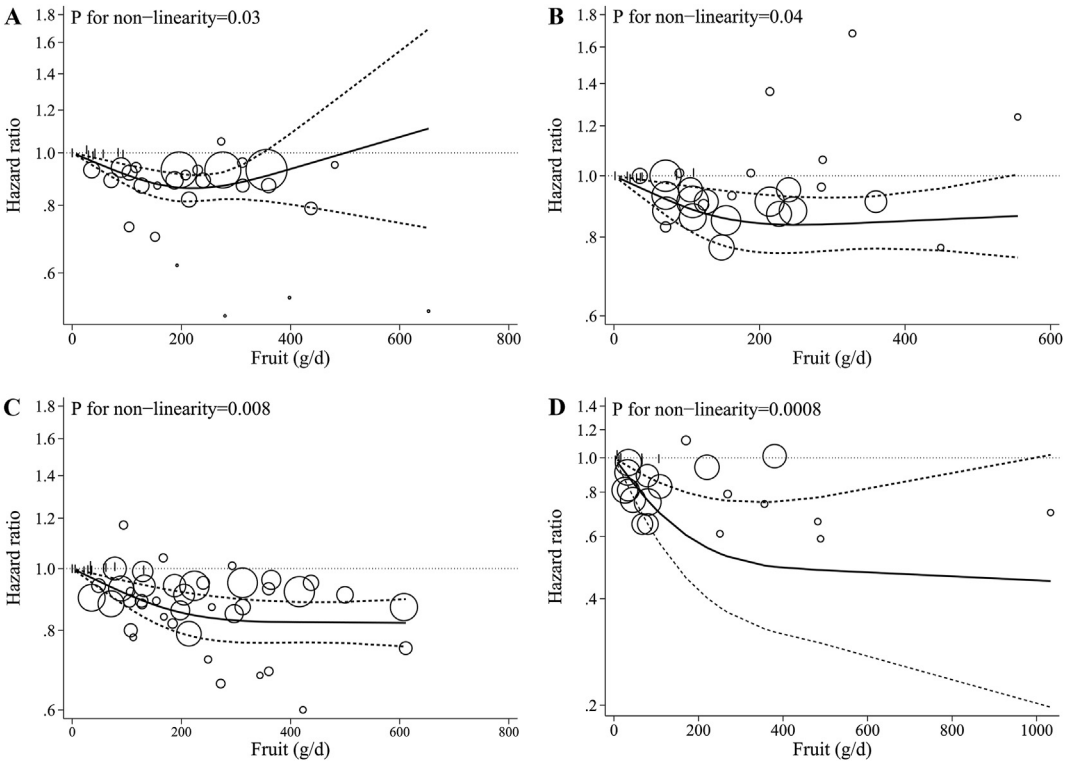

FIGURE 3. Nonlinear dose-response relationships between daily intake of fruit and cardiovascular disease incidence (A), coronary heart disease incidence (B), stroke incidence (C), and stroke mortality (D). Solid line represents the nonlinear dose response, and dotted lines represent the 95% confidence interval. Circles represent hazard ratio point estimates for fruit intake categories from each study, with circle sizes proportional to the inverses of standard errors. Small vertical lines represent baseline fruit intake categories for each study.

In the dose-response analysis, the summary HR per 80 g/d increment was 0.94 (95% CI: 0.92, 0.97; $I^2 = 68\%$, *P*-heterogeneity < 0.00001) (Table 1, Supplemental Figure 28). There was an inverse linear relationship between fruit intake and the risk of CVD mortality (*P*-nonlinearity = 0.71) (Figure 4A).

Fruit intake and stroke mortality

Seven studies (6 publications) investigated the association between fruit intake and risk of stroke-associated mortality, comprising 331,437 participants, of whom 5459 died of stroke. Fruit intake ranged from 8 to 1033 g/d. The summary HR for the highest category compared with the lowest category of fruit intake was 0.77 (95% CI: 0.67, 0.90; $I^2 = 63\%$, *P*-heterogeneity = 0.01) (Table 1, Supplemental Figure 12). In the sensitivity analyses, we were able to remove some of the heterogeneity by omitting the Multiethnic Cohort (78) from the meta-analysis (HR: 0.73; 95% CI: 0.65, 0.82; $I^2 = 26\%$, *P*-heterogeneity = 0.24). However, omitting this or any other study did not alter the significance or direction of the association (Supplemental Table 7).

In the dose-response analysis, the summary HR per 80 g/d increment was 0.83 (95% CI: 0.74, 0.93; $I^2 = 88\%$, *P*-heterogeneity < 0.00001) (Table 1, Supplemental Figure 29). The association was nonlinear: risk decreased sharply in a linear manner as fruit intake increased to 200 g/d, falling slightly further until 400 g/d, above which it remained relatively constant (*P*-nonlinearity = 0.0008) (Figure 3D).

Intake of 100% fruit juice and CVD incidence

Only 2 studies investigated the association between fruit juice intake and risk of CVD, comprising 58,091 participants, of whom 4166 were diagnosed with CVD. Fruit juice intake ranged from 0 to 267 mL/d. The summary HR for the highest compared with the lowest category of fruit juice intake was 0.98 (95% CI: 0.89, 1.08; $I^2 = 0\%$, *P*-heterogeneity = 0.62) (Table 1, Supplemental Figure 13).

Intake of 100% fruit juice and CHD incidence

Three studies investigated the association between fruit juice intake and risk of CHD, comprising 187,201 participants, of whom 11,585 were diagnosed with CHD. Fruit juice intake ranged from 0 to 350 mL/d. The summary HR for the highest category compared with the lowest category of fruit juice intake was 0.88 (95% CI: 0.74, 1.04; $I^2 = 28\%$, *P*-heterogeneity = 0.25) (Table 1, Supplemental Figure 14), indicating no significant association. Similarly, the dose-response analysis indicated a summary HR per 100 mL/d increment of 0.97 (95% CI: 0.94, 1.01; $I^2 = 0\%$, *P*-heterogeneity = 0.42) (Table 1, Supplemental Figure 30). There was an inverse linear relation between fruit juice intake and the risk of CHD incidence (*P*-nonlinearity = 0.20) (Figure 4B).

Intake of 100% fruit juice and CVD mortality

Only 1 study investigated the association between fruit juice intake and risk of CVD-associated mortality, with 30,458 participants, of whom 294 died of CVD. Fruit juice intake ranged from 5 to 585 mL/d. No association between fruit juice intake and CVD-associated mortality was found: the summary HR for the highest compared with the lowest category of fruit juice intake was 0.81 (95% CI: 0.52, 1.27) (Table 1).

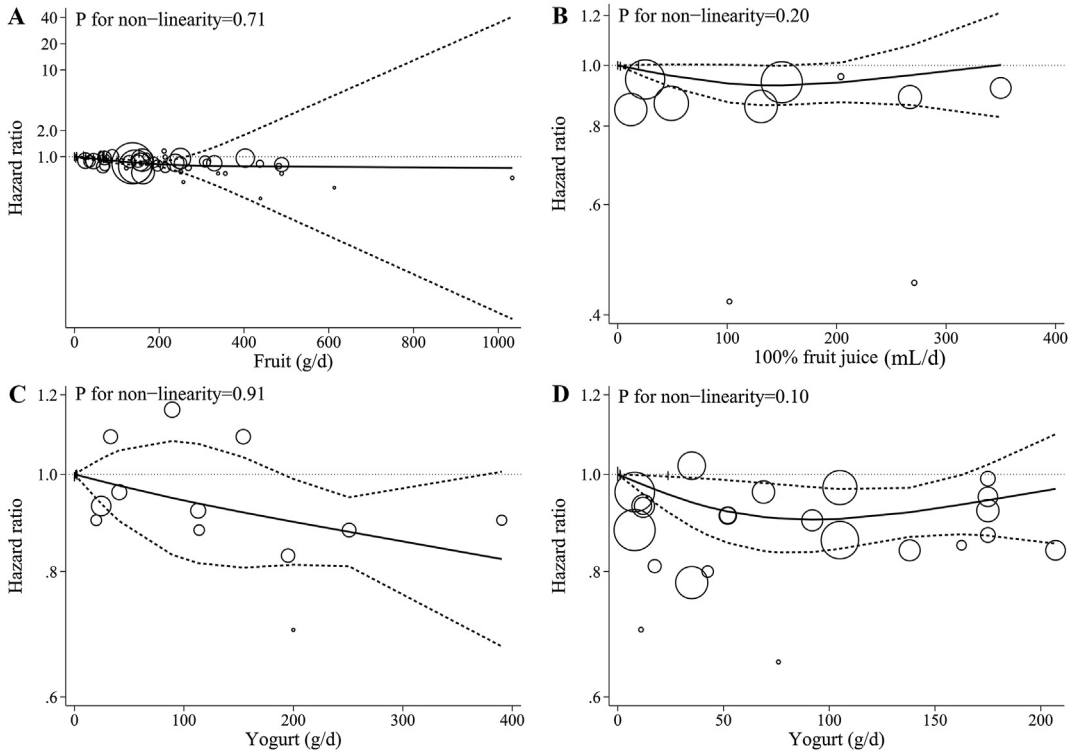

FIGURE 4. Nonlinear dose-response relationships between daily intake of fruit and cardiovascular disease mortality (A), 100% fruit juice and coronary heart disease incidence (B), yogurt and cardiovascular disease incidence (C), and yogurt and cardiovascular disease mortality (D). Solid line represents the nonlinear dose response, and dotted lines represent the 95% confidence interval. Circles represent hazard ratio point estimates for fruit intake categories from each study, with circle size proportional to the inverses of standard errors. Small vertical lines represent baseline food intake categories for each study.

Intake of 100% fruit juice and CHD mortality

Two studies investigated the relationship between fruit juice intake and CHD-associated mortality, comprising 47,929 participants, of whom 1497 died of CVD. Juice intake ranged from 0 to 341 mL/d. No association between fruit juice intake and CVD mortality was found: the summary HR for the highest compared with the lowest category of fruit juice intake was 1.07 (95% CI: 0.83, 1.40; $I^2 = 64\%$, *P*-heterogeneity = 0.09) (Table 1, Supplemental Figure 15).

Yogurt intake and CVD incidence

Five studies investigated the association between yogurt intake and risk of CVD, comprising 187,201 participants, of whom 11,585 experienced CVD. Yogurt intake ranged from 0 to 390 g/d. The summary HR for the highest category compared with the lowest category of yogurt intake was 0.92 (95% CI: 0.84, 1.02; $I^2 = 60\%$, *P*-heterogeneity = 0.04) (Table 1, Supplemental Figure 16). The sensitivity analysis identified 1 study [93] whose removal from the meta-analysis led to a significant inverse association between yogurt intake and risk of CVD (HR: 0.88; 95% CI: 0.83, 0.93; $I^2 = 45\%$, *P*-heterogeneity = 0.879) (Supplemental Table 7).

In the dose-response analysis, the summary HR per 80 g/d increment was 0.98 (95% CI: 0.94, 1.02; $I^2 = 54\%$, *P*-heterogeneity = 0.07) (Table 1, Supplemental Figure 31). There was an inverse linear relationship between yogurt intake and the risk of CVD incidence (*P*-nonlinearity = 0.91) (Figure 4C).

Yogurt intake and CVD mortality

Seven studies (6 publications) investigated the association of yogurt intake and risk of CVD-associated mortality, comprising 245,728 participants, of whom 11620 died of CVD. Yogurt intake ranged from 0 to 207 g/d. The summary HR for the highest category compared with the lowest category of yogurt intake was 0.90 (95% CI: 0.83, 0.98), with low heterogeneity ($I^2 = 0\%$, *P*-heterogeneity = 0.89) (Table 1, Supplemental Figure 17). This result did not change substantially when each of the studies was omitted from the meta-analysis (Supplemental Table 7).

In the dose-response analysis, the summary HR per 80 g/d increment was 0.96 (95% CI: 0.93, 0.99; $I^2 = 0\%$, *P*-heterogeneity = 0.84) (Table 1, Supplemental Figure 32). There was an inverse linear relationship between yogurt intake and the risk of CVD mortality (*P*-nonlinearity = 0.10) (Figure 4D).

Intake of breakfast cereals and CVD mortality

Only 2 studies investigated an association between eating breakfast cereal and risk of CVD, comprising 453,632 participants, of whom 12,664 died of CVD. The summary HR for the highest category compared with the lowest category of cereal intake was 0.80 (95% CI: 0.70, 0.90; $I^2 = 55\%$, *P*-heterogeneity = 0.14) (Table 1, Supplemental Figure 18).

Intake of cakes and cookies and CVD incidence

Two studies investigated the association between consumption of cakes or cookies and risk of CVD, comprising 49,976 participants, of whom 3286 were diagnosed with CVD. Intake of

cakes and cookies ranged from 0 to 79 g/d. No association between intake and CVD-associated mortality was found: the summary HR for the highest compared with the lowest intake category was 0.91 (95% CI: 0.80, 1.05; I^2 = 23%, *P*-heterogeneity = 0.25) (Table 1, Supplemental Figure 19). Similarly, the summary HR per 50-g/d increment was 0.93 (95% CI: 0.86, 1.01; I^2 = 0%, *P*-heterogeneity = 0.43) (Table 1, Supplemental Figure 33).

Intake of confectionaries and CVD incidence

Two studies investigated the association of confectionary intake and the risk of CVD, comprising 49,976 participants, of whom 3286 were diagnosed with CVD. Confectionary intake ranged from 0 to 76 g/d. No association between intake and risk of CVD was found: the summary HR for the highest compared with the lowest category of intake was 1.08 (95% CI: 0.95, 1.23; I^2 = 0%, *P*-heterogeneity = 0.80) (Table 1, Supplemental Figure 20). Similarly, the summary HR per-50 g/d increment was 1.06 (95% CI: 0.96, 1.16; I^2 = 0%, *P*-heterogeneity = 0.92) (Table 1, Supplemental Figure 34).

Supplemental Table 6 tabulates the detailed subgroup analysis stratified by whether adjusting for some important dietary factors and lifestyle factors (age, socioeconomic status, education level, body mass index, physical activity, hypertension, dyslipidemia, smoking, alcohol consumption, a family history of CVD, energy intake, and dietary factors). The results suggested the associations remained significant in the subgroup with studies adjusting for these factors.

GRADE assessment

Supplemental Tables 8–14 summarize the certainty of the evidence by GRADE. The evidence for the correlation between SSB intakes and stroke incidence or CVD mortality was graded as moderate. However, the inverse correlation between SSB intakes and the CVD or CHD incidence was graded as low. The evidence for the correlation between fruit intake and CVD, CHD, and stroke incidence was rated as moderate, whereas the correlation of fruit intake with CVD mortality was rated as low. The certainty of evidence for the correlation between yogurt intake and CVD mortality was moderate, whereas it was low for CVD incidence. The certainty of the evidence for the correlation between consumptions of fruit juice, breakfast cereals, cakes and cookies, or confectionary and the risk of CVD was rated as very low.

Discussion

Primary findings

In this study, we investigated whether different food sources of fructose have potentially different associations with risk of CVD, CHD, stroke, and associated mortality. To verify the hypothesis, we performed a dose-response meta-analysis of 64 publications containing 45 unique prospective cohort studies. For the incidence of CVD, CHD, and stroke, only SSB intakes demonstrated a harmful association. By contrast, fruit and yogurt showed a protective association from in a pairwise meta-analysis or dose-response meta-analysis. In addition, only the fruit intake showed asignificant effect in the nonlinear dose-response analysis. We found a relatively J-shaped relationship between fruit intake and CVD incidence: risk was the lowest at fruit intake of 200 g/d, followed by a slight and linear increase along with the increase of fruit intake until the fruit intake reached 400 g/d. No protective association with CVD was found once the fruit intake was greater than 400 g/d. Similarly, SSB intakes showed a harmful association with CVD mortality, whereas intake of fruit, yogurt, and breakfast cereals demonstrated a protective association in the pairwise meta-analysis or dose-response meta-analysis. In the nonlinear dose-response analysis, the associated risk of stroke mortality reduced when fruit intake was up to 200 g/d, and it continued to fall until 400-g/d intake, above which it remained relatively constant. We did not find the association between the risk of CVD and intake of 100% fruit juice, confectionary, or cakes and cookies.

Findings in the context of existing literature

We found a harmful association between SSB intakes and CVD, CHD, and stroke incidence. In addition, we found a harmful association between SSB intakes and CVD mortality, which was in line with previous meta-analyses [11,21], although the association was weaker than that of CVD incidence. Our dose-response analysis indicated a negative linear relationship between SSB intake and CVD morbidity and mortality, such that even low intake was harmful. These results indicated that individuals should minimize their consumption of SSBs, particularly those with cardiovascular risk factors. In the subgroup analysis, we found the association between SSB intakes and stroke incidence was stronger in studies including female participants but no significant association between the 2 factors in studies with male participants. Unlike this study, the meta-analysis by Bechthold et al. [101] showed that the association was no longer statistically significant in studies including female participants. For the subgroup with female participants, one of the differences between the study by Bechthold et al. and this study is that we included more studies in this analysis, one of which was the California Teachers Study [47]. The California Teachers Study included 106, 178 female study participants and had a weighted 20% in the meta-analysis. The more included participants and a wider range of SSB intakes may contribute to the difference of the results and made our results seem more reliable.

Our observation of protective associations between fruit intakes and risk of CVD, CHD, and stroke is consistent with previous meta-analyses [21, 102–104]. However, we observed a J-shaped dose-dependent association with a threshold of 400 g/d for fruit intake to be beneficial, and these results are inconsistent with a previous meta-analysis [103]. Our results may be more reliable because we included more studies and explored a wider range of fruit intake. The results suggested that daily fruit intake should not exceed 400g/d. Surprisingly, our subgroup analysis showed that the protective association was stronger in studies with <10 years' follow-up duration compared with those ≥10 years' follow-up. A meta-analysis by Kazemi et al. [21] published a similar result. Most of the included studies only completed the dietary assessment at baseline and did not perform a resurvey during the follow-up. The diet might have changed during long-term follow-up (range, 5–29 years), which potentially partially contributed to the finding.

In contrast to protective associations with intake of whole fruit, we did not observe healthy associations between intake of 100% fruit juices and CVD morbidity and mortality. This may reflect that 100% fruit juices contain less fiber and higher caloric

density than fresh fruits. Fruit juices may have a complex effect on disease risk: a meta-analysis linked their low intake to lower risk of stroke [105], whereas a cross-sectional study linked intake to elevated intrahepatic lipids [106]. More prospective cohort studies and intervention studies are warranted to clarify associations between consumption of 100% fruit juice and cardiovascular health.

We did not detect a significant association between yogurt intake and risk of CVD, whereas 2 meta-analyses showed a protective association [107, 108]. We would have come to a similar conclusion had we omitted the NutriNet-Santé study [93]. The NutriNet-Santé study analyzed a more inclusive category of "yogurt-like dairy products," which also contained curd cheese and petit-suisses, which may alter the apparent association with CVD.

This study focused on dietary sources of fructose; however, other aspects of diet and lifestyle can also influence the risk of cardiovascular outcomes. For example, people who consume more SSBs may also be more likely to eat a "western-style" diet. In addition, they may be more likely to lead a relatively sedentary lifestyle. Given this, we did a detailed subgroup analysis stratified by whether adjusting for some important dietary factors and lifestyle factors. Nevertheless, we found that associations remained significant in the subgroup with studies adjusting for many potential confounders: age, socioeconomic status, education level, body mass index, physical activity, hypertension, dyslipidemia, smoking, alcohol consumption, a family history of CVD, energy intake, and dietary factors. However, socioeconomic status seemed to exert a particularly strong influence on the association between fruit intake and risk of stroke. In the subgroup analysis, there was huge heterogeneity between subgroups stratified by adjustment for socioeconomic status. In addition, there was no heterogeneity between studies while a stronger association in the subgroup adjusting for socioeconomic status. The results showed socioeconomic status might be an important confounding. However, most of the included studies did not adjust for socioeconomic status. Our results highlight that future prospective studies need to consider this factor more carefully as a confounder to isolate the real associations from the confounding factors.

We calculated the percentage of included studies that have included some common and potential confounders as a confounding factor. Few studies adjusted for socioeconomic status, dyslipidemia, fish consumption, and a family history of CVD, which suggested that future prospective studies should consider them as confounding factors.

Strengths and limitations

There are several strengths to this study. First, we investigated intake of fructose-containing foods and drinks instead of individual fructose, which was in line with the focus of dietary guidelines and allowed our results to be translated more directly into dietary recommendations. Second, we investigated the association between major food sources of fructose and CVD incidence and the long-term risk of death due to CVD, which allowed us to include more studies and provide a more comprehensive assessment of the association between fructose and CVD. Third, we investigated risk to cardiovascular health in general as CVD and specifically as CHD or stroke. Fourth, we tested a potential nonlinear dose-response correlation between the food intake of various sources of fructose and CVD risks using the 1-stage mixed-effects meta-analysis, which is more flexible and accurate and avoids excluding studies reporting less than 3 exposure categories. Finally, we assessed the certainty of the evidence using the GRADE and confirm that several of our observed associations were supported by a moderately strong evidence.

However, our results should be interpreted with caution in light of several limitations. First, the observational nature of the included studies implies greater risk of confounding. Although we had performed the subgroup analysis stratified by adjustment for dietary and lifestyle factors and the associations observed persisted in the subgroup with studies adjusting for those factors, such factors may vary during follow-up in a nonrandom way, which might bias our analysis. In addition, many of the included studies did not adjust for socioeconomic status, but our analysis indicates that this factor may be important. Second, we expressed intake of fructose-containing foods, and the definitions and compositions of these foods may have varied in various studies. Most included studies provided data as the amount of food intake rather than fructose intake. Future prospective studies should aim for standardizing fructose intake according to actual fructose in specific foods according to their local food composition. Third, as noted earlier, most studies assessed dietary intake of fructose only at baseline and not again during follow-ups. Finally, we identified few studies that investigated breakfast cereals, confectionary, or cakes and cookies. More studies are needed to clarify relationships between intake of these types of food and risk of CVD.

Conclusions

We found that even low intake of SSBs is associated with elevated CVD morbidity and mortality, whereas intake of yogurt, fruit, and breakfast cereals seems to be associated with reduced risk of CVD. However, the potential health benefits of these foods may not be infinite: our analysis suggests that consuming more than 400 g of fruit per day is not associated with further reduction in CVD morbidity. Our study extends and nuances the literature on health effects of fructose by showing that its dietary origin modulates its influence on the risk of CVD, CHD, and stroke and associated mortality. Our findings should be considered when developing dietary guidelines to reduce intake of added sugars, especially fructose, for improving cardiovascular health.

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Author disclosures

The authors report no conflicts of interest.

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YGZ: drafted the search strategy; TTS, YBZ, LD: performed the literature search, data extraction, and data analyses; TTS, YGZ, QL, TL: interpreted the results; TTS: drafted the manuscript; QL, TL: critically reviewed the manuscript and take primary responsibility for the final content; and all authors: read and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advnut.2022.12.002.

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