Association of Major Food Sources of Fructose-Containing Sugars With Incident Metabolic Syndrome
A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE Sugar-sweetened beverages (SSBs) are associated with increased risk of metabolic syndrome (MetS). However, the role of other important food sources of fructose-containing sugars in the development of MetS remains unclear.

OBJECTIVE To examine the association of major food sources of fructose-containing sugars with incident MetS.

DATA SOURCES MEDLINE, Embase, and Cochrane Library were searched from database inception to March 24, 2020, in addition to manual searches of reference lists from included studies using the following search terms: sugar-sweetened beverages, fruit drink, yogurt, metabolic syndrome, and prospective study.

STUDY SELECTION Inclusion criteria included prospective cohort studies of 1 year or longer that investigated the association of important food sources of fructose-containing sugars with incident MetS in participants free of MetS at the start of the study.

DATA EXTRACTION AND SYNTHESIS Study quality was assessed using the Newcastle-Ottawa Scale. Extreme quantile risk estimates for each food source with MetS incidence were pooled using a random-effects meta-analysis. Interstudy heterogeneity was assessed (Cochran Q statistic) and quantified (I² statistic). Dose-response analyses were performed using a 1-stage linear mixed-effects model. The certainty of the evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation). Results were reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.

MAIN OUTCOMES AND MEASURES Pooled risk ratio (RR) of incident MetS (pairwise and dose response).

RESULTS Thirteen prospective cohort studies (49 591 participants [median age, 51 years; range, 6-90 years]; 14 205 with MetS) that assessed 8 fructose-containing foods and MetS were included. An adverse linear dose-response association for SSBs (RR for 355 mL/d, 1.14; 95% CI, 1.05-1.23) and an L-shaped protective dose-response association for yogurt (RR for 85 g/d, 0.66; 95% CI, 0.58-0.76) and fruit (RR for 80 g/d, 0.82; 95% CI, 0.78-0.86) was found. Fruit juices (mixed and 100%) had a U-shaped dose-response association with protection at moderate doses (mixed fruit juice: RR for 125 mL/d, 0.58; 95% CI, 0.42-0.79; 100% fruit juice: RR for 125 mL/d, 0.77; 95% CI, 0.61-0.97). Honey, ice cream, and confectionary had no association with MetS incidence. The certainty of the evidence

(continued)
Abstract (continued)

was moderate for SSBs, yogurt, fruit, mixed fruit juice, and 100% fruit juice and very low for all other food sources.

CONCLUSIONS AND RELEVANCE The findings of this meta-analysis suggest that the adverse association of SSBs with MetS does not extend to other food sources of fructose-containing sugars, with a protective association for yogurt and fruit throughout the dose range and for 100% fruit juice and mixed fruit juices at moderate doses. Therefore, current policies and guidelines on the need to limit sources of free sugars may need to be reexamined.


Introduction

Metabolic syndrome (MetS) is a cluster of major health risk factors associated with an increased incidence of type 2 diabetes and cardiovascular disease. Although the definition and criteria for identifying MetS can vary, all definitions consider important risk factors, including large waist circumference, elevated blood pressure, low high-density lipoprotein level, elevated levels of triglycerides, and hyperglycemia.

Fructose-containing sugars (eg, sucrose and high-fructose corn syrup) in the diet have been implicated as potential contributing factors to increased MetS risk. There is strong evidence that sugar-sweetened beverages (SSBs), a major source of fructose in the North American diet, are associated with increased incident MetS. The role of other important food sources of fructose-containing sugars in the development of MetS, however, has yet to be fully elucidated. This systematic review and dose-response meta-analysis of prospective cohort studies examines the association of food sources of fructose-containing sugars and incident MetS and evaluates the strength and quality of the evidence using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).

Methods

Data Sources and Searches

This meta-analysis followed the Cochrane Handbook for Systematic Reviews of Interventions. Results were reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. The study protocol was registered at ClinicalTrials.gov. Data sources included MEDLINE, Embase, and the Cochrane Library from database inception to March 24, 2020. Manual search of the reference lists from included studies supplemented the database search. Search terms reflected the most consumed food sources of fructose-containing sugars (based on national surveys that outlined the leading fructose-containing added or free sugar foods) (eg, sugar-sweetened beverages, fruit drink, and yogurt), the outcome of interest (eg, metabolic syndrome), and the study design (eg, prospective study) (eTable 1 in the Supplement).

Study Selection

Prospective cohort studies of 1 year or longer that investigated the association of major food sources of fructose-containing sugars with incident MetS in participants free of MetS at baseline were included (eTable 1 in the Supplement). If multiple publications of the same cohort provided results on the same outcome with overlapping groups of individuals, the longest follow-up study was included. Abstracts and unpublished studies were excluded.
Data Extraction and Quality Assessment

Two independent reviewers (Z.S.A. and T.A.K) extracted relevant data, including sample size, participant characteristics, food source of fructose-containing sugars, exposure levels, follow-up duration, number of MetS cases, covariates in fully adjusted models, and the relative risk (RR) with 95% CIs of incident MetS per category of intake, median dose in each category, and funding source, dual-sequentially. Studies were assessed for risk of bias using the Newcastle-Ottawa Scale. A maximum of 9 points could be awarded, with 0 points indicating lowest study quality and 9 points indicating highest study quality. A score of 6 points was the minimum threshold for the study to be considered higher quality. Disagreements were resolved by consensus or by involving a third person (J.L.S.). The GRADE approach was used to assess the overall certainty and strength of the evidence, ranging from high to very low certainty (eAppendix I in the Supplement).

Statistical Analysis

Pairwise meta-analyses and sensitivity analyses were conducted in R software, version 3.6.1 (R Foundation for Statistical Computing) using dmetar. Dose-response analyses were conducted in Stata software, version 16 (StataCorp) using drmeta. Each food source of fructose-containing sugar was considered as an independent exposure. Risk ratios (RRs) of extreme quantiles from the most adjusted models were used for pairwise analyses. When studies used continuous RRs per dose, we imputed the extreme quantiles from other publications of the same or similar cohort. Hazard ratios and odds ratios were converted to RRs based on the recommended method by Zhang and Yu (eAppendix 2 in the Supplement).

Summary estimates were determined by natural log transforming and pooling the RRs using the DerSimonian and Laird random-effects model. A fixed-effects model was used if the number of studies was 5 or fewer. Unit-of-analysis error (for studies that appeared more than once in the same food source analysis) was addressed by dividing participants equally among the multiple comparisons and readjusting the log SEs. Interstudy heterogeneity was assessed using the Cochran Q ($\chi^2$) statistic and quantified by the $I^2$ statistic, where $I^2$ of 50% or greater and $p < .10$ determined by the Q statistic represented evidence of substantial heterogeneity. Sources of heterogeneity were assessed by sensitivity analyses that involved the systematic removal of each study for food sources with more than 2 cohorts. If 10 or more cohort comparisons were available, a priori subgroup analyses were performed.

If 10 or more cohort comparisons were available, studies were assessed for publication bias by visual inspection of funnel plots and formal testing using the Begg and Egger tests, with significance set at $p < .10$. In the presence of publication bias, the Duval and Tweedie trim and fill method was used. Dose responses were modeled using RRs (95% CIs) from dose categories to determine the shape of the association between the dose of the fructose-containing foods and the risk of MetS (eAppendix 3 in the Supplement). Doses were defined as the mean consumption in each reported category or quantile. We reported nonlinear associations for a study if results of the Wald test for departure from linearity were significant at $p < .10$ (2-sided). The significance for the main pooled RR for the pairwise analyses was based on $p < .05$.

Results

Search Results

Thirteen reports (49 591 participants and 14 205 cases) with data from 8 unique prospective cohorts met the inclusion criteria (Figure 1). Eight major food sources of fructose-containing sugars were identified, including SSBs (7 cohort comparisons; 20 480 participants and 7406 cases), mixed fruit juice (3 cohort comparisons; 3062 participants and 1322 cases),
100% fruit juice (2 cohort comparisons; 5464 participants and 1389 cases\(^{31,32,40}\)), fruit (4 cohort comparisons; 10 074 participants and 3002 cases \(^{30,33,40}\)), yogurt (5 cohort comparisons; 19 057 participants and 3877 cases \(^{29,30,35,39}\)), honey (1 cohort; 3616 participants and 590 cases \(^{30}\)), ice cream (1 cohort; 3616 participants and 590 cases \(^{30}\)), and confectionary (2 cohort comparisons; 1476 participants and 250 cases \(^{30}\)). Prospective cohort studies that assessed grain and grain-based products or other fruit- or dairy-based products with incident MetS were not identified.

**Study Characteristics**

The Table gives the characteristics of the 13 prospective cohort studies.\(^ {28-40}\) Studies included data from the US, Spain, Iran, and South Korea. Participants ranged from adolescents to older adults (median age, 51 years; range, 6-90 years). Appelhans et al\(^ {28}\) exclusively studied a female cohort. The mean (SD) duration of follow-up was 5.7 (3.3) years (range, 2.0-14.0 years). Fruit juice was considered to be mixed fruit juice if the study combined fruit drinks and fruit juice or did not specify the kind of fruit juice (100% fruit juice or fruit drink). Yogurt was considered a source of fructose given that more than 70% of the yogurt products are flavored\(^ {41}\) and consumers prefer yogurt products with a moderate (approximately 7%-10%) concentration of added sucrose.\(^ {42-44}\) MetS was defined using the Adult Treatment Panel III,\(^ {31,34-38,40}\) harmonized criteria,\(^ {28-30,32,39}\) or a continuous scale\(^ {33}\) (eAppendix 4 in the Supplement). All studies were agency funded.

All studies, except for the study by Cheraghi et al,\(^ {30}\) adjusted for age and multiple prespecified primary confounding variables, including sex, markers of obesity, smoking, family history of MetS, energy or calorie intake, diabetes, physical activity, and alcohol intake (eTable 2 in the Supplement). Between 4 and 26 variables were adjusted for in fully adjusted models of the 12 studies\(^ {28,29,31-40}\) that detailed their statistical process.

**Risk of Bias**

None of the studies were rated as high risk of bias (eTable 3 in the Supplement). Statistical tests for publication bias could not be assessed for any food source because of 10 or fewer cohort comparisons.

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**Figure 1. Diagram of Study Selection**

[Diagram showing the selection process with numbers and categories, such as reports identified, included in the analysis, excluded, and reasons for exclusion.]

MetS indicates metabolic syndrome.
## Table. Characteristics of Prospective Cohort Studies Investigating Dietary Intake of Food Sources of Fructose-Containing Sugars and MetS

<table>
<thead>
<tr>
<th>Source</th>
<th>Cohort name</th>
<th>Country</th>
<th>Follow-up duration, y</th>
<th>Sex</th>
<th>No. of participants</th>
<th>No. of MetS cases</th>
<th>Baseline age range, y</th>
<th>Dietary assessment</th>
<th>Food source</th>
<th>MetS assessment</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appelhans et al,28 2017</td>
<td>SWAN</td>
<td>US</td>
<td>14a</td>
<td>Female</td>
<td>1401</td>
<td>268</td>
<td>42-52</td>
<td>FFQ (interviewer administered)</td>
<td>SSB</td>
<td>Harmonized criteria</td>
<td>Agency</td>
</tr>
<tr>
<td>Babio et al,29 2015</td>
<td>PREDIMED</td>
<td>Spain</td>
<td>3.2b</td>
<td>Both</td>
<td>1868</td>
<td>930</td>
<td>Male: 55-80; female: 60-80.</td>
<td>SFFQ</td>
<td>Yogurt</td>
<td>Harmonized criteria</td>
<td>Agency</td>
</tr>
<tr>
<td>Cheraghi et al,30 2016</td>
<td>TLGS</td>
<td>Iran</td>
<td>2.05b</td>
<td>Both</td>
<td>3616</td>
<td>590</td>
<td>≥20</td>
<td>FFQ (interviewer administered)</td>
<td>Fruit, yogurt, ice cream, honey</td>
<td>Harmonized criteria</td>
<td>Agency</td>
</tr>
<tr>
<td>Duffey et al,31 2010</td>
<td>CARDIA</td>
<td>US</td>
<td>7a</td>
<td>Both</td>
<td>3596</td>
<td>459</td>
<td>18-30</td>
<td>SFQ (interviewer administered)</td>
<td>100% fruit juice</td>
<td>ATP III</td>
<td>Agency</td>
</tr>
<tr>
<td>Ferreira-Pêgo et al,32 2016</td>
<td>PREDIMED</td>
<td>Spain</td>
<td>3.24b</td>
<td>Both</td>
<td>1868</td>
<td>930</td>
<td>55-80</td>
<td>SFQ</td>
<td>SSB, mixed fruit juice, 100% fruit juice</td>
<td>Harmonized criteria</td>
<td>Agency</td>
</tr>
<tr>
<td>Hur et al,33 2016</td>
<td>KoCAS</td>
<td>South Korea</td>
<td>4a</td>
<td>Both</td>
<td>770</td>
<td>345</td>
<td>9-10</td>
<td>3-d FR</td>
<td>Fruit sugar, beverage sugar</td>
<td>cMET</td>
<td>Agency</td>
</tr>
<tr>
<td>Kang and Kim,34 2017</td>
<td>KoGES</td>
<td>South Korea</td>
<td>5.7c</td>
<td>Both</td>
<td>5797</td>
<td>2129</td>
<td>40-69</td>
<td>SFFQ</td>
<td>SSB</td>
<td>ATP III</td>
<td>Agency</td>
</tr>
<tr>
<td>Kim and Kim,35 2017</td>
<td>KoGES</td>
<td>South Korea</td>
<td>5.7c</td>
<td>Both</td>
<td>5510</td>
<td>2103</td>
<td>40-69</td>
<td>SFFQ</td>
<td>Yogurt</td>
<td>ATP III</td>
<td>Agency</td>
</tr>
<tr>
<td>Lim and Kim,36 2019</td>
<td>KoGES</td>
<td>South Korea</td>
<td>8a</td>
<td>Both</td>
<td>5688</td>
<td>2067</td>
<td>40-69</td>
<td>SFFQ</td>
<td>Fruit</td>
<td>ATP III</td>
<td>Agency</td>
</tr>
<tr>
<td>Lutsey et al,37 2008</td>
<td>ARIC</td>
<td>US</td>
<td>9a</td>
<td>Both</td>
<td>9514</td>
<td>3782</td>
<td>45-64</td>
<td>FFQ</td>
<td>SSB</td>
<td>ATP III</td>
<td>Agency</td>
</tr>
<tr>
<td>Mirmiran et al,38 2014</td>
<td>TLGS</td>
<td>Iran</td>
<td>3a</td>
<td>Both</td>
<td>1476</td>
<td>249</td>
<td>19-70</td>
<td>SFFQ</td>
<td>Biscuits and cakes, candies and chocolate, SSB</td>
<td>ATP III with specific waist circumference cutoffs for Iranian adults</td>
<td>Agency</td>
</tr>
<tr>
<td>Mirmiran et al,38 2015</td>
<td>TLGS</td>
<td>Iran</td>
<td>3.6d</td>
<td>Both</td>
<td>424</td>
<td>47</td>
<td>6-18</td>
<td>SFFQ</td>
<td>SSB, mixed fruit juice</td>
<td>ATP III adapted definition for adolescents</td>
<td>Agency</td>
</tr>
<tr>
<td>Sayón-Orea et al,39 2015</td>
<td>SUN</td>
<td>Spain</td>
<td>6a</td>
<td>Both</td>
<td>8063</td>
<td>306</td>
<td>20-90</td>
<td>SFFQ</td>
<td>Yogurt</td>
<td>Harmonized criteria</td>
<td>Agency</td>
</tr>
</tbody>
</table>

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; ATP III, Adult Treatment Panel III; CARDIA, Coronary Artery Risk Development in Young Adults; cMET, continuous MetS score; FFQ, Food Frequency Questionnaire; FR, food records; KoCAS, Korean Child Adolescents Cohort Study; KoGES, Korean Genome and Epidemiology Study; MetS, metabolic syndrome; PREDIMED,Prevención con Dieta Mediterránea; TLGS, Tehran Lipid and Glucose Study; SFFQ, Semiquantitative Food Frequency Questionnaire; SSB, sugar-sweetened beverage; SUN, Sequimiento University of Navarra; SWAN, Study of Women's Health Across the Nation.

a Mean value.
b Median value.

c Harmonized criteria of the American Heart Association/National Heart, Lung, and Blood Institute, and the International Diabetes Federation definitions for metabolic syndrome.
d Agency funding is that from government, university, or not-for-profit health agency.
Important Food Sources of Fructose-Containing Sugars and Incident MetS

Figure 2 and eFigures 1 through 8 in the Supplement illustrate the association between food sources of fructose-containing sugars and incident MetS. Intake of SSBs was associated with an increased risk of incident MetS (RR, 1.20; 95% CI, 1.06-1.36), with evidence of significant heterogeneity\(^\text{15}\) (\(I^2 = 68\%\); \(P = .005\) determined by the \(Q\) statistic). Fruit and yogurt intake had an inverse association with incident MetS (fruit: RR, 0.91; 95% CI, 0.89-0.93; \(I^2 = 0\%\); \(P = .78\) determined by the \(Q\) statistic; yogurt: RR, 0.83; 95% CI, 0.77-0.90; \(I^2 = 65\%\); \(P = .02\) determined by the \(Q\) statistic). No association was found between mixed fruit juice, 100% fruit juice, honey, ice cream, or confectionary with MetS incidence.

Sensitivity Analyses
eTable 5 in the Supplement details the sensitivity analysis after systematic removal of each cohort study for food sources with more than 2 studies. Results for SSBs did not alter in direction and significance of association (eg, maintained an adverse association with MetS incidence) or the evidence of heterogeneity. Similar results were found for mixed fruit juice and fruit, where removal of each study maintained no association for mixed fruit juice and a significant protective association for fruit. Heterogeneity in both mixed fruit juice and fruit remained nonsignificant. Removal of the study by Cheraghiet al\(^\text{30}\) resulted in nonsignificant evidence of interstudy heterogeneity for yogurt; however, it did not significantly affect the pooled estimate. Because none of the comparisons had 10 or more cohorts, subgroup analyses were not performed.

Dose Response

Figure 2 and Figure 3 show the dose-response association of each food source and incident MetS. Data from 6 cohorts,32,34,36-38 with a dose range of 0 to 680 mL/d, demonstrated an adverse linear dose-response association between SSB intake and MetS (RR for 355 mL/d, 1.14; 95% CI, 1.05-1.23), with no evidence for departure from linearity (\(P = .27\)) (Figure 3).

Data for mixed fruit juice (2 cohorts32,38) and 100% fruit juice (1 cohort37) indicate a U-shaped, significant, nonlinear dose-response association with incident MetS, with the curve suggesting a maximum protection between 75 and 150 mL. There was no protective association after 200 mL/d for mixed fruit juice intake and after 175 mL/d for 100% fruit juice. The estimated RR for 125 mL/d was 0.58 (95% CI, 0.42-0.79) for mixed fruit juice and 0.77 (95% CI, 0.61-0.97) for 100% fruit juice.

Data from 2 cohorts40 with a dose range of 0 to 600 g/d found a significant L-shaped, protective, nonlinear dose response for fruit intake and incident MetS, suggesting a sharp reduction of RR until 450 g/d. The estimated RR for 240 g (3 servings) was 0.61 (95% CI, 0.55-0.68).

Data from 3 cohorts29,35 with a dose range of 0 to 129 g/d of yogurt intake found an L-shaped, protective, nonlinear dose-response association with incident MetS, with the curve suggesting a sharp reduction of RR until 80 g/d. The estimated RR for 85 g (one-third cup serving) was 0.66 (95% CI, 0.58-0.76).

Confectionary data from 2 cohorts37 with a dose range of 8 to 84 g/d found no evidence of a dose-response association with incident MetS (RR per 50 g, 1.18; 95% CI, 0.98-1.42). Relevant data were not available to assess the dose-response association for honey and ice cream.

GRADE Assessment

The GRADE certainty of evidence was moderate for adverse association for SSBs and protective association for mixed fruit juice, 100% fruit juice, fruit, and yogurt with MetS risk attributable to upgrades for dose-response gradient (Figure 2 and eTable 4 in the Supplement). Although both SSBs and 100% fruit juice had substantial interstudy heterogeneity (\(I^2 = 68\%\) for SSBs and 73% for fruit juice), the RR estimates for SSB studies were all in the same direction with considerable overlap. In addition, the heterogeneity observed with 100% fruit juice was explained by the nonlinear dose-response model. Therefore, these 2 food sources were not downgraded for inconsistency. The certainty of evidence of no association was very low for honey, ice cream, and confectionary because...
Figure 2. Summary Superplot for the Association Between Important Food Sources of Fructose-Containing Sugars and Incident Metabolic Syndrome

<table>
<thead>
<tr>
<th>Food source and comparison</th>
<th>No. of cases/ No. of participants</th>
<th>Risk ratio (95% CI)</th>
<th>P</th>
<th>Heterogeneity</th>
<th>Favors positive association</th>
<th>Favors adverse association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar-sweetened beverage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme quantiles</td>
<td>7/125 mL</td>
<td>1.21 (1.06-1.31)</td>
<td>.005</td>
<td>68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear DRM per 3.5 mL</td>
<td></td>
<td>1.14 (1.05-1.23)</td>
<td>.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed fruit juice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme quantiles</td>
<td>3/125 mL</td>
<td>1.13 (0.91-1.41)</td>
<td>.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlinear DRM at 50 mL</td>
<td></td>
<td>0.67 (0.54-0.83)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlinear DRM at 125 mL</td>
<td></td>
<td>0.58 (0.42-0.79)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlinear DRM at 200 mL</td>
<td></td>
<td>0.87 (0.69-1.09)</td>
<td>&lt;.001</td>
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<td></td>
<td></td>
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<tr>
<td>100% Fruit juice</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Extreme quantiles</td>
<td>2/100% Fruit juice</td>
<td>1.02 (0.92-1.13)</td>
<td>.66</td>
<td>73%</td>
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<tr>
<td>Nonlinear DRM at 50 mL</td>
<td></td>
<td>0.82 (0.72-0.94)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlinear DRM at 125 mL</td>
<td></td>
<td>0.77 (0.61-0.97)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlinear DRM at 200 mL</td>
<td></td>
<td>1.14 (0.90-1.45)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme quantiles</td>
<td>4/100% Fruit juice</td>
<td>0.91 (0.89-0.93)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlinear DRM at 80 g</td>
<td></td>
<td>0.82 (0.78-0.86)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlinear DRM at 240 g</td>
<td></td>
<td>0.61 (0.55-0.68)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlinear DRM at 480 g</td>
<td></td>
<td>0.53 (0.47-0.60)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yogurt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme quantiles</td>
<td>5/100% Fruit juice</td>
<td>0.83 (0.77-0.90)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nonlinear DRM at 35 g</td>
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<td>0.76 (0.69-0.84)</td>
<td>&lt;.001</td>
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<tr>
<td>Nonlinear DRM at 60 g</td>
<td></td>
<td>0.68 (0.60-0.78)</td>
<td>&lt;.001</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nonlinear DRM at 85 g</td>
<td></td>
<td>0.66 (0.58-0.76)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honey</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Extreme quantiles</td>
<td>1/350 mL</td>
<td>1.00 (0.50-2.00)</td>
<td>.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ice cream</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme quantiles</td>
<td>1/350 mL</td>
<td>0.94 (0.84-1.06)</td>
<td>.31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confectionary</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Extreme quantiles</td>
<td>2/350 mL</td>
<td>1.21 (0.92-1.60)</td>
<td>.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear DRM per 50 g</td>
<td></td>
<td>1.18 (0.98-1.42)</td>
<td>.07</td>
<td></td>
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</tr>
</tbody>
</table>

Pooled risk estimate is represented by the data markers. P values of 50% or greater (P >.10 determined by the Q statistic) indicate substantial heterogeneity, and risk ratios greater than 1.00 indicate an adverse association. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) of prospective cohort studies are rated as low certainty of evidence and can be downgraded by 5 domains and upgraded by 3 domains. The filled black squares indicate downgrade and/or upgrades for each outcome. DRM indicate dose response meta-analysis; NA, not applicable.
of downgrades for serious imprecision, indirectness for honey, ice cream, and confectionary with no upgrades.

**Discussion**

In our systematic review and meta-analysis, 13 prospective cohort studies (including 49,591 participants and 14,205 MetS cases) found that SSB intake was associated with an increased risk for MetS incidence, whereas yogurt and fruit were associated with a reduced risk. Mixed fruit juice and 100% fruit juice had a U-shaped association with MetS, presenting a protective association between 75 and 150 mL/d and an adverse association for more than 175 to 200 mL/d. No association was found between honey, ice cream, and confectionary and MetS incidence.

The adverse association of SSB intake and MetS incidence in our study is consistent with the current literature. Previous meta-analyses found a 20% and 46% increased MetS risk with higher SSB consumption from 3 prospective and 8 cross-sectional studies, respectively. Our findings expand on current findings by the inclusion of 7 prospective cohorts and the assessment of dose response, which found a 14% increased risk of MetS incidence per 355-mL daily serving of SSBs.

The association between SSB and incident MetS may reflect a general unhealthy lifestyle whereby individuals with greater SSB intake are likely to have a poorer diet quality, higher caloric intake, and a sedentary lifestyle. Furthermore, SSBs are a source of liquid calories, which can have a lower effect on satiety compared with solid foods, resulting in increased energy intake, weight gain, and downstream complications related to MetS. Although the prospective studies included...
in our SSB analysis controlled for potential confounding factors, all except 1 study controlled for total energy intake, and 2 studies did not adjust for adiposity, an important risk factor and component of MetS. Thus, residual and unmeasured confounding could have contributed to the observed adverse association.

Conversely, yogurt had a protective association against MetS incidence, with a dose-dependent benefit with intakes of 60 to 80 g/d. The nonlinear findings indicate that the association above 85 g/d plateaus, and data are lacking to suggest any benefit associated with increasing intake beyond this dose. The role of yogurt, or more broadly dairy intake, and MetS has gained attention during the past decade. A meta-analysis highlighted that higher dairy consumption was inversely associated with MetS incidence by 14% among 7 prospective cohorts with a dose-response reduction with incremental intake. Our findings broadly concur with these results. This protective association of yogurt may be attributable to its rich micronutrient composition. Calcium, a major nutrient in yogurt, decreases fat absorption, lowers triglyceride concentration, improves the overall ratio of high-density lipoprotein to low-density lipoprotein. In addition, dairy-derived saturated fats have anti-inflammatory properties and potentially improve insulin sensitivity and glycemic response.

Furthermore, the probiotic bacteria found in yogurt products have been linked to modulating gut microbiota through the reduction of pathogenic bacteria while increasing metabolite production and modulating various inflammatory reactions, all of which can aid in reducing the risk of MetS.

Similarly, fruit consumption presented a protective association against MetS incidence, with the greatest dose benefit at 300 to 450 g/d (equivalent to 3-5 servings). Fruit intake is protective for some components of MetS, including waist circumference and blood pressure; however, evidence on the dose range with MetS is limited. Most fruit intake and MetS studies are cross-sectional in design or are assessed in combination with vegetable intake, making it difficult to determine the association of specific fructose-containing fruits with MetS. One such meta-analysis of cross-sectional studies found that fruit intake had a protective association with MetS risk.

We identified a U-shaped dose-dependent association with mixed fruit juice and 100% fruit juice intake, showing protective associations against MetS with intakes less than 200 mL. The benefit of 100% fruit juice seen at moderate doses may be attributable to the range of fruit-derived nutrients and bioactive compounds in fruit juice, and the potential for harm at higher doses may be attributable to the consumption of excess calories outweighing any benefit of these bioactive nutrients.

Mixed fruit juices are a combination of fruit drinks (which are similar to SSBs because they are sugary drinks without the accompanying nutrients) and 100% fruit juice. The observed moderate doses of intake may represent the beneficial nutrients from natural fruit within the mixed fruit juice, thus indicating an association similar to that of 100% fruit juices rather than SSBs. The lack of linear association in 100% fruit juice and mixed fruit juice underscores that without consideration of the dose-response association, a naive analysis of extreme intakes assumes a false-linear association and fails to detect important dose ranges for protection or harm.

Furthermore, honey, ice cream, and confectionary intake was not associated with MetS incidence. Although animal models suggest potential protective effects of honey in MetS, to our knowledge, only 1 prospective cohort study assessed honey with MetS incidence and found no significant association. Similarly, the current limited evidence indicates that ice cream and confectionary were not significantly associated with MetS incidence. Future data might clarify our association, particularly for confectionaries, for which CIs did not eliminate significant harm.

The protective and neutral association in our results highlight 2 important considerations. First, the small beneficial effects of some foods might be driven by catalytic doses of fructose intake. Second, the food composition is important. SSBs are without beneficial nutrients and thus offer an unchecked source of fructose-containing sugar, whereas in other foods (eg, yogurt), nutrients other than sugars (eg, polyphenols, minerals, and fiber) may offer protection that might overcome harms from added sugars. More data are needed to enable a complete dose-response assessment and
reveal dose ranges for increased or reduced risk, depending on the balance between nutrient
matrices vs excess sugars.

**Strengths and Limitations**

There are numerous strengths associated with our study. To our knowledge, this study is the first
meta-analysis to comprehensively compare major food sources of fructose-containing sugars with
incident MetS in prospective cohort studies. We conducted a thorough literature search, performed
quantitative synthesis, and assessed the certainty of the evidence using GRADE. Selected studies
included a large sample size, long follow-up durations, and adjustment for multiple lifestyle factors.
We also assessed dose responses for all food sources and identified ranges and cutoffs for benefit
and harm.

This study also had some limitations. The observational nature of prospective cohort studies
may result in unmeasured and residual confounding and may suffer from reverse causality. Thus,
GRADE evaluation for observational studies is low certainty of evidence. Although SSBs, yogurt, and
100% fruit juice had substantial interstudy heterogeneity, we did not consider this as a serious
inconsistency. The estimates were all in the same direction, and there was considerable overlap for
SSB and yogurt. The nonlinear dose-response model explained the heterogeneity for yogurt and
100% fruit juice. Honey, ice cream, and confectionary were downgraded for serious indirectness for
the inability to assess inconsistency because only 1 study was available for each exposure.
Furthermore, they were downgraded for serious imprecision, indicating no association with MetS
incidence in the extreme quantile analysis. The CIs were wide and could not conclude clinically
important harm for confectionary or clinically important benefit or harm for honey and ice cream. In
our dose-response analysis, we found a significant linear dose response of harm for SSBs and a
nonlinear dose response of benefit for mixed fruit juice, 100% fruit juice, fruit, and yogurt, leading to
an upgrade for the certainty of evidence. Data were not available for grain and grain-based products,
a leading source of sugar.

**Conclusions**

Our study provides supporting evidence that increased SSB consumption is associated with MetS
incidence. Generalizing statements on the adverse effects of fructose-containing sugars, however,
cannot be extrapolated to other major food sources of fructose-containing sugars. Furthermore, our
dose-response assessment found that mixed and 100% fruit juice presented consistent dosage for
benefit that align with some national nutrition guidelines, suggesting that a 150-mL intake may
contribute toward the recommended daily fruit consumption. Thus, well-intentioned policies
and guidelines to limit sources of free sugars, such as fruit juice or sweetened yogurts, based on
evidence from SSBs may need to be reexamined with a food-based lens, such as those of the new
Canada's Food Guide or Scientific Advisory Committee on Nutrition.

Additional prospective studies are needed to improve our estimates and better understand the
dose-response association between important food sources of fructose-containing sugars and MetS.
Moreover, high-quality, large randomized clinical trials are needed on other fructose-containing
foods. Furthermore, studies of whole diets and dietary patterns that consist of various food sources
of fructose-containing sugars with cardiometabolic-related health outcomes can also contribute to
the evidence of the association of these diets with MetS.
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Author Contributions: Dr Sievenpiper had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Semnani-Azad, Khan, Sievenpiper.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Semnani-Azad, Khan.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Semnani-Azad, Khan, Blanco Mejia.

Obtained funding: Sievenpiper.

Administrative, technical, or material support: Blanco Mejia, Kendall, Hanley.

Supervision: Sievenpiper.

Conflict of Interest Disclosures: Dr Khan reported receiving grants from the Canadian Institutes of Health Research and the International Life Science Institute and nonfinancial support from the Calorie Control Council outside the submitted work. Dr de Souza reported receiving grants from the Canadian Foundation for Dietetic Research, the Canadian Institutes for Health Research, the Hamilton Health Sciences Corporation, and the Hamilton Health Sciences Corporation/Population Health Research Institute; personal fees and nonfinancial support from the World Health Organization; personal fees from McMaster Children's Hospital; and speaker fees from the University of Toronto, the College of Family Physicians of Canada, Royal College, and McMaster Children's Hospital. Dr de Souza also served as an external resource person to the World Health Organization's Nutrition Guidelines Advisory Group on trans fats, saturated fats, and polyunsaturated fats. The World Health Organization paid for his travel and accommodation to attend meetings from 2012-2017 to present and discuss this work. He also serves as an independent director of the Helderleigh Foundation (Canada). Dr Kendall reported receiving grants from the Advanced Food Materials Network, the Agriculture and Agri-Foods Canada, the Canadian Institutes of Health Research, the Canola Council of Canada, and the National Dried Fruit Trade Association; grants and nonfinancial support from Almond Board of California, Barilla, the International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd, Pulse Canada, and Unilever; grants, nonfinancial support, and travel support from the International Nut and Dried Fruit Council; nonfinancial support and travel support from the American Peanut Council; nonfinancial support from the California Walnut Commission, Danone, Kellogg Canada, Nutrartis, Primo, Quaker, Unico, and Upfield; travel support from the International Pasta Organization, the Oldways Preservation Trust, and The Peanut Institute; and personal fees from the McCormick Science Institute outside the submitted work and serving on the scientific advisory board for the International Pasta Organization, McCormick Science Institute, and Oldways Preservation Trust. Dr Kendall is a member of the International Carbohydrate Quality Consortium, Executive Board of the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes, and the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the European Association for the Study of Diabetes and is a director of the Toronto 3D Knowledge Synthesis and Clinical Trials Foundation. Dr Hanley reported receiving grants from Dairy Farmers of Canada outside the submitted work. Dr Sievenpiper reported receiving grants from the Canadian Institutes of Health Research, Diabetes Canada, Canadian Institutes of Health Research, Canadian Foundation for Innovation, Ontario Research Fund, Province of Ontario Ministry of Research and Innovation and Science, PSI Foundation, Bantering and Best Diabetes Centre, American Society for Nutrition; grants from the International Nut and Dried Fruit Council Foundation, the National Dried Fruit Trade Association, The Tate and Lyle Nutritional Research Fund at the University of Toronto, The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers), and the Nutrition Trialists Fund at the University of
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**REFERENCES**


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