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ORIGINAL ARTICLE

Relation of Total Sugars, Sucrose, Fructose, and Added Sugars With the Risk of Cardiovascular Disease: A Systematic Review and Dose-Response Meta-analysis of Prospective Cohort Studies

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Abstract

Objective: To determine the association of total and added fructose-containing sugars on cardiovascular (CVD) incidence and mortality.

Methods: MEDLINE, EMBASE and Cochrane Library were searched from January 1, 1980, to July 31, 2018. Prospective cohort studies assessing the association of reported intakes of total, sucrose, fructose and added sugars with CVD incidence and mortality in individuals free from disease at baseline were included. Risk estimates were pooled using the inverse variance method, and dose-response analysis was modeled.

Results: Eligibility criteria were met by 24 prospective cohort comparisons (624,128 unique individuals; 11,856 CVD incidence cases and 12,224 CVD mortality cases). Total sugars, sucrose, and fructose were not associated with CVD incidence. Total sugars (risk ratio, 1.09 [95% confidence interval, 1.02 to 1.17]) and fructose (1.08 [1.01 to 1.15]) showed a harmful association for CVD mortality, there was no association for added sugars and a beneficial association for sucrose (0.94 [0.89 to 0.99]). Dose-response analyses showed a beneficial linear dose-response gradient for sucrose and nonlinear dose-response thresholds for harm for total sugars (133 grams, 26% energy), fructose (58 grams, 11% energy) and added sugars (65 grams, 13% energy) in relation to CVD mortality ($P<.05$). The certainty of the evidence using GRADE was very low for CVD incidence and low for CVD mortality for all sugar types.

Conclusion: Current evidence supports a threshold of harm for intakes of total sugars, added sugars, and fructose at higher exposures and lack of harm for sucrose independent of food form for CVD mortality. Further research of different food sources of sugars is needed to define better the relationship between sugars and CVD.

Registration: clinicaltrials.gov, NCT01608620

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Fructose-containing sugars (sucrose, fructose) have been implicated as important drivers of the epidemic of obesity, diabetes, and cardiovascular disease (CVD),[1] resulting in recommendations from major public health agencies[2-5] and diabetes and heart associations[6-9] to set upper limits for sugars, especially for added or free fructose-containing sugars, and policy initiatives from government regulators to label and tax these sugars.[10-14] Much of the evidence supporting these recommendations and policies derives from data on sugar-sweetened beverages (SSBs), the

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Affiliations are at the end of this article.

largest source of fructose-containing sugars in the United States and Canadian diets.[15,16] Although systematic reviews and meta-analyses of prospective cohort studies have shown adverse associations of SSBs with weight gain, diabetes, and hypertension,[17-20] the same has not been seen for the fructose-containing sugars they contain.[18,21,22] Whether the reported adverse associations of SSBs with CVD[23-26] hold for different fructose-containing sugars independent of food form is unclear.[27] Our objective was to conduct a systematic review and meta-analysis of prospective cohort studies using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to determine the role of total or added fructose-containing sugars in the development of CVD.

MATERIALS AND METHODS

We conducted a systematic review and dose-response meta-analysis following the methodology from the Cochrane Handbook for Systematic Reviews and Interventions[28] and reported the results according to the MOOSE (meta-analysis of observational studies in epidemiology) guidelines[29] and the PRISMA guidelines.[30] The study protocol was registered (ClinicalTrials.gov identifier, NCT01608620).

Data Sources and Searches

We searched MEDLINE, EMBASE, and the Cochrane Library (from January 1, 1980, to July 31, 2018) for relevant studies with restrictions for prospective cohort studies according to a prevalidated list. The search strategy is presented in Supplemental Table S1 (available online at http://www.mayoclinicsproceedings.org). We supplemented the search with manual searches and reference lists of relevant articles. Authors were contacted for additional data and clarification.

Study Selection

We included prospective cohort studies in humans investigating the association between reported intakes of fructose-containing sugars (total sugars, fructose, sucrose, and added sugars) and CVD (incidence and mortality) in people free of the disease at baseline. Total sugar was defined as the sum of all monosaccharides (glucose, fructose, and galactose) and disaccharides (sucrose, lactose, and maltose).[31,32] Added sugars were defined as the sum of all monosaccharides and disaccharides used in processed and prepared foods and drinks and as sugars added to foods but not naturally occurring sugars such as in fruits and fruit juices.[31,33]

Data Extraction

Two reviewers (T.A.K. and A.A.) independently reviewed the articles and extracted relevant data. The main outcomes were CVD mortality and CVD incidence, both as a combined outcome or separated as coronary heart disease and stroke outcomes expressed as risk ratios (RR) with 95% confidence intervals (95% CI).

Risk of Bias

We assessed the risk of bias using Newcastle-Ottawa Scale. Up to 9 points were awarded based on cohort selection (max 4 points), the comparability of cohort (max 2 points), and adequacy of the outcome measures (max 3 points).[34] Studies achieving 7 points or more were considered high quality. We resolved disagreements at every stage by consensus and involving a third person (J.L.S.), if required.

Data Synthesis

All data were analyzed using Stata version 15.1 (StataCorp, College Station, Texas). RRs comparing extreme quantiles from the most adjusted models were used for analyses. When studies used continuous relative risk per dose, we imputed the extreme quantiles from other publications of the same cohort or a similar available cohort. Because of the low incidence of CVD, odds ratio (OR) and hazard ratio (HR) were treated as RRs. To obtain summary estimates, we natural log-transformed the RRs and pooled them using DerSimonian and Laird random-effects

models.[35] Separate analyses were performed for CVD incidence and mortality. Studies reporting coronary heart disease and stroke incidence were analyzed as CVD incidence. We conducted dose-response meta-analyses using methods of Greenland and Longnecker[36] (Supplemental Methods 1) in units of grams per day. When significant nonlinear association was present, we regarded the threshold for harm or protective association when the estimated nonlinear RR crossed the null (RR = 1). We report dose-response threshold in grams but also as % energy based on a 2000 kcal diet and rounded down to the nearest whole number. Heterogeneity was assessed by the Cochran Q statistic and quantified by the I^2 statistic. An $I^2 \geq 50\%$ and $P < .10$ was considered evidence of substantial heterogeneity.[28,37] To explore sources of heterogeneity, we performed sensitivity analyses involving the systematic removal of each study, restricting analyses to studies using validated measures of sugars intake and restricting analyses to studies using original (nonimputed) data. If ≥10 cohort comparisons were available, we performed prespecified subgroup analyses by sex, follow-up, type of CVD outcome for CVD incidence, Newcastle-Ottawa scale for the risk of bias and funding source. If ≥10 cohort comparisons were available, we assessed publication bias by visual inspection of funnel plots and using the Begg's and the Egger's tests.[38,39]

Grading of the Evidence

We assessed the certainty in our estimates using GRADE.[40] Included observational studies started as low certainty by default and then were downgraded or upgraded based on a prespecified criteria. Criteria to downgrade included study limitations (risk of bias), inconsistency (substantial unexplained heterogeneity), indirectness (factors that limit generalizability), imprecision (95% CI cross a minimally important difference of 5% [RR 0.95-1.05]), and publication bias (significant evidence of small-study effects). Criteria to upgrade certainty of evidence included a large magnitude of effect (RR > 2 or RR < 0.5 in the absence of plausible confounders), a dose-response gradient, and attenuation by plausible confounding factors.

Role of the Funding Sources

None of the sponsors had a role in any aspect of the current study, including design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or decision to publish.

RESULTS

Search Results

Supplemental Figure S1 shows the flow of literature. Of the 1980 reports, we included 11 reports of 10 unique prospective cohort studies (24 cohort comparisons).[27,31-33,41-47] Twelve cohort comparisons (249,788 unique participants and 11,856 cases)[27,32,41-45] assessed the relation of total sugars (8 studies), sucrose (3 studies), and fructose (1 study) with CVD incidence. Another 12 cohort comparisons (374,340 unique participants and 12,224 cases)[31,33,46,47] assessed the relation of total sugars (4 studies), added sugars (4 studies), and sucrose (2 studies) and fructose (2 studies) with CVD mortality.

Study Characteristics

The Table shows the characteristics of the 10 included prospective cohort studies. Studies were from Europe, United States, and Australia. The median age of participants was 60 years (range, 21 to 79 years). Eight studies were in healthy people, whereas 1 was in participants with diabetes[47] and 1 in patients with chronic kidney failure.[46] There were more female than male participants, with 3 exclusively female cohorts.[27,32,42] Median follow-up was 11 years (range, 8 to 16 years) for CVD incidence and 13 years (range, 9 to 15 years) for CVD mortality. Ascertainment of cases was done by medical record linkage for all studies except NHANES (National Health and Nutrition Examination Survey)[33]; Blue Mountains Eye study,[46] which used probabilistic matching; and Women's Health Initiative,[32] which used self-report. Median intakes for total

TABLE. Characteristics of Prospective Cohort Studies Investigating the Dietary Intake of Total Sugars, Sucrose, Fructose, and Added Sugars, and Cardiovascular Incidence and Mortality

Cohort	Outcome	Sex	Participants	Cases	Person-years	Age range (years)	Country	Median follow-up (years)	Exposure measurement	Outcome measure	Quantile divisions	Exposure (Median range of intake/day)	NOS[a]	Funding source
Incident CVD[a]														
EPIC-Morgen (Healthy) Burger, 2011[41]	Incident CHD[a]	M[a]	8855	581	127,961	21 to 64	Holland	12 (1995 to 2007)	Validated 79-item FFQ[a]	Medical record linkage	Per SD	Total sugars (M) (111 ± 25 grams) Total sugars (F) (106 ± 29 grams)[b]	9	Agency[c]
		F[a]	10,753	300	105,375									
	Incident stroke	M	8855	120	127,961									
		F	10,753	109	105,375									
EPIC-PROSPECT Beulens, 2007[42]	Incident CVD	F	15,714	799	157,140	49 to 70	Holland	10 (1995-2005)	Validated 77-item SFFQ[a]	Medical record linkage	Quartile (4 vs. 1)	Total Sugars (Carbohydrates 162 to 227 grams)	8	Agency
EPICOR Study Sieri, 2010[43]	Incident CHD	M	15,171	305	119,851	49 to 51	Italy	8 (1995-2003)	Validated SFFQ (Varence, Turin, Florence); Validated SFFQ via interview (Ragusa & Naples)	Medical record linkage	Quartile (4 vs. 1)	Total Sugars (118 to 243 grams)	8	Agency
		F	32,578	158	257,366									
Women's Health Initiative Taveska, 2018[32]	Incident CVD	F	64,751	5802	NA	50 to 79	USA	16	122-item SFFQ	Self-report followed by medical record	Per 20% increase	Total sugars (79 to 95 g/1000 kcal)	7	Agency
Malmo Diet Study Sonestedt, 2015; Warfa 2016[44,45]	Incident CVD	M	10,048	1694	140,672	44 to 74	Sweden	14 (recruitment 1991 to 1996)	7-d food diary, SQ 168-item FFQ, diet history interview	Medical record linkage	Quintile (5 vs. 1)	Sucrose	8	Agency
		F	16,397	1227	229,558									
Nurses Health Study Liu, 2000[27]	Incident CHD	F	75,521	761	729,472	38 to 63	USA	10 (1984 to 1994)	Validated 126-item SFFQ	Medical record linkage	Quartile (5 vs. 1)	Total sugars, total sucrose, total fructose (carbohydrates 144 to 226 grams)	8	Agency

Continued on next page

TABLE. Continued

Cohort	Outcome	Sex	Participants	Cases	Person-years	Age range (years)	Country	Median follow-up (years)	Exposure measurement	Outcome measure	Quantile divisions	Exposure (Median range of intake/day)	NOS[a]	Funding source
Fatal CVD														
Blue Mountains Eye Study Iff, 2014[46]	CVD mortality	Mixed	2664	318	33,644	65 ± 9.2	Australia	15 (1992 to 2007)	Validated 145-item SFFQ	Probabilistic matching to National Death Index	Per 100 grams	Sucrose	8	Agency
EPIC-Morgan (Diabetic) Burger, 2012[47]	CVD mortality	Mixed	6192	181	56,969	20 to 60+	Europe (France, Spain, Holland, Germany, Italy, Sweden, Denmark, UK)	9 (Recruitment 1992 to 2000)	Quantitative Dietary Questionnaire (France, Spain, Holland, Germany, Italy); Local SFFQ (Denmark, Sweden, UK)	Medical record linkage	Per SD	Total sugars (Mean ± SD, 84.6 ± 31 grams	8	Agency
NIH-AARP Diet Health Study Tasevska, 2014[31]	CVD mortality	M	206,371	7488	2,682,823	50 to 71	USA	13 (1995 to 2008)	124-item SFFQ	Medical record linkage	Quintile (5 vs. 1)	Total sugars[d] (80 to 224 grams), sucrose (31 to 83 grams), fructose (32 to 99 grams), Added sugars (33 to 106 grams)	8	Agency
		F	147,380	3406	1,915,940									
NHANES Yang, 2014[33]	CVD mortality	M	5639	434	78,028	57 ± 6.7	USA	15 (1988-2006)	24-hour dietary recall	Probabilistic matching to National Death Index	Quintile (5 vs. 1)	Added sugars (7.4% to 25.2% calories from added sugars)	8	Agency
		F	6094	397	85,011									

[a]CHD = coronary heart disease; CVD = cardiovascular disease; SFFQ = Semiquantitative Food-Frequency Questionnaire; FFQ = Food-Frequency Questionnaire; M = males; F = females; NOS = Newcastle Ottawa Scale for risk of bias.

[b]Mean ± SD.

[c]Agency funding is that from government, university or not-for-profit health agency sources.

[d]Estimated grams based upon a 2000 kcal/day die.

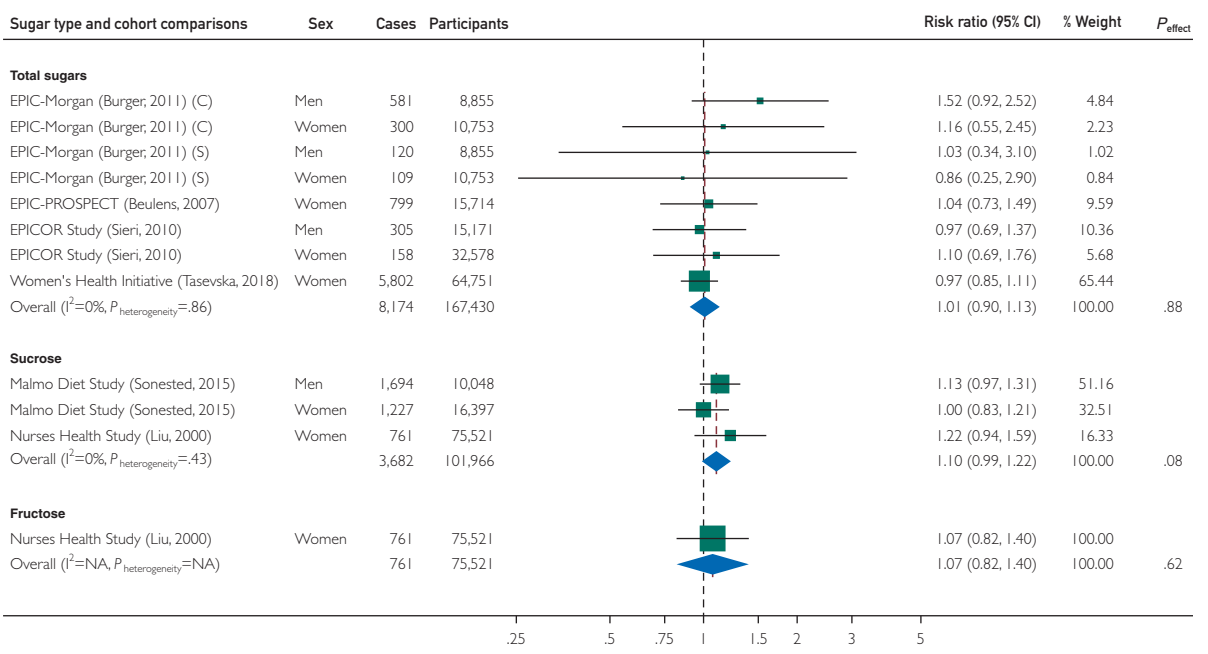


FIGURE 1. Relation between intake of sugars and cardiovascular incidence (highest vs lowest level of intake). The **green squares** with **black horizontal lines** represent risk ratio for each cohort comparison. The **blue diamonds** represent the pooled risk estimate for each sugar. Values of $I^2 \geq 50\%$ with $P_{heterogeneity} < .10$ indicate substantial heterogeneity.[28,37] Values greater than 1.0 indicate an adverse association. Results are from random-effects model. CI = confidence interval, C = CHD (coronary heart disease), S = stroke.

sugars, sucrose, fructose and added sugars were 97 g/day (range, 16 to 135 g/day), 50 g/d (range, 21 to 102 g/d), 47 g/d (range, 23 to 79 g/d), and 63 g/d (range 16 to 135 g/d), respectively. Dietary intake was assessed by validated food frequency questionnaires (FFQs) in all studies except NHANES,[33] which used 24-hour recall, and the Malmo Diet study,[44] which used both FFQs and 7-day food diaries. All studies were agency funded.

Supplemental Table S2 shows the statistical adjustments performed in the included studies. All studies adjusted for the prespecified primary confounding variable age, and 8 of the 10 cohort studies[27,31-33,41,42,47] adjusted for at least 7 of 9 of the important secondary confounding variables including sex, family history, smoking, markers of adiposity, energy intake, physical activity, presence of diabetes, hypertension (or related medications), and dyslipidemia (or related medications).

Risk of Bias Assessment

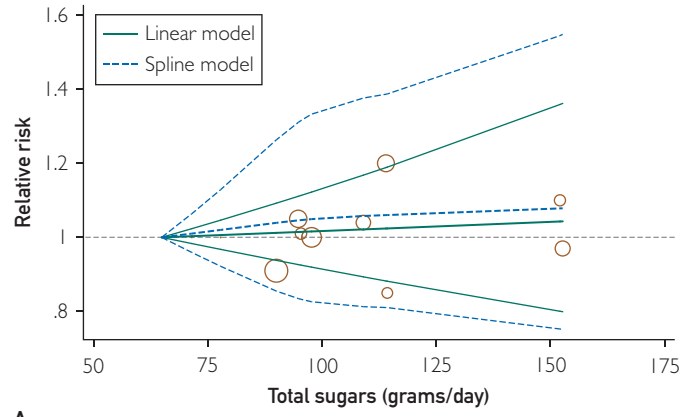
Supplemental Table S3 shows the Newcastle-Ottawa scale scores for the included studies. None of the studies was rated as high risk of bias. Publication bias could not be assessed for any of the sugars with both CVD incidence and CVD mortality, as all had ≤10 cohort comparisons.

Sugars and CVD Incidence

Figure 1 shows the relation of total sugars, sucrose, and fructose with CVD incidence, comparing the highest vs the lowest levels of exposure. There was no association of total sugars (RR 1.01, [95% CI, 0.90, 1.13], I^2=0%), sucrose (RR 1.10, [95% CI, 0.99, 1.22], I^2=0%), or fructose (RR 1.07, [95% CI, 0.82, 1.40], I^2=NA) with CVD incidence, with no evidence of heterogeneity. There were no data available for the association of added sugars with CVD incidence.

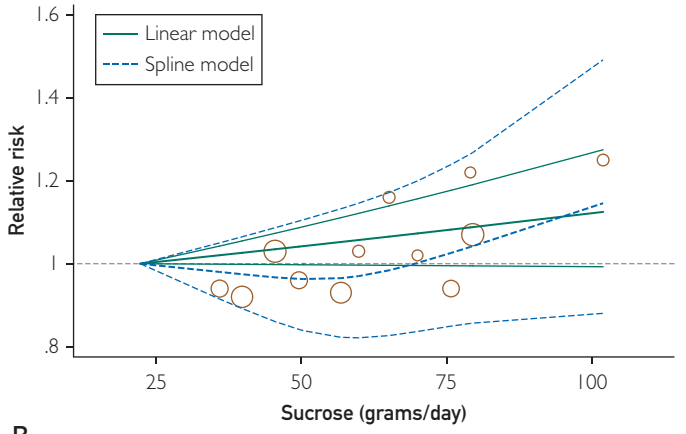
Figure 2(A-C) shows the dose-response analyses for total sugars, sucrose, and

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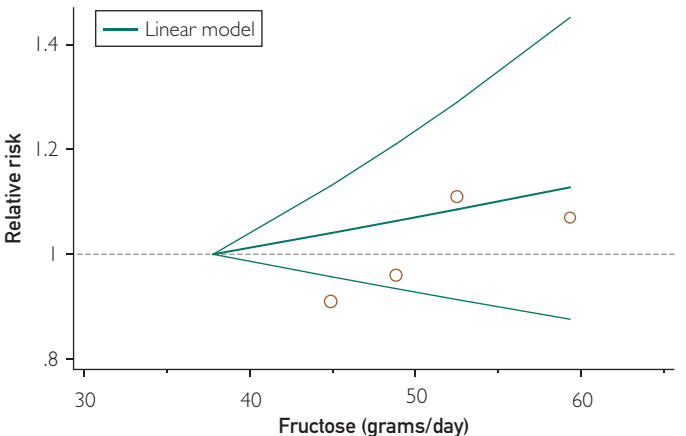
A

Linear RR per 50 grams of usual intake from total sugars: 1.02 [95% CI, 0.88 to 1.19]; *P*=.76
Departure from linearity *P*=.82



B

Linear RR per 50 gram usual intake from added sugars: 1.08 [95% CI, 0.99 to 1.16]; *P*=.07
Departure from linearity *P*=.14



C

Linear RR per 50 grams usual intake from fructose: 1.32 [95% CI, 0.74 to 2.38]; *P*=.35

FIGURE 2. Dose-response relationship between intake of (a) total sugars, (b) sucrose, (c) fructose with cardiovascular incidence. **Green solid and blue dashed lines** represent the linear and nonlinear spline models, respectively, along with their confidence intervals. The **brown circles** represent the relative risk-point estimates for the different doses from each study; the size of the **circle** is related to inverse of the variance. There were not sufficient data to calculate nonlinear dose response for fructose.

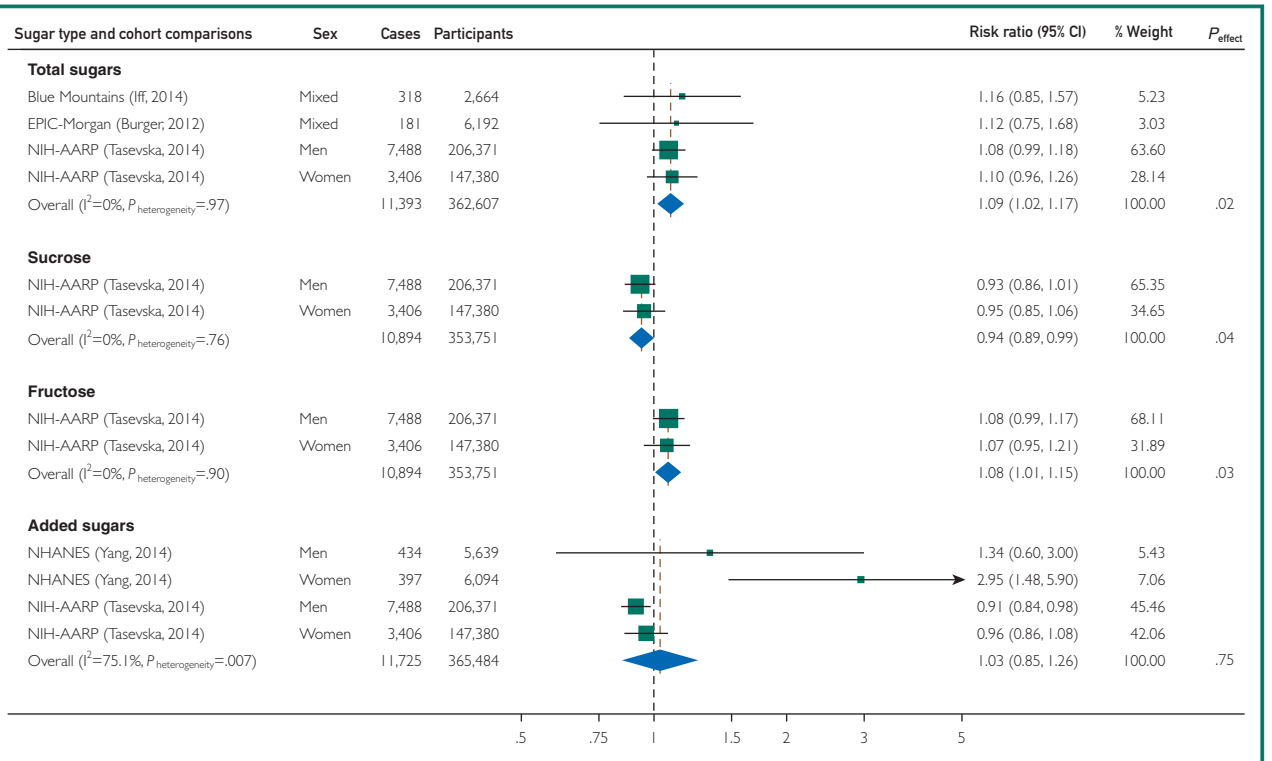


FIGURE 3. Relation between intake of sugars and cardiovascular mortality (highest vs lowest level of intake). The **green squares with black horizontal lines** represent risk ratio for each cohort comparison. The **blue diamonds** represent the pooled risk estimate for each sugar. Values of $I^2 \geq 50\%$ with $P_{heterogeneity} < .10$ indicate substantial heterogeneity.[28,37] Values greater than 1.0 indicate an adverse association. Results are from random-effects model. CI = confidence interval.

fructose with CVD incidence. Linear and nonlinear dose-response analyses were nonsignificant across the 3 sugars.

Sugars and CVD Mortality

Figure 3 shows the relation of total sugars, sucrose, fructose, and added sugars with CVD mortality, comparing the highest vs the lowest levels of exposure. Total sugars (RR 1.09, [95% CI, 1.02, 1.17]; I^2=0%) and fructose (RR 1.08, [95% CI, 1.01, 1.15]; I^2=0%) were associated with increased CVD mortality, whereas sucrose was associated with decreased CVD mortality (RR 0.94, [95% CI, 0.89, 0.99]; I^2=0%), with no evidence of heterogeneity. There was no association between added sugars and cardiovascular mortality (RR 1.03, [95% CI, 0.85, 1.26]) with evidence of substantial heterogeneity (I^2=75%, P=.007).

Figure 4(A-D) shows the dose-response analyses for total sugars, sucrose, fructose, and added sugars with CVD mortality. Nonlinear models fit best the data for total sugars (P=.001), fructose (P=.007), and added sugars (P<.001). These models identified thresholds for harm of 133 grams per day (26% of total energy) for total sugars (RR per 50 grams before threshold, 0.99 [95% CI, 0.25, 3.9]; RR_{50g} after threshold 1.17, [95% CI, 1.08, 1.27]), 58 grams per day (11% of total energy) for fructose (RR_{50g} before threshold, 0.97, [95% CI, 0.09, 11.0]; RR_{50g} after threshold 1.39, [95% CI, 1.18, 1.63]), and 65 grams/day (13% of total energy) for added sugars (RR_{50g} before threshold 0.97, [95% CI, 0.33, 5.13]; RR_{50g} after threshold 1.17, [95% CI 1.06, 1.28]). A linear inverse dose-response model fits the data best for sucrose with a RR_{50g} reduction of 7% (RR, 0.93 [95% CI, 87, 0.99]).

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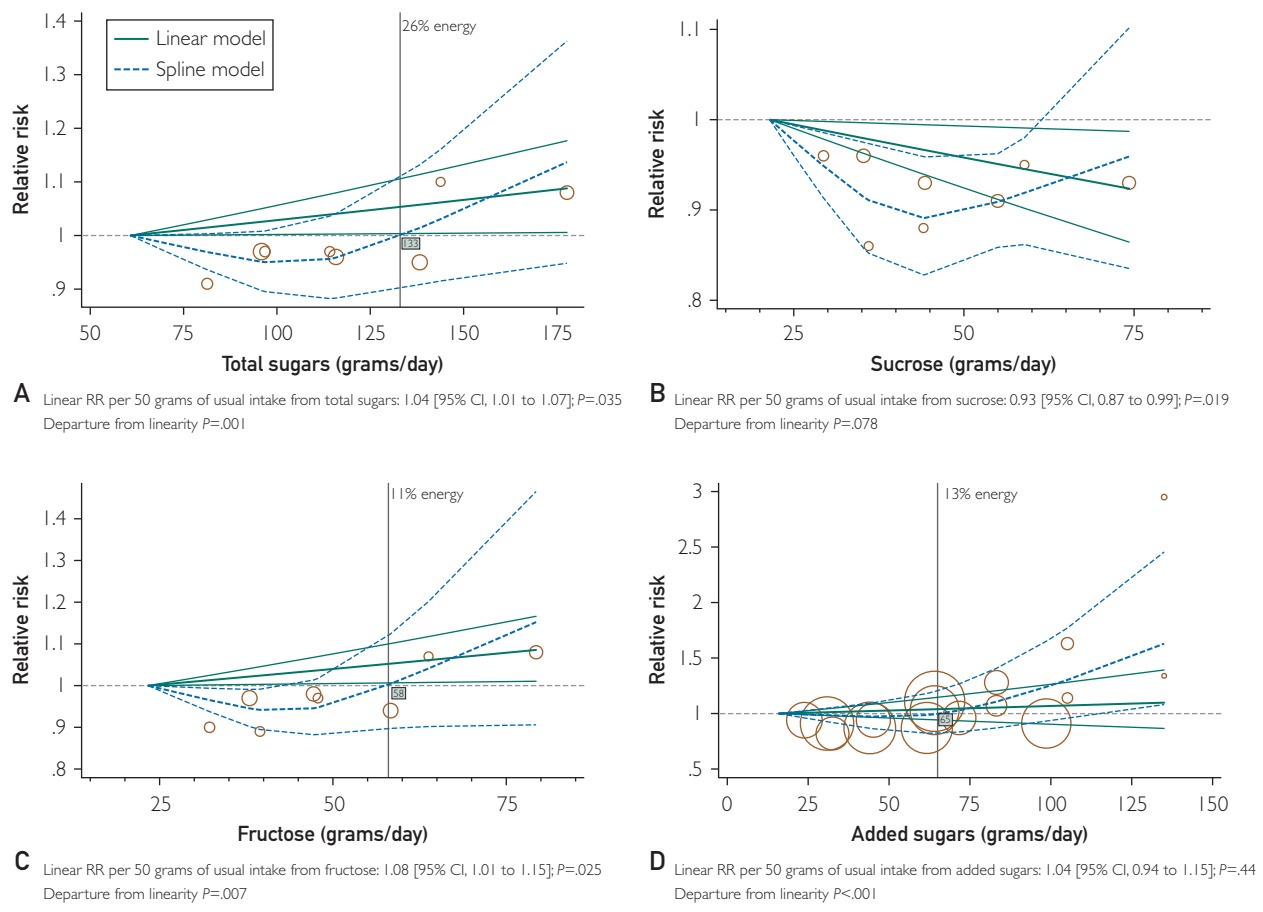


FIGURE 4. Dose-response relationship between intake of (a) total sugars, (b) sucrose, (c) fructose, and (d) added sugars with cardiovascular mortality. **Green solid and blue dashed lines** represent the linear and nonlinear spline models, respectively, along with their confidence intervals. The **brown circles** represent the relative risk-point estimates for the different doses from each study; the size of the **circle** is related to inverse of the variance. The **light green box** with a number is the threshold intake in grams where RR crosses 1; the equivalent threshold in % energy is based upon a 2000 kcal diet.

Sensitivity Analyses

Supplemental Tables S4 and S5 show the sensitivity analyses involving the systematic removal of each study for CVD incidence and mortality, respectively. The removal of the Malmo Diet Study (women) study[44] changed the significance of the association between sucrose and CVD incidence from nonsignificant to significant (RR 1.15, [95% CI, 1.01, 1.31]) without changing the direction or magnitude of the association or the evidence for heterogeneity. The removal of NIH-AARP (National Institutes of Health/American Association of Retired Persons) study[31] in men changed the association between total sugars and CVD mortality from significant to nonsignificant (RR 1.10 [95% CI, 0.99, 1.25]) without changing the magnitude, or direction of the association. Removal of either of the NIH-AARP study[31] in men or women changed the association between fructose and CVD mortality (RR 1.07 [95% CI, 0.95, 1.21] and RR 1.08 [95% CI, 0.99, 1.17], respectively) and sucrose and CVD mortality (RR 0.95 [95% CI, 0.85, 1.06] and RR 0.93 [95% CI, 0.86, 1.01], respectively) from significant to nonsignificant without changing the magnitude or direction of the association. The removal of NHANES (women) study[33] changed the direction and significance of the association between added sugars and

CVD mortality from a nonsignificant association to a protective association (RR 0.93, CI, 0.87, 0.99) and explained all of the heterogeneity (I^2=0%, P=.50).

Supplemental Figures S2 and S3 show the sensitivity analyses restricting analyses to studies using validated measures of sugars intake, and Supplemental Figures S4 and S5 show the sensitivity analyses restricting analyses to studies using original (nonimputed) extreme quantile data for CVD incidence and mortality. The sensitivity analyses did not change the significance, magnitude, or direction of the association or the evidence for heterogeneity for any of the sugars-outcome relationships.

Subgroup Analyses and Publication Bias

Subgroup analyses and publication bias were not undertaken as there were <10 cohort comparisons available.

GRADE Assessment

Supplemental Table S6 shows a summary of the GRADE assessments for CVD incidence. The certainty of the evidence for the lack of association of total sugars, fructose and sucrose with CVD incidence was rated as very low because of a downgrade for serious imprecision for total sugars and sucrose and both imprecision and indirectness for fructose.

Supplemental Table S7 shows a summary of the GRADE assessments for CVD mortality. The certainty of the evidence for the adverse association of total sugars, fructose, and added sugars with CVD mortality was rated as low, owing to a downgrade for serious imprecision and upgrade for a nonlinear dose response threshold in each case. The certainty of the evidence for the protective association of sucrose with CVD mortality was rated as low, owing to a downgrade for serious imprecision and an upgrade for a linear dose-response gradient.

DISCUSSION

Main Findings

We conducted a systematic review and dose-response meta-analysis of 10 unique prospective cohort studies (24 cohort comparisons) in 624,128 individuals involving 11,856 cases of CVD incidence and 12,224 cases of CVD mortality of the relation of total and added fructose-containing sugars with CVD risk. Total sugars, sucrose, and fructose were not associated with CVD incidence in extreme quantile analyses or in linear and nonlinear dose-response models. A harmful association of total sugars, fructose, and added sugars with CVD mortality was seen in nonlinear dose-response models with a threshold for harm above intakes of 133 grams (26% energy) for total sugars, 58 grams (11% energy) for fructose, and 65 grams (13% energy) for added sugars. No harmful association was seen at lower intakes of these sugars or at any dose for sucrose with the relationship between sucrose and CVD mortality best explained by an inverse linear dose-response gradient in which 50 grams (10% energy) increase in sucrose was associated with a 7% reduction in CVD mortality.

Findings in the Context of Existing Literature

We were unable to reproduce the same adverse associations seen between SSBs and CVD outcomes. Unlike the previous systematic reviews and meta-analyses of SSBs,[23,26,48] we did not find an association among total sugars, fructose, or sucrose with CVD incidence. The nonlinear dose response for total sugars, fructose, and added sugars with CVD mortality and protective inverse linear dose response for sucrose with CVD mortality also did not agree with the evidence of a linear dose response reported between SSBs and CVD outcomes.[23] Although our extreme quantile analyses showing an adverse association of total sugars and fructose with CVD mortality agree with similar analyses between SSBs and CVD, the presence of a nonlinear dose response suggests that excess energy may be a necessary cofactor. The lack of association of added sugars with CVD mortality in extreme quantile analyses supports this view, as the overall result was driven heavily by the larger NIH-AARP Diet Health study,[31] in which the mean energy from added sugars

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in the highest quantile was lower than that in NHANES (17% vs 27% energy), close to the level below, in which no harm was seen in the nonlinear dose-response analyses. At high doses, sugars may increase CVD risk, mainly through provision of excess energy. This is also suggested by a study in postmenopausal women that used biomarker calibrated total sugar intake energy and CVD and showed no association when adjusted for energy.[32]

The nonlinear dose-response thresholds for total sugars, fructose, and added sugars suggest the food sources of sugars may be an important consideration. SSBs may account for the signal for harm at high intakes, as SSBs represent the most important food source of these sugars.[49] The observed protective linear dose response between sucrose and CVD mortality may also represent a contribution of solid as opposed to liquid food sources. Whereas fructose as part of high-fructose corn syrup tends to act as a proxy for SSBs, sucrose tends to be found more in solid foods.[50] Total solid food sources of added sugars[31] and important food sources of sucrose[16,51]—such as grains and grain-based products, fruit and fruit products, and sweetened dairy and dairy products—have shown protective associations with CVD mortality.[52-56] The protective association of sucrose with CVD mortality may therefore reflect important contributions from these other food sources.

In addition to the role of excess calories and food sources, several other possible mechanisms may explain our variable results. Collinearity effects may be an important source of residual confounding. High consumers may have different diet and lifestyle patterns, factors for which adjustment in the analyses might not be adequate. For example, it is well recognized that high SSBs consumers tend to consume more calories, smoke more, exercise less, and have a poorer diet quality.[57] Another possibility is a hormetic response to sugars intake, implying a benefit at low doses that becomes harmful at higher doses. Hormesis is thought be a general phenomenon of a biphasic dose response exemplified by low dose-stress adaptation to environmental challenges, such as dietary factors,[58] on biological systems and that is now increasingly recognized as a possible explanation of the lack of benefit of many nutrients at higher doses.[59-62] Finally, the possibility of reverse causality cannot be ruled out. People at high risk of CVD may avoid sugars as a preventive strategy, decreasing the risk associated with sugars and explaining the observed null or protective associations.

Strengths and Limitations

The strengths of our study are that we identified all available prospective cohorts through a systematic search strategy, performed quantitative synthesis, and assessed the certainty of the evidence using the GRADE system. We had a large sample size, long duration of follow-up, and adjustment for many dietary and lifestyle factors in the included studies. Another strength is we undertook linear and nonlinear dose-response analyses for all sugars to explore dose-response gradients and thresholds. We found significant dose responses resulting in upgrades of the certainty of evidence for the adverse associations of total sugars, fructose, and added sugars and protective association of sucrose with CVD mortality

Our systematic review and meta-analysis has several limitations. First, the included prospective cohort studies were observational in nature, and so one cannot discount the possibility of measured and unmeasured residual confounding. In addition, the validity of self-reported dietary consumption is limited,[63-65] as it is argued that it represents only a collection of memories of perception of dietary intake, leading to its possible implausibility due to misestimations.[66-68] Estimates of sugar dose in our paper are based upon self-reported dietary recall and should be inferred in light of this limitation. This is the reason why the GRADE starts at "low certainty," which means that our confidence in the estimate is very limited, as the true effect might be substantially different.[69] Second, there was evidence of substantial heterogeneity among estimates of the association of added sugars with CVD mortality.

We did not, however, downgrade the evidence for serious inconsistency, as the evidence of substantial heterogeneity was explained by the removal of NHANES data in women[33] in sensitivity analyses, and the significant nonlinear dose-response threshold showed that the adverse associations driving the heterogeneity were restricted to higher intakes of added sugars (above 65 grams or 13% energy). Finally, we downgraded all summary estimates for imprecision. There was evidence of serious imprecision for the associations of all sugar types with CVD incidence and mortality outcomes. Although there was no association of total sugars, fructose, and sucrose with CVD incidence, the CIs were wide and could not rule out clinically important harm for total sugars and sucrose and clinically important benefit or harm for fructose. The CIs also could not rule out unimportant associations that were less than the prespecified minimally important difference for the associations of total sugars, fructose, and sucrose with CVD mortality and both clinically important benefit and harm for the lack of association of added sugars with CVD mortality.

Balancing the strengths and limitations, the evidence was assessed by GRADE as very low certainty for the lack of association of all fructose-containing sugars with CVD incidence and low certainty for the adverse associations of total sugars, fructose, and added sugars with CVD mortality and protective association of sucrose with CVD mortality. Applying the same criteria, the evidence for the adverse association of SSBs with CVD incidence would be similarly rated as low certainty.[23-26]

Implications

Public health recommendations and policy initiatives to reduce sugars[2-14] derive largely from data on SSBs, which assumes a linear association. Our work provides evidence to the contrary, suggesting that SSBs may not be a good proxy for understanding the association of fructose-containing sugars with CVD. The J-shaped dose-response curves obtained for the association of total sugars, fructose, and added sugars with CVD mortality suggest that these sugars may be associated with both benefit and harm. There appears to be slight reductions in risk with low intakes followed by sharp increases in risk as the number of calories provided by sugars increase. This relationship implies that there is a "sweet spot," where sugar intake represents the best compromise of caloric intake and risk. This threshold for harm starts at around 65 grams for added sugars and, assuming a median 2000 kcal diet,[3] translates to a 13% of total energy, a level that is higher than the 5% to 10% upper limit of intake of added/free sugars recommended by major public health agencies[2-5] and being used to set policy.[10-14] Our findings are consistent with the view that excess intake of calories from added sugars, such as SSBs, are associated with harm and cannot rule out a benefit at intakes <65 grams per day (13% energy) for other important food sources. A more nuanced approach to guidance may be needed as dietary guidance moves away from nutrient-based recommendations toward more food and dietary pattern-based recommendations.[70-72]

CONCLUSIONS

Our systematic review and dose-response meta-analysis of the available prospective cohort studies show a nonlinear dose-response association with CVD mortality for reported intakes of total sugars, fructose, and added sugars with thresholds for harm at high levels of intake. Sucrose did not show an adverse association with CVD mortality, and there was no association of fructose-containing sugars of any type with CVD incidence. Our certainty in the estimates is generally weak, and further research is very likely to change the estimates. Our findings suggest a higher-dose threshold for harmful association for added sugars compared with the current recommendations, implying that different food sources may differently contribute at different doses. More research is needed to assess whether the association of linear dose-response thresholds seen for SSBs in the literature hold across other important food sources of

sugars such as grain and grain-based products, fruit and fruit products, and sweetened dairy and dairy products.

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Drs Sievenpiper and Khan were responsible for the conception and design and analysis and interpretation of the data. Drs Khan, Blanco Mejia, and Sievenpiper drafted the article. Drs

Khan, Tayyiba, Agarwal, Blanco Mejia, de Souza, Wolever, Leiter, Kendall, Jenkins, and Sievenpiper were responsible for critical revision of the article for important intellectual content.

Final approval of the article was completed by Drs Khan, Tayyiba, Agarwal, de Souza,. Blanco Mejia, Wolever, Leiter, Kendall, Jenkins, and Sievenpiper. Drs Khan and de Souza provided statistical expertise, and Drs Leiter, Kendall, Jenkins, and Sievenpiper obtained funding.

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Drs Khan, Tayyiba, Agarwal, de Souza, Blanco Mejia, and Sievenpiper collected and assembled data.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CI** = confidence interval; **CVD** = cardiovascular disease; **GRADE** = Grading of Recommendations Assessment, Development, and Evaluation; **RR** = risk ratio; **SSB** = sugar-sweetened beverage

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