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Original Research Article

Important food sources of fructose-containing sugars and adiposity: A systematic review and meta-analysis of controlled feeding trials

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ABSTRACT

Background: Sugar-sweetened beverages (SSBs) providing excess energy increase adiposity. The effect of other food sources of sugars at different energy control levels is unclear.

Objectives: To determine the effect of food sources of fructose-containing sugars by energy control on adiposity.

Methods: In this systematic review and meta-analysis, MEDLINE, Embase, and Cochrane Library were searched through April 2022 for controlled trials ≥2 wk. We prespecified 4 trial designs by energy control: substitution (energy-matched replacement of sugars), addition (energy from sugars added), subtraction (energy from sugars subtracted), and ad libitum (energy from sugars freely replaced). Independent authors extracted data. The primary outcome was body weight. Secondary outcomes included other adiposity measures. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of evidence.

Results: We included 169 trials (255 trial comparisons, $n = 10{,}357$) assessing 14 food sources at 4 energy control levels over a median 12 wk. Total fructose-containing sugars increased body weight (MD: 0.28 kg; 95% CI: 0.06, 0.50 kg; $P_{MD} = 0.011$) in addition trials and decreased body weight (MD: −0.96 kg; 95% CI: −1.78, −0.14 kg; $P_{MD} = 0.022$) in subtraction trials with no effect in substitution or ad libitum trials. There was interaction/influence by food sources on body weight: substitution trials [fruits decreased; added nutritive sweeteners and mixed sources (with SSBs) increased]; addition trials [dried fruits, honey, fruits (≤10%E), and 100% fruit juice (≤10%E) decreased; SSBs, fruit drink, and mixed sources (with SSBs) increased]; subtraction trials [removal of mixed sources (with SSBs) decreased]; and ad libitum trials [mixed sources (with/without SSBs) increased]. GRADE scores were generally moderate. Results were similar across secondary outcomes.

Conclusions: Energy control and food sources mediate the effect of fructose-containing sugars on adiposity. The evidence provides a good indication that excess energy from sugars (particularly SSBs at high doses ≥20%E or 100 g/d) increase adiposity, whereas their removal decrease adiposity. Most other food sources had no effect, with some showing decreases (particularly fruits at lower doses ≤10%E or 50 g/d). This trial was registered at clinicaltrials.gov as NCT02558920 (https://clinicaltrials.gov/ct2/show/NCT02558920).

Keywords: adiposity, body weight, fructose, sugars, food sources, sugar-sweetened beverages, systematic review, meta-analysis

Abbreviations: GRADE, Grading of Recommendations Assessment; Development, and Evaluation; MD, mean difference; MID, minimally important difference; ROB, risk of bias; SMD, standardized mean difference; SSB, sugar-sweetened beverages; VAT, visceral adipose tissue.

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Introduction

Sugar consumption is as a public health concern, with a focus on those containing fructose owing to its unique metabolism and its implied contribution toward obesity and the related downstream cardiometabolic implications. Fructose is believed to act as an unregulated substrate for de novo lipogenesis, bypassing negative feedback control, unlike its glucose counterpart. This mechanism is postulated to impair other metabolic signaling and lead to increased adiposity [1,2]. Animal models, ecological studies, and some fructose overfeeding trials have been conducted with levels of exposure much greater than population intake and they support these proposed mechanisms and report the harmful effects of fructose-containing sugar consumption. However, systematic review and meta-analyses of controlled trials have demonstrated that harmful effects on some cardiometabolic outcomes, such as body weight, are only observed when fructose-containing sugars are consumed as excess energy [3–7]. Furthermore, there is some evidence that the effect of fructose-containing sugars on adiposity may differ for different food sources. For example, sugar-sweetened beverages (SSBs) providing excess energy consistently show increases in body weight and are associated with an increased risk of obesity [8–10], whereas other food sources of fructose-containing sugars such as fruit are not associated with a harm but rather a benefit [11]. It remains uncertain whether there is any relationship between other food sources of fructose-containing sugars and adiposity at different levels of energy control. To inform public health guidance and policy on sugars, the American Society for Nutrition commissioned a systematic review and meta-analysis of controlled trials on the effect of different food sources of fructose-containing sugars at different levels of energy control on body weight and other measures of global and abdominal adiposity with an assessment of the certainty of evidence using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

Methods

We followed the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3) [12] to conduct this systematic review and meta-analysis and reported our results following the PRISMA guidelines [13]. The study protocol was registered at clinicaltrials.gov (NCT02558920).

Data sources and search strategy

We conducted a systematic search in MEDLINE, Embase, and the Cochrane Central Register of Controlled Studies databases through 4 April 2022. Supplemental Tables 1 and 2 present the search strategy. There were no language restrictions. Validated filters were applied [14]. The searches were supplemented with manual searches of the reference lists from the included trials.

Study selection

We included randomized and nonrandomized controlled feeding trials in humans of all health backgrounds and ages, with intervention periods ≥14 d [9], investigating the effect of orally consumed fructose-containing sugars from various food sources compared with control diets free or lower in fructose-containing sugars on body weight and measures of global (BMI ad body fat) and abdominal adiposity (waist circumference, WHR, and visceral adipose tissue [VAT]). We excluded studies of liquid meal replacement interventions and studies of interventions or comparators of rare sugars that contain fructose (e.g., isomaltulose, melezitose, and turanose) or were low-calorie epimers of fructose (e.g., allulose, tagatose, and sorbose). Reports were initially excluded based on a review of their titles and abstracts by a single reviewer. Those reports that remained were then excluded based on a review of the full-text reports by at least 2 of the reviewers (LC, AC, SA-C, DL, AA, QL, FA-Y, XQ, SB, NM, VH), leaving the final set of reports to be included in our syntheses. We prespecified the following 4 study designs based on energy control: *1*) "substitution" trials, in which energy from the food sources of fructose-containing sugars was substituted for other non–fructose-containing macronutrients under energy-matched conditions; *2*) "addition" trials, in which excess energy from the food sources of fructose-containing sugars was added to the background diet compared with the same diet alone without the excess energy (with or without the use of nonnutritive/low-calorie sweeteners to match sweetness); *3*) "subtraction" trials, in which energy from the food sources of fructose-containing sugars was subtracted from background diets compared with the original background diets through displacement by water or low-calorie sweeteners or elimination altogether; and *4*) "ad libitum" trials, in which energy from the food sources of fructose-containing sugars was freely replaced with other non–fructose-containing macronutrients without any strict control of either the study foods or the background diets, allowing for free replacement of energy. In reports containing more than 1 eligible trial comparison, we included each available trial comparison separately.

Data extraction

At least 2 reviewers independently extracted data from eligible studies. Relevant information included food source of fructose-containing sugars, number of participants, setting, participant health status, study design, level of feeding control, randomization, comparator, fructose-containing sugar type, macronutrient profile of the diets, follow-up duration, energy balance, funding source, and outcome data. Supplemental Table 3 summarizes the definitions of the different food sources of fructose-containing sugars. The authors were contacted for missing outcome data when it was indicated that an adiposity outcome was measured but not reported. Graphically presented data were extracted from figures using the Plot Digitizer [15].

Risk of bias assessment

Included studies were assessed for the risk of bias (ROB) independently and in duplicate by ≥2 reviewers using the Cochrane ROB Tool [16]. Assessment was performed across 6 domains of bias (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other). The ROB for each domain was assessed as "low" (proper methods taken to reduce bias), "high" (improper methods creating bias), or "unclear" (insufficient information provided). The other domain applied only to crossover trials; "high" ROB was given when there was no washout between interventions; otherwise, the trial was rated as low. Reviewer discrepancies were resolved by consensus or arbitration by the senior author (JLS).

Outcomes

The primary outcome was body weight. Secondary outcomes included measures of global (BMI and body fat) and abdominal adiposity (waist circumference, WHR, VAT). Mean differences (MDs) between the intervention and control arm and their standard errors

(SEs) were extracted for each eligible trial comparison. If unavailable, they were derived from available data using published formulas [12] (chapter 6). Mean pairwise differences in change-from-baseline values were preferred over end values, when available. When median data were provided, they were converted to mean data with corresponding variances using methods developed by Luo et al. [17] and Wan et al. [18]. When no variance data were available, the standard deviation was borrowed from a trial similar in size, participants, and nature of intervention, including food source and dose [19]. When an outcome was not reported, but the variables to calculate that variable was, the outcome was calculated using a standard formula (body weight and height were used to calculate BMI; BMI and height were used to calculate the body weight; body fat mass (in kilograms) and total body weight (in kilograms) were used to calculate percentage body fat; and waist and hip measurements were used to calculate the WHR).

Data syntheses and analyses

We used the Stata software (version 16.1; StataCorp) for all analyses. As our primary research question was to assess the effect of different food sources of fructose-containing sugars at different energy control levels, we performed separate pairwise meta-analyses for each of the 4 prespecified designs by energy control level (substitution, addition, subtraction, and ad libitum trials) and assessed the interaction (variation in the effect estimates) by food source of fructose-containing sugars within each energy control level using the Cochrane Handbook recommended standard Q test for subgroup differences using meta-regression (significance at $P < 0.10$) [20–22]. In the absence of interaction, we also assessed the influence of the food source. If 1 food source had ≥50% of the weight in a pooled analysis, we determined the food source to have a disproportionate influence on the analysis. If ≤3 food sources provided 100% of the weight in the pooled analysis, we determined that we could not rule out an influence of the food source. In these scenarios, there is an important influence because we cannot draw conclusions regarding the effect of total fructose-containing sugars independent of the food source.

The principal effect measures were the mean pairwise differences in change-from-baseline (or alternatively, end differences) between the intervention arm providing a source of fructose-containing sugars and the comparator/control arm (devoid of or low in fructose-containing sugars) in each study (significance at $P < 0.05$). Data were analyzed using the generic inverse variance method with the DerSimonian and Laird random-effects model [12,23]. A fixed-effects model was used when <5 trial comparisons were available [24]. Paired analyses were applied to all crossover trials with the use of a within-individual correlation coefficient between the treatments of 0.5 as described by Elbourne et al. to calculate SEs [25–27]. Data were expressed as MDs with 95% CIs for all outcomes with the exception of VAT, in which data were expressed as standardized mean differences (SMDs) [28]. To mitigate a unit-of-analysis error, when arms of trials with multiple intervention or control arms were used more than once, the corresponding sample size was divided by the number of times it was used for the calculation of the standard error [29].

Heterogeneity was assessed by visual inspection of the forest plots and using the Cochrane Q statistic and quantified using the I^2 statistic [12] (chapter 10). We considered an $I^2 \geq 50\%$ and $P_Q < 0.10$ as evidence of substantial heterogeneity [12] (chapter 10). Sources of heterogeneity were explored by sensitivity analyses, including individual trial influence, altering the pairwise comparison correlation coefficient, and subgroup analyses. The individual trial influence analysis systematically removed each trial comparison from the meta-analysis with recalculation of the summary effect estimate. A trial whose removal explained the heterogeneity or changed the significance, direction, or magnitude of the effect by more than the minimally important difference (MID) for each outcome [prespecified as 0.5 kg for body weight, 0.2 kg/m^2 for BMI, 2% for body fat, 0.5 cm for waist circumference, 0.02 for WHR [30,31], and 0.08 SMD for VAT (5% of the baseline in SMD units)] was considered an influential trial. To determine whether the overall results were robust to the use of different correlation coefficients in crossover trials, we also conducted sensitivity analyses using correlation coefficients of 0.25 and 0.75. Furthermore, we conducted sensitivity analyses where we removed those trial comparisons in which nonmean summary statistics (e.g. medians) were used to estimate means. If ≥10 trials were available [21,32], we conducted subgroup analyses to explore sources of heterogeneity using meta-regression (significance at $P_Q < 0.05$). A priori subgroup analyses were conducted by participant health status, whether randomization was used (yes, no), energy balance of the intervention relative to the basal diet (neutral, positive, and negative), baseline outcome levels, fructose sugar type (fructose, sucrose, fruit, high-fructose corn syrup, and mixed type), comparator, study design, follow-up duration, feeding control (dietary advice and supplemented, metabolic), fructose-containing sugar dose, sugar regulatory designation (naturally occurring, added, and mixed), sugar food form (solid, liquid, and mixed), funding, and ROB. Post hoc subgroup analyses were conducted by the type of imputation performed for deriving variances (change from the baseline and end differences), data source (reported, plot digitized, calculated, and author provision of data), and weight maintenance (yes/no). Meta-regression analyses were used to assess the significance of each subgroup categorically and, when applicable, continuously.

If ≥6 trial comparisons were available [33], then we assessed linear and nonlinear (restricted cubic splines) dose-response relationships (significance at $P < 0.05$) using meta-regression. We also assessed nonlinear dose-response threshold effects with 3 prespecified spline knots at important public health thresholds of 5% [34,35], 10% [35,36], and 25% [37] total energy (%E).

If ≥10 trials were available, then we assessed for the presence of small-study effects (publication bias) by visual inspection of contour-enhanced funnel plots and formal testing with Egger [38] and Begg [39] tests (significance at $P < 0.10$) [40]. If there was evidence of small-study effects (publication bias), then we quantified the size of the potential publication bias or other causes of asymmetry by adjusting for the funnel plot asymmetry and assessing the effect of small-study effects using the trim-and-fill method of Duval and Tweedie [41].

Certainty of the evidence

The certainty of the evidence was assessed using the GRADE approach and software (GRADEpro GDT, McMaster University and Evidence Prime) [42]. The assessments were conducted by at least 2 of the independent reviewers (LC, DL, AA, SA-C), and discrepancies were resolved by consensus or arbitration by the senior author (JLS). The evidence was rated as high, moderate, low, or very low certainty. The included controlled trials were initially rated as high certainty by default and then downgraded or upgraded based on prespecified criteria. Reasons for downgrading the evidence included ROB (assessed by the Cochrane ROB Tool [16]), inconsistency (substantial unexplained interstudy heterogeneity: $I^2 > 50\%$ and $P_Q < 0.10$), indirectness (presence of factors that limit the generalizability of the results), imprecision (the 95% CI for effect estimates overlap the MID

for benefit or harm), and publication bias (significant evidence of small-study effects). The reason for upgrading the evidence was the presence of a significant dose-response gradient [43–48]. The importance of the magnitude of the pooled estimates was assessed using our prespecified MIDs and the effect size categories according to the GRADE guidance [42,49–51] as follows: a large effect (≥5× MID); moderate effect (≥2× MID); small important effect (≥1× MID); and trivial/unimportant effect (<1 MID).

Results

Search results

Figure 1 shows the flow of the literature. We retrieved 10,182 reports from databases and manual searches, 9612 of which were excluded based on the title or abstract. Of the 497 reports reviewed in full text, 169 reports of controlled feeding trials (255 trial comparisons, $n = 10{,}357$) met the eligibility criteria [52–220]. These trials included 14 different food sources of fructose-containing sugars [SSB; sweetened dairy; sweetened dairy alternative (soy); 100% fruit juice; fruit drink; fruit; dried fruit; mixed fruit forms; sweetened cereal grains and bars; sweets and desserts; honey; added nutritive (caloric) sweetener; mixed sources (with SSBs), and mixed sources (without SSBs)] across 4 energy control levels: substitution (126 trial comparisons); addition (104 trial comparisons); subtraction (13 trial comparisons); and ad libitum (12 trial comparisons). The mixed sources (without SSBs) food category includes those trials in which the intervention included more than one of the food sources, excluding SSBs (e.g., sweets and desserts and fruits).

Trial characteristics

Table and Supplemental Table 4 summarize the trial characteristics. Trial sizes ranged from a median of 13 participants (range: 5–159) in ad libitum trials to 68 participants (range: 7–318) in subtraction trials. Participants were a mix of adults with and without obesity or with a diagnosed chronic condition (e.g., diabetes) or at elevated risk for CVD (e.g., dyslipidemia and metabolic syndrome). There were approximately equal ratios of both sexes in all trial categories. Most participants were middle-aged adults, with ages ranging from a mean of 32 y (range: 21–43 y) in subtraction trials to 44 y (range: 22–70 y) in substitution trials. Most trials were conducted in an outpatient setting (85%–100%), performed in North American and European countries, and were parallel in design (55% in substitution, 63% in addition, 69% in subtraction, and 25% in ad libitum trials). Feeding control was mostly supplemented for substitution (56%), addition (90%), subtraction (31%), and ad libitum (33%) trials. The energy intake in the ad libitum trials was usually held within reasonable limits (e.g. the energy intake was required to be between 75% and 125% of predicted daily energy requirements [190]). Most studies were randomized (69%–83%). The dose of fructose-containing sugars ranged from a median of 11% (range: 1%–33%) in addition trials to 18% (range: 5%–30%) of total energy intake in ad libitum trials. The follow-up duration ranged from a mean of 7 wk in addition trials (range: 2–24 wk) to 22 wk in subtraction trials (range: 2–48 wk). Most trials were funded by agency sources (government, not-for-profit health agency, or university sources) for substitution (31%), addition (57%), and subtraction (38%) trials, with agency and industry sources for ad libitum trials (50%). The comparators for substitution trials were mostly starch comparators (50/126, 40%), followed by glucose (25/126, 20%) and mixed comparators (24/126, 19%), diet alone for addition trials (64/104, 62%), nonnutritive sweetener for subtraction (5/13, 38%), and starch for ad libitum trials (6/12, 50%). The main food sources were mixed sources (with SSBs) (44/126, 35%) for substitution, SSBs (23/104, 22%) and 100% fruit juice (23/104, 22%) followed by fruit (20/104, 19%) for addition, SSBs (7/13, 54%) for subtraction, and mixed sources (with SSBs) (10/12, 83%) for ad libitum trials.

Risk of bias

Supplemental Figures 1–6 show a summary of the ROB assessments of the included trials. Across energy designs, most trials were assessed as having unclear ROB in random sequence generation (31%–46%) and allocation concealment (46%–57%) domains due to unclear and/or incomplete reporting, while there was a fairly close split between unclear and low assessments for blinding (31%–92% unclear) incomplete outcome data (55%–100%), and selective outcome reporting (0%–51%) domains. Most crossover trials were assessed as having low ROB in the "other" (carryover effects) domain (76% in substitution, 79% in addition, 100% in subtraction and 85% in ad libitum trials). Fewer studies were assessed as having high ROB, for random sequence generation (27%–50%), allocation concealment (30%–50%), blinding of participants and personnel (0%–8%), incomplete outcome data (0%–2%), selective outcome reporting (0%–2%), and other (carryover effects) (0%–50%) ROB domains. Thus, there was no overall serious ROB in most trial comparisons except for in substitution and addition trials of total fructose-containing sugars for body weight and VAT, respectively, and trials of SSBs for BMI, sweetened cereal grains and bars for body fat and WHR, and honey for waist circumference, where the overall pooled estimate was driven by high ROB trials.

Primary outcome

Figure 2 and Supplemental Figures 7–12 present the effect of different food sources of fructose-containing sugars on the primary outcome, body weight, at 4 levels of energy control. Total fructose-containing sugars resulted in an increase in body weight for addition trials (90 trials; MD: 0.28 kg; 95% CI: 0.06, 0.50 kg; $P_{MD} = 0.011$; substantial heterogeneity: $I^2 = 57.4\%$; $P_Q < 0.001$), whereas there was a reduction in the body weight in subtraction trials (13 trials; MD: −0.96 kg; 95% CI: −1.78, −0.14 kg; $P_{MD} = 0.022$; substantial heterogeneity: $I^2 = 69.0\%$; $P_Q < 0.001$), and no effect in substitution (119 trials; MD: 0.04 kg; 95% CI: −0.07, 0.16 kg; $P_{MD} = 0.469$; no substantial heterogeneity: $I^2 = 2.7\%$; $P_Q = 0.401$) and ad libitum trials (12 trials; MD: 0.77 kg; 95% CI: −0.29, 1.82 kg; $P_{MD} = 0.154$; substantial heterogeneity: $I^2 = 79.9\%$; $P_Q < 0.001$).

An interaction by food source was detected in the substitution ($P < 0.001$), addition ($P < 0.001$), and ad libitum ($P < 0.001$) trials. In substitution trials, fruit (10 trials; MD: −0.38 kg; 95% CI: −0.57, −0.20 kg; $P_{MD} < 0.001$; no heterogeneity: $I^2 = 0.0\%$; $P_Q = 0.708$) resulted in a decrease in the body weight, whereas added nutritive (caloric) sweetener (13 trials; MD: 0.66 kg; 95% CI: 0.13, 1.19 kg; $P_{MD} = 0.014$; no heterogeneity: $I^2 = 0.0\%$; $P_Q = 0.968$) and mixed sources (with SSBs) (42 trials; MD: 0.27 kg; 95% CI: 0.09, 0.45 kg; $P_{MD} = 0.003$; no substantial heterogeneity: $I^2 = 0.0\%$; $P_Q = 0.675$) resulted in an increase in the body weight, whereas no other food sources showed an effect with variable directions of effect. In addition trials, because dose was a major explanatory factor of the effect size for fruit and 100% fruit juice (please see the "Subgroup analyses" section), the data for ≤10%E and >10%E for these 2 foods were presented separately. Moreover, 100% fruit juice (at ≤10%E) (9 trials; MD: −1.30 kg; 95% CI: −2.38, −0.22 kg; $P_{MD} = 0.018$; no substantial heterogeneity: $I^2 = 20.2\%$; $P_Q = 0.263$); fruits (at ≤10%E) (14 trials;

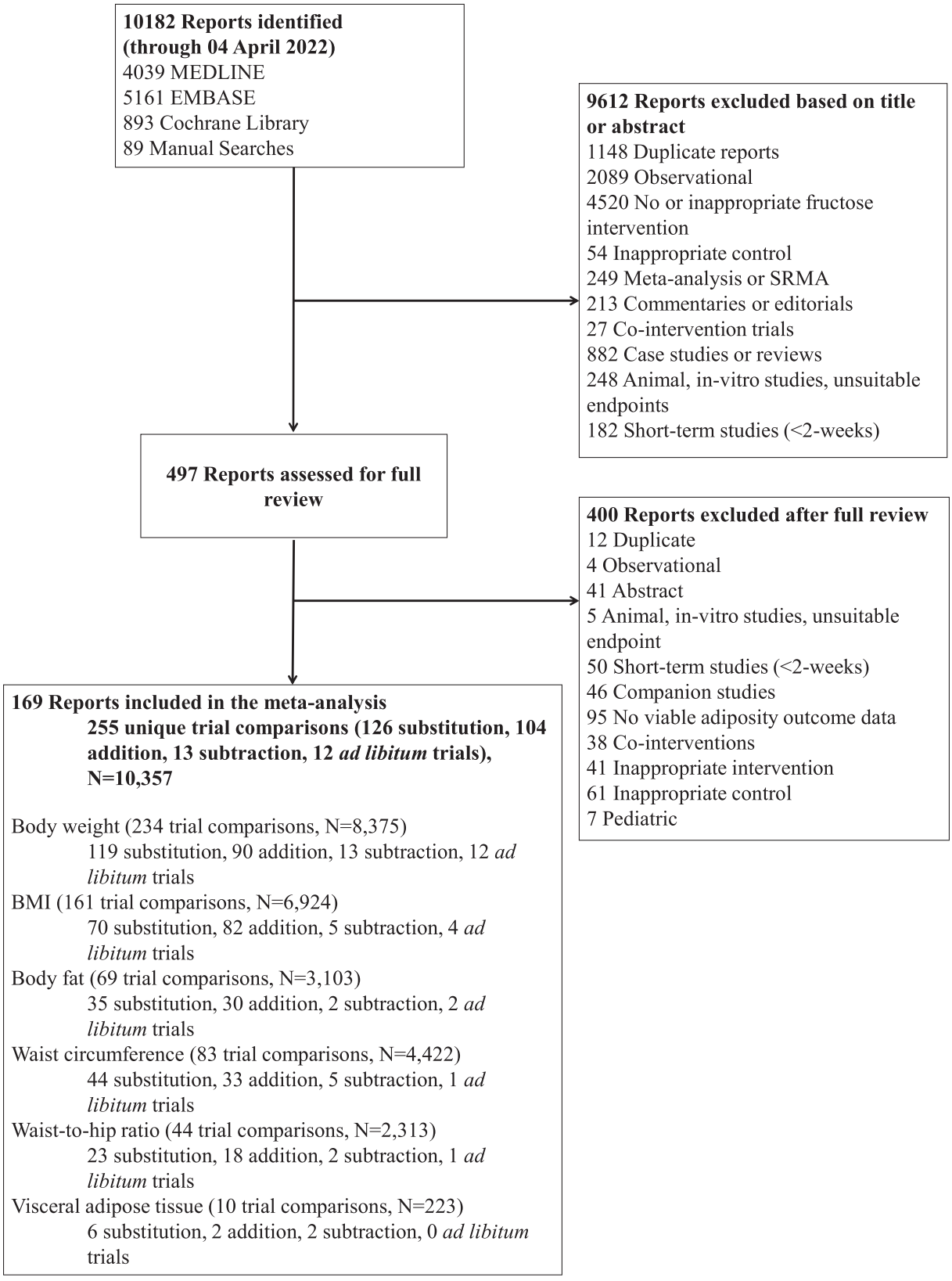

FIGURE 1. The flow of literature on the effect of food sources of fructose-containing sugars and adiposity. SRMA, systematic review, and meta-analysis.

MD: −0.60 kg; 95% CI: −1.19, −0.01 kg; $P_{MD} = 0.048$; no heterogeneity: $I^2 = 0.0\%$; $P_Q = 1.000$); dried fruits (3 trials; MD: −1.29 kg; 95% CI: −2.01, −0.57 kg; $P_{MD} < 0.001$; no heterogeneity: $I^2 = 0.0\%$; $P_Q = 0.913$); and honey (5 trials; MD: −1.65 kg; 95% CI: −2.46, −0.85 kg; $P_{MD} < 0.001$; no heterogeneity: $I^2 = 0.0\%$; $P_Q = 0.653$) resulted in a decrease in the body weight, whereas SSBs (21 trials; MD: 0.49 kg; 95% CI: 0.24, 0.74 kg; $P_{MD} < 0.001$; no substantial heterogeneity: $I^2 = 40.0\%$; $P_Q = 0.029$), fruit drinks (14 trials; MD: 0.90 kg;

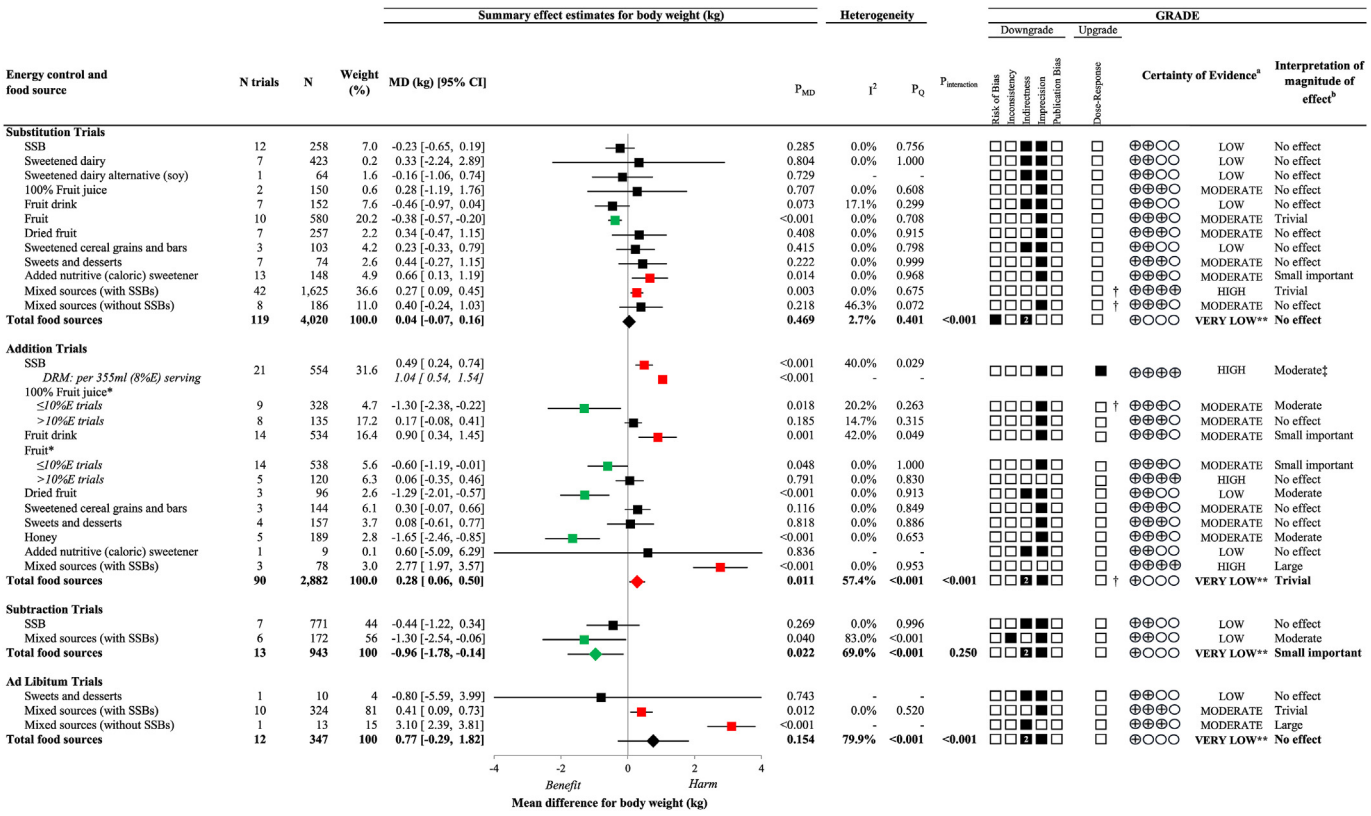

FIGURE 2. A summary plot for the effect of different food sources of fructose-containing sugars on the body weight. Data are weighted mean differences (95% CIs) for the summary effects of individual food sources and total food sources on body weight. Analyses conducted using generic, inverse variance random-effects models (at least 5 trials available), or fixed-effects models (fewer than 5 trials available). Between-study heterogeneity was assessed by the Cochrane Q statistic, where $P_Q < 0.100$ was considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered evidence of substantial heterogeneity. The effects of total fructose-containing sugars are denoted by the bolded lines, with the effect estimates as diamonds. The effects of individual food sources are denoted by the nonbolded lines, with the effect estimates as squares. Any statistically significant reductions are highlighted in green and significant increases in red. The GRADE of randomized controlled trials are rated as "high" certainty of evidence and can be downgraded by 5 domains and upgraded by 1 domain. The white squares represent no downgrades, the filled black squares indicate a single downgrade or upgrades for each outcome, and the black square with a white "2" indicates a double downgrade for each outcome. DRM, dose-response model; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MD, mean difference; N, number; ROB, risk of bias; SSB, sugar-sweetened beverage. (A) Because all included trials were randomized or nonrandomized controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded or upgraded based on prespecified criteria. Criteria for downgrades included risk of bias (ROB) (downgraded if most trials were considered to be at high ROB); inconsistency (downgraded if there was substantial unexplained heterogeneity: $I^2 \geq 50\%$; $P_Q < 0.10$); indirectness (downgraded if there were factors absent or present relating to the participants, interventions, or outcomes that limited the generalizability of the results); imprecision [downgraded if the 95% CI crossed the minimally important difference (MID) for harm or benefit set at 0.5 kg for body weight, 0.2 kg/m^2 for BMI, 2% for body fat, 0.5 cm for waist circumference, and 0.02 for waist-to-hip ratio] [30,31]; and publication bias (downgraded if there was evidence of publication bias based on the funnel plot asymmetry and/or significant Egger or Begg test ($P < 0.10$), with confirmation by adjustment using the trim-and-fill analysis of Duval and Tweedie [41]). The criteria for upgrades included a significant dose-response gradient. (B) For the interpretation of the magnitude, we used the MIDs (see A) to assess the importance of magnitude of our point estimate using the effect size categories according to the new GRADE guidance. Then, we used the MIDs to assess the importance of the magnitude of our point estimates using the effect size categories according to the GRADE guidance [42,49,51] as follows: a large effect (≥5× MID); moderate effect (≥2× MID); small important effect (≥1× MID); and trivial/unimportant effect (<1 MID). *Because categorical subgroup analyses by dose for 100% fruit juice and fruit in addition trials for body weight showed significant interaction (with a threshold at 10%E), and dose is a major domain of the assessment of certainty of evidence, we presented the data separately for ≤10%E and >10%E, rather than present the total pooled analysis and downgrade for serious inconsistency. **Where there was a significant interaction by food source in substitution and addition trials and SSBs and/or mixed sources (with SSBs) were the sole food sources in subtraction and ad libitum trials, we performed the GRADE analysis for each individual food source. † Not upgraded for dose response. Please see Supplementary Tables 10 and 11 for details. ‡The interpretation of the magnitude of the effect was based on the linear dose-response gradient (Supplementary Table 11).

95% CI: 0.34, 1.45 kg; $P_{MD} = 0.001$; no substantial heterogeneity: $I^2 = 42.0\%$; $P_Q = 0.049$), and mixed sources (with SSBs) (3 trials; MD: 2.77 kg; 95% CI: 1.97, 3.57 kg; $P_{MD} < 0.001$; no heterogeneity: $I^2 = 0.0\%$; $P_Q = 0.953$) resulted in an increase in the body weight. However, no other food sources showed a significant effect, with varying directions of effect. In ad libitum trials, mixed sources (with SSBs) (10 trials; MD: 0.41 kg; 95% CI: 0.09, 0.73 kg; $P_{MD} = 0.012$; no heterogeneity: $I^2 = 0.0\%$; $P_Q = 0.520$) and mixed sources (without SSBs) (1 trial; MD: 3.10 kg; 95% CI: 2.39, 3.81 kg; $P_{MD} < 0.001$) resulted in an increase in body weight, whereas sweets and desserts showed no significant effect. Although the interaction by food source in subtraction trials was not significant, we assessed the influence by food source as the reduction in body weight was driven by a sole food source: mixed sources (with SSBs) (6 trials; MD: −1.30 kg; 95% CI: −2.54, −0.06 kg; $P_{MD} = 0.040$; substantial heterogeneity: $I^2 = 83.0\%$; $P_Q < 0.001$).

Secondary outcomes

Figures 3–7 and Supplemental Figures 13–33 present the effect of different food sources of fructose-containing sugars on our secondary outcomes, including BMI, body fat, waist circumference, WHR, and VAT at 4 levels of energy control. In substitution trials, there was generally no overall effect on any outcome; however, there was significant interaction by food source ($P < 0.05$) for BMI and influence by food source for WHR, where 1 food source (fruits) had the most (63.2%) of the weight in the pooled analysis. Fruits resulted in a decrease in the BMI, and mixed sources (with SSBs) resulted in an increase in the BMI and WHR. In addition to trials, total fructose-containing sugars resulted in an increase in the BMI and body fat, with no effect on the waist circumference, WHR, or VAT. A significant interaction by food sources was found in addition to trials for the BMI, body fat, and waist circumference and an influence of food sources on the WHR where fruits (79.5%) had the most of the weight of the

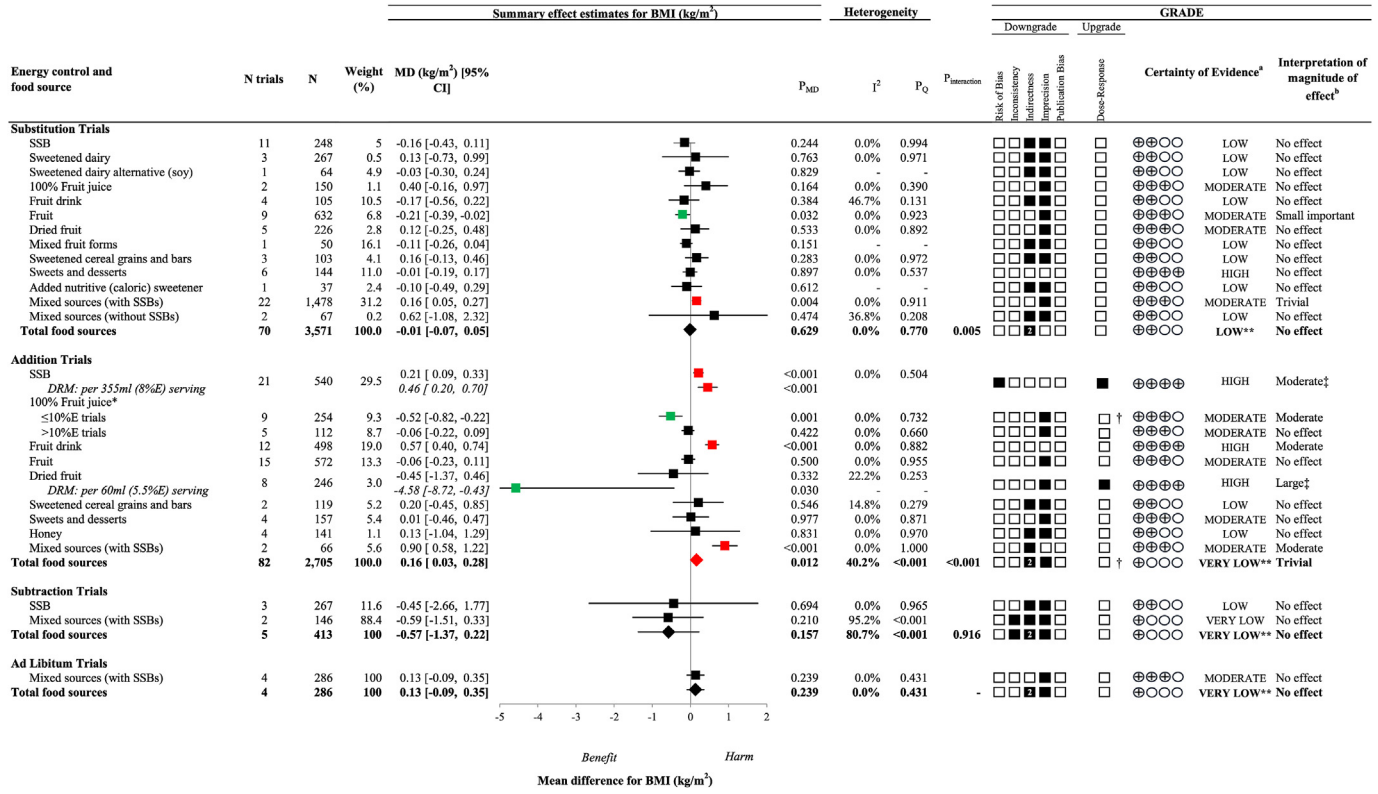

FIGURE 3. A summary plot for the effect of different food sources of fructose-containing sugars on the BMI. Data are weighted mean differences (95% CIs) for the summary effects of individual food sources and total food sources on BMI. Analyses conducted using generic, inverse variance random-effects models (at least 5 trials available) or fixed-effects models (fewer than 5 trials available). Between-study heterogeneity was assessed by the Cochrane Q statistic, where $P_Q < 0.100$ was considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered evidence of substantial heterogeneity. The effects of total fructose-containing sugars are denoted by the bolded lines, with the effect estimates as diamonds. The effects of individual food sources are denoted by the nonbolded lines, with the effect estimates as squares. Any statistically significant reductions are highlighted in green and significant increases in red. The GRADE of randomized controlled trials are rated as "high" certainty of evidence and can be downgraded by 5 domains and upgraded by 1 domain. The white squares represent no downgrades, filled black squares indicate a single downgrade or upgrades for each outcome, and black squares with a white "2" indicates a double downgrade for each outcome. DRM, dose-response model; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MD, mean difference; N, number; ROB, risk of bias; SSB, sugar-sweetened beverage. (A) Because all included trials were randomized or nonrandomized controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded or upgraded based on prespecified criteria. Criteria for downgrades included risk of bias (ROB) (downgraded if the most trials were considered to be at high ROB); inconsistency (downgraded if there was substantial unexplained heterogeneity: $I^2 \geq 50\%$; $P_Q < 0.10$); indirectness (downgraded if there were factors absent or present relating to the participants, interventions, or outcomes that limited the generalizability of the results); imprecision [downgraded if the 95% CI crossed the minimally important difference (MID) for harm or benefit set at 0.5 kg for body weight, 0.2 kg/m^2 for BMI, 2% for body fat, 0.5 cm for waist circumference, and 0.02 for waist-to-hip ratio] [30,31]; and publication bias (downgraded if there was evidence of publication bias based on the funnel plot asymmetry and/or significant Egger or Begg test ($P < 0.10$), with confirmation by adjustment using the trim-and-fill analysis of Duval and Tweedie [41]). The criteria for upgrades included a significant dose-response gradient. (B) For the interpretation of the magnitude, we used the MIDs (see A) to assess the importance of magnitude of our point estimate using the effect size categories according to the new GRADE guidance. Then, we used the MIDs to assess the importance of the magnitude of our point estimates using the effect size categories according to the GRADE guidance [42,49,51] as follows: a large effect (≥5× MID); moderate effect (≥2× MID); small important effect (≥1× MID); and trivial/unimportant effect (<1 MID). *Because categorical subgroup analyses by dose for 100% fruit juice in addition trials for BMI showed a significant interaction (with a threshold at 10%E), and dose is a major domain of the assessment of certainty of evidence, we presented the data separately for ≤10%E and >10%E, rather than presenting the total pooled analysis and downgrade for serious inconsistency. **Where there was a significant interaction by food source in substitution and addition trials and SSBs and/or mixed sources (with SSBs) were the sole food sources in subtraction and ad libitum trials, we performed the GRADE analysis for each individual food source. †Not upgraded for dose response. Please see Supplementary Tables 10 and 12 for details. ‡The interpretation of the magnitude of the effect was based on the linear dose-response gradient (Supplementary Table 12).

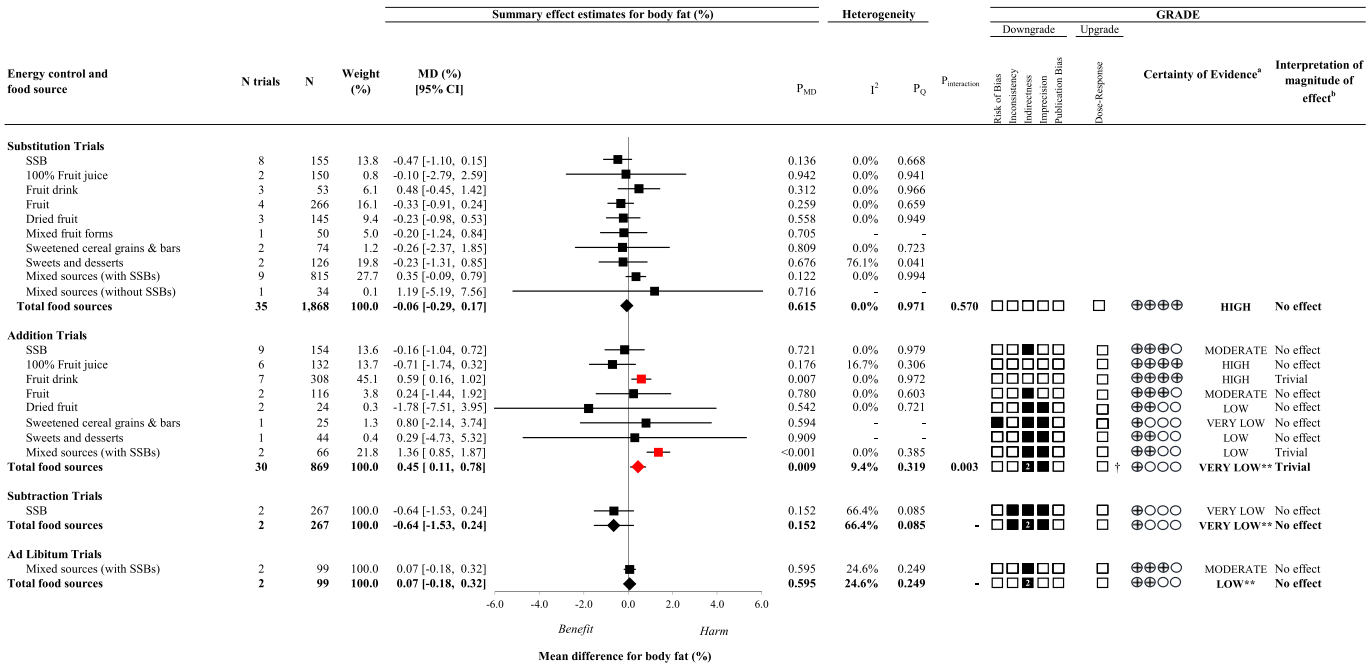

FIGURE 4. A summary plot for the effect of different food sources of fructose-containing sugars on the body fat. Data are weighted mean differences (95% CIs) for the summary effects of individual food sources and total food sources on body fat. Analyses conducted using generic, inverse variance random-effects models (at least 5 trials available) or fixed-effects models (fewer than 5 trials available). Between-study heterogeneity was assessed by the Cochrane Q statistic, where $P_Q < 0.100$ was considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered evidence of substantial heterogeneity. The effects of total fructose-containing sugars are denoted by the bolded lines, with the effect estimates as diamonds. The effects of individual food sources are denoted by the nonbolded lines, with the effect estimates as squares. Any statistically significant reductions are highlighted in green and significant increases in red. The GRADE of randomized controlled trials are rated as "high" certainty of evidence and can be downgraded by 5 domains and upgraded by 1 domain. The white squares represent no downgrades, the filled black squares indicate a single downgrade or upgrades for each outcome, and the black square with a white "2" indicates a double downgrade for each outcome. DRM, dose-response model; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MD, mean difference; N, number; ROB, risk of bias; SSB, sugar-sweetened beverage. (A) Because all included trials were randomized or nonrandomized controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded or upgraded based on prespecified criteria. Criteria for downgrades included risk of bias (ROB) (downgraded if the most trials were considered to be at high ROB); inconsistency (downgraded if there was substantial unexplained heterogeneity: $I^2 \geq 50\%$; $P_Q < 0.10$); indirectness (downgraded if there were factors absent or present relating to the participants, interventions, or outcomes that limited the generalizability of the results); imprecision [downgraded if the 95% CI crossed the minimally important difference (MID) for harm or benefit set at 0.5 kg for body weight, 0.2 kg/m^2 for BMI, 2% for body fat, 0.5 cm for waist circumference, and 0.02 for waist-to-hip ratio] [30,31]; and publication bias (downgraded if there was evidence of publication bias based on the funnel plot asymmetry and/or significant Egger or Begg test ($P < 0.10$), with confirmation by adjustment using the trim-and-fill analysis of Duval and Tweedie [41]). The criteria for upgrades included a significant dose-response gradient. (B) For the interpretation of the magnitude, we used the MIDs (see A) to assess the importance of magnitude of our point estimate using the effect size categories according to the new GRADE guidance. Then, we used the MIDs to assess the importance of the magnitude of our point estimates using the effect size categories according to the GRADE guidance [42,49,51] as follows: a large effect (≥5× MID); moderate effect (≥2× MID); small important effect (≥1× MID); and trivial/unimportant effect (<1 MID). **Where there was a significant interaction by food source in addition trials and SSBs and/or mixed sources (with SSBs) were the sole food sources in subtraction and ad libitum trials, we performed the GRADE analysis for each individual food source. †Not upgraded for dose response. Please see Supplementary Tables 10 and 13 for details.

analyses. Because dose was a major explanatory factor for the effect of 100% fruit juice on BMI and WHR, the data for ≤10%E and >10%E for this food were presented separately. Moreover, 100% fruit juice (at ≤10%E) resulted in a decrease in the BMI, whereas increases were seen for the effects of SSBs on the BMI; fruit drinks on the BMI and body fat; mixed sources (with SSBs) on the BMI, body fat, and waist circumference; and 100% fruit juice (at >10%E) on the WHR. In subtraction trials, the removal of total fructose-containing sugars resulted in a reduction in the waist circumference and WHR, with no effect on other secondary outcomes. Because there were only 1–2 food sources in subtraction trials across all outcomes, there was an important influence by food sources, where the removal of mixed sources (with SSBs) resulted in a reduction in the waist circumference and WHR. In ad libitum trials, total fructose-containing sugars did not affect any outcome, and although there was an influence of food source because there were only 1–2 food sources per outcome, neither had any effect. There was no overall effect of total fructose-containing sugars on VAT, and although there was the influence of food sources due to too few food sources, none were significant.

Sensitivity analyses

Supplemental Figures 34–37 present the individual trial influence analyses on the effect of total fructose-containing sugars at the 4 levels of energy control on the primary outcome, body weight. The removal of the study by either Mann et al. [155] or Vazquez-Duran et al. (water arm) [211] resulted in a loss of significance for the decrease in the body weight in subtraction trials, and removal of the study by Mann et al. [155] provided a partial explanation of the evidence of substantial heterogeneity. Removal of a single trial comparison resulted in a gain of significance and explained heterogeneity in ad libitum trials [205].

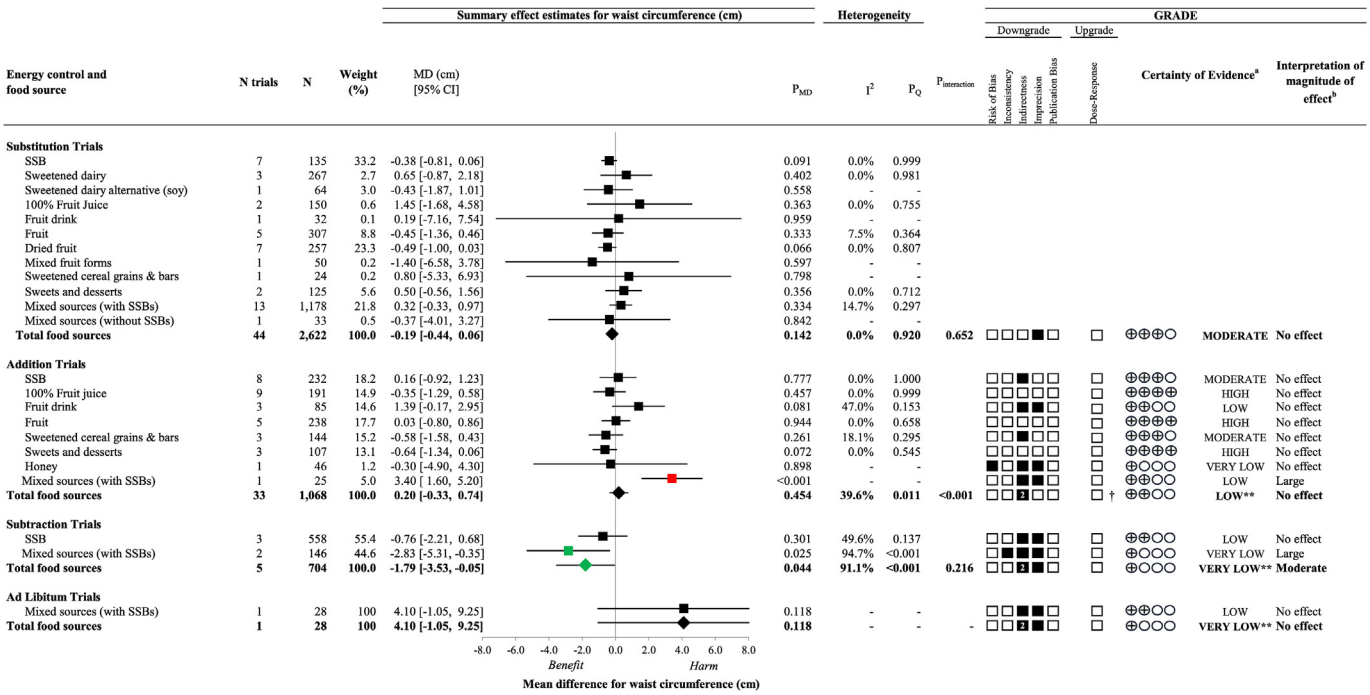

FIGURE 5. A summaryplot for the effect of different food sources of fructose-containing sugars on the waist circumference. Data are weighted mean differences (95% CIs) for the summary effects of individual food sources and total food sources on the waist circumference. Analyses conducted using generic, inverse variance random-effects models (at least 5 trials available) or fixed-effects models (fewer than 5 trials available). Between-study heterogeneity was assessed by the Cochrane Q statistic, where $P_Q < 0.100$ was considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered evidence of substantial heterogeneity. The effects of total fructose-containing sugars are denoted by the bolded lines, with the effect estimates as diamonds. The effects of individual food sources are denoted by the nonbolded lines, with the effect estimates as squares. Any statistically significant reductions are highlighted in green and significant increases in red. The GRADE of randomized controlled trials are rated as "high" certainty of evidence and can be downgraded by 5 domains and upgraded by 1 domain. The white squares represent no downgrades, filled black squares indicate a single downgrade or upgrades for each outcome, and the black square with a white "2" indicates a double downgrade for each outcome. DRM, dose-response model; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MD, mean difference; N, number; ROB, risk of bias; SSB, sugar-sweetened beverage. (A) Because all included trials were randomized or nonrandomized controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded or upgraded based on prespecified criteria. Criteria for downgrades included risk of bias (ROB) (downgraded if most trials were considered to be at high ROB); inconsistency (downgraded if there was substantial unexplained heterogeneity [$I^2 \geq 50\%$; $P_Q < 0.10$]; indirectness (downgraded if there were factors absent or present relating to the participants, interventions, or outcomes that limited the generalizability of the results); imprecision [downgraded if the 95% CI crossed the minimally important difference (MID) for harm or benefit set at 0.5 kg for body weight, 0.2 kg/m^2 for BMI, 2% for body fat, 0.5 cm for waist circumference, and 0.02 for waist-to-hip ratio] [30,31]; and publication bias (downgraded if there was evidence of publication bias based on the funnel plot asymmetry and/or significant Egger or Begg test ($P < 0.10$), with confirmation by adjustment using the trim-and-fill analysis of Duval and Tweedie [41]). The criteria for upgrades included a significant dose-response gradient. (B) For the interpretation of the magnitude, we used the MIDs (see A) to assess the importance of magnitude of our point estimate using the effect size categories according to the new GRADE guidance. Then, we used the MIDs to assess the importance of the magnitude of our point estimates using the effect size categories according to the GRADE guidance [42,49,51] as follows: a large effect (≥5× MID); moderate effect (≥2× MID); small important effect (≥1× MID); and trivial/unimportant effect (<1 MID). **Where there was a significant interaction by food source in addition trials and SSBs and/or mixed sources (with SSBs) were the sole food sources in subtraction and ad libitum trials, we performed the GRADE analysis for each individual food source. †Not upgraded for dose response. Please see Supplementary Table 10 for details.

Supplemental Figures 38–62 present the individual trial influence analyses on the effect of individual food sources, for those analyses that showed evidence of an interaction or influence by food sources, on the primary outcome, body weight. Removal of a single trial comparison resulted in a loss of significance for the increase with added nutritive (caloric) sweeteners [78] and gain of significance for an increase with fruit drinks [117] in substitution trials; a loss of significance for the reduction with 100% fruit juices (≤10%E) [109,137], dried fruits [120], and honey [66]; a gain of significance for an increase with 100% fruit juices (>10%E) [178] in addition trials; and a loss of significance for the reduction with mixed sources (with SSBs) [155,211] in subtraction trials and for the increase with mixed sources (with SSBs) [158] in ad libitum trials.

Supplemental Table 5 tabulates sensitivity analyses for the different correlation coefficients (0.25 and 0.75) used in paired analyses of crossover trials for the body weight. The use of these different correlation coefficients did not alter the direction, magnitude, or significance of the effect or evidence for heterogeneity with the following exceptions: loss of significance for the effect of mixed sources (with SSBs) on the body weight in ad libitum trials (10 trials; MD: 0.35 kg; 95% CI: −0.15, 0.84 kg; $P_{MD} = 0.167$; $I^2 = 11.3\%$; $P_Q = 0.339$) with the use of 0.75; and gain of significant and substantial heterogeneity for SSBs ($I^2 = 53.4\%$; $P_Q = 0.002$) and fruit drinks ($I^2 = 53.3\%$; $P_Q = 0.010$) on the body weight in substitution trials with the use of 0.75.

Supplemental Table 6 presents the sensitivity analyses for the removal of trial comparisons in which nonmean summary statistics

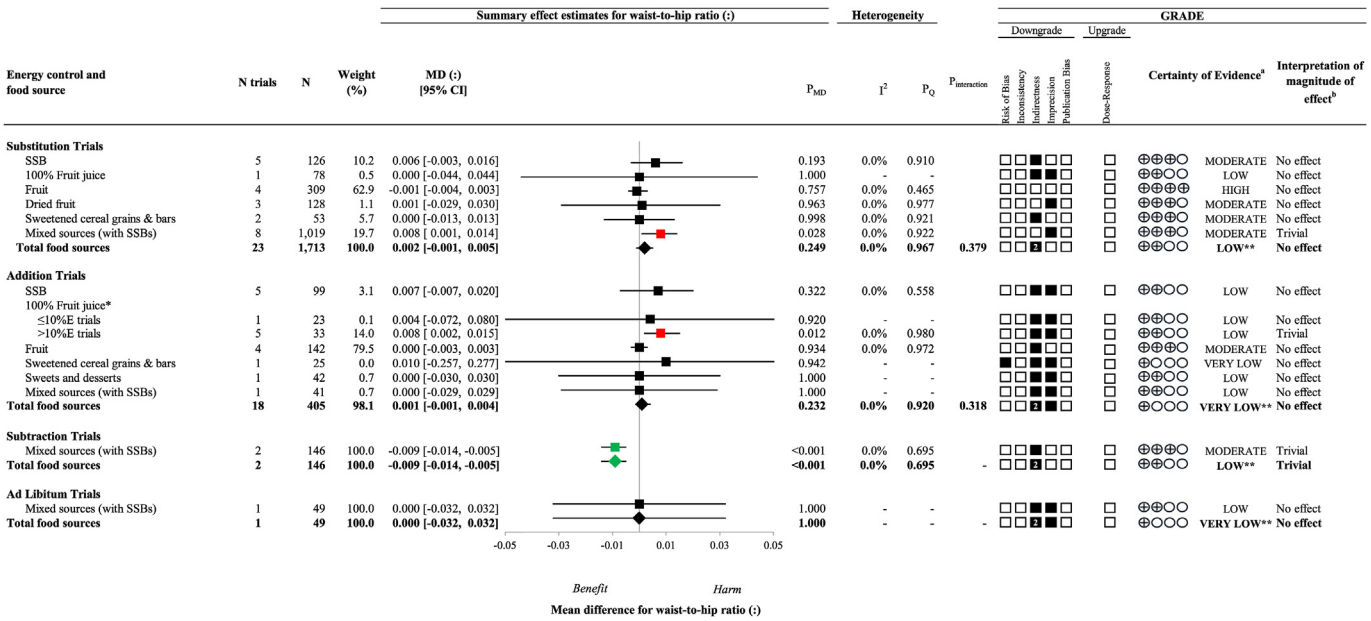

FIGURE 6. A summary plot for the effect of different food sources of fructose-containing sugars on the waist-to-hip ratio. Data are weighted mean differences (95% CIs) for the summary effects of individual food sources and total food sources on the waist-to hip ratio. Analyses conducted using generic, inverse variance random-effects models (at least 5 trials available) or fixed-effects models (fewer than 5 trials available). Between-study heterogeneity was assessed by the Cochrane Q statistic, where $P_Q < 0.100$ was considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered evidence of substantial heterogeneity. The effects of total fructose-containing sugars are denoted by the bolded lines, with the effect estimates as diamonds. The effects of individual food sources are denoted by the nonbolded lines, with the effect estimates as squares. Any statistically significant reductions are highlighted in green and significant increases in red. The GRADE of randomized controlled trials are rated as "high" certainty of evidence and can be downgraded by 5 domains and upgraded by 1 domain. The white squares represent no downgrades, filled black squares indicate a single downgrade or upgrades for each outcome, and the black square with a white "2" indicates a double downgrade for each outcome. DRM, dose-response model; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MD, mean difference; N, number; ROB, risk of bias; SSB, sugar-sweetened beverage. (A) Because all included trials were randomized or nonrandomized controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded or upgraded based on prespecified criteria. Criteria for downgrades included risk of bias (ROB) (downgraded if most trials were considered to be at high ROB); inconsistency (downgraded if there was substantial unexplained heterogeneity: $I^2 \geq 50\%$; $P_Q < 0.10$); indirectness (downgraded if there were factors absent or present relating to the participants, interventions, or outcomes that limited the generalizability of the results); imprecision [downgraded if the 95% CI crossed the minimally important difference (MID) for harm or benefit set at 0.5 kg for body weight, 0.2 kg/m^2 for BMI, 2% for body fat, 0.5 cm for waist circumference, and 0.02 for waist-to-hip ratio] [30,31]; and publication bias (downgraded if there was evidence of publication bias based on the funnel plot asymmetry and/or significant Egger or Begg test ($P < 0.10$) with confirmation by adjustment using the trim-and-fill analysis of Duval and Tweedie [41]). The criteria for upgrades included a significant dose-response gradient. (B) For the interpretation of the magnitude, we used the MIDs (see A) to assess the importance of magnitude of our point estimate using the effect size categories according to the new GRADE guidance. Then, we used the MIDs to assess the importance of the magnitude of our point estimates using the effect size categories according to the GRADE guidance [42,49,51] as follows: a large effect (≥5× MID); moderate effect (≥2× MID); small important effect (≥1× MID); and trivial/unimportant effect (<1 MID). *The overall analysis for 100% fruit juice showed a significant increase in WHR; however, this was driven by 5 of the 6 trials with >10%E. Because there was a significant interaction (with a threshold at 10%E) by dose in categorical subgroup analyses for 100% fruit juice in addition to trials for body weight and BMI and dose is a major domain of the assessment of certainty of evidence, we presented the data separately for ≤10%E and >10%E, rather than presenting the total pooled analysis. **1 food source contributed most of the weight in the analysis (fruit = 63% weight in substitution and 80% in addition trials), thus limiting the ability to assess differences in food sources. Mixed sources (with SSBs) were the sole food source in subtraction and ad libitum trials. Therefore, we performed a GRADE analysis for each individual food source for each energy control.

were used to estimate the mean for body weight and secondary outcomes. There were 2 trial comparisons, of mixed sources (with SSBs), in substitution trials, and 3 trial comparisons, 2 of SSBs and 1 of sweets and desserts, in addition trials. The removal of these trials did not alter the significance and direction of magnitude of the effect.

Supplemental Figures 63–124 present the sensitivity analyses for the secondary outcomes. For total fructose-containing sugars, the removal of a single trial comparison resulted in a loss of significance for the increase in the body fat [56,118] and the reduction in the waist circumference in subtraction trials [204,211], a gain of significance for the decrease in the waist circumference [92] in substitution trials, the increase in the WHR [93] in addition trials, and the reduction in the BMI [211] and body fat [115] in subtraction trials, and a partial explanation of heterogeneity for the BMI in subtraction trials [211]. For individual food sources for those analyses that showed evidence of an interaction or influence by food source for secondary outcomes, removal of a single trial comparison resulted in a loss of significance for the reduction in the BMI with fruits [113,148] in substitution trials and 100% fruit juice (at ≤10%E) [137] in addition trials, for the increase in the body fat with mixed sources (with SSBs) [56] in addition trials, and for the increase in the WHR with mixed sources (with SSBs) [92] in substitution trials and with 100% fruit juice (at >10%E) [178] in addition trials; and a gain of significance for the increase in the BMI with fruit drinks [212] in substitution trials and the decrease in the BMI with dried fruits [57] in addition trials, the increase in waist circumference with fruit drinks [119] in addition trials, and the

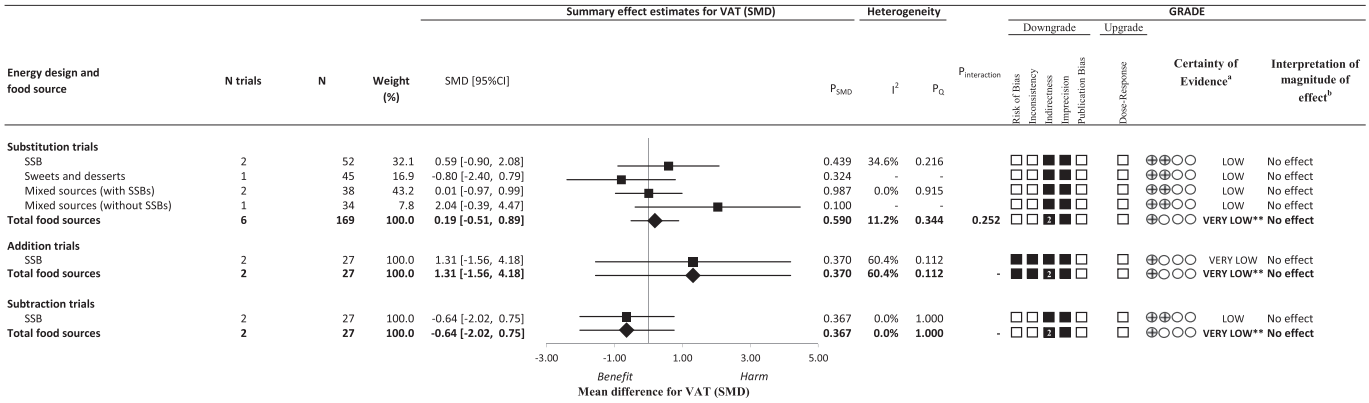

FIGURE 7. A summary plot for the effect of different food sources of fructose-containing sugars on VAT. Data are weighted mean differences (95% CIs) for the summary effects of individual food sources and total food sources on VAT. Analyses conducted using generic, inverse variance random-effects models (at least 5 trials available) or fixed-effects models (fewer than 5 trials available). Between-study heterogeneity was assessed by the Cochrane Q statistic, where $P_Q < 0.100$ was considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered evidence of substantial heterogeneity. The effects of total fructose-containing sugars are denoted by the bolded lines, with the effect estimates as diamonds. The effects of individual food sources are denoted by the nonbolded lines, with the effect estimates as squares. Any statistically significant reductions are highlighted in green and significant increases in red. The GRADE of randomized controlled trials are rated as "high" certainty of evidence and can be downgraded by 5 domains and upgraded by 1 domain. The white squares represent no downgrades, filled black squares indicate a single downgrade or upgrades for each outcome, and the black square with a white "2" indicates a double downgrade for each outcome. DRM, dose-response model; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MD, mean difference; N, number; SMD, standardized mean difference; ROB, risk of bias; SSB, sugar-sweetened beverage; VAT, visceral adipose tissue. (A) Because all included trials were randomized or nonrandomized controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded or upgraded based on prespecified criteria. Criteria for downgrades included risk of bias (ROB) (downgraded if most trials were considered to be at high ROB); inconsistency (downgraded if there was substantial unexplained heterogeneity: $I^2 \geq 50\%$; $P_Q < 0.10$); indirectness (downgraded if there were factors absent or present relating to the participants, interventions, or outcomes that limited the generalizability of the results); imprecision [downgraded if the 95% CI crossed the minimally important difference (MID) for harm or benefit set at 0.5 kg for body weight, 0.2 kg/m^2 for BMI, 2% for body fat, 0.5 cm for waist circumference, 0.02 for waist-to-hip ratio [30,31], and 0.08 SMD for VAT (5% of baseline SMD); and publication bias (downgraded if there was evidence of publication bias based on the funnel plot asymmetry and/or significant Egger or Begg test ($P < 0.10$) with confirmation by adjustment using the trim-and-fill analysis of Duval and Tweedie [41]). The criteria for upgrades included a significant dose-response gradient. (B) For the interpretation of the magnitude, we used the MIDs (see A) to assess the importance of magnitude of our point estimate using the effect size categories according to the new GRADE guidance. Then, we used the MIDs to assess the importance of the magnitude of our point estimates using the effect size categories according to the GRADE guidance [42,49,51] as follows: a large effect (≥5× MID); moderate effect (≥2× MID); small important effect (≥1× MID); and trivial/unimportant effect (<1 MID). **Where there were 2 or few food sources (other than mixed sources), we performed the GRADE analysis for each individual food source.

reduction in the BMI with mixed sources (with SSBs) [211] and in the body fat [115] and waist circumference [115] with SSBs in subtraction trials.

Supplemental Tables 7–10 present sensitivity analyses for the different correlation coefficients (0.25 and 0.75) used in paired analyses of crossover trials for secondary outcomes. The use of these different correlation coefficients did not alter the direction, magnitude, or significance of the effect or evidence for heterogeneity for any outcomes across food sources and levels of energy control, with the following exceptions: loss of significance for the increase in the body weight with mixed sources (with SSBs) in ad libitum trials and the increase in the body fat with total fructose-containing sugars in addition trials with the use of 0.75; gain of significance for the increase in the waist circumference with total fructose-containing sugars with the use of 0.75, the decrease in the BMI with 100% fruit juice in addition trials with the use of 0.25, and the increase in the waist circumference with fruit drinks in addition trials with either 0.25 or 0.75; and gain of significant and substantial heterogeneity for SSBs and fruit drinks on the body weight in substitution trials and total fructose-containing sugars on the waist circumference in addition trials with the use of 0.75.

Subgroup analyses

Supplemental Figures 125–136 present the subgroup analyses and continuous meta-regression analyses for the effect of total fructose-containing sugars, where there were at least 10 trial comparisons, on the primary outcome, body weight. There was significant effect modification by fructose-containing sugar type (generally, trials providing fruit or honey showed reductions, whereas those providing sucrose, high-fructose corn syrup, and/or mixed type showed increases, and others showed no effect in substitution and addition trials), regulatory designation (trials providing naturally occurring sugars showed reductions, whereas those providing added or mixed type showed increases in substitution and addition trials), sugar form matrix (trials providing liquid sugars showed reductions in substitution trials but increases in addition trials, whereas those providing mixed types showed increases in both), follow-up (trials of >8 wk showed increases in addition trials, whereas trials of ≤8 wk showed reductions in subtraction trials), funding (trials with industry funding showed increases in substitution trials whereas trials with agency and industry funding showed increases in ad libitum trials, with others showing no effect), and continuous age (trials in participants with a greater mean age showed a greater body weight gain in addition and ad libitum trials).

Supplemental Figures 137–163 present the subgroup analyses and continuous meta-regression analyses for the effect of individual food sources of fructose-containing sugars on the primary outcome, body weight. There was a significant effect modification by the baseline body weight (trials with a baseline body weight greater than the median) showed greater reductions for fruit in substitution trials and a greater increase for fruit drinks in addition trials), randomization [randomized trials showed a greater increase for mixed sources (with

SSBs) in substitution trials and for fruit drinks in addition trials], design [parallel trials showed greater increases for mixed sources (with SSBs) in substitution trials and crossover trials showed greater increases for fruit drinks in addition trials], and allocation concealment (low ROB trials showed greater reductions for fruits in substitution trials, and low or unclear ROB trials showed greater increases for fruit drinks in addition trials).

Supplemental Figures 164–187 present the subgroup analyses and continuous meta-regression analyses for the effect of total fructose-containing sugars, where there were at least 10 trial comparisons, on secondary outcomes. There was a significant effect modification involving multiple (at least 3) outcomes by dose (trials providing sugars at ≤10%E showed reductions, whereas trials providing sugars at >10%E showed increases), sugar form matrix (trials providing liquid and mixed forms of sugar showed increases), feeding control (metabolic trials showed increases), comparator (trials using nonnutritive sweetener or starch comparators showed increases), and design (crossover trials showed increases than the parallel trials) in addition trials. A number of other subgroup analyses showed subgroup differences for individual outcomes across levels of energy control, without any discernable pattern.

Supplemental Figures 188–201 present the subgroup analyses and continuous meta-regression analyses for the effect of individual food sources on secondary outcomes. There were no subgroup analyses for the body fat, waist circumference, WHR, or VAT because there was no interaction by food source or <10 trial comparisons available across all 4 levels of energy control. Subgroup analyses by food sources were conducted only for the BMI in substitution and addition trials. There were no subgroup differences for any food source in the substitution trials. There was a significant effect modification for the effect of SSBs and 100% fruit juice on the BMI in addition to trials by incomplete outcome reporting (low ROB trials showed greater increases or decreases, respectively), funding (trials with agency funding showed greater increases or reductions, respectively), and continuous age (trials with younger participants showed greater increases or less reductions, respectively).

Dose-response analyses

Supplemental Figures 202–229 present linear and nonlinear dose-response analyses for the primary outcome, body weight. In the substitution trials, there was no dose response for the effect of total fructose-containing sugars. There was an inverse linear dose response ($P_{linear} = 0.023$) for mixed sources (with SSBs), which was driven by a single trial [135] ($P_{linear} = 0.356$, after removal), and a positive linear ($P_{linear} = 0.037$) and nonlinear ($P_{nonlinear} = 0.002$) dose response for mixed sources (without SSBs), which was driven by a single trial [110] ($P_{linear} = 0.905$; $P_{nonlinear} = 0.518$, after removal). In addition trials, there was a positive linear dose response for total fructose-containing sugars ($P_{linear} < 0.001$), which was driven by the significant interaction by a food source, with higher doses of SSBs ($P_{linear} < 0.001$) and 100% fruit juice ($P_{linear} = 0.004$; $P_{nonlinear} < 0.001$) resulting in greater increases in the body weight. The relationship for 100% fruit juice was dependent on the dose threshold. There was a significant positive linear dose response at doses ≤10%E ($P_{linear} = 0.006$), with doses across the entire dose-response range (up to 10%E) showing reductions in the body weight, where smaller doses resulted in greater reductions. In the subtraction and ad libitum trials, there were no dose responses for total fructose-containing sugars or any food source.

Supplemental Figures 230–270 present linear and nonlinear dose-response analyses for secondary outcomes. Total fructose-containing sugars showed a positive linear dose response for the BMI, body fat, and waist circumference in addition trials ($P_{linear} < 0.001$, $P_{linear} < 0.001$, and $P_{linear} = 0.004$, respectively); however, each of these exhibited a significant interaction by food sources. In addition trials, there was a positive linear dose response for the effect of SSBs on the BMI ($coef_{linear}$: 0.46 kg/m^2; 95% CI: 0.20, 0.70; $P < 0.001$ per 355 mL serving, 8%E), where higher doses of SSBs resulted in greater increases in the BMI; a positive linear dose response for the effect of 100% fruit juice at doses ≤10%E on the BMI ($coef_{linear}$: 0.91 kg/m^2; 95% CI: 0.05, 1.77; $P = 0.038$ per 125 mL serving, 3%E) with most doses across the dose-response range (up to 10%E) showing reductions in the BMI, where smaller doses resulted in greater reductions; and a significant inverse linear dose-response gradient for the effect of dried fruits on the BMI ($coef_{linear}$: −4.58 kg/m^2; 95% CI: −8.72, −0.43; $P = 0.030$ per 60 mL serving, 5.5%E), where larger doses of dried fruits resulted in greater reductions in the BMI.

Small-study effects

Supplemental Figures 271–289 present the contour-enhanced funnel plots and publication bias and trim-and-fill (where applicable) assessments for all outcomes where there were ≥10 trials available. There was an evidence of the funnel plot asymmetry for total fructose-containing sugars on the body weight ($P = 0.037$) and BMI ($P = 0.067$) in the substitution trials. However, adjustment for the funnel plot asymmetry with the imputation of 3 missing trials by the trim-and-fill method of Duval and Tweedie did not alter the direction, magnitude, or significance of the effect, suggesting that there was no meaningful influence of publication bias on the results (original MD for body weight: 0.04 kg; 95% CI: −0.07, 0.16; $P = 0.469$; imputed MD: 0.08 kg; 95% CI: −0.06, 0.22; $P = 0.265$; original MD for BMI: −0.01 kg/m^2; 95% CI: −0.07, 0.05; $P = 0.628$; imputed MD: −0.02 kg/m^2; 95% CI: −0.08, 0.04; $P = 0.537$).

GRADE assessment

Figures 2–7 and Supplemental Tables 11–17 present the GRADE assessments. The certainty of evidence for the effect of total fructose-containing sugars on the primary outcome, body weight, was very low in the substitution (no effect), addition (trivial increase), subtraction (small important reduction), and ad libitum (no effect) trials, owing to double downgrades for indirectness across the 4 levels of energy control and single downgrades for imprecision in addition, subtraction, and ad libitum trials and serious ROB in substitution trials.

Because there was an evidence of a significant interaction or influence by food sources, the certainty of evidence was assessed for the individual food sources. The certainty of evidence was moderate for fruits (trivial reduction) and added nutritive sweeteners (small important increase) owing to a downgrade for imprecision and high for mixed sources (with SSBs) (trivial increase) in substitution trials; high for SSBs (moderate increase) and mixed sources (with SSBs) (large increase), moderate for 100% fruit juice in trials with ≤10%E and honey (moderate reductions) and fruit drinks (small important increase) owing to downgrades for imprecision, and low for dried fruits (moderate reduction) owing to downgrades for indirectness and imprecision in addition trials; low for mixed sources (with SSBs) (moderate reduction) owing to downgrades for inconsistency and imprecision in subtraction trials; and moderate for mixed sources (with and without SSBs) (trivial and large reductions, respectively) owing to a downgrade for imprecision and indirectness, respectively, in ad libitum trials. The certainty of evidence for the remaining food sources that showed no effect was

generally moderate, ranging from high to low, owing to downgrades for inconsistency, indirectness, and/or imprecision.

The certainty of evidence for the effect of total fructose-containing sugars on secondary outcomes was either low or very low owing to double downgrades for indirectness in each analysis and at least a single downgrade for ROB, inconsistency, or imprecision, with the exception of high for the body fat (no effect) with no downgrades and moderate for the waist circumference (no effect) owing to a downgrade for imprecision in substitution trials.

If there was an evidence of a significant interaction or influence by food sources, the certainty of evidence was assessed for individual food sources. In substitution trials, the certainty of evidence was moderate for the effect of fruits on the BMI (small important reduction) and mixed sources (with SSBs) on the BMI and WHR (trivial increases) owing to downgrades for imprecision. In addition trials, the certainty of evidence was high for the effect of SSBs (moderate increase), fruit drinks (moderate increase), and dried fruits (large reduction) on the BMI, owing to a downgrade for serious ROB and upgrade for linear dose response for SSBs and a downgrade for imprecision and an upgrade for linear dose response for dried fruits; high for the effect of fruit drinks (trivial increase) on the body fat; moderate for the effect of 100% fruit juice in trials with ≤10%E (moderate reduction) and mixed sources (with SSBs) (moderate increase) on the BMI owing to downgrade for imprecision and indirectness, respectively; low for the effect of mixed sources (with SSBs) on the body fat (trivial increase) and waist circumference (large increase) owing to downgrades for indirectness and imprecision; and low for 100% fruit juice in trials >10%E on the WHR (trivial increase) owing to downgrades for indirectness and imprecision. In subtraction trials, the certainty of evidence was moderate for mixed sources (with SSBs) on the WHR (trivial reduction) owing to a downgrade for indirectness and very low for mixed sources (with SSBs) on the waist circumference (large reduction) owing to downgrades for inconsistency, indirectness, and imprecision. The certainty of evidence for the remaining food sources that showed no effect was generally moderate, ranging from high to very low, owing to downgrades for the ROB, inconsistency, indirectness, and/or imprecision.

Discussion

We conducted a systematic review and meta-analysis of 169 reports (255 trial comparisons) in 10,357 adult participants with or without obesity and who had or are at risk for cardiometabolic diseases of the effects of 14 different food sources of fructose-containing sugars [SSB; sweetened dairies; sweetened dairy alternatives (soy); 100% fruit juice; fruit drinks; fruits; dried fruits; mixed fruit forms; sweetened cereal grains and bars; sweets and desserts; honey; added nutritive (caloric) sweeteners; mixed sources (with SSBs); and mixed sources (without SSBs)], with a median dose of 9% to 20% of total energy across 4 different levels of energy control over a median follow-up of 6–18 wk. Total fructose-containing sugars led to trivial increases in the body weight (0.28 kg), BMI (0.16 kg/m^2), and body fat (0.45%) in addition trials and small important reductions in the body weight (−0.96 kg) and moderate reductions in the waist circumference (−1.79 cm) and WHR (−0.009) in subtraction trials. There was no effect of total fructose-containing sugars in substitution or ad libitum trials on any marker of adiposity. There was an evidence of interaction or influence by the food source in most analyses. Fruits at a median dose of 6%E (doses ranging from 3.2%E to 14.6%E) led to moderate reductions in the body weight (−0.38 kg) and small important reductions in the BMI (−0.21 kg/m^2) in substitution trials, whereas fruits at lower doses that did not exceed the public health threshold of 10% E led to small important reductions in the body weight (−0.60 kg) in addition trials. Moreover, 100% fruit juice at lower doses (≤10% E) led to moderate reductions in the body weight (−1.30 kg) and BMI (−0.52 kg/m^2), dried fruits at a median dose of 3%E (doses ranging from 1.4%E to 3.8%E) led to moderate reductions in the body weight (−1.29 kg) and large reductions in the BMI with an evidence of a linear dose-response gradient [1 serving (60 mL, 5.5%E) was associated with a BMI reduction of 4.58 kg/m^2], and honey at a median dose of 9%E (doses ranging from 3.2%E to 33%E) led to moderate reductions in the body weight (−1.65 kg) in addition trials. In addition, 100% fruit juice at doses >10%E led to trivial increases in the WHR (0.008). Added nutritive (caloric) sweeteners at a median dose of 10%E (doses ranging from 5%E to 22% E) led to small important increases in the body weight (0.66 kg) in substitution trials. SSBs providing excess energy at a median dose of 21%E (doses ranging from 7%E to 25%E) led to moderate increases in the body weight and BMI with evidence of a linear dose-response gradient [1 serving (355 mL, 8%E) was associated with a body weight increase of 1.04 kg and a BMI increase of 0.46 kg/m^2] in addition trials. Fruit drinks providing excess energy at a median dose of 18%E (doses ranging from 5%E to 25%E) led to small important increases in the body weight (0.9 kg) and moderate increases in the BMI (0.57 kg/m^2) in addition trials. Mixed sources (with SSBs) at a median dose of 20%E (doses ranging from 4%E to 95%E) led to trivial increases in the body weight (0.27 kg), BMI (0.16 kg/m^2), and WHR (0.008) in substitution trials. This same food source providing excess energy at a median dose of 24%E (doses ranging from 23%E to 28%E) led to large increases in the body weight (2.77 kg) and moderate increases in BMI (0.90 kg/m^2) in addition trials and consumed ad libitum at a median dose of 22%E (doses ranging from 6%E to 30%E) led to trivial increases in the body weight (0.41 kg), whereas its removal at a median dose of 11%E led to moderate reductions in the body weight (−1.30 kg), large reductions in the waist circumference (−2.83 cm), and trivial reductions in the WHR (−0.009) in subtraction trials. Other categories of food sources of fructose-containing sugars assessed showed no significant effects on markers of adiposity.

Findings in relation to the literature

Our results for total fructose-containing sugars are similar to a previous systematic review and meta-analysis on the effects of fructose on the body weight [7], where a significant increase in body weight was observed when consumed as excess calories but was without effect in substitution trials. This study builds on the previous study over a decade ago because it pooled a much larger number of trials (n = 31 and n = 118 substitution trial comparisons; n = 10 and n = 108 addition trial comparisons) and explores interaction by food source. Furthermore, the increasing effect of SSBs providing excess energy on the body weight and BMI, with an evidence of a positive linear dose response, has been consistently reported in the literature [3,6,8,9].

The advantages and lack of harm observed for certain food sources of fructose-containing sugars agrees with previous observations. A systematic review and meta-analysis of controlled trials of berries, which were the predominant type of fruit in the included trials, showed similar reductions in BMI, and reductions in glycemic control, blood lipids, blood pressure, and inflammation [221]. Similar improvements were shown for fruits in this systematic review and meta-analysis of the effect of food sources of fructose-containing sugars on the glycemic control [6]. This line of evidence is supported by a systematic review and meta-analysis of prospective cohort studies, which demonstrated an inverse association between fruit intake and weight change [11].

TABLE
Summary of trial characteristics[1]

Trial characteristics	Substitution trials	Addition trials	Subtraction trials	Ad libitum trials
Trial comparisons (*n*)	126	104	13	12
Study size, median *n* (range)	25 (5–595)	29 (7–158)	68 (7–318)	13 (5–159)
Health status (No. of studies)	NW = 8, MW = 34, OW/OB = 36, diabetes = 26, MetS = 4, dyslipidemia = 3, NAFLD = 3, pre-DM = 5, CKD = 2, coronary artery disease = 1, IBS = 1, higher CVD risk = 1, HTN = 1, osteoarthritis = 1	NW = 9, MW = 40, OW/OB = 31, diabetes = 8, MetS = 3, dyslipidemia = 5, NAFLD = 1, higher CVD risk = 1 , RA = 1, MW with gall stones = 1, HIV = 3, PCOS = 1	MW = 5, OW/OB = 5, dyslipidemia = 1, post-MI = 2	NW = 4, MW = 4, OW/OB = 1, diabetes = 1, MetS = 1, dyslipidemia = 1
Male:female ratio (%)[2]	54:46	48:52	55:45	46:54
Age (y), mean (range)[2]	44 (22–70)	38 (20–66)	32 (21–43)	38 (25–47)
Country (No. of comparisons)	Antarctic = 1, Australia = 1, Brazil = 9, Denmark = 2, Finland = 6, France = 4, Germany = 2, Greece = 3, India = 2, Iran = 4, Ireland = 1, Israel = 1, Italy = 2, Mexico = 3, Netherlands = 2, New Zealand = 1, Poland = 3, South Africa = 4, Spain = 2, Sweden = 3, Switzerland = 7, UK = 27, USA = 36	Australia = 1, Bahrain = 1, Brazil = 4, Canada = 5, China = 1, Denmark = 9, Finland = 1, Germany = 3, Greece = 1, India = 2, Indonesia = 1, Italy = 2, Iran = 7, Malaysia = 3, Mexico = 2, Netherlands = 2, New Zealand = 2, Norway = 1, Scotland = 2, Serbia = 3, Spain = 2, Switzerland = 6, Thailand = 3, Turkey = 2, UK = 7, USA = 31	Mexico = 3, South Africa = 2, Switzerland = 2, UK = 2, USA = 4	Antarctic = 2, Denmark = 4, Germany = 1, Netherlands = 1, Scotland = 1, UK = 3
Setting (%; inpatients:outpatients:inpatients/outpatients)	6:85:9	3:91:6	0:100:0	0:100:0
Baseline BW (kg), mean (range)[2,3]	81 (55–111)	76 (55–102)	82 (65–103)	80 (62–91)
Baseline BMI (kg/m^2), mean (range)[2,4]	28 (21–36)	27 (21–39)	30 (25–37)	28 (23–32)
Study design (%), crossover:parallel	45:55	38:63	31:69	75:25
Feeding control (%), met:supp:DA:met, supp:supp, DA	19:56:23:2:0	4:90:1:5:0	8:31:38:0:23	33:33:25:8:0
Randomization (%), yes:no:partial[5]	78:22:0	71:29:0	69:31:0	83:17:0
Fructose-containing sugar dose (% of total energy intake), mean (range)	16 (1–95)	11 (1–33)	16 (5–24)	18 (5–30)
Follow-up duration (wk), mean (range)	10 (2–52)	7 (2–24)	22 (2–48)	12 (2–24)
Funding sources (%), A:I:A,I:NR	31:21:29:18	57:10:27:7	38:15:15:31	17:25:50:8
Fructose-containing sugar type (No. of comparisons)	Fructose = 28, sucrose = 60, HFCS = 3, fruit = 21, mixed type = 14	Fructose = 9, sucrose = 28, HFCS = 8, fruit = 51, honey = 5, mixed type = 3	Sucrose = 7, HFCS = 4, mixed type = 2	Sucrose = 10, mixed type = 2
Sugar regulatory designation (No. of comparisons)	Naturally occurring = 21, added = 62, mixed designation = 43	Naturally occurring = 52, added = 49, mixed designation = 3	Added = 8, mixed designation = 4	Added = 2, mixed designation = 10
Comparator (No. of comparisons)	Starch = 50, glucose = 25, lactose = 7, maltodextrin = 3, fat = 14, protein = 2, diet alone = 1, mixed comparator = 24	NNS = 25, water = 9, diet alone = 64, starch = 1, glucose = 1, fat = 1, mixed comparator = 3	NNS = 5, water = 4, diet alone = 4	Starch = 6, fat = 2, NNS = 2, glucose = 2
Food sources of fructose-containing sugars (No. of comparisons)	SSB = 12, sweetened dairy = 7, sweetened dairy alternative (soy) = 1, 100% fruit juice = 2, fruit drink = 7, fruit = 11, dried fruit = 8, mixed fruit form = 1, sweetened cereal grains and bars = 3, sweets and desserts = 8, added nutritive (caloric) sweetener = 14, mixed sources (with SSBs) = 44, mixed sources (without SSBs) = 8	SSB = 23, 100% fruit juice = 23, fruit drink = 14, fruit = 20, dried fruit = 8, sweetened cereal grains and bars = 3, sweets and desserts = 4, honey = 5, added nutritive (caloric) sweetener = 1, mixed sources (with SSBs) = 3	SSB = 7, mixed sources (with SSBs) = 6	Sweets and desserts = 1, mixed sources (with SSBs) = 10, mixed sources (without SSBs) = 1

A, agency; A,I, agency and industry; BW, body weight; CKD, chronic kidney disease; DA, dietary advice; HFCS, high-fructose corn syrup; HTN, hypertension; I, industry; IBS, irritable bowel syndrome; MetS, metabolic syndrome; MW, mixed weight; NAFLD, nonalcoholic fatty liver disease; No, number; NNS, nonnutritive sweetener; NR, not reported; NW, normal weight; OW/OB, overweight or obese; PCOS, polycystic ovarian syndrome; PreDM, prediabetes mellitus; RA, rheumatoid arthritis; SSB, sugar-sweetened beverage.

[1] Values are rounded to the nearest whole number.

[2] Based on trial comparisons that reported data.

[3] Based on trial comparisons that reported baseline data ($n = 27$ trials missing baseline BW in substitution trials; $n = 10$ trials missing baseline BW addition trials; $n = 2$ trials missing baseline BW in subtraction trials; $n = 1$ trial missing baseline BW in ad libitum trials).

[4] Based on trial comparisons that reported baseline data ($n = 27$ trials missing baseline BMI in substitution trials; $n = 4$ trials missing baseline BMI addition trials; $n = 3$ trials missing baseline BMI in subtraction trials; $n = 3$ trials missing baseline BMI in ad libitum trials).

[5] Partial randomization was assigned to a trial comparison that randomized only selected participants.

Dried fruit, which are nutritionally equivalent to fresh fruits in smaller serving sizes [222], also have evidence to support improvements in cardiometabolic risk factors [223,224]. The reductions in the body weight and BMI from 100% fruit juice at lower doses (≤10%E), and increases in the WHR at higher doses (>10%E), agrees with systematic reviews and meta-analyses of prospective cohort studies, which have demonstrated U-shaped associations between 100% fruit juice intake and various cardiometabolic outcomes including incident hypertension [225], metabolic syndrome [226], and cardiovascular event risk [227] where protection is seen at low to moderate doses. Evidence showing fruit juice is associated with weight gain has modeled the relationship linearly and not assessed nonlinear relationships or threshold effects [228]. The reductions in body weight observed for honey is supported by a recent systematic review and meta-analysis of honey, which found a nonsignificant reduction of −0.92 kg in the body weight along with improvements in other cardiometabolic risk factors [229]. These findings may be explained by honey's rare sugar content. Honey contains up to 14% by weight (in milligrams per gram) [230] rare sugars, notably allulose, tagatose, and isomaltulose, all of which have shown improvements in cardiometabolic risk factors [231–233]. Finally, the lack of harm observed for sweetened cereal grains and bars agrees with systematic reviews and meta-analyses of sources of whole grains and fiber [234,235]. The implication that any harm from the fructose-containing sugars was offset by the benefit of cereal grains, nuts, and dried fruits contained in the cereal grains and bars.

These advantages and/or the lack of harm may be partly explained by the food matrix. Dietary fiber can be higher and GI can be lower in some food sources of fructose-containing sugars. Fruits and dried fruits, which showed reductions, and sweetened cereal grains and bars, which failed to show an increase in markers of adiposity, generally have a higher fiber (e.g., apples 4 g/medium; berries 4 g/cup; raisins 2 g/40 g box; and fruit and nut bar, 5 g/bar) and lower GI (e.g., apples 38; berries 28; raisins 57; fruit and nut bar, 40) [236]. Meanwhile, SSBs added nutritive sweeteners, and mixed sources (with SSBs), which showed increases in markers of adiposity, would be expected to be lower in fiber and higher in GI. There is evidence that low GI diets may improve measures of adiposity, as demonstrated in a recent systematic review and meta-analysis of low GI/load diets, in which similar reductions in the body weight and BMI resulted from low GI than in higher GI diets [237]. Low GI foods and foods high in fiber may reduce circulating insulin and related incretin hormones, thus increasing satiety after meals, delaying hunger, and a reducing subsequent energy intake [238–242].

The predominant subgroup effects we identified support the significant interactions between food sources of fructose-containing sugars observed. The significant effect modification by fructose-containing sugar type, regulatory designation, and dose in substitution and addition trials reflect the significant reductions seen with fruits, dried fruits, and 100% fruit juice, and increases seen with SSBs, added nutritive (caloric) sweeteners, and mixed sources (with SSBs). Fruits (fructose-containing sugar type subgroup), naturally occurring sugars (regulatory designation subgroup), and lower doses (categorical dose subgroup) generally showed reductions in markers of adiposity. Meanwhile, sucrose and fructose (fructose-containing sugar type subgroup), added sugars (regulatory designation subgroup), and higher doses (categorical dose subgroup) generally showed increased in markers of adiposity.

Strengths and weaknesses

There are several strengths in our systematic review and meta-analysis. First, we conducted a comprehensive and reproducible

search and selection process of the literature examining the effect of food sources of fructose-containing sugars on adiposity. Second, we collated and synthesized the totality of available evidence from a large body (169 reports, 255 trial comparisons, $n = 10{,}357$) of controlled intervention studies, which give the greatest protection against bias. Third, we had comprehensive exploration of possible sources of heterogeneity. Fourth, we evaluated the shape and strength of the dose-response relationships. Fifth, we assessed the overall quality of evidence using the GRADE assessment approach.

Our analyses also presented limitations. First, there was evidence for a serious ROB in several of the analyses. We downgraded body weight in substitution trials, BMI in addition to trials of SSBs, body fat, and WHR addition trials of sweetened cereal grains and bars, waist circumference of honey in addition trials, and VAT addition trials of SSBs for serious ROB. Second, there was an evidence of indirectness. The significant interaction or influence of food source in all substitutions (except for the body fat and waist circumference) and addition trials and the limited number of food sources of fructose-containing sugars available in all subtraction and ad libitum trials [only 1 or 2 food sources available (SSBs and/or mixed sources)] in the pooled analyses for total fructose-containing sugars meant the results could not be generalized to all food sources. Therefore, we double downgraded for very serious indirectness in these analyses and rated the evidence separately for individual food sources. The downgrades for the indirectness of individual food sources were related to insufficient trial comparisons, which limited generalizability related to participant type. The absence of long-term trials (>1- y diet duration) might be another reason to downgrade for serious indirectness; however, we did not make this downgrade and made our conclusions specific to medium-term intake, reflecting the median 12-wk follow-up duration of the included trials. We also cannot rule out an effect of modification by sex and ethnicity. Although we did not conduct subgroup analyses by sex and ethnicity, the effect estimates from trials from different countries or with data presented separately by sex did not appear to differ meaningfully from the pooled estimates, so we did not downgrade for serious indirectness in either case. Third, there was evidence of inconsistency in a few of the pooled estimates. In most subtraction analyses of mixed sources (with SSBs), we downgraded for serious inconsistency owing to substantial unexplained heterogeneity. Finally, there was an evidence of imprecision in almost all pooled analyses. We downgraded for serious imprecision owing to the crossing of the prespecified MID, which meant that clinically important benefits and/or harm could not be ruled out.

Weighing the strengths and limitations, the certainty of evidence was moderate for the decreasing effect of fruit in substitution trials, generally moderate (high to low) for the decreasing effect of honey, dried fruits, and fruits and 100% fruit juice (at ≤10%E) in addition trials and the increasing effect of added nutritive (caloric) sweeteners and mixed sources (with SSBs) in substitution trials, high for the increasing effect of SSBs in addition trials, low for the decreasing effect of the removal of mixed sources (with SSBs) in subtraction trials, moderate for the increasing effect of the mixed sources (with and without SSBs) in ad libitum trials, and generally moderate (very low to high) for the effect of all other comparisons on markers of adiposity.

Implications

Our findings demonstrate the importance of focusing on foods, dietary patterns, and the energy conditions under which they are consumed, rather than recommending limits on total fructose-containing sugars. Dietary guidelines have shifted away from a focus on single nutrients (sugars, fat, etc.) toward a dietary pattern-based approach [243]. This shift has been well supported by the Global Burden of Disease Study, which concludes that a policy focus on increased intake of foods that are the most important contributors to the global burden of morbidity and mortality, such as fruits and whole grains, might have a comparatively larger benefit rather than a focus on sugars and fat [244]. Currently, obesity, diabetes, and cardiovascular guidelines generally recommend adhering to plant-based Mediterranean, vegetarian, Portfolio, dietary approaches to stop hypertension, and low GI dietary patterns, which emphasize some food sources of fructose-containing sugars (fruits, vegetables, and whole grains), whereas limiting others (sweets and SSBs) [245–250]. Our research aligns with these dietary patterns by supporting the selection of food sources of fructose-containing sugars, which include fresh fruits, 100% fruit juice at low to moderate intake (≤10%E), and dried fruits and limiting the intake of SSBs, especially when providing excess energy.

Conclusions

In conclusion, the effect of fructose-containing sugars on adiposity seems to be mediated by both energy control and fructose-containing food source in adults with or without obesity and who have or are at risk of cardiometabolic diseases over the medium term (12 wk). The evidence provides a good indication that excess energy intake at high doses (≥20%E or ≥100 g/d) from SSBs, other sugary beverages, and mixed sources (with SSBs) leads to generally moderate increases in adiposity, whereas the removal of energy from mixed sources (with SSBs) leads to generally moderate decreases in adiposity. Most other food sources, with the exception of mixed sources (with SSBs) at high doses (≥20%E or ≥100 g/d), show no harmful effects irrespective of energy control, with some sources even showing generally moderate beneficial effects (fruits, 100% fruit juice, dried fruits, and honey at lower doses of ≤10%E or ≤50 g/d). The main sources of uncertainty across the analyses were imprecision and indirectness with a lack of food sources assessed in subtraction and ad libitum trials. To address these uncertainties, there remains a need for more large, high-quality randomized trials assessing a broader variety of food sources of fructose-containing sugars. In the meantime, these findings suggest that policy and guideline makers should consider the role of energy control and food source for the prevention and management of obesity.

Author Contribution

The authors' responsibilities were as follows—JLS, LC, VLC, SBM, RJdS, TMSW, LAL, CWCK, DJAJ: designed the research (project conception, development of overall research plan, and study oversight); LC, AC, SA-C, AA, DL, FA-Y, XQ, SB, NM, EL, VH: conducted the research (hands-on conduct of the experiments and data collection); LC, SA-C, AA, DL, TAK, AZ: analyzed the data or performed the statistical analysis; LC, JLS: wrote the paper; LC, JLS: had primary responsibility for the final content and take responsibility for the integrity of the data and the accuracy of the data analysis; JLS, DJAJ: supervised the study; and all authors: contributed to the critical revision of the manuscript for important intellectual content and read and approved the final version of the manuscript. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Conflict of Interest

JLS is a member of the Journal's Editorial Board and played no role in the Journal's evaluation of the manuscript. LC was a Mitacs-Elevate postdoctoral fellow jointly funded by the Government of Canada and the Canadian Sugar Institute (September 2019–August 2021). She was previously (2010–2018) employed as a casual clinical coordinator at INQUIS Clinical Research, Ltd. (formerly Glycemic Index Laboratories, Inc.), a contract research organization. AC and AA have received funding from a Toronto 3D MSc Scholarship award. SA-C was funded by a Canadian Institutes of Health Research (CIHR) Canadian Graduate Scholarships Master's Award, the Loblaw Food as Medicine Graduate Award, the Ontario Graduate Scholarship, and the CIHR Canadian Graduate Scholarship Doctoral Award. She avoids consuming NSBs and SSBs and has received an honorarium from the international food information council (IFIC) for a talk on artificial sweeteners, the gut microbiome, and the risk for diabetes. NM was a former employee of Loblaw Companies Limited and current employee of Enhanced Medical Nutrition. She has completed consulting work for contract research organizations, restaurants, start-ups, the International Food Information Council, and the American Beverage Association, all of which occurred outside of the submitted work. TAK has received research support from the Canadian Institutes of Health Research (CIHR), the International Life Science Institute (ILSI), and the National Honey Board. He has taken honorarium for lectures from International Food Information Council (IFIC) and Institute for the Advancement of Food and Nutrition Sciences (IAFNS; formerly ILSI North America). FA-Y is a part-time Research Assistant at INQUIS Clinical Research, Ltd., a contract research organization. DL reports receiving a stipend from the University of Toronto Department of Nutritional Sciences Graduate Student Fellowship, University of Toronto Fellowship in Nutritional Sciences, University of Toronto Supervisor's Research Grant—Early Researcher Awards, and Dairy Farmers of Canada Graduate Student Fellowships; a scholarship from St. Michael's Hospital Research Training Centre, and a University of Toronto School of Graduate Studies Conference Grant. AZ is a part-time Research Associate at INQUIS Clinical Research, Ltd., a contract research organization, and has received funding from a BBDC Postdoctoral Fellowship. She has received consulting fees from the GI found. RJdS has 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 WHO paid for his travel and accommodation to attend meetings from 2012–2017 to present and discuss this work. He has also performed contract research for the CIHR's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the World Health Organization for which he received remuneration. He has received speaker's fees from the University of Toronto and McMaster Children's Hospital. He has held grants from the Canadian Foundation for Dietetic Research, Population Health Research Institute, and Hamilton Health Sciences Corporation as a principal investigator and is a co-investigator on several funded team grants from the CIHR. He has served as an independent director of the Helderleigh Foundation (Canada). He serves as a member of the Nutrition Science Advisory Committee to Health Canada (Government of Canada) and is a co-opted member of the Scientific Advisory Committee on Nutrition Subgroup on the Framework for the Evaluation of Evidence (Public Health England).

TMSW was previously a part owner and now is an employee of INQUIS and received an honorarium from Springer/Nature for being an Associate Editor of the European Journal of Clinical Nutrition. CWCK has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada, Almond Board of California, Barilla, CIHR, Canola Council of Canada, International Nut and Dried Fruit Council, International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd, the Peanut Institute, Pulse Canada, and Unilever. He has received in-kind research support from the Almond Board of California, Barilla, California Walnut Commission, Kellogg Canada, Loblaw Companies, Nutrartis, Quaker (PepsiCo), the Peanut Institute, Primo, Unico, Unilever, and WhiteWave Foods/Danone. He has received travel support and/or honoraria from the Barilla, California Walnut Commission, Canola Council of Canada, General Mills, International Nut and Dried Fruit Council, International Pasta Organization, Lantmannen, Loblaw Brands, Ltd., the Nutrition Foundation of Italy, Oldways Preservation Trust, Paramount Farms, the Peanut Institute, Pulse Canada, Sun-Maid, Tate & Lyle, Unilever, and White Wave Foods/Danone. He has served on the scientific advisory board for the International Tree Nut Council, the International Pasta Organization, McCormick Science Institute, and Oldways Preservation Trust. He is a founding member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes, is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD and is a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation.

DJAJ has received research grants from Saskatchewan & Alberta Pulse Growers Associations, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies, Ltd., Unilever Canada and Netherlands, Barilla, the Almond Board of California, Agriculture and Agri-food Canada, Pulse Canada, Kellogg's Company, Canada, Quaker Oats, Canada, Procter & Gamble Technical Centre, Ltd., Bayer Consumer Care, Pepsi/Quaker, International Nut & Dried Fruit Council, Soy Foods Association of North America, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Soy Nutrition Institute (SNI), the Canola and Flax Councils of Canada, the Calorie Control Council, the CIHR, the Canada Foundation for Innovation and the Ontario Research Fund. He has received in-kind supplies for trials as a research support from the Almond Board of California, Walnut Council of California, the Peanut Institute, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, and WhiteWave Foods. He has been on the speaker's panel, served on the scientific advisory board and/or received travel support and/or honoraria from Nutritional Fundamentals for Health (NFH)-Nutramedica, Saint Barnabas Medical Center, The University of Chicago, 2020 China Glycemic Index International Conference, Atlantic Pain Conference, Academy of Life Long Learning, the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies, Ltd., the Griffin Hospital (for the development of the NuVal scoring system), the Coca-Cola Company, Epicure, Danone, Diet Quality Photo Navigation, Better Therapeutics (FareWell), Verywell, True Health Initiative, Heali AI Corp, Institute of Food Technologists, SNI, Herbalife Nutrition Institute, Saskatchewan & Alberta Pulse Growers Associations, Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands,

Solae, Kellogg, Quaker Oats, Procter & Gamble, Abbott Laboratories, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, Agri-Culture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Soy Foods Association of North America, the Nutrition Foundation of Italy, Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society, the American Society of Nutrition, Arizona State University, Paolo Sorbini Foundation, and the Institute of Nutrition, Metabolism and Diabetes. He received an honorarium from the United States Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013 Award for Excellence in Research from the International Nut and Dried Fruit Council. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association. He is a member of the ICQC. His wife, Alexandra L Jenkins, is a director and partner of INQUIS Clinical Research for the Food Industry. His 2 daughters, Wendy Jenkins and Amy Jenkins, have published a vegetarian book that promotes the use of the foods described in this study, The Portfolio Diet for Cardiovascular Risk Reduction (Academic Press/Elsevier 2020 ISBN:978-0-12-810510-8). His sister, Caroline Brydson, received funding through a grant from St. Michael's Hospital Foundation to develop a cookbook for 1 of his studies. He is also a vegan. JLS has received research support from the Canadian Foundation for Innovation, Ontario Research Fund, Province of Ontario Ministry of Research and Innovation and Science, Canadian Institutes of health Research (CIHR), Diabetes Canada, American Society for Nutrition (ASN), International Nut and Dried Fruit Council (INC) Foundation, National Honey Board [the US Department of Agriculture (USDA) honey "Checkoff" program], Institute for the Advancement of Food and Nutrition Sciences (IAFNS), Pulse Canada, Quaker Oats Center of Excellence, The United Soybean Board (the USDA soy "Checkoff" program), 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), The Plant Protein Fund at the University of Toronto (a fund that has received contributions from IFF), and The Nutrition Trialists Fund at the University of Toronto (a fund established by an inaugural donation from the Calorie Control Council). He has received food donations to support randomized controlled trials from the Almond Board of California, California Walnut Commission, Peanut Institute, Barilla, Unilever/Upfield, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, WhiteWave Foods/Danone, Nutrartis, Soylent, and Dairy Farmers of Canada. He has received travel support, speaker fees, and/or honoraria from ASN, Danone, Dairy Farmers of Canada, FoodMinds LLC, Nestlé, Abbott, General Mills, Comité Européen des Fabricants de Sucre, Nutrition Communications, International Food Information Council, Calorie Control Council, the International Sweeteners Association, the International Glutamate Technical Committee, Phynova, and Brightseed. He has or has had ad hoc consulting arrangements with Perkins Coie LLP, Tate & Lyle, Phynova, and INQUIS Clinical Research. He is a former member of the European Fruit Juice Association Scientific Expert Panel and a former member of the Soy Nutrition Institute (SNI) Scientific Advisory Committee. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the study of Diabetes, Canadian Cardiovascular Society, and Obesity Canada/Canadian Association of Bariatric Physicians and Surgeons. He serves or has served as an unpaid member of the Board of Trustees and an unpaid scientific advisor for the Carbohydrates Committee of IAFNS. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His spouse is an employee of AB InBev. XYQ, SB, NM, VH, EL, SBM, VLC, and LAL declare no competing interests.

Data Availability

The data described in the manuscript, code book, and analytic code will be made available on a request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.01.023.

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