Food sources of fructose-containing sugars and glycemic control: A systematic review and meta-analysis of controlled intervention studies in people with and without diabetes

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Keywords:	fructose, HFCS, sucrose, glycemic control, diabetes, meta-analysis

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WHAT THIS PAPER ADDS

What is already known

- Current dietary guidelines recommend a reduction to <5-10% energy in free sugars, especially fructose-containing sugars from sugars-sweetened beverages (SSBs).
- Fructose-containing sugars from SSBs have shown an adverse association with diabetes incidence in systematic reviews and meta-analyses of prospective cohort studies and free fructose adding excess energy to diets has shown an adverse effect on glycemic control in systematic reviews and meta-analyses of controlled intervention studies.
- As dietary guidelines shift from a focus on single nutrients to a focus on dietary patterns, it is unclear whether the evidence for SSBs and excess energy from fructose holds for other important food sources of fructose-containing sugars at different levels of energy control.

What this study adds

- Our systematic review and meta-analysis of 152 controlled intervention studies suggests that most food sources of fructose-containing sugars do not have an adverse effect on glycemic control in energy-matched substitutions for other macronutrients but several food sources do have adverse effects when adding excess energy to the diet, especially SSBs.
- While awaiting further research, public health professionals should be aware that adverse effects of fructose-containing sugars on glycemic control appear to be mediated by energy and food source.

ABSTRACT

Objective: As dietary guidelines move to more dietary pattern-based recommendations, it is unclear whether the the evidence supporting current recommendations to reduce added or free sugars, especially fructose-containing sugars from sugars-sweetened beverages (SSBs), holds for all food sources of these sugars. We conducted a synthesis of controlled intervention studies to assess the effect of different food sources of fructose-containing sugars on glycemic control at different levels of energy control.

Design: Systematic review and meta-analysis

Data Sources: MEDLINE, EMBASE, and The Cochrane library through May 29, 2017.

Eligibility criteria for selecting studies: We included controlled intervention studies of ≥ 7-days duration assessing the effect of food sources of fructose-containing sugars on glycemic control in people with and without diabetes. We prespecified 4 study designs based on energy control: substitution studies (sugars in energy matched comparisons with other macronutrients); addition studies (excess energy from sugars added to diets); subtraction studies (energy from sugars subtracted from diets); and *ad libitum* studies (sugars freely replaced by other macronutrients without control for energy). Outcomes were HbA1c, fasting blood glucose, and fasting blood glucose insulin.

Data extraction and synthesis: Four independent reviewers extracted relevant data and assessed risk of bias. Data were pooled using the inverse variance method and expressed as mean differences with 95% confidence intervals (95% CIs). The overall certainty of the evidence was assessed using GRADE.

Results: 152 controlled intervention studies (N=4,979) met eligibility criteria. In substitution studies, total food sources of fructose-containing sugars decreased HbA1c (-0.18% [-0.29, -0.06%], low quality evidence) without affecting fasting blood glucose (low quality evidence) or insulin (low quality evidence), while individual food sources showed decreasing (fruit juice), null (fruit, SSBs, baked goods, added sweeteners) or increasing (sweetened-milk, mixed sources) effects on fasting blood insulin. In

addition studies, total food sources increased fasting blood insulin (4.68 pmol/L [95% CI, 1.40, 7.96], low quality evidence) without affecting HbA1c (low quality evidence) or fasting blood glucose (low quality evidence), while individual food sources showed increasing effects on both fasting blood glucose (SSBs and fruit juice) and insulin (SSBs, mixed sources). In *ad libitum* studies, total food sources derived exclusively from mixed food sources (inclusive of SSBs) increased fasting blood insulin (7.24pmol/L [0.47, 14.00], moderate quality evidence), while neither total nor individual food sources affected HbA1c (low quality evidence) or fasting blood glucose (moderate quality evidence). There was no evidence of benefit in subtraction studies, although the effect was unstable (low to moderate quality evidence).

Conclusions: Energy control and food source appear to mediate the effect of fructose-containing sugars on glycemic control. Whereas most food sources of fructose-containing sugars do not have an adverse effect in energy-matched substitutions with other macronutrients, several food sources of fructose-containing sugars, especially SSBs, adding excess energy to diets or in free replacement for other macronutrients do have adverse effects. More studies are needed to improve our confidence in the estimates.

Registration: ClinicalStudies.gov identifier, NCT02716870.

INTRODUCTION

The role of sugars in the development of cardiometabolic disease is actively debated (1, 2). In particular, fructose has recently emerged as a serious public health concern, as ecological parallels have been drawn between the introduction of high fructose corn syrup (HFCS) as a popular sweetener during the 1970s and global rises in obesity and diabetes prevalence (3, 4).

Despite early considerations for the use of fructose as an alternative sweetener in people with diabetes due to its observed potential to lower postprandial glycemic excursions when compared to isocaloric amounts of starch (5), a mounting body of evidence has suggested that fructose may be particularly detrimental to metabolic health, even more so than other sugars (6). This view has received support from ecological evidence(4) as well as animal (7-9) and select human intervention studies(10-12). However, higher levels of evidence from systematic reviews and meta-analyses of controlled human intervention studies have failed to demonstrate adverse glycemic effects unique to fructose, and have even shown a beneficial effect on glycated blood proteins of fructose in isocaloric substitution for other carbohydrates in the diet in people with diabetes (13).

Whether there exists a causal link between fructose and the development of diabetes and related cardiometabolic co-morbidities continues to be contested, though much less appreciated in this debate are the consumption patterns and levels at which fructose is normally consumed in the diet. Fructose is rarely consumed in isolation under real world conditions (14). It is present in a variety of food sources containing comparable amounts of glucose, and the proportion of fructose co-ingested with glucose has been suggested to influence fructose metabolism (15). In its most commonly consumed form, sucrose (table sugar), fructose is part of a disaccharide with glucose in a 50:50 ratio. HFCS is also a glucose-fructose mix, with varying fructose content (42-55% molecular weight) in a free, unbound

monosaccharide form. Similarly, less refined sources of fructose-containing sugars, including honey, agave and maple syrup, are composed of varying proportions of fructose and glucose, while natural sources of fructose present in various fruit and vegetables also co-exist with glucose. These fructose-containing sugars are found in the diet in a variety of food sources, ranging from "nutrient poor" sources of added sugars such as sugars-sweetened beverages (SSBs), to "nutrient dense" sources of bound sugars such as fruit. Evidence from prospective cohorts on diabetes risk have shown differential associations depending on the food source of the sugars (positive associations with SSBs (16, 17) and inverse association with fruit (18, 19)).

As dietary guidelines shift from nutrient-based recommendations to more food and dietary pattern-based recommendations(20, 21) , it is important to understand the role of the food matrix in modifying the effect of fructose-containing sugars. Current recommendations from the WHO, U.S., and England have focussed on the reduction of added or free sugars to <5-10% energy (20, 22, 23), especially free fructose-containing sugars from sugars-sweetened beverages (SSBs) (20). Whether the evidence for added or free sugars and SSBs can be generalized to all food sources of fructose-containing sugars in relation to their effects on surrogate markers of type 2 diabetes has not yet been determined. We conducted a systematic review and meta-analysis of controlled intervention studies to determine the effect of food sources of fructose-containing sugars at different levels of energy control on glycemic control in people with and without diabetes.

METHODS

This systematic review and meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews and interventions(24), with all results reported according to the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines (25). The study protocol was registered at ClinicalStudies.gov, (identification number, NCT02716870).

Data Sources

Medline, EMBASE and the Cochrane Central Register of Controlled Studies were searched through May 29, 2017 using the following search terms: fructose OR dietary sucrose, OR HFCS OR sugar OR sugar* sweetened beverage* OR honey AND glyc?em* OR insulin OR HbA1c OR fructosamine OR blood glucose OR gly* albumin (**Supplementary Table 1**). Validated filters from McMaster University Health Information Research Unit were applied to limit the database search to controlled studies only (26), and electronic searches were supplemented with manual searches of references from included studies.

Study Selection

We included reports of controlled intervention studies lasting ≥7 days investigating the effect of diets of fructose-containing sugars (fructose, sucrose, HFCS, honey, syrups) from various food sources compared with control diets free of or lower in fructose-containing sugars on outcome measures of glycemic control (fasting glucose, fasting insulin, and HbA1c) in people with and without diabetes. We excluded reports of studies of meal replacements and studies of interventions of rare sugars that contained fructose (e.g. isomaltulose or melzitose) or were low-calorie epimers of fructose (e.g. allulose, tagatose, sorbose) or studies that used these sugars as the comparator. Four study designs based on the control of energy were prespecified: 1) 'substitution' studies, in which food sources of fructose-containing sugars were compared with food sources of other non-fructose-containing macronutrients under energy matched conditions (isocaloric comparison); (2) 'addition' studies, in which excess energy from food sources of fructose-containing sugars was added to background diets compared to the same background diets alone without the excess energy from fructose-containing sugars with or without the

use of low-calorie sweeteners to match sweetness (hypercaloric comparison); (3) 'subtraction' studies, in which energy from food sources of fructose-containing sugars was subtracted from background diets through displacement by water and/or low-calorie sweeteners, or by eliminating the food sources of fructose-containing sugars altogether compared with the original background diets (hypocaloric comparison); and (4) '*ad libitum*' studies, in which food sources of fructose-containing sugars were compared with food sources of other non-fructose-containing macronutrients without any strict control of either the study foods or the background diets to allow for free replacement of the energy from fructose-containing sugars with the energy from other macronutrients (free-feeding comparison). Reports containing both randomized and non-randomized controlled intervention studies were included. An intervention study was considered non-randomized if the authors explicitly stated that a method of randomization was not used or randomization was not reported in the allocation of participants to the intervention or control treatments in parallel designs or the sequence of the treatments in crossover designs. In reports containing more than one study comparison, we included all available study comparisons.

Patient involvement

No patients were involved in the design of this study.

Data Extraction

Data from included reports were individually extracted at least twice by four separate reviewers. Relevant information included number of participants, setting, underlying disease status of participants, study design, level of feeding control, randomization, comparator, fructose-containing sugars type, food sources of fructose-containing sugars, macronutrient profile of the diets, follow-up duration, energy balance, and funding sources. The three outcome variables were HbA1c, fasting blood glucose, and

fasting blood insulin. HbA1c was reported instead of total glycated blood proteins as originally indicated in our protocol (identification number, NCT02716870), as mean differences for these values were considered more clinically relevant and did not require the use of standardized mean differences needed to the different glycated blood proteins. Authors were contacted for missing outcome data when it was indicated that an outcome was measured but not reported. In the absence of numerical values for outcome measurements and inability to obtain the original data from authors, values were extracted from figures using Plot Digitizer where available(21). All discrepancies between reviewers were resolved through consensus or, where necessary, arbitration by the senior author.

Study quality

Included studies were assessed for risk of bias by at least 2 of the reviewers using the Cochrane Collaboration Risk of bias Tool(27). Final assessments were based on consensus between reviewers.

Data Synthesis and Analysis

We used Review Manager (RevMan) version 5.2 (Copenhagen, Denmark) for primary analyses and Stata (version 12, College Station, TX, USA) for subgroup, dose response, and publication bias analyses. We performed separate analyses for the 4 prespecified study designs based on the control of energy (substitution, addition, subtraction, and *ad libitum* studies) and stratified analyses by food sources of sugars for each of three outcome variables (HbA1c, fasting blood glucose, and fasting blood insulin). The principal effect measure was the mean pair-wise difference (MD) in change from baseline (or, when not available, the post-treatment value) between the food sources of fructose-containing sugars arm and the comparator arm with results reported as mean differences (MD) with 95% confidence intervals (CI). We extracted the estimates of the MD and corresponding 95% confidence intervals for each outcome.Change-from-baseline differences were preferred over end differences and paired analyses

were applied to all crossover trials with the use of a within-individual correlation coefficient between treatments of 0.5 as described by Elbourne et al.(28). When at least two studies provided data, we performed a DerSimonian and Laird random effects meta-analysis, which yields conservative confidence intervals around effect estimates in the presence of heterogeneity. When less than 5 studies were available for analysis, we also considered fixed effect estimates. Heterogeneity was assessed by the Cochran Q test (significant at P<0.10) and quantified by the I^2 statistic (range 0%-100%)(29). The interaction of fructose-containing sugars x food source was assessed using the Chi-square statistic. Other sources of heterogeneity were explored using sensitivity and subgroup analyses. We carried out sensitivity analyses by systematically removing each study from the meta-analyses and recalculating the summary association. A study whose removal explained the heterogeneity, changed the significance of the effect, or altered the effect size by 10% or more, was considered an influential study. If ≥10 studies per outcome were available (30, 31), then we conducted a priori subgroup and analyses using meta-regression. Categorical subgroup analyses were done for energy balance (positive, neutral, negative), comparator (starch, glucose, fat, lactose, maltrodextrin, diet alone, water, non-nutritive sweeteners, protein, mixed sources), fructose-containing sugars type (fruit, sucrose, fructose, HFCS, honey), fructose-containing sugars dose (≤10%, >10% energy (22, 32)), baseline values for HbA1c (≤7%, >7%), fasting glucose (≤5.5, >5.5 mmol/L based on median values) and insulin (≤96.6, >96.6 pmol/L based on median values), age (≤18, >18), study design (crossover, parallel), follow-up duration (< 8weeks, ≥ 8 weeks) , randomization (yes, no), level of feeding control (supplemented, dietary advice and metabolically controlled), underlying disease status (diabetes, overweight/ obese, metabolic syndrome criteria, otherwise healthy), and individual domains of risk of bias (sequence generation, allocation concealment, blinding of participants/ personnel and outcome assessors, incomplete outcome data, selective outcome reporting). Continuous dose response analyses were performed using meta-regression to assess linear dose-response gradients and non-linear meta-regression (MKSPLINE procedure) with knots

at the public health thresholds of 5% (22, 23), 10% (22, 33), and 25% (34) energy to assess non-linear dose-threshold effects. If ≥10 studies per outcome were available(35), then we assessed publication bias by inspection of funnel plots and formal testing with the Egger and Begg tests. If there was evidence of publication bias, then we used the Duval and Tweedie trim and fill method to adjust for funnel plot asymmetry by imputing missing study data (36).

Grading of the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty in our estimates and produce evidence profiles (37) using GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University, Canada, 2015). Evidence was graded as high, moderate, low or very low quality. Included controlled intervention studies were graded as high quality evidence by default and downgraded based on pre-specified criteria. Criteria to downgrade evidence included risk of bias (assessed through the Cochrane Risk of Bias tool), inconsistency (substantial unexplained heterogeneity, I^2>50%, P<0.10), indirectness (presence of factors that limited the generalizability of the results), imprecision (the 95% CI for pooled effect estimates crossed a minimally important difference [MID] for benefit or harm for HbA1c [±0.3%], fasting blood glucose [±0.5 mmo/L], and fasting blood insulin [±10 pmol/L]), and publication bias (significant evidence of publication bias).

RESULTS

Search Results

The systematic search and selection of literature is shown in **Figure 1.** 4,180 reports were identified from database and manual searches, of which 3,882 were excluded based on title and abstract. 257 reports were reviewed in full, of which an additional 140 reports were excluded for failure to meet the

eligibility criteria. 117 reports of controlled intervention studies (5, 11, 12, 38-153) including a total of 152 study comparisons in 4,979 participants were included in the final analysis.

Study Characteristics

A summary of the mean study characteristics is presented by the 4 prespecified study designs (substitution, addition, subtraction, and *ad libitum* studies) in **Table 1**, with a breakdown of individual study characteristics in **Supplementary Table 2**. Study sizes were relatively small, ranging from a median of 15 participants (range 6-318) in subtraction studies to 39 (range 8-236) participants in *ad libitum* studies. The majority of studies were performed in an outpatient setting, with almost half of all substitution (43/103), addition (12/35) and subtraction (1/5) studies conducted in the USA, and all *ad libitum* studies conducted in European countries. Participants tended to be middle aged, with approximately equal ratios of males to females in substitution, addition and *ad libitum* studies, but proportionately more females in subtraction studies. Most studies were conducted in those with diabetes (36%) or otherwise healthy participants (27%) in substitution studies; otherwise healthy (38%) or overweight/obese (31%) in addition studies; overweight or obese (80%) in subtractions studies; and otherwise healthy (43%) in *ad libitum* studies. Most studies were randomized (71% of substitution studies, 66% of addition studies, 80% of subtraction studies and 100% of *ad libitum* studies). Follow up duration was relatively short, ranging from a median of 5 weeks (range 1- 52 weeks) in substitution studies to 12 weeks (range 1-36 weeks) in subtraction studies. Fructose-containing sugars doses ranged from a median of 12.2% (range 7.7-25.0%) of total energy intake in addition studies to 23% (range 13.0-26.0%) of total energy intake in *ad libitum* studies, and were mostly in the form of mixed food sources in substitution (45/110) and *ad libitum* (6/7) studies while most addition (12/35) and subtraction (4/5) studies used sugars-sweetened beverages. Most studies were funded by agency sources (government, not-for-profit health agency or university sources), except for *ad libitum* trails which were primarily funded by agency-industry funding.

Study quality

A summary of the risk of bias assessments by the Cochrane Risk of Bias Tool is shown in **Supplementary Figure 1**. Owing to poor reporting standards, most studies were assessed as having unclear risk of bias across the 5 domains of bias. Few studies were assessed as having high risk of bias with only 19.3%, 22.7%, 1.7%, 7.6% of studies assessed as high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and incomplete outcome data, respectively. Overall, no serious risk of bias was detected.

Outcomes: HbA1c

The effect of different food sources of fructose-containing sugars on HbA1c are shown in **Figure 2** and **Supplementary Figures 2-5**. Total fructose-containing sugars independent of food sources showed a significant decreasing effect on HbA1c in substitution studies (32 study comparisons, MD=-0.18% [95% CI, -0.29, -0.06], p<0.01, substantial heterogeneity [I^2=82%, p <0.001]). There was no significant effect in addition (6 study comparisons, substantial heterogeneity [I^2=83%, p<0.001]), subtraction (1 study comparison) or *ad libitum* (1 study comparison) studies. There was no fructose-containing sugars x food source interaction in the substitution, addition, subtraction or *ad libitum* studies.

Sensitivity analyses for HbA1c are presented in **Supplementary table 3.** The removal of each study did not explain the heterogeneity or change the significance of the effect.

A priori subgroup analyses for HbA1c are presented in **supplementary figures 6 and 7** and dose-response analyses for HbA1c are presented in **Supplementary Figure 8 and 9**. *A priori* subgroup analyses

did not reveal any effect modification in substitution studies. There was also no evidence of a dose-response gradient or threshold.

No subgroup or dose-response analyses were conducted for addition, subtraction or *ad libitum* studies, as less than 10 studies were available for these analyses.

Outcomes: Fasting Blood Glucose

The effect of different food sources of fructose-containing sugars on fasting blood glucose are shown in **Figure 3** and **Supplementary Figures 10-13**. Total fructose-containing sugars independent of food sources had no effect on fasting blood glucose in substitution studies (101 study comparisons, substantial heterogeneity [I^2=65, p<0.001]), addition studies (28 study comparisons, substantial heterogeneity [I^2=71, p<0.001]), subtraction studies (4 study comparisons, substantial heterogeneity [I^2=59, p=0.06]) or *ad libitum* studies (6 study comparisons, no evidence of heterogeneity). There was a significant fructose-containing sugars x food source interaction in addition studies (P<0.001): SSBs (11 study comparisons, MD= 0.12 mmol/L [95% CI, 0.03, 0.22], substantial heterogeneity [I^2=74], p<0.001) and fruit juice (2 study comparisons, MD= 0.29 mmol/L [95% CI, 0.09, 0.49], no evidence of heterogeneity) showed a significant increasing effect, while fruit (7 study comparisons), fruit drinks (3 study comparisons), sweetened chocolate (1 study comparison), added sweeteners (3 study comparisons), and mixed sources (1 study comparison) showed no significant effect on fasting blood glucose. No fructose-containing sugars x food source interactions were seen in the substitution, subtraction or *ad libitum* studies.

Sensitivity analyses for fasting blood glucose are presented in **Supplementary Table 3.** Removal of anyone of 6 addition studies (38, 46, 72, 105, 114, 123) changed the significance from non-significant

to significant but did not change the magnitude or direction of the effect or the evidence of substantial heterogeneity. Removal of the subtraction study by Campos et al. 2015 (group 2 [G2]) (60) involving 15 participants over 12 weeks explained all of the heterogeneity, changing the direction but not the lack of significance of the effect on fasting blood glucose. Finally, removal of the subtraction study by Tate et al. 2012 (149) involving 318 participants over 6 months explained all of the heterogeneity but did not change the direction or lack of significance of the effect on fasting blood glucose (MD= 0.20 pmol/L [95% CI, 0.00, 0.40], p=0.05, no evidence of heterogeneity [I^2=32%, P=0.23]).

A priori subgroup analyses for fasting blood glucose are presented in **Supplementary Figures 14-17** and dose-response analyses for fasting blood glucose are presented in **Supplementary Figure 8 and 9**. There was significant effect modification by fructose-containing sugars dose, baseline fasting blood glucose, feeding control, and underlying disease status in the substitution studies (P≤0.05). Categorical subgroup analyses by dose showed a greater decreasing effect at doses ≤10% energy than >10% energy (P=0.01), although there was no evidence of a continuous linear dose-response gradient by meta-regression or dose threshold with knots at 5%, 10%, or 25% energy by the MKSPLINE procedure. Subgroup analyses by baseline fasting blood glucose showed a greater decreasing-effect on fasting blood glucose when the baseline fasting blood glucose was >5.5 mmol/L than ≤5.5mmol/L (P<0.01). Finally, subgroup analyses by level of feeding control showed a greater decreasing effect in studies using supplementation or dietary advice as the methods of feeding control than in studies using metabolic control (provision of all study foods) as the method of feeding control in pairwise comparisons (P<0.05). None of the subgroups explained the substantial heterogeneity in the substitution studies.

A significant subgroup effect was also observed in addition studies. There was significant effect modification by baseline fasting blood glucose (P<0.05). Subgroup analyses by baseline fasting blood glucose levels showed a greater decreasing effect when the baseline fasting blood glucose was >5.5 mmol/L than ≤5.5 mmol/L (P=0.01). This subgroup did not explain the substantial heterogeneity in in the addition studies.

No subgroup or dose-response analyses were conducted for subtraction or *ad libitum* comparisons as less than 10 studies were available for these analyses.

Outcomes: Fasting Blood Insulin

The effect of different food sources of fructose-containing sugars on fasting blood insulin are shown in **Figure 4** and **Supplementary Figures 18-21**. Total fructose-containing sugars independent of food sources had an increasing effect on fasting blood insulin in addition studies (23 study comparisons, MD=4.68 pmol/L [95% CI, 1.40, 7.96], p< 0.01, substantial heterogeneity [I^2=58%, p<0.001]) and *ad libitum* studies (4 study comparisons, MD=7.24 pmol/L [95% CI, 0.47, 14.00], p=0.04, no evidence of heterogeneity [I^2=0%, p=0.46). There was no effect in substitution (72 studies) or subtraction (3 studies, substantial heterogeneity [I^2=79, p<0.01]). There was a significant fructose-containing sugars x food source interaction in substitution studies (P<0.001): fruit juice (1 study comparison, MD=-13.89 pmol/L [95%CI, -27.50, -0.28], P=0.05) showed a decreasing effect; sweetened low-fat milk (2 study comparisons, MD=18.95 pmol/L [95%CI, 9.09, 28.80], P<0.001, no evidence of heterogeneity) and mixed sources (25 study comparisons, MD=7.74 pmol/L [95%CI, 2.94, 12.53], P<0.01, no substantial heterogeneity) showed an increasing effect; and fruit (7 study comparisons, no evidence of heterogeneity), dried fruit (2 study comparisons), SSBs (17 study comparisons), baked goods, sweets, and desserts (10 study comparisons, no evidence of heterogeneity), and added sweeteners (8 study

comparisons, substantial heterogeneity [I^2=83, p<0.001]) showed no significant effect on fasting blood insulin. There was also a significant fructose-containing sugars x food source interaction in addition studies (P=0.02): SSBs (13 study comparisons, MD=6.17 pmol/L [95% CI, 1.55, 10.78], p <0.001, substantial heterogeneity [I^2=65, p<0.001]), and mixed sources (1 study comparison, MD=13.00 pmol/L [95% CI, 0.81, 25.19], p=0.04) showed an increasing effect, while fruit (6 study comparisons, no evidence of heterogeneity) and fruit juice (3 study comparisons, no evidence of heterogeneity) showed no significant effect on fasting blood insulin. No fructose-containing sugars x food source interactions were seen in the *ad libitum* studies (although mixed sources was the exclusive food source of fructose-containing sugars) or subtraction studies.

Sensitivity analyses for fasting blood insulin are presented in **Supplementary table 3.** Removal of the subtraction study by Campos et al. (G2) (60) involving 15 participants explained nearly all of the heterogeneity, changing the significance and magnitude but not the direction of the effect (MD= -39.54 pmol/L [95% CI, -75.02, -4.06], p =0.03, no evidence of heterogeneity [I^2=1%, P=0.31]). Removal of the *ad libitum* study by Raben et al. 2000 (C) (124) involving 16 participants eliminated the evidence for the significance but not the direction of the effect or lack of heterogeneity.

A priori subgroup analyses for fasting blood insulin are presented in **supplementary figures 22-25** and dose-response analyses for fasting blood insulin are presented in **Supplementary Figure 8 and 9**. There was significant effect modification by level of feeding control and risk of bias for blinding of participants, personnel and outcome assessors in the substitution studies (P<0.05). Subgroup analyses by level of feeding control showed a greater increasing effect in studies using dietary advice as the method of feeding control than in studies using supplementation as the method of feeding control (P=0.04). Subgroup analyses by risk of bias for blinding of participants, personnel and outcome assessors showed

a greater increasing effect in studies with a low risk of bias than those with an unclear risk of bias (P=0.01). None of the subgroups explained the substantial heterogeneity in the substitution studies. No subgroup or dose-response analyses were significant in the addition studies, and no subgroup analyses were conducted for the subtraction or *ad libitum* studies, as less than 10 studies were available for these analyses.

Publication Bias

The publication bias assessment is shown in **Supplementary Figure 26**. There was no evidence of publication bias through visual inspection of funnel plots or formal testing with the Egger and Begg tests for the effect of food sources of fructose containing sugars on HbA1c, fasting blood glucose, or fasting blood insulin for all analyses where ≥10 studies were available..

GRADE Assessment

A summary of the overall quality of evidence assessment for the effect of total fructose-containing sugars independent of food source on the outcome measures of glycemic control is shown in **Table 2.** The certainty in the evidence was variable for HbA1c (low, low, low, and low), fasting blood glucose (low, low, moderate, and moderate) and fasting blood insulin (low, low, low, and moderate) across substitution, addition, subtraction, and *ad libitum* studies, respectively. Evidence for HbA1c was downgraded for inconsistency in substitution and addition studies, indirectness in subtraction and *ad libitum* studies, and for imprecision in substitution, addition, subtraction and ad libitum studies. Evidence for fasting blood glucose was downgraded for inconsistency in substitution and addition studies, and for imprecision in substitution, addition, subtraction and ad libitum studies. Similarly, evidence for fasting blood insulin was downgraded for inconsistency in the substitution, addition, and subtraction studies, and for imprecision in substitution, addition, subtraction and ad libitum studies.

DISCUSSION

Our systematic review and meta-analysis of 154 studies involving 5,136 participants with and without diabetes showed variable effects of food sources of fructose-containing sugars on three outcome measures of glycemic control at median doses ranging from 10-23% energy over median follow-up durations of 4-12 weeks. Four types of study designs were identified based on energy control. In substitution studies, total food sources of fructose-containing sugars in energy matched comparisons with other macronutrients (mainly refined starches) showed a beneficial effect on HbA1c with no effects on fasting blood glucose or insulin, while individual food sources showed decreasing (fruit juice), null (fruit, SSBs, baked goods, added sweeteners) or increasing (sweetened-milk, mixed sources) effects on fasting blood insulin. In addition studies, total food sources of fructose-containing sugars supplementing diets with excess energy compared to the same diet alone without the excess energy showed a harmful effect on fasting blood insulin without affecting HbA1c or fasting blood glucose, while individual food sources showed harmful effects on both fasting blood glucose (SSBs and fruit juice) and insulin (SSBs, mixed sources). In the *ad libitum* studies, total food sources of fructose-containing sugars freely replacing other macronutrients showed a harmful effect on fasting blood insulin (for which the effect was derived exclusively from mixed food sources inclusive of SSBs) without affecting HbA1c or fasting blood glucose. No effect of food sources of fructose-containing sugars was observed in subtraction studies.

Sources of heterogeneity

Methodological and clinical sources of heterogeneity had an influence on our results. Sensitivity analyses revealed evidence of instability in the significance of our pooled estimates. Removal of anyone of 6 studies (38, 46, 72, 105, 114, 123) changed the significance from non-significant to significant for fasting blood glucose in the addition studies, while the removal of a study by Raben et al. 2000 (C) (124)

changed the significance from significant to non-significant for fasting blood insulin in the *ad libitum* studies. None of the studies explained any of the heterogeneity. Removal of the study by Campos et al. (G2) (60), however, did both explaining the heterogeneity and changing the significance of the effect. This sensitivity analysis revealed a consistent decreasing effect of reducing excess calories from fructose-containing sugars on fasting blood insulin in subtraction studies. The reason for the strong influence of this study is unclear. As Campos et al. (G2) (60) was a small study (n=15) that received most of the weight in the analysis (>50%), it is possible that its true within-study variances were seriously underestimated, leading to an important outlier effect on the pooled estimate for fasting blood insulin (154).

Subgroup analyses also revealed evidence of effect modification under certain conditions. Greater improvements in fasting blood glucose were observed in participants with higher baseline fasting glucose in substitution and addition studies, suggesting a regression-to-the-mean phenomenon. These effects were concordant with the observed subgroup modification by underlying disease status in addition studies, demonstrating a greater decreasing effect on fasting blood glucose in patients with diabetes. Although a significant subgroup effect by level of feeding control and age were also observed in addition studies where fasting blood glucose was significantly reduced when dietary advice was the method of feeding control or the age of participants was ≤ 18 years, only one study was available for each of these analyses and neither analysis explained the substantial heterogeneity. The relevance of the subgroup analysis for feeding control is also brought into question by the finding of an opposite result for fasting blood insulin in substitution studies. The categorical subgroup analyses revealed a significant effect modification by dose, whereby fasting blood glucose was lower at doses of ≤10% energy, suggesting that intakes that meet current recommendations to consume no more than 10% of energy from sugars (22, 33) may have advantages. These results, however, are difficult to interpret in

the absence of a linear dose response gradient or dose threshold effect in continuous analyses at this threshold or the other public health thresholds of 5% (22, 23) and 25% (34).

Results in the context of other studies

Our findings agree with two other previously conducted systematic reviews and meta-analyses of controlled intervention studies which demonstrated a beneficial effect of the isocaloric substitution of fructose for other carbohydrates on glycated blood proteins in participants with (equivalent to ~0.53% reduction in HbA1c)(13) and without (fructose intake <90 g/d significantly improved HbA1c dependent on dose, study duration and severity of dysglycemia) diabetes (155). Although the modest decrease of -0.14% in HbA1c from our analysis did not exceed the clinically meaningful threshold of 0.3% proposed by the U.S Food and Drug administration for the development of new drugs for diabetes as observed in the previous meta-analysis (32), our findings suggest that food sources of fructose-containing sugars may have modest benefits for long term glycemic control when they replace other macronutrients on a calorie-for-calorie basis. On the other hand, our results suggest that food sources of fructose-containing sugars providing excess energy to the diet may raise fasting blood insulin agreeing with the findings from our previous systematic reviews and meta-analyses that fructose providing excess energy increases insulin resistance (156).

Our data also agree with evidence from prospective cohort studies of the relation of fructose-containing sugars with diabetes risk. While we failed to observe an adverse association of total fructose-containing sugars independent of food source with incident diabetes in an earlier systematic review and meta-analysis of the available prospective cohort studies (157), differential associations have been shown for different food sources of sugars. Systematic reviews and meta-analyses of prospective cohort studies have shown an adverse association with SSBs (16, 17) but a protective association with fruit (18, 19),

associations which are consistent with our findings of an increasing effect of SSBs on fasting blood glucose and insulin in addition studies and a non-significant decreasing effect of fruit on HbA1c in substitution studies.

Potential mechanisms

Several proposed mechanisms may explain the observed beneficial effect of food sources of fructose-containing sugars on HbA1c when substituted for other calories in the diet. Fructose has a relatively low glycemic index (GI) of 16 compared to reference carbohydrates such as starch with a GI of 100 (158). As a majority of the comparators used in substitution studies were in the form of starch, replacement of these high-GI carbohydrates with fructose may have reduced the overall GI of the diet, leading to long term glycemic improvement through alleviation of pancreatic stress (159, 160). The low GI of fruit may explain why it was the main food source driving of a significant improvement in HbA1c in substitution studies, especially when compared to intermediate GI food sources such as SSBs or sweets, which provide calories from sugars in the absence of any nutritional value. The higher fiber content of fruit may contribute to lower postprandial glycemic excursions. Particularly, viscous gels formed by the pectin in fruit may delay gastric emptying and slow down the release of sugars (161). A secondary analysis of a randomized controlled trial of the effect of a 6-month low-GI intervention showed that low-GI fruit intake was the strongest predictor of the reduction in HbA1c in people with type 2 diabetes (162). Whether or not low-GI food sources of fructose-containing sugars would show similar effects when compared to other low-GI carbohydrate foods, including legumes or some whole grains, remains to be determined as there is a lack of studies using high quality carbohydrate comparators. While a low-GI mechanism may have contributed to the observed decrease in HbA1c in the substitution studies), especially as it relates to fruit, it did not extend to improvements in fasting blood glucose and insulin. Although the summary effects for both endpoints tended to be in the direction of benefit (with the

possibility of additional studies providing sufficient power to confirm any beneficial effects), a mechanism that targets postprandial excursions in glucose and insulin would not necessarily be expected to lead to meaningful improvements in these fasting measurements which are more determined by changes in insulin sensitivity (163).

An alternative mechanism accounting for the observed beneficial effects of food sources of fructose-containing sugars on HbA1c in substitution studies relates to a "catalytic" effect of fructose whereby fructose metabolites have regulatory actions on glucokinase and hepatic glucose uptake. There is evidence that small catalytic fructose doses of ≤10g/meal (a level obtainable from fruit) may improve glycaemia by the ability of fructose-1-P to up regulate glucokinase activity through the glucokinase regulatory protein, resulting in decreased hepatic glucose production (164) and increased glycogen synthesis(165). The relevance of this mechanism is unclear. It would be expected to have disproportionally greater effect on fasting blood glucose and insulin than HbA1c, the opposite of what we found. The doses of fructose in most of the included studies were also much higher than the catalytic doses (10g/meal) shown to have benefit, although categorical subgroup analyses did show lower fasting blood glucose at doses of ≤10% energy (≤50g/day). How dietary fructose interacts with glucose at the level of hepatic glucose homeostasis remains largely under-explored.

The increase in insulin in the absence of an adverse effect on HBA1c or fasting blood glucose with sweetened low-fat milk in the substitution studies may relate to an isolated insulinotropic effect of dairy proteins. The ability of protein, especially dairy proteins, co-ingested with carbohydrate to stimulate glucose stimulated insulin secretion has been well described (166-168). This isolated finding does not necessarily imply harm, as sweetened and unsweetened low-fat dairy, especially in the form of yogurt, is associated with decreased risk of weight gain and diabetes incidence (169).

In contrast, the observed adverse effects of food sources of fructose-containing sugars on glycemic control in addition studies appear to be largely driven by the energy contribution of the sugars. Fructose-containing sugars supplementing diets with excess calories may promote ectopic weight gain, contributing to downstream insulin resistance and impaired glycemic control. Related effects have been reported in systematic reviews and meta-analyses of controlled intervention studies of fructose overfeeding for body weight (170), blood pressure(171), uric acid levels (172), markers of Non-Alcoholic Fatty Liver Disease (NAFLD)(173) and postprandial triglycerides (174). Although fructose more than other carbohydrates (because of its ability to enter glycolysis as an unregulated substrate) has been proposed to increase de novo lipogenesis (DNL) leading to weight gain and its downstream cardiometabolic disturbances, this mechanism has been shown to be a minor pathway for fructose disposal (175). It is also not unique to fructose-containing sugars per se and weight gain with metabolic disturbances would be expected for the overconsumption of food sources of other dietary macronutrients (176).

The lack of a protective effect of interventions to reduce excess energy from food sources of fructose-containing sugars in subtraction studies is unclear. It may represent compensation, in which the decrease in energy from food sources of fructose-containing sugars are compensated by replacement with energy from other food sources or spontaneous changes in physical activity that decrease energy expenditure preventing weight loss and its downstream metabolic benefits. Compensation may have been more apparent in these studies as they had the longest median follow-up (12-weeks). It may explain why longer term (median follow-up,~ 1 year) subtraction studies designed to displace excess energy from SSBs have only shown a weight-loss benefit in specific subgroups of overweight or obese individuals (177). The instability in the significance of the pooled effect estimates may have also played a

role. Removal of the studies Campos et al. (G2) (60) explained the heterogeneity revealing significant decreasing effects on fasting insulin, suggesting that this study may have masked a true benefit of interventions to reduce fructose-containing sugars.

Implications

As dietary guidelines shift from a focus on individual nutrients towards a focus on foods and dietary patterns, our findings may have implications for guiding recommendations on important food sources of fructose-containing sugars in the prevention and management of diabetes. As various food sources of fructose-containing sugars tended to demonstrate improvements on HbA1c, encouraging the consumption food sources of sugars such as fruit, yogurt, and whole grain cereals to replace foods high in refined starches within the recommendation to consume no more than 10% of energy from free sugars (22, 32) may be an effective strategy for improving glycemic control, especially in people with diabetes. As SSBs tended to impair fasting blood glucose and insulin when adding excess energy to the diet, public health strategies to reduce consumption of this food source of fructose-containing sugars may be useful, especially as SSBs provide empty calories in absence of any nutritional "value". While these findings highlight the role of food sources of fructose-containing sugars on glycemic control, other important cardiometabolic parameters should also be taken into consideration in future syntheses.

Strengths and Limitations

Our systematic review and meta-analysis has several strengths, including: 1) a comprehensive and reproducible search and selection process of the literature examining the effect of food sources of fructose-containing sugars on glycemic control, 2) collation and synthesis of the totality of the available evidence from a large body (152 studies, n=4,979) of controlled intervention studies which give the greatest protection against bias (noting that results did not differ between randomized and non-

randomized studies), and 3) an assessment of overall quality of evidence using the GRADE assessment approach.

Several of our analyses presented limitations. First, despite the inclusion of a large number of studies, there was a limited number of studies using particular food sources. For example, there were no study comparisons available for sweetened breakfast cereals or yogurt and only one study comparison was available for sweetened chocolate and two study comparisons for sweetened low-fat milk for any of the analyses. Many analyses also had only one or two study comparisons available for inclusion: baked goods, sweets and desserts for HbA1c in substitution and addition studies (1 study); fruit juice for fasting blood glucose and insulin in substitution studies (1 study); mixed sources for fasting blood glucose and insulin in addition studies (1 study); SSBs for HbA1c in substitution studies (2 studies); and fruit juice for fasting blood glucose in additions studies (2 studies). As a result, we elected only to do GRADE assessments for total food sources. Second, substantial unexplained heterogeneity was present in all analyses for the substitution studies, as well as the addition studies for HbA1c, fasting blood glucose, and fasting blood insulin. Although there was also substantial heterogeneity present in the subtraction studies for HbA1c, fasting blood glucose and insulin, and *ad libitum* studies for HbA1c, the removal of individual studies during sensitivity analyses explained this heterogeneity, and so we did not downgrade for inconsistency. Third, serious indirectness was present in some analyses as only one trial in 240 overweight and obese women was available in the HbA1c subtraction analysis, and similarly, one trial in 10 patients with diabetes was available in the HbA1c *ad libitum* analysis. Although the small sample sizes of the included studies (median sample sizes ranged from 15 participants in subtraction studies to 39 participants in *ad libitum* studies) are another potential source of indirectness, we did not downgrade the evidence for indirectness owing to the very large number of included studies (152 study comparisons) representing a diverse range of study conditions and metabolic phenotypes across a large

total number of participants (n=4,979). We also did not downgrade for indirectness based on the relatively short duration of follow-up (median follow-up, 5-12 weeks), as we felt that it was sufficient to assess the question of harm (a decision shared with an earlier WHO commissioned review of the evidence for sugars and body weight (178). Finally, there was evidence of serious imprecision in all of the analyses. As the 95% CIs crossed the MIDs for HbA1c, fasting blood glucose and fasting blood insulin, these analyses were downgraded for serious imprecision.

Weighing the strengths and limitations, we graded the certainty in the evidence using GRADE from low quality for HbA1c, low to moderate quality for fasting blood glucose and low to moderate quality for fasting blood insulin across the four study designs based on energy control.

CONCLUSION

In conclusion, the effects of food sources of fructose-containing sugars on glycemic control appear to be both energy and food source dependent. Most food sources of fructose-containing sugars substituted for equal amounts of calories from other macronutrient sources (mainly refined starches) led to improvements in HbA1c without adversely affecting fasting blood glucose or insulin. However, when several food sources of fructose-containing sugars added excess energy to the diet, especially SSBs, significant increases in fasting blood glucose and insulin were observed. The same was also seen for the effect of mixed food sources (inclusive of SSBs) of fructose-containing sugars freely replacing other macronutrients on fasting blood insulin without an adverse effect on HbA1c or fasting blood glucose. The anticipated benefit of interventions to reduce the excess energy from sugars, however, was not seen reliably, suggesting that compensatory behaviours may be an important consideration. The lack of any harm and even advantages were most pronounced in those with higher HbA1c and fasting blood glucose baseline levels or who had diabetes. While our findings may suggest that common food sources

of fructose-containing sugars do not have adverse effects on glycemic control in energy matched replacement of other less sugary foods, our GRADE assessment suggests that more research is likely to have an important influence on many of our estimates. More high quality studies using a greater variety of food sources of fructose-containing sugars are required to assess the durability of these effects under free living conditions. While awaiting these data, policy and guidelines makers should consider the influence of energy control and food source in the development recommendations to reduce sugars for the prevention and management of diabetes.

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CONTRIBUTIONS

VLC, SBM and JLS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: VLC, JLS and DJAJ. Acquisition, analysis and interpretation of data: VLC, EV, SBM, AIC, VH, LAL, TMSW, TAK, DJAJ and JLS. Drafting of the manuscript: VLC. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: VLC and SBM. Study supervision: JLS and DJAJ.

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EXCLUSIVE LICENCE

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TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ETHICS APPROVAL

Not required.

DATA SHARING STATEMENT

No additional data are available.

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Figures and Tables

Figure 1. Flow of literature for the effect of food sources of fructose-containing sugars on glycemic control.

Figure 2. Summary super-plot for the effect of food sources of fructose-containing sugars on HbA1c. N= Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for summary effects of individual food sources and total on HbA1c. Analyses were conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using the Cochran's Q statistic (chi-square) at a significance level of P<0.10.

Figure 3. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood glucose. N= Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for summary effects of individual food sources and total on fasting blood glucose. Analyses were conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using the Cochran's Q statistic (chi-square) at a significance level of P<0.10.

Figure 4. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood insulin. N= Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for summary effects of individual food sources and total on fasting blood insulin. Analyses were conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of P<0.10.

Table 1. Summary of Study Characteristics

Study Characteristics	Substitution Studies	Addition Studies	Subtraction Studies	*Ad libitum* Studies
Study Comparisons (N)	110	35	5	7
Study Size (participants)[1]	16 (5-595)	20 (6-63)	15 (6-318)	39 (8-236)
Male: Female[2]	40: 60	46: 54	12: 88	41: 59
Age (years)[3]	40.0 (25.1-53.8)	36.2 (27.4-49.4)	33.5 (29.1-41.9)	38 (34-39.8)
Setting (Inpatient: Outpatient: Inpatient/outpatient)[2]	10: 75: 15	3: 89: 9	0: 100: 0	0: 100: 0
Baseline Fasting Glucose (mmol/L)[3]	5.0 (4.8-5.3)	5.1 (4.9-5.4)	5.1 (5.1-5.2)	4.9 (4.9-5.4)
Baseline Fasting Insulin (pmol/L)[3]	89.6 (56.7-126.8)	50.4 (40.6-81.4)	109.8 (97.8-121.7)	32.8 (32.1-45.9)
Baseline HbA1c (%)[3]	7.5 (6.8-8.5)	6.8 (5.5-7.1)	N/A[4]	N/A[4]
Study Design (Crossover: Parallel)[2]	62: 38	49: 51	20: 80	57: 43
Feeding Control (Met: Supp: DA)[2]	43: 42: 15	13: 80: 7	0: 70: 30	50: 37.5: 12.5
Randomization (Yes: No)[2]	71: 29	66: 34	80: 20	100: 0
Fructose-Containing Sugars Dosage (%E)[3]	14.5 (8.9-22.0)	12.2 (7.7-25.0)	15.0 (11.3-15.0)	23.0 (13.0-26.0)
Follow-Up Duration (Weeks)[1]	5 (1-52)	6 (1-24)	12 (1-36)	8 (2-76)
Funding Sources (A: I: AI: NR)[2]	32: 17: 29: 22	49: 9: 34: 9	60: 40: 0: 0	0: 17: 50: 33
Fructose-Containing Sugars Type (N)	Fructose=47; Fruit=19; HFCS=3; Sucrose=48; Honey=2	Fructose=8; Fruit=13; HFCS=1; Honey=4; Sucrose=9	Sucrose= 5; HFCS=4	Fructose=1; Sucrose=7
Comparator (N)	Fat=7; Glucose=23; Lactose=5; Maltodextrin=1; Mixed Comparator=14; Protein=1; Starch=53; Diet alone=5; Water=1	Diet alone=27; Sweetener=4; Water=5	Water=2; Sweetener=3; No sucrose=1	Fat=2; Mixed comparator=2; Starch=4; Sweetener=3
Food Sources of Fructose-Containing Sugars	Fruit=13; Dried Fruit=5; Fruit Juice=1; SSBs=21; Sweetened Low-Fat Milk=2; Baked Goods, Sweets and Desserts=11; Added Sweeteners=12; Mixed Sources= 45;	Fruits=10; Fruit Juice=3; Fruit Drink=3; SSBs=12; Sweetened Chocolate=1; Baked Goods, Sweets and Desserts=1; Added Sweeteners=4; Mixed Sources=1	Mixed Sources=1; SSBs=4	Baked Goods, Sweets and Desserts=1; Mixed Sources=6

A=agency; AI=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; Met=metabolic; N=number of studies; NR=not reported; SSBs=sugars-sweetened beverages; Supp=supplemented

[1,2,3]Values are reported as Medians and ranges[1], percent ratios[2] or Interquartile Ranges (IQR)[3].

[4]Baseline data were only reported for one study.

Table 2. GRADE Quality of Evidence Assessment

Quality assessment							Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
HbA1c in Substitution Studies							
32	randomized and non-randomized studies	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	⊕⊕OO LOW
HbA1c in Addition Studies							
6	randomized and non-randomized studies	no serious risk of bias	serious[3]	no serious indirectness	serious[4]	none	⊕⊕OO LOW
HbA1c in Subtraction Studies							
1	randomized and non-randomized studies	no serious risk of bias	no serious inconsistency[5]	serious[6]	serious[7]	none[8]	⊕⊕OO LOW
HbA1c in *Ad libitum* Studies							
1	randomized and non-randomized studies	no serious risk of bias	no serious inconsistency[5]	serious[9]	serious[10]	none[8]	⊕⊕OO LOW
Fasting Blood Glucose in Substitution Studies							
101	randomized and non-randomized studies	no serious risk of bias	serious[11]	no serious indirectness	serious[12]	none	⊕⊕OO LOW
Fasting Blood Glucose in Addition Studies							
28	randomized and non-randomized studies	no serious risk of bias	serious[13]	no serious indirectness	serious[14]	none	⊕⊕OO LOW
Fasting Blood Glucose in Subtraction Studies							
4	randomized and non-randomized studies	no serious risk of bias	no serious inconsistency[15]	no serious indirectness	serious[16]	none[8]	⊕⊕⊕O MODERATE
Fasting Blood Glucose in *Ad libitum* Studies							
6	randomized and non-randomized studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[17]	none[8]	⊕⊕⊕O MODERATE
Fasting Blood Insulin in Substitution Studies							
72	randomized and non-randomized studies	no serious risk of bias	serious[18]	no serious indirectness	serious[19]	none	⊕⊕OO LOW
Fasting Blood Insulin in Addition Studies							
23	randomized and non-randomized studies	no serious risk of bias	serious[20]	no serious indirectness	serious[21]	none	⊕⊕⊕OO LOW
Fasting Blood Insulin in Subtraction Studies							
3	randomized and non-randomized studies	no serious risk of bias	serious[22]	no serious indirectness	serious[23]	none[8]	⊕⊕⊕OO LOW
Fasting Blood Insulin in *Ad libitum* Studies							
4	randomized and non-randomized studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[24]	none[8]	⊕⊕⊕O MODERATE

[1] Serious inconsistency for the effect of fructose-containing sugars on HbA1c in substitution studies, as there was evidence of significant interstudy heterogeneity (I^2=82%, p<0.0001).

[2] Serious imprecision for the effect of fructose-containing sugars on HbA1c in substitution studies, as the 95% CI [-0.29, -0.06 %] overlaps the minimally important difference (MID) for HbA1c (±0.3%), including clinically unimportant benefit (≥ -0.3%).

[3] Serious inconsistency for the effect of fructose-containing sugars on HbA1c in addition studies, as there was evidence of significant interstudy heterogeneity (I^2=83%, p<0.0001).

[4]Serious imprecision for the effect of fructose-containing sugars on HbA1c in addition studies, as the 95% CI [-0.41, 0.50 %] overlaps the MID for HbA1c (±0.3%), including both clinically important benefit (≤ -0.3%) and harm (≥0.3%).

[5]Inconsistency cannot be exlcluded since we were not able to test for heterogeneity due to lack of studies (only 1 study included in the analysis).

[6]Serious indirectness for the effect of fructose-containing sugars on HbA1c in subtraction studies, as only 1 study in 240 overweight/ obese females was available for analysis.

[7]Serious imprecision for the effect of fructose-containing sugars on HbA1c in subtraction studies, as the 95% CI [-0.04, 0.14 %] overlaps the MID for HbA1c (±0.3%), including clinically unimportant benefit (≥ -0.3%).

[8]Bias cannot be excluded since we were unable to test for funnel plot asymmetry due to lack of power (<10 studies included in the analysis).

[9]Serious indirectness for the effect of fructose-containing sugars on HbA1c in *ad libitum* studies, as only 1 study in 10 participants with type 1 diabetes mellitus was available for analysis.

[10]Serious imprecision for the effect of fructose-containing sugars on HbA1c in *ad libitum* studies, as the 95% CI [-0.38, 0.42 %] overlaps the MID for HbA1c (±0.3%), including both clinically important benefit (≤ -0.3%) and harm (≥0.3%).

[11]Serious inconsistency for the effect of fructose-containing sugars on fasting blood glucose in substitution studies, as there was evidence of significant interstudy heterogeneity (I^2=65%, p<0.0001).

[12] Serious imprecision for the effect of fructose-containing sugars on fasting blood glucose in substitution studies, as the 95% CI [-0.02, 0.05 mmol/L] overlaps the MID for fasting blood glucose (±0.5 mmol/L), including clinically unimportant benefit (≥ -0.5 mmol/L).

[13]Serious inconsistency for the effect of fructose-containing sugars on fasting blood glucose in addition studies, as there was evidence of significant intersudy heterogeneity (I^2=71%, p<0.0001).

[14] Serious imprecision for the effect of fructose-containing sugars on fasting blood glucose in addition studies, as the 95% CI [-0.00, 0.15 mmol/L] overlaps the MID for fasting blood glucose (±0.5 mmol/L), including clinically unimportant benefit (≥ -0.5 mmol/L).

[15]No serious inconsistency for the effect of fructose-containing sugars on fasting blood glucose in subtraction studies, as the removal of Tate et al. 2012 explained most of the heterogeneity (I^2=32%, p=0.23), without changing the direction or significance of the effect on fasting blood glucose (MD= 0.20 mmol/L [95% CI, 0.00, 0.40 mmol/L], p =0.05) and the removal of Campos et al. 2015 (G2) explained all the heterogeneity (I^2=0%, p=0.78), changing the direction, but not the lack of significance of the effect on fasting blood glucose (MD=-0.02 mmol/L [95% CI, -0.11, 0.07mmol/L], p=0.63).

[16] Serious imprecision for the effect of fructose-containing sugars on fasting blood glucose in subtraction studies, as the 95% CI [-0.07, 0.10 mmol/L] overlaps the MID for fasting blood glucose (±0.5 mmol/L), including clinically unimportant benefit (≥ -0.5 mmol/L).

[17] Serious imprecision for the effect of fructose-containing sugars on fasting blood glucose in ad libitum studies, as the 95% CI [-0.07, 0.04 mmol/L] overlaps the MID for fasting blood glucose (±0.5 mmol/L), including clinically unimportant benefit (≥ -0.5 mmol/L).

[18]Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin in substitution studies, as there was evidence of significant interstudy heterogeneity (I^2=60%, p<0.001).

[19]Serious imprecision for the effect of fructose-containing sugars on fasting blood insulin in substitution studies, as the 95% CI [-0.24, 4.82 pmol/L] overlaps the MID for fasting blood insulin (±10 mmol/L), including clinically unimportant benefit (≥ -10 pmol/L).

[20]Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin in addition studies, as there was evidence of significant interstudy heterogeneity (I^2=58%, p<0.001).

[21]Serious imprecision for the effect of fructose-containing sugars on fasting blood insulin in addition studies, as the 95% CI [-1.40, 7.96 pmol/L] overlaps the MID for fasting blood insulin (±10 mmol/L), including clinically unimportant benefit (≥ -10 pmol/L).

[22]Serious inconsistency for the effect of fructose-containing sugars on fasting plasma insulin in subtraction studies. Although the evidence of significant interstudy heterogeneity (I^2=79%, p<0.01) was explained by the removal of the study by Campos et al. 2015 (G2) (I^2=1%, p=0.31), the conclusion changed for the significance (from non-significant to significant) and magnitude (from smaller to larger) of the effect on fasting blood insulin (MD=-39.54 pmol/L [95% CI, -75.02, -4.06 pmol/L], p=0.03).

[23] Serious imprecision for the effect of fructose-containing sugars on fasting plasma insulin in subtraction studies, as the 95% CI [-22.83, 26.83 pmol/L] overlaps the MID for fasting blood insulin (±10 mmol/L), including both clinically important benefit (<10 pmol/L) and harm (>10 pmol/L). Only 3 studies involving 33 participants were available for analysis.

[24] Serious imprecision for the effect of fructose-containing sugars on fasting plasma insulin in *ad libitum* studies, as the 95% CI [0.47 to 14.00] overlaps the MID for fasting blood insulin (±10 mmol/L), including clinically unimportant harm (>10 pmol/L).

Supplementary Tables and Figures

SUPPLEMENTARY TABLES

Supplementary Table 1. Search strategy for the effect of food sources of fructose-containing sugars on glycemic control.

Supplementary Table 2. Characteristics of included intervention studies of the effect of food sources of fructose-containing sugars on glycemic control.

Supplementary Table 3. Select sensitivity analyses in which the systematic removal of an individual study altered the significance of the effect estimate or the evidence for heterogeneity.

SUPPLEMENTARY FIGURES

Supplementary Figure 1. Risk of bias summary for the effect of food sources of fructose-containing sugars on glycemic control.

Supplementary Figure 2. Forest plot for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on HbA1c.

Supplementary Figure 3. Forest plot for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on HbA1c.

Supplementary Figure 4. Forest plot for subtraction studies investigating the effect of removing calories from the diet in the form of food sources of fructose-containing sugars on HbA1c.

Supplementary Figure 5. Forest plot for ad libitum studies investigating the effect of freely replacing calories from food sources of fructose-containing sugars with other dietary sources on HbA1c.

Supplementary Figure 6. Subgroup analyses for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on HbA1c.

Supplementary Figure 7. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on HbA1c.

Supplementary Figure 8. Linear meta-regression analyses for the effect of fructose-containing sugars dose (%E) on glycemic control in substitution and addition studies..

Supplementary Figure 9. Non-linear meta-regression analyses for the effect of fructose-containing sugars dose (%E) on glycemic control in substitution and addition studies.

Supplementary Figure 10. Forest plot for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose.

Supplementary Figure 11. Forest plot for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood glucose.

Supplementary Figure 12. Forest plot for subtraction studies investigating the effect of removing calories from the diet in the form of fructose-containing food sources on fasting blood glucose.

Supplementary Figure 13. Forest plot for ad libitum studies investigating the effect of freely replacing calories from food sources of fructose-containing sugars with other dietary sources on fasting blood glucose.

Supplementary Figure 14. Subgroup analyses for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose.

Supplementary Figure 15. Subgroup analyses for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood glucose.

Supplementary Figure 16. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose.

Supplementary Figure 17. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for addition studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose.

Supplementary Figure 18. Forest plot for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood insulin.

Supplementary Figure 19. Forest plot for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood insulin.

Supplementary Figure 20. Forest plot for subtraction studies investigating the effect of removing calories from the diet in the form of food sources of fructose-containing sugars on fasting blood insulin.

Supplementary Figure 21. Forest plot for ad libitum studies investigating the effect of freely replacing calories from food sources of fructose-containing sugars with other dietary sources on fasting blood insulin.

Supplementary Figure 22. Subgroup analyses for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood insulin.

Supplementary Figure 23. Subgroup analyses for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood insulin.

Supplementary Figure 24. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood insulin.

Supplementary Figure 25. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood insulin.

Supplementary Figure 26. Publication bias funnel plots for the effect of food sources of fructose-containing sugars on glycemic control in substitution and addition studies.

Supplementary Table 1. Search strategy for the effect of food sources of fructose-containing sugars on glycemic control.

Database and search terms		
Medline	**Embase**	**The Cochrane library of control studies**
1 exp Fructose/ 2 exp Dietary Sucrose/ 3 HFCS.mp. 4 sugar.mp. 5 sugar* sweetened beverage*.mp. 6 exp Honey/ 7 glyc?em*.mp. 8 exp insulin/ 9 HbA1c.mp or exp hemoglobin A, glycosylated/ 10 fructosamine.mp. 11 exp blood glucose/ 12 gly*albumin.mp. 13 1 or 2 or 3 or 4 or 5 or 6 14 7 or 8 or 9 or 10 or 11 or 12 15 13 and 14 16 limit 15 to animals 17 15 not 16 18 clinical trial.mp. 19 clinical trial.pt. 20 random:.mp. 21 tu.xs. 22 18 or 19 or 20 or 21 23 17 and 22	1 exp Fructose/ 2 exp sucrose/ 3 HFCS.mp. 4 exp sugar/ 5 sugar* sweetened beverage*.mp. 6 exp Honey/ 7 exp glycemic control/ or glyc?em*.mp. 8 exp insulin/ 9 HbA1c.mp or exp hemoglobin A1c/ 10 fructosamine blood level/ or fructosamine.mp. 11 exp glucose blood level/ 12 exp glucosylated albumin/ or gly*albumin.mp. 13 1 or 2 or 3 or 4 or 5 or 6 14 7 or 8 or 9 or 10 or 11 or 12 15 13 and 14 16 limit 15 to animals 17 15 not 16 18 limit 17 to animal studies 19 17 not 18 20 random:.tw. 21 clinical trial:.mp. 22 exp health care quality/ 23 20 or 21 or 22 24 19 and 23	1 Fructose/ 2 Dietary Sucrose/ 3 HFCS.mp. 4 sugar.mp. 5 sugar* sweetened beverage*.mp. 6 Honey/ 7 glyc?em*.mp. 8 Insulin/ 9 HbA1c.mp, hemoglobin A or glycosylated/ 10 fructosamine.mp. 11 blood glucose/ 12 gly*albumin.mp. 13 1 or 2 or 3 or 4 or 5 or 6 14 7 or 8 or 9 or 10 or 11 or 12 15 13 and 14

For all databases, the original search date was November 3rd 2015; updated search was performed on May 29th 2017.

Supplementary Table 2. Characteristics of included intervention studies of the effect of food sources of fructose-containing sugars on glycemic control

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control[a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Substitution Studies (Isocaloric comparison)																		
Fruit																		
Agebratt et al. 2016	30 H (18 M, 12 W)	23.5 (3.7)		22.3 (1.9)	OP, Sweden				P	Supp	Yes						8 wk	A
Intervention	15 H (7 M, 8 W)		66.5 kg (8.7)	22.2 (1.6)		5.1 (0.4)	53.7 (21.5)	5.1 (2.4)				25.6 (~3.8)	Fruit	7 cal/kg bw/ day of fruit	NR	Neutral		
Control	15 H (11 M, 4 W)		73.6 kg (9.0)	22.5 (2.3)		5.3 (0.5)	50.6 (20.1)	5.1 (2.5)					Fat	7 cal/kg bw/ day of walnuts				
Basu et al. 2010 (BB)		49.8 (15.3)	-	37.8 (11.2)	OP, USA	-	-	-	P	Supp	Yes				NR	Positive	8 wk	A, I
Intervention	25 MetS (2 M, 23 W)	51.5 (15.0)		38.1 (7.5)								30 (~6) [l]	Fruit	Freeze dried blueberry beverage				
Control	23 MetS (2 M, 21 W)	48.0 (15.8)		37.5 (14.4)									Water	Water				
Basu et al. 2010 (SB)		46.7 (16.6)	102.3 kg (9.5)	37.8 (8.9)	OP, USA	5.1 (0.7)	-	-	P	Supp	Yes					Positive	8 wk	A, I
Intervention	15 MetS (0 M, 15 W)	48.0 (20.5)	102.0 kg (11.6)	39.0 (7.7)		5.2 (0.8)						~14.6 (~3.2) [f]	Fruit	Freeze dried strawberry beverage	45:37:13			
Control	12 MetS (2 M, 10 W)	45.0 (10.4)	102.7 kg (6.6)	36.4 (10.4)		5.0 (0.7)							Water	Water	46:35:15			
Christensen et al. 2013		58 (12)	91.8 kg (16.9)	32 (5.5)	OP, Denmark	6.6 (1.1)	-	-	P	DA	Yes				NR	Negative	12 wk	NR
Intervention	32 DM2 (18 M, 14 W)	59 (12)	92.4 kg (17)	32 (5)		6.74 (1.2)						~23.1 (~4.6) [f]	Fruit	Incorporate ≥ 2 fruit/d into diet				
Control	31 DM2 (13 M, 18 W)	57 (12)	91.2 kg (17)	32(6)		6.53 (1.1)							Mixed Comparator	Incorporate ≤ 2 fruit/d into diet				
Conceição et al. 2003		44.0 (4.5)		-	OP, Brazil	5.2 (0.9)	74.7 (57.3)	-	P	Supp	Yes				55:30:15	Negative	12 wk	I
Intervention	26 OW/OB, HCL (0 M, 26 W)	43.7 (4.8)	77.7 kg (10.8)			5.3 (1.0)	85.4 (62.5)					Apple, 22.8 (~5.6) ; pear, 19.2 (~3.8)	Fruit	300 g/d apple, 300g/d pear				
Control	9 OW/OB, HCL (0 M, 9 W)	45.0 (3.8)	78.9 kg (9.7)			5.1 (0.6)	43.8 (17.4)						Mixed Comparator	Oat Cookie				
Hegde et al. 2013		58.0 (9.2)	-	24.9 (3.9)	OP, India	8.3 (2.5)	-	8.0 (1.4)	P	DA	No				NR	Positive	3 mo	A
Intervention	60 DM2	58.5 (9.6)		24.4 (3.9)		7.9 (1.5)		8.0 (1.3)				~16.5 (~3.3) [f]	Fruit	Incorporate 2 fruit/d into regular diet				
Control	63 DM2	57.5 (8.9)		25.3 (3.9)		8.6 (3.1)		8.0 (1.5)					Mixed Comparator	Regular diet				
Kolehmainen et al. 2012		51.7 (6.5)			OP, Finland	6.0 (0.7)	103.5 (64.7)	-	P	Supp	Yes					Neutral	8 wk	A
Intervention	15 MetS (5 M, 10 W)	53 (6)	85.4 kg (12.1)	31.4 (4.7)		6.1 (0.9)	100.7 (70.8)					~18.8 (~4.0) [g]	Fruit	200 g/d bilberry puree and 40 g/d dried bilberries equivalent to 400 g/d fresh bilberries	~52:31:17			
Control	12 MetS (3 M, 9 W)	50 (7)	93.1 kg (10.8)	32.9 (3.4)		5.8 (0.4)	107.0 (59.0)						Starch	Other Carbohydrates	~50:34:16			
Lehtonen et al. 2010		42.9 (35-52)	-		OP, Finland	5.0 (0.4)	57.3 (27.9)	5.3 (0.2)	P	Supp	Yes					Neutral	20 wk	A, I
Intervention	28 OW (0 M, 28 W)			29.3 (2.2)		5.1 (0.4)	55.6 (27.1)	5.3 (0.2)				~14.7 (~3.3) [g]	Fruit	163 g/d fresh berries	~50:32:17			
Control	22 OW (0 M, 22 W)			29.5 (1.8)		4.9 (0.4)	59.0 (29.2)	5.2 (0.2)					Mixed comparator	Snacks	~46:35:19			
Lehtonen et al. 2011 [BB]	80 OW/OB (0 M, 80 W)	44.2 (6.2)	81.6 kg (8.5)	29.6 (2.1)	OP, Finland	5.3 (0.4)	53.5 (24.3)	-	C	Supp	No				NR	Neutral	~34 d	A, I
Intervention	80											~3.6 (~0.7) [g]	Fruit	100 g/d of bilberries or sea buckthorn berries				
Control	40												Diet alone	Berry extract, berry oil				
Madero et al. 2011	131 OW/OB (29 M, 102 W)	38.3 (8.8)	80.9 kg (13.4)	32.4 (4.5)	OP, Mexico	5.0 (1.2)	125.1 (70.8)	-	P	DA	Yes				50:30:15	Negative	6 wk	A
Intervention	65 OW/OB (15 M, 50 W)	40.2 (8.1)	79.1 kg (13.4)	32.8 (4.5)		4.9 (1.2)	125.5 (71.1)					~60 (~14)	Fruit	Fruits				
Control	66 OW/ OB (14 M, 52 W)	37.6 (9.3)	82.7 kg (13.3)	32.9 (4.5)		5.1 (1.2)	124.7 (71.1)					<10-20	Starch	Low fructose diet substituted with cereal products				
Moazen et al. 2013	36 DM2 (13 M, 23 W)	51.6 (11.1)			OP, Iran	10.0 (4.1)	-	7.3 (1.7)	P	Supp	Yes					Neutral	6 wk	A, I
Intervention	19 DM2	51.9 (8.3)	75.8 kg (9.3)	27.3 (3.3)		8.9 (2.8)		7.2 (1.6)				~14.6 (~3.2)	Fruit	Freeze dried strawberry beverage equivalent to 500 g fresh strawberries				
Control	17 DM2	51.2 (13.9)	73.0 kg (11.8)	28.7 (4.2)		11.2 (5.0)		7.5 (1.9)					Lactose	Sugar-free strawbery flavored beverage with lactose				
Rodriguez et al. 2005		32.6 (5.8)			OP, Spain	5.1 (0.5)	46.1 (44.3)	-	P	DA	Yes				55:30:15	Negative	8 wk	A
Intervention	7 OB (0 M, 7 W)		91.6 kg (6.0)	34.2 (2.6)		5.2 (0.5)	52.8 (59.0)					~45.0 (13.8)	Fruit	High fruit diet				
Control	8 OB (0 M, 8 W)		91.1 kg (13.0)	35.6 (3.3)		5.0 (0.5)	40.3 (29.2)					~12.6 (4.0)	Starch	Low fruit diet with substitution for other carbohydrates				
Singh et al. 1997		50.5 (8.5)		-	OP, India	6.1 (0.6)	-	-	P	Supp	Yes					Neutral	24 wk	NR
Intervention	52 HTN, HCL (43 M, 9 W)	49.1 (7.5)	67.8 kg (9.6)			6.1 (0.6)						~36.8 (~7) [f]	Fruit	412 g/d guava	63:23:14			
Control	49 HTN, HCL (45 M, 4 W)	52.0 (9.2)	69.2 kg (11.4)			6.1 (0.6)							Mixed comparator	Refined CHO, saturated fat and cholesterol	57:29:14			

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control[a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Dried Fruit																		
Anderson et al. 2014		60.6			OP, USA	5.3 (0.6)	-	5.9 (0.4)	P	Supp	Yes				NR	Neutral	12 wk	I
Intervention	31 MetS (12 M, 19 W)	60.3	86.3 kg (12.2)	30.0 (2.8)		5.3 (0.7)		5.9 (0.4)				~60 (~12)	Fruit	84 g/d raisins				
Control	15 MetS (9 M, 6 W)	61.1	85.2 kg (12.4)	29.2 (2.3)		5.2 (0.3)		5.8 (0.5)					Mixed comparator	Processed snacks				
Bays et al. 2015		58.4			OP, USA	8.5 (1.8)	88.6 (93.8)	7.4 (0.9)	P	Supp	Yes				NR	Neutral	12 wk	I
Intervention	27 DM2 (17 M, 10 W)	58	-	34 (5)		9.0 (1.9)	97.2 (111.1)	7.6 (1.0)				~60 (~12)	Fruit	84 g/d raisins				
Control	19 DM2 (10 M, 9 W)	59	-	37 (7)		7.8 (1.5)	76.4 (62.5)	7.1 (0.6)					Mixed comparator	Processed snacks				
Kaliora et al. 2016	55 NAFLD (23 M, 32 W)				OP, Greece				P	DA	YES				50:30:20	Neutral	24 wk	I
Intervention	28 NAFLD (13 M, 15 W)	50.7 (10.9)	85.7 (14.3)	29.7 (22.2)		5.3 (0.7)	109.7 (50.0)	5.8 (0.5)				36 (7.5)	Fruit	36 g/d currant				
Control	27 NAFLD (10 M, 17 W)	51.6 (9.4)	82.0 (3.0)	29.1 (21.8)									Diet alone	Diet alone				
Kanellos et al. 2014		63.4 (7.3)		-	OP, Greece	7.8 (1.9)	-	6.7 (0.8)	P	Supp	Yes				NR	Neutral	24 wk	A, I
Intervention	26 DM2 (15 M, 11 W)	63.7 (6.3)	83.4 kg (13.8)			7.7 (1.3)		6.5 (0.6)				~24.5 (~4.9)	Fruit	36 g/d raisins				
Control	22 DM2 (10 M, 12 W)	63.0 (8.5)	81.2 kg (14.3)			7.9 (2.4)		6.9 (0.9)					Mixed Comparator	Snacks				
Lehtonen et al. 2011 [SB]	80 OW/OB (0 M, 80 W)	44.2 (6.2)	81.6 kg (8.5)	29.6 (2.1)	OP, Finland	5.3 (0.4)	53.5 (24.3)	-	C	Supp	No				NR	Neutral	~34 d	A, I
Intervention	80											~3.6 (~0.7)[g]	Fruit	100 g/d of bilberries or sea buckthorn berries				
Control	40												Diet alone	Berry extract, berry oil				
Fruit Juice																		
Ribeiro et al. 2017	78 OB (24 M, 54 W)	36 (1.0)	-	33 (3.0)	OP, Brazil	4.8 (0.5)	104.2 (41.7)	-	P	Supp	Yes	44 (~8.8)						
Intervention	39 OB	37 (1.0)		33 (3.0)		4.8 (0.6)	104.2 (41.7)						Fruit	Orange Juice	NR	Negative	12 wk	A,I
Control	39 OB	33 (1.0)		35 (4.0)		4.7 (0.3)	104.2 (41.7)						Mixed comparator	Energy equivalent food item				
SSBs																		
Aeberli et al. 2011 (HD)	29 H (29 M, 0 W)	26.3 (6.6)	73.7 kg (8.8)	22.4 (1.9)	OP, Switzerland	4.5 (0.5)	-	-	C	Supp	Yes	80 (~13)				Neutral	3 wk	A, I
Intervention													Fructose, sucrose	Fructose SSB, sucrose SSB	~55:32:13			
Control													Glucose	Glucose SSB	~57:31:13			
Aeberli et al. 2011 (MD)	29 H (29 M, 0 W)	26.3 (6.6)	73.7 kg (8.8)	22.4 (1.9)	OP, Switzerland	4.5 (0.5)	-	-	C	Supp	Yes	40 (~7)				Neutral	3 wk	A, I
Intervention													Fructose	Fructose SSB	~51:35:14			
Control													Glucose, starch	Glucose SSB, low fructose diet	~49:35:15			
Aeberli et al. 2013	9 H (9 M, 0 W)	22.8 (1.7)	-	22.6 (1.4)	OP, Switzerland	-	-	-	C	Supp	Yes	80 (~14)				Neutral	3 wk	A
Intervention													Fructose, sucrose	Fructose SSB, sucrose SSB	~55:31:15			
Control													Glucose	Glucose SSB	54:31:14			
Beck-Nielsen et al. 1980	15 H	(21-25)		-	OP, Denmark	5.5 (0.6)	37.5 (29.8)	-	P	Supp	Yes				44:38:18	Positive	7 d	A, I
Intervention			61.5 kg (9.9)			5.2 (0.6)	27.8 (19.6)					250 (~33)	Fructose	Fructose dissolved in water				
Control			60.9 kg (7.4)			5.8 (0.5)	48.6 (36.7)						Glucose	Glucose dissolved in water				
Heden et al. 2014 (AJCN-H)	20 H (9 M, 11 W)	18.3 (1.5)	70.5 kg (11.3)	23.9 (3.3)	OP, USA	-	-	-	C	Supp	Yes	50 (~10)			NR	Positive	2 wk	A
Intervention													Fructose	Fructose SSB				
Control													Glucose	Glucose SSB				
Heden et al. 2014 (AJCN-OW/OB) (XX)	20 OW/ OB (11 M, 9 W)	17.4 (1.7)	88.0 kg (16.7)	30.8 (6.1)	OP, USA	-	-	-	C	Supp	Yes	50 (~10)			NR	Positive	2 wk	A
Intervention													Fructose	Fructose SSB				
Control													Glucose	Glucose SSB				
Heden et al. 2015	7 OW/ OB (3 M, 4 W)	18 (1.1)	93.6 kg (10.6)	34.6 (4.2)	OP, USA	-	-	-	C	Supp	Yes	50 (~10)			NR	Positive	2 wk	A
Intervention													Fructose	Fructose SSB with walking (≥12000 steps per day)				
Control													Glucose	Glucose SSB with walking (≥12000 steps per day)				

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control [a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet [c]	Energy Balance [d]	Follow-Up	Funding Sources [e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Jin et al. 2014	21 OW (11 M, 10 W)	13.5 (2.5)		-	OP, USA	5.3 (1.1)	234.5 (176.4)	-	P	Supp	Yes				NR	Neutral	4 wk	A
Intervention	9 OW (3 M, 6 W)	14.2 (2.6)	82.3 kg (5.6)			5.5 (0.8)	211.1 (89.4)					99 (~20)	Fructose	Fructose SSB				
Control	12 OW (8 M, 4 W)	13.0 (2.5)	82.0 kg (4.27)			5.0 (1.3)	252.1 (233.5)						Glucose	Glucose SSB				
Johnston et al. 2013 (T1)	32 OW (32 M, 0 W)	34 (9.9)			OP, UK	4.6 (0.3)	112.1 (38.5)	-	P	Met	Yes				55:30:15	Neutral	2 wk	A
Intervention	15 OW (15 M, 0 W)	35 (11)	96.8 kg (7.4)	30.0 (1.4)		4.5 (0.2)	124.3 (35.4)					~221 (25)	Fructose	Fructose dissolved in water				
Control	17 OW (17 M, 0 W)	33 (9)	93.9 kg (8.7)	28.9 (1.7)		4.7 (0.4)	101.4 (38.9)						Glucose	Glucose dissolved in water				
Johnston et al. 2013 (T2)	32 OW (32 M, 0 W)	34 (9.9)			OP, UK	4.6 (0.3)	112.1 (38.5)	-	P	Supp	Yes				NR	Positive	2 wk	A
Intervention	15 OW (15 M, 0 W)	35 (11)	96.8 kg (7.4)	30.0 (1.4)		4.5 (0.2)	124.3 (35.4)					~221 (25)	Fructose	Fructose dissolved in water				
Control	17 OW (17 M, 0 W)	33 (9)	93.9 kg (8.7)	28.9 (1.7)		4.7 (0.4)	101.4 (38.9)						Glucose	Glucose dissolved in water				
Koivisto and Yki-Järvinen 1993	10 DM2 (4 M, 6 W)	61 (10)	81.9 kg (15.4)	27.5 (4.1)	IP, Finland				C	Met	Yes				50:30:20	Neutral	4 wk	A, I
Intervention			82.0 kg (15.8)			9.7 (3.2)	83 (44.3)	9.0 (1.6)				~55 (~10)	Fructose	Fructose dissolved in water				
Control			81.8 kg (15.8)			10.0 (2.5)	89 (60.1)	9.5 (1.9)					Glucose	Glucose dissolved in water				
Maersk et al. 2012	22 OW/OB (9 M, 13 W)	38 (8)	96.2 kg (13.8)	31.6 (2.8)	OP, Denmark	5.4 (0.7)	74.2 (59.3)	-	P	Supp	Yes				NR	Neutral	6 mo	A, I
Intervention	10 OW/OB (6 M, 4 W)	39 (6)	97.8 kg (12.5)	31.3 (2.9)		5.4 (0.6)	54.3 (26.7)					~106 (~21)	Sucrose	Cola				
Control	12 OW/OB (3 M, 9 W)	38 (9)	94.7 kg (15.3)	31.9 (2.8)		5.4 (0.8)	92.6 (74.9)						Lactose	Semi-skim milk				
Mark et al. 2014	73 OW (0 M, 73 W)	39.7 (8.6)	92.0 kg (12.6)	32.7 (4.3)	OP, Denmark	5.5 (0.6)	58.9 (40.2)	-	P	Supp	Yes				~20:45:34	Neutral	4 wk	A
Intervention	35 OW (0 M, 35 W)					5.4 (0.4)	58.2 (43.6)					60 (~13.6)	Fructose	Fructose dissolved in water				
Control	38 OW (0 M, 38 W)					5.5 (0.4)	62.6 (36.3)						Glucose	Glucose dissolved in water				
McAteer et al. 1987	10 DM2	64.4 (54-71)	59.3 kg (5.4)	-	OP, Ireland	-	-	-	C	Supp	No				42:38:20	Neutral	4 wk	I
Intervention												43.7 (11.6)	Fructose	Fructose dissolved in water with lemon or orange flavor				
Control												10.6 (2.8)	Starch	Starch containing foods				
Ngo Sock et al. 2010	11 H (11 M, 0 W)	24.6 (2)	71.9 kg (5.3)	(19-25)	OP, Switzerland	5.0 (0.4)	54.0 (11.9)	-	C	Met	Yes				55:30:15	Positive	7 d	A
Intervention												~214 (35)	Fructose	20% fructose solution				
Control													Glucose	20% glucose solution				
Schwarz et al. 2015	8 H (8 M, 0 W)	42 (8.5)	-	24.4 (4.5)	IP, USA	4.3 (0.3)	34.7 (33.4)	-	C	Met	No				50:35:15	Neutral	9 d	A
Intervention												~112.5 (~22.5)	Fructose	Fructose SSB				
Control													Starch	Isocaloric exchange of fructose for CCHO				
Silbernagel et al. 2011	20 H (12 M, 8 W)	30.5 (8.9)		25.9 (2.3)	OP, Germany	4.85 (0.3)	47.9 (29.2)	-	P	Supp	Yes				50:35:15	Positive	4 wk	A
Intervention	10 H (7 M, 3 W)	32.8 (9.3)	80.3 kg (9.1)	25.5 (2.2)		4.8 (0.3)	45.4 (36.7)					150 (~22)	Fructose	Fructose dissolved in water				
Control	10 H (5 M, 5 W)	28.2 (8.4)	80.7 kg (7.5)	26.2 (2.4)		4.9 (0.2)	50.6 (20.9)						Glucose	Glucose dissolved in water				
Stanhope et al. 2011 (AJCN)	32 OW/OB (16 M, 16 W)	53.7 (8.1)	85.9 kg (10.5)	29.3 (2.9)	IP/ OP, USA	4.9 (0.2)	99.2 (45.0)	-	P	Met/ Supp	No					Positive	8 wk	A
Intervention	17 OW/ OB(9 M, 8 W)	52.5 (9.3)	85.8 kg (10.7)	29.3 (2.6)		4.9 (0.2)	99.2 (45.0)					158 (25)	Fructose	Fructose SSB	~55:30:15			
Control	15 OW/OB (7 M, 8 W)	55.1 (6.6)	86.1 kg (10.6)	29.4 (3.2)		4.9 (0.4)	104.1 (55.9)						Glucose	Glucose SSB	~55:30:15			
Stanhope et al. 2011 (JCEM)	48 (27 M, 21 W)	27.6 (7.1)	76.0 kg (13.1)	25.5 (4.0)	IP/OP, USA	4.9 (0.4)	96.6 (55.0)	-	P	Met/ Supp	No				55:30:15	Neutral	2 wk	A
Intervention	32 (18 M, 14 W)	27.9 (7.1)	75.6 kg (12.8)	25.2 (4.3)		4.9 (0.4)	96.0 (64.4)					~125 (25)	Fructose, HFCS	Fructose SSB, HFCS SSB				
Control	16 (9 M, 7 W)	27.0 (7.2)	76.8 kg (14.1)	26.2 (3.6)		4.9 (0.4)	97.9 (30.4)						Glucose	Glucose SSB				
Swarbrick et al. 2008	7 OW/OB (0 M, 7 W)	(50-72)	75.7 kg (24.3)	29.1 (5.8)	IP, USA	4.6 (1.1)	58 (48)	-	C	Met	No				55:30:15	Neutral	10 wk	A
Intervention												~125 (25)	Fructose	Fructose SSB (12 % solution flavored with unsweetened drink mix)				
Control													Starch	Complex CHO sources (bread, rice, pasta)				
Vaisman et al. 2006	25 DM2	62.3 (10.1)			OP, Israel	11.47 (3.6)	348.3 (231.8)	8.47 (0.8)	P	Supp	Yes	22.5 (~5)			NR	Neutral	3 mo	NR
Intervention	12 DM2	65.4 (10.7)	82.9 kg (10.9)	29.5 (3.9)		11.3 (3.6)	357.0 (319.5)	8.6 (0.9)					Fructose	Fructose dissolved in water				
Control	13 DM2	59.5 (9.1)	83.4 kg (17.6)	30.5 (5.2)		11.7 (3.7)	340.3 (117.4)	8.4 (0.8)					Maltodextrin	Maltodextrin dissolved in water				
Sweetened Low-Fat Milk																		
Lowndes et al. 2015- Fructose	95 OW/ OB (43 M, 52 W)	36.0 (11.5)	74.3 kg (12.5)	26.0 (3.5)	OP, USA	5.0 (0.4)	55.1 (40.8)	-	P	Supp	Yes					Neutral	10 wk	I
Intervention	30 OW/OB (16 M, 14 W)	35.6 (10.4)	74.3 kg (13.1)	26.0 (3.8)		4.9 (0.4)	55.6 (31.9)					~49.5 (9)	Fructose	Fructose sweetened milk	~52:29:20			
Control	65 OW/OB (27 M, 38 W)	36.2 (12.0)	74.3 kg (12.3)	26.1 (3.4)		5.1 (0.5)	54.9 (44.8)						Glucose, lactose	Glucose sweetened milk, unsweetened milk	~52:30:19			

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control [a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet [c]	Energy Balance [d]	Follow-Up	Funding Sources [e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Lowndes et al. 2015-Sucrose	92 OW/ OB (36 M, 56 W)	35.2 (11.5)	72.5 kg (13.1)	26.0 (3.5)	OP, USA	5.0 (0.4)	58.5 (35.9)	-	P	Supp	Yes					Neutral	10 wk	I
Intervention	61 OW/OB (26 M, 35 W)	35.2 (11.1)	72.7 kg (13.6)	26.0 (3.5)		4.9 (0.4)	60.6 (36.2)					sucrose, HFCS: ~109.7 (18)	Sucrose, HFCS	Sucrose or HFCS sweetened milk (18% E)	~55:28:18			
Control	31 OW/OB (10 M, 21 W)	35.3 (12.5)	72.3 kg (12.2)	26.0 (3.5)		5.0 (0.4)	54.2 (35.4)						Diet alone	Unsweetened milk (9% E)	~49:32:20			
Baked Goods, Desserts and Sweets																		
Behall et al. 1980 (non-OC)	6 (0 M, 6 W)	(19-25)	63 kg	-	OP, USA			-	C	Met	No	~214 (~43)			51:36:13	Neutral	4 wk	A
Intervention						4.4 (0.4)	141.7 (35.7)						Sucrose	Sucrose Pattie				
Control						4.4 (0.3)	147.2 (66.3)						Starch	Starch Pattie				
Behall et al. 1980 (OC)	6 (0 M, 6 W)	(19-25)	64 kg	-	OP, USA			-	C	Met	No	~214 (~43)			51:36:13	Neutral	4 wk	A
Intervention						4.4 (0.4)	132.6 (42.5)						Sucrose	Sucrose Pattie				
Control						4.8 (0.7)	179.9 (42.5)						Starch	Starch Pattie				
Claesson et al. 2009	25 H (11 M, 14 W)	23.4 (2.7)	68.0 kg (6.7)	22.2 (1.7)	OP, Sweden	4.7 (0.4)	26 (13)	-	P	Supp	Yes					Positive	2 wk	A
Intervention	12 H (5 M, 7 W)	23.2 (3.5)	67.3 kg (7.6)	22.2 (1.4)		4.7 (0.5)	27 (11)					278 (~37)	Sucrose	Candy	65:21:10			
Control	13 H (6 M, 7 W)	23.6 (1.8)	68.7 kg (6.1)	22.2 (2.0)		4.7 (0.3)	24 (15)					92 (~12)	Fat	Peanuts	32:48:18			
Costa et al. 2005	10 DM1 (7 M, 3 W)	(14-18)	58.5 kg (11.8)	21.7 (3.2)	OP, Brazil	-	-	8.3	C	DA	No					Neutral	4 mo	I
Intervention												~37.5 (~6.2)	Sucrose	Sweets	50:30:20			
Control													Starch	Other CHO sources	48:32:21			
Hallfrisch et al. 1983 HI	12 HI (12 M, 0 W)	39.5 (7.3)	81.4 kg (8.0)	-	IP/OP, USA	-	164.6 (19.0)	-	C	Met	No				43:42:15	Neutral	5 wk	NR
Intervention												~50.6 (7.5), ~101.3 (15) [h]	Fructose	Fructose wafer				
Control													Starch	Starch wafer				
Hallfrisch et al. 1983 H	12 H (12 M, 0 W)	39.8 (8.3)	80.5 kg (11.1)	-	IP/OP, USA	-	145.2 (19.2)	-	C	Met	No				43:42:15	Neutral	5 wk	NR
Intervention												~50.6 (7.5), ~101.3 (15) [h]	Fructose	Fructose wafer				
Control													Starch	Starch wafer				
Jones et al. 2014		26.2 (7.2)	69.0 kg (16.0)	23.6 (3.7)	OP, USA			-	P	Supp	Yes				NR	Neutral	12 wk	I
Intervention	25 H					4.8 (0.3)	59.4 (46.3)					6 (~1.2)	Sucrose[i]	Honey roasted peanuts				
Control	25 H					4.8 (0.5)	48.7 (30.4)						Fat	unsalted peanuts				
Kelsay et al. 1974	8 H (0 M, 8 W)	(18-23)	(43.6-65.3 kg)	-	OP, USA	-	-	-	C	Met	Yes			Sucrose	50:38:12	Neutral	4 wk	NR
Intervention												~212.5 (~42)	Sucrose	Uncooked fondant pattie made with fat and sucrose				
Control													Glucose	Uncooked fondant pattie made with fat and glucose				
Malerbi et al. 1996	16 DM2 (7 M, 9 W)	54.2 (9.2)	65.7 kg (8.1)	25.6 (2.8)	OP, Brazil	7.2 (1.5)	57.9 (41.3)	7.5 (1.0)	C	Met	No					Neutral	4 wk	I
Intervention												63.2 (20)	Fructose	85% of fructose incorporated into a papaya frozen cream sorbet, remaining 15% from natural sources such as fruits and vegetables	55:30:15			
Control													Starch	Starch contianing foods	50:35:15			
Reiser et al. 1989 (HI)	10 HI (10 M, 0 W)	47.4	85 kg	25.7	IP/OP, USA	-	-	-	C	Met	No				51:36:13	Neutral	5 wk	NR
Intervention												168 (20)	Fructose	Fructose fondant				
Control													Starch	Starch muffin				
Reiser et al. 1989 (H)	11 H (11 M, 0 W)	38.10	79 kg	24.4	IP/OP, USA	-	-	-	C	Met	No				51:36:13	Neutral	5 wk	NR
Intervention												168 (20)	Fructose	Fructose fondant				
Control													Starch	Starch muffin				
Added Sweeteners																		
Abdulrhman et al. 2013	20 DM1 (10 M, 10 W)	11.4 (4.2)	105 % IBW (12.1)	-	OP, Egypt	9.4 (1.1)	-	7.2 (0.8)	C	Supp	Yes				NR	Neutral	12 wk	NR
Intervention												~26.6 (~4.0)	Honey	Honey added to diet				
Control													Diet alone	Regular diet				
Bantle et al. 2000	24 H (12 M, 12 W)	41.3 (13.5)		25.1 (2.4)	OP, USA	5.1 (0.5)	-	-	C	Met	Yes	~85 (17)			55:30:15	Neutral	6 wk	A
Intervention			74.1 kg (7.3)										Fructose	Baked goods, beverages, breakfast cereals				
Control			74.1 kg (6.9)										Glucose	Baked goods, beverages, breakfast cereals				
Despland et al. 2017	8 H (8 M 0 W)	-	73.7 kg (5.7)	23.8 (2.3)	IP/ OP, Switzerland	-	-	-	C	Met	Yes				55:30:15	Neutral	7-8 d	A,I
Intervention												~150 (30)	Honey, HFCS	25% starch substituted for robinia honey or fructose+glucose solution comparable to honey composition				
Control													Starch	Starch				

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control[a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Emanuele et al. 1986	5 DM2, HLP (5 M, 0 W)	59 (6.7)	117 % IBW (14.5)	-	OP, USA				C	Met	Yes					Neutral	4 wk	NR
Intervention			93 kg (24.6)			13.2 (3.2)	187.5 (155.3)	-				220 (~39)	Sucrose	220 g/d sucrose added to beverages and cereals, gelatin desserts, artificially flavored beverages, jelly spreads	63:22:15			
Control			94 kg (22.4)			10.4 (3.1)	145.8 (77.6)	-				≤ 3 (~≤0.5)	Mixed comparator	Isocaloric low sucrose (≤ 3 g/d), low CHO diet	38:39:22			
Grigoresco et al. 1988	8 DM2 (5 M, 3 W)	40 (6.9)	74.3 kg (12.4)	26.1 (3.3)	OP, France	8.0 (1.4)	168.1 (95.2)	6.8 (1.6)	C	Supp	Yes				50:30:20	Neutral	8 wk	A, I
Intervention												30 (8)	Fructose	30 g powdered fructose packs added to food and beverages				
Control													Starch	Fructose exchanged for 30 g starch				
Jellish et al. 1984		59.5 (9.6)	92.6 kg (19.2)	-	IP, USA	11.7 (4.0)	166.7 (106.2)	-	P	Met	Yes					Neutral	4 wk	NR
Intervention	18 DM2 (18 M, 0 W)	60.7 (8.9)	92.4 kg (19.4)									120 (~21), 220 (~39) [n]	Sucrose	Hot beverages, cereals, gelatin desserts, jelly spreads, beverages	50:35:15, 65:21:14 [m]			
Control	8 DM2 (8 M, 0 W)	59.5 (9.6)	92.6 kg (19.2)									≤ 3 (~1)	Mixed comparator	Isocaloric low sucrose diet	37:41:22			
Koh et al. 1988 (IGT)	9 IGT (3 M, 6 W)	54 (18)	74.5 kg (15)	-	OP, USA	-	-	-	C	Supp	No					Neutral	4 wk	NR
Intervention												~64 (15)	Fructose	Fructose packets added to Fruit juice, milk, water or baked goods	~53:32:16			
Control													Glucose	Glucose packets added to Fruit juice, milk, water or baked goods				
Koh et al. 1988 (NGT)	9 H (3 M, 6 W)	50 (15)	65.9 kg (13.6)	-	OP, USA	-	-	-	C	Supp	No					Neutral	4 wk	NR
Intervention												~78.5 (15)	Fructose	Fructose packets added to Fruit juice, milk, water or baked goods	~53:32:16			
Control													Glucose	Glucose packets added to Fruit juice, milk, water or baked goods				
Lock et al. 1980	18 (18 M, 0 W)	(31-62)	-	-	OP, England	-	-	-	C	Supp	No					Neutral	12 mo	NR
Intervention												60 (~10.2)	Sucrose	Crystalline and powdered sucrose	41:42:13			
Control													Glucose	Crystalline and powdered dried glucose syrup	42:41:14			
Malerbi et al. 1996	16 DM2 (7 M, 9 W)	54.2 (9.2)	65.7 kg (8.1)	25.6 (2.8)	OP, Brazil	7.2 (1.5)	57.9 (41.3)	7.5 (1.0)	C	Met	No					Neutral	4 wk	I
Intervention												77.8 (19)	Sucrose	Sucrose used to sweeten fruits, milk, beverages and coffee	55:30:15			
Control													Starch	Starch contianing foods	50:35:15			
Osei et al. 1987	18 DM2 (3 M, 15 W)	57 (8.6)	82.7 kg (13.5)	-	OP, USA	12.7 (3.2)	-	11.51 (2.5)	P	Supp	Yes				50:35:15	Neutral	12 wk	A, I
Intervention	9 DM2 (2 M, 7 W)	57 (8.7)	82.8 kg (15.6)			12.4 (4.0)		11.5 (1.5)				60 (~10)	Fructose	Crystalline fructose added to cereals and non-alcoholic beverages				
Control	9 DM2 (1 M, 8 W)	57 (9.0)	82.5 kg (12.0)			12.9 (2.3)		11.5 (3.3)					Starch	ADA recommended diet - mostly CCHO as souce of carbohydrates				
Osei et al. 1989	13 DM2 (5 M, 8 W)	54 (11)		29.6 (9.4)	OP, USA		-		C	Supp	Yes				50:35:15	Neutral	6 mo	A, I
Intervention			87.7 kg (27.4)			12.6 (4.0)		11.3 (1.4)				60 (15)	Fructose	Crystalline fructose incorporated into cereals and non-alcoholic beverages				
Control			88.3 kg (20.9)			11.0 (0.4)		10.4 (2.5)					Starch	ADA recommended diet - mostly CCHO as souce of carbohydrates				
Mixed Sources																		
Abraira et al. 1988	18 DM2 (17 M, 1 W)			-	IP, USA	8.7 (3.4)	149.3 (142.6)	-	P	Met	Yes	220 (~38)			50:35:15	Neutral	1 mo	I
Intervention	9 DM2 (9 M, 0 W)	61.4 (4.8)	85.4 kg (22.2)			8.2 (3.0)	132.0 (145.8)						Sucrose	Beverages, gelatin desserts, cereals				
Control	9 DM2 (8 M, 1 W)	61.4 (7.2)	82.6 kg (18.1)			9.2 (3.8)	166.7 (145.8)						Starch	Bread, potatoes, pasta				
Anderson et al. 1989	14 DM2 (14 M, 0 W)	60 (15.0)	112 % DBW (15)	-	IP/OP, USA	11.2 (4.2)	-	10.6 (1.9)	C	Met	No	~55 (12)			55:20:25	Neutral	24 wk	A, I
Intervention													Fructose	Cookies, lemonade-flavored drink, crystalline fructose				
Control													Starch	Starch containing foods				

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control[a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Bantle et al. 1986 (DM1)	12 DM1 (6 M, 6 W)	23 (15-32)	103 % MRW (82-123)	-	IP, USA	-	-	9.9 (1.8)	C	Met	Yes	~137 (21)			55:30:15	Neutral	8 d	A, I
Intervention													Fructose, sucrose	Baked goods, beverages, breakfast cereals				
Control													Starch	Starch containing foods				
Bantle et al. 1986 (DM2)	12 DM2 (5 M, 7 W)	62 (36-80)	129 % MRW (106-160)	-	IP, USA	-	-	8.5 (2.4)	C	Met	Yes	~137 (21)		Fructose, sucrose	55:30:15	Neutral	8 d	A, I
Intervention													Fructose, sucrose	Baked goods, beverages, breakfast cereals				
Control													Starch	Starch containing foods				
Bantle et al. 1992 (DM1)	6 DM1 (3 M, 3 W)	23 (18-34)	102 % MRW (97-111)	-	IP/OP, USA		-	8.1 (0.3)	C	Met	Yes	~120 (20)			55:30:15	Neutral	28 d	A, I
Intervention						10.6 (4.0)							Fructose	Baked goods, beverages, breakfast cereals				
Control						10.3 (4.2)							Starch	Starch containing foods				
Bantle et al. 1992 (DM2)	12 DM2 (4 M, 8 W)	62 (40-72)	136 % MRW (99-170)	-	IP/OP, USA		-	7.2 (2.1)	C	Met	Yes	~120 (20)			55:30:15	Neutral	28 d	A, I
Intervention						9.3 (2.3)							Fructose	Baked goods, beverages, breakfast cereals				
Control						8.2 (1.4)							Starch	Starch containing foods				
Bantle et al. 1993	12 DM2 (4 M, 8 W)	62 (40-72)		-	OP, USA		-		C	Met	Yes	~114 (19)			55:30:15	Neutral	28 d	A, I
Intervention			86.0 kg (22.5)			8.7 (2.5)		7.2 (1.1)					Sucrose	Baked goods, beverages, breakfast cereals				
Control			86.9 kg (22.2)			8.2 (1.4)		7.2 (1.5)					Starch	Starch containing foods				
Black et al. 2006	13 H (13 M, 0 W)	33 (11)	86.0 kg (12.3)	26.6 (3.2)	OP, UK	4.8 (0.4)	-	5.7 (0.4)	C	Met	Yes	~199 (25)			55:33:12	Neutral	6 wk	A
Intervention													Sucrose	High sucrose diet (25% E)				
Control													Starch	Low sucrose diet (10% E)				
Blayo et al. 1990	14 DM1, 6 DM2	46.9 (13.1)	-	22.6 (1.9)	OP, France	9.8	-	8.8	P	Supp	Yes				55:30:15	Neutral	12 mo	A, I
Intervention	8 DM1, 4 DM2	49.5 (14.1)		23.0 (2.1)		9.4		7.8				~25 (5)	Fructose, sucrose	20-30 g sugar/d in drinks, desserts, meals				
Control	6 DM1, 2 DM2	43.0 (11.0)		22.0 (1.6)		10.4		9.5					Starch	Isocaloric substitution of sugar with starch				
Brymora et al. 2012	28 CKD (17 M, 11 W)	59 (15)	85.8 kg (11.5)	29.9 (4.2)	OP, Poland	5.4 (0.7)	77.8 (42.4)	-	C	DA	No				55:30:15	Neutral	6 wk	A
Intervention												~56 (~10)	Fructose, sucrose	Regualr diet				
Control												12 (~2)	Starch	Isocaloric low fructose diet through reduction of fruits and added sugars				
Brynes et al. 2003	17 OW/ OB (17 M, 0 W)	45 (8)	-	29.3 (4.0)	OP, London	-	-	-	C	Supp	Yes	132 (~22)				Neutral	24 d	I
Intervention													Sucrose	Table sugar	51:33:16			
Control													Fat, starch	Olive oil, instant potato, wholegrain rye bread	~43:39:18			
Buysschaert et al. 1987	10 DM1 (5 M, 5 W)	52 (12.6)	124 % IBW (22)	-	OP, Belgium	-	-	9.5 (1.3)	C	Met	Yes				45:35:20	Neutral	3 mo	NR
Intervention												19 (~5.4)	Sucrose	Sucrose incorporated into desserts and/ or soft drinks				
Control													Starch	Conventional diabetic diet				
Cooper et al 1988	17 DM2 (6 M, 11 W)	62.2 (14.0)	69.1 kg (2.8)	26.0 (3.0)	OP, Australia	8.9 (2.8)	100.0 (50.4)	8.1 (1.7)	C	Supp	Yes				NR	Positive	6 wk	I
Intervention												28 (8.2)	Sucrose	28 g sucrose added to hot beverages, fruit juice, milk, cereals, stewed fruit				
Control													Starch	30 g starch and saccharin added to hot beverages, fruit juice, milk, cereals, stewed fruit				
Coulston et al. 1985	11 DM2 (5 M, 6 W)	62 (6.6)	-	27.8 (2.3)	OP, USA	7.8 (1.7)	-	-	C	Met	No					Neutral	15 d	A
Intervention												~80 (16)	Sucrose	Sucrose added diet	53:29:18			
Control												~5 (1)	Starch	Sucrose free diet	51:30:19			
Dunnigan et al. 1970	8 CND, 1 CAD (6 M, 3 W)	51.8 (8.1)	63.1 kg (10.5)	-	IP, Scotland	-	-	-	C	Met	No				45:40:15	Neutral	4 wk	NR
Intervention												169 (~34)	Sucrose	70% CHO intake as sucrose				
Control													Starch	85% CHO intake as wheat, potato or maize starch				
Fry et al. 1972	19 (19 M, 0 W)	24.7 (20.8-40.8)	76.9 kg (8.4)	-	OP, Antartica	-	-	-	C	Met	No				44:43:13	Neutral		NR
Intervention												97 (~13)	Sucrose	Sucrose-containing diet			18 wk	
Control													Glucose	Sucrose-free diet with glucose syrup and calcium cyclamate			14 wk	

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control [a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet [c]	Energy Balance [d]	Follow-Up	Funding Sources [e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Hendler et al. 1986	6 OB (0 M, 6 W)	(20-44)	(56-126 % IBW)	-	OP, USA	-	-	-	C	Met	No					Negative	15 d	A, I
Intervention												~190 (95)	Sucrose	High sucrose diet	96:04:00			
Control													Protein	High protein diet	96:04:00			
Lewis et al. 2013	13 OW/ OB (9 M, 4 W)	46.1 (6.9)	92 kg (10.5)	31.7 (3.2)	OP, UK	5.2 (0.7)	-	-	C	Met	Yes	~101.8 (15)				Neutral	6 wk	I
Intervention													Sucrose	High sucrose diet (15% E)	~55:33:12			
Control													Starch	Low sucrose diet (5% E)	~55:33:12			
Liu et al. 1984	10 HTG (4 M, 6 W)		-		IP, USA	-	-	-	P	Met	Yes				40:41:19	Neutral	15 d	A
Intervention	5 HTG	52 (4.5)		29.6 (4.5)								~65 (13)	Sucrose	13 % sucrose diet				
Control	5 HTG	55 (4.5)		28.9 (4.0)								~45 (9)	Starch	9 % sucrose diet				
Maki et al. 2015	34 DM2 (17 M, 17 W)	53.8 (12.2)	-	32.2 (4.7)	OP, USA	5.5 (0.5)	56.0 (21.0)	-	C	Supp	Yes					Neutral	6 wk	A, I
Intervention												~92 (~17)	Sucrose	Non-diet soda and non-dairy pudding	57:29:15			
Control													Lactose	2% milk and sugar-free low fat yogurt	47:33:19			
Paganus et al. 1987 (CG)	8 DM1 (3 M, 5 W)	12.3 (10.7-14.8)	-	-	OP, Finland	-	-	-	C	Met	Yes				50:30:20	Neutral	3 wk	I
Intervention												37 (~7.4)	Fructose	Marmalade, grain fruit bar, pure fructose sweetener				
Control													Starch	Isocaloric exchange of fructose for other carbohydrates				
Paganus et al. 1987 (SG)	22 DM1 (9 M, 13 W)	12.2 (8.9-15.9)	-	-	OP, Finland	-	-	-	C	Met	Yes				50:30:20	Neutral	3 wk	I
Intervention												37 (~7.4)	Fructose	Marmalade, grain fruit bar, pure fructose sweetener				
Control													Starch	Isocaloric exchange of fructose for other carbohydrates				
Paineau et al. 2008					OP, France	-	-	-	P	DA	Yes				-	Negative	8 mo	A, I
Intervention	297 (55 M, 242 W)	40.4 (5.3)	66.8 kg (13.5)	24.2 (4.5)								~80.1 (~17.6) j	Sucrose	Reduced fat, increased CCHO				
Control	298 (48 M, 250 W)	40.3 (5.4)	67.3 kg (16.0)	24.6 (5.7)									Starch	Reduced fat, reduced sugar, increased CCHO to maintain isocaloric CHO intake				
Pelkonen et al. 1972	10 DM1 (5 M, 5 W)	25.5 (19-70)	99 % RBW (90-118)	-	IP, Finland	-	-	-	C	Met	No				40:40:20	Neutral	10 d	A
Intervention												75 (15)	Fructose	Fructose incorporated into main meals replacing starch				
Control													Starch	Starch incorporated into main meals				
Peterson et al. 1986 (DM1)	12 DM1 (10 M, 2 W)	52 (11)	-	24.9 (21.2-27.9)	OP, UK	-	-	-	C	DA	Yes				50:30:20	Neutral	6 wk	NR
Intervention												45 (~9.4)	Sucrose	45 g CCHO replaced by sucrose in food				
Control													Starch	British Diabetic Association recommended diet				
Peterson et al. 1986 (DM2)	11 DM2 (7 M, 4 W)	56 (9)	-	24.7 (20.1-28.0)	OP, UK	-	-	-	C	DA	Yes				50:30:20	Neutral	6 wk	NR
Intervention												45 (~9.4)	Sucrose	45 g CCHO replaced by sucrose				
Control													Starch	British Diabetic Association recommended diet				
Porta et al. 1989	16 DM2 (8 M, 8 W)	60 (9.7)	-		OP, Italy	8.5 (2.2)	-	5.8 (1.1)	P	Supp	Yes					Neutral	6 mo	A
Intervention	8 DM2 (4 M, 4 W)	60 (8.5)		27.4 (3.1)		9.3 (2.5)		6.0 (1.4)				~38.1 (10)	Sucrose	10% of starch replaced by sucrose in 2 main meals, coffee, tea, fruit	54:28:18			
Control	8 DM2 (4 M, 4 W)	60 (11.3)		28.2 (2.5)		7.7 (1.7)		5.6 (0.8)					Starch	Traditional diabetic diet	55:28:18			
Rath et al. 1974	6 H (6 M, 0 W)	21.5 (2.7)	65.8 kg (10.2)	-	IP, Prague	-	-	-	C	Met	No					Neutral	24 d	NR
Intervention												400 (52.5)	Sucrose	High sugar diet (400 g/d sugar)	72:16:12			
Control												120 (17.1)	Mixed comparator	Control diet (120 g/d sugar)	50:33:17			
Reiser et al. 1986 (W)	9 H (0 M, 9 W)	(27-48)	-	-	IP/OP, USA	4.9 (1.2)	128.5 (45.8)	-	C	Met	No				50:35:15	Neutral	6 wk	NR
Intervention												141.8 (~21)	Sucrose	High sugar diet (20 %E)				
Control													Starch	Low sugar diet with isocaloric exchange of sugar for CCHO				

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control [a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet [c]	Energy Balance [d]	Follow-Up	Funding Sources [e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Reiser et al. 1986 (M)	10 H (10 M, 0 W)	(24-56)	107 % DBW	-	IP/OP, USA	5.2 (0.6)	123.6 (24.2)	-	C	Met	No				50:35:15	Neutral	6 wk	NR
Intervention												141.8 (~21)	Sucrose	High sugar diet (20 %E)				
Control													Starch	Low sugar diet with isocaloric exchange of sugar for CCHO				
Santacore et al. 1990	12 DM1 (6 M, 6 W)	27 (16-46)	-	22.3 (19.8-25)	OP, Italy	-	-	6.9 (1.0)	C	Met	Yes				52:31:17	Neutral	2 mo	NR
Intervention								6.8 (1.0)				30 (~6)	Sucrose	Sucrose added to foods and mixed meals				
Control								6.9 (1.0)					Starch	High glycemic index bread				
Souto et al. 2013	33 DM1 (21 M, 12 W)	21.7 (5)	-		OP, Brazil	10.0 (3.8)	-	7.6 (1.6)	P	DA	Yes					Negative	3 mo	NR
Intervention	15 DM1 (8 M, 7 W)			24.0 (2.6)		10.9 (3.6)		8.0 (2.1)				~162 (27)	Sucrose	Sucrose containing foods	58:26:20			
Control	18 DM1 (12 M, 6 W)			22.4 (2.7)		9.4 (3.9)		7.3 (1.1)					Starch	Isocaloric exchange of sucrose for other carbohydrates	53:24:20			
Sunehag et al. 2002 (P1-AD)	12 H (6 M, 6 W)	14.5 (1.1)	55.5 kg (10.7)	20.2 (3.1)	IP/ OP, Italy	-	-	-	C	Met	Yes					Neutral	7 d	A
Intervention												~74.9 (~12.1)	Fructose	High CHO low fat diet (20% CHO from fructose)	60:25:15			
Control												~39.8 (~6.3)	Mixed comparator	Low CHO high fat diet (20% CHO from fructose)	30:55:15			
Sunehag et al. 2002 (P1-PP)	12 H (6 M, 6 W)	8.0 (1.0)	26.1 kg (4.5)	15.7 (1.3)	IP/ OP, Italy	-	-	-	C	Met	Yes					Neutral	7 d	A
Intervention												~50.6 (~12.1)	Fructose	High CHO low fat diet (20% CHO from fructose)	60:25:15			
Control												~27.7 (~6.3)	Mixed comparator	Low CHO high fat diet (20% CHO from fructose)	30:55:15			
Sunehag et al. 2002 P2	12 H (6 M, 6 W)	14.8 (1.3)	60.3 kg (11.1)	21.8 (3.9)	IP/ OP, Italy	-	-	-	C	Met	Yes					Neutral	7 d	A
Intervention												~150.3 (~23.8)	Fructose	High CHO low fat diet (40% CHO from fructose)	60:25:15			
Control												~40.4 (~6.5)	Starch	High CHO low fat diet (10% CHO fructose)	60:25:15			
Sunehag et al. 2008	6 OB (3 M, 3 W)	15.2 (1.2)	98.4 kg (18.4)	35 (4.9)	OP, USA	-	-	-	C	Met	Yes				60:25:15	Neutral	7 d	A, I
Intervention												~149.1 (24)	Fructose	White bread, fruit, fruit juice, canned fruit in heavy syrup, candy, soft drinks				
Control												~38 (6)	Starch	Isocaloric exchange of fructose from other carbohydrates				
Surwit et al. 1997	42 OB (0 M, 42 W)	40.2 (7.6)			OP, England	4.9 (0.6)	-	-	P	Met	Yes					Negative	6 wk	A, I
Intervention	20 OB (0 M, 20 W)	40.6 (8.2)	96.1 kg (13.7)	35.9 (4.8)		5.0 (0.7)						121.2 (58.0)	Sucrose	High-sucrose, low fat diet	73:11:19			
Control	22 OB (0 M, 22 W)	40.3 (7.3)	96.7 kg (12.6)	34.9 (4.4)		4.9 (0.6)						11.8 (6.0)	Starch	Low-sucrose, low fat diet	71:11:20			
Swanson et al. 1992	14 H (7 M, 7 W)	34 (19-60)		-	IP/ OP, USA	5.1 (0.4)	-	5.0 (0.4)	C	Met	Yes			Fructose	55:30:15	Neutral	28 d	A, I
Intervention			68.6 kg (3.1)			4.9 (0.4)		5.1 (0.4)				100 (20)	Fructose	Crystalline fructose added to baked goods, beverages, breakfast cereals, and natural fructose in fruits and vegetables				
Control			68.5 kg (3.0)			5.2 (0.4)		4.9 (0.4)				14 (<3)	Starch	Bread, potatoes, wheat and corn flour, oats				
Szanto et al. 1969	19 H (19 M, 0 W)	28 (21-44)	73.1 kg (58.5-81.5)	-	OP, UK	3.8 (3.4-4.5)	153 (97.2-180.6)	-	C	DA	No				NR	Neutral	2 wk	A
Intervention												438 (~52)	Sucrose	High sucrose diet				
Control													Starch	High starch diet				
Van Meijl et al. 2011	35 OW/OB (10 M, 25 W)	49.5 (13.2)	-	32.0 (3.8)	OP, Netherlands	5.68 (0.6)	-	-	C	Supp	Yes					Neutral	8 wk	I
Intervention												70.2 (~12.8) [l]	Sucrose	Fruit Juice (600 mL), fruit biscuits (43 g)	53:30:16			
Control													Lactose	Low fat milk (500 mL), low fat yogurt (150 g)	46:33:19			
Volp et al. 2007 (G1)	10 H (0 M, 10 W)	22.5 (2.1)			OP, Brazil	-	-	-	P	DA	Yes					Neutral	14 d	A
Intervention	5 H (0 M, 5 W)		54.9 (48.8-64.5) [k]	21.7 (20.2-25.0) [k]								110 (~22)	Sucrose	High sucrose diet	59:28:13			
Control	5 H (0 M, 5 W)		55.8 (48.0-65.6) [k]	21.3 (19.4-24.8) [k]								10 (~2)	Fat	High fat diet	42:45:13			

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline FBG, mmol/L (SD or range)	Baseline FBI, pmol/L (SD or range)	Baseline HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
Volp et al. 2007 (G2)	10 OW (0 M, 10 W)	21.8 (2.8)			OP, Brazil	-	-	-	P	DA	Yes					Neutral	14 d	A
Intervention	5 OW (0 M, 5 W)		73.9	29.1								130 (~23)	Sucrose	High sucrose diet	59:28:13			
Control	5 OW (0 M, 5 W)		72	28.7								10 (2)	Fat	High fat diet	42:45:13			
Volp et al. 2008 (G1)	6 H (0 M, 6 W)	21 (19-24) [k]	-	21.4 (20.2-22.8) [k]	OP, Brazil	5.5 (5.2-5.8)	89.6 (59.7-100.0)	-	C	DA	Yes					Neutral	14 d	AI
Intervention												~81.1 (18.4)	Sucrose	High sucrose diet	65:22:16			
Control												~11.2 (2.6)	Fat	High fat diet	50:36:17			
Volp et al. 2008 (G2)	6 OW/OB (0 M, 6 W)	21 (19-22) [m]	-	28.6 (25.1-32.1) [m]	OP, Brazil	5.9 (5.4-6.0)	124.3 (77.1-157.0)	-	C	DA	Yes					Neutral	14 d	A, I
Intervention												~47.1 (8.8)	Sucrose	High sucrose diet	63:26:15			
Control												~10.5 (2.4)	Fat	High fat diet	53:31:16			
Yudkin et al. 1972	11 (11 M, 0 W)	29 (21-44)	-	-	OP, England	-	-	-	C	DA	No					Neutral		I
Intervention												441 (~53)	Sucrose	Substitute sugar for starch from regular diet	~59:30:10		2 wk	
Control												148 (~18)	Starch	Regular diet	~58:30:10		1 wk	
Addition Studies (Hypercaloric comparison)																		
Fruit																		
Basu et al. 2010 (BB)		49.8 (15.3)	-	37.8 (11.2)	OP, USA	-	-	-	P	Supp	Yes				NR	Neutral	8 wk	A, I
Intervention	25 MetS (2 M, 23 W)	51.5 (15.0)		38.1 (7.5)								30 (~6) [n]	Fruit	Freeze dried blueberry beverage				
Control	23 MetS (2 M, 21 W)	48.0 (15.8)		37.5 (14.4)									Water	Water				
Basu et al. 2010 (SB)		46.7 (16.6)	102.3 kg (9.5)	37.8 (8.9)	OP, USA	5.1 (0.7)	-	-	P	Supp	Yes					Neutral	8 wk	A, I
Intervention	15 MetS (0 M, 15 W)	48.0 (20.5)	102.0 kg (11.6)	39.0 (7.7)		5.2 (0.8)						~14.6 (~3.2) [g]	Fruit	Freeze dried strawberry beverage	45:37:13			
Control	12 MetS (2 M, 10 W)	45.0 (10.4)	102.7 kg (6.6)	36.4 (10.4)		5.0 (0.7)							Water	Water	46:35:15			
Cressey et al. 2014 (DM2)	15 DM2	52.8 (5.23			OP, Thailand			-	C	Supp	No					Positive		A
Intervention			61.8 kg (13.3)	25.8 (4.7)		7.3 (2.5)	97.2 (117.4)					~18.1 (~3.3) [f]	Fruit	1 banana/d (250 g)	~57:25:18		4 wk	
Control			62.3 kg (13.0)	25.9 (4.6)		6.7 (1.7)	117.4 (122.2)						Diet alone	No banana	~53:29:19		8 wk	
Cressey et al. 2014 (H)		36.4 (12.0)	51.3 kg (6.1)	20.2 (2.7)	OP, Thailand	4.6 (0.5)	-	-	P	Supp	Yes					Positive		A
Intervention	7 H	41 (13.7)	54.5 kg (5.6)	21.5 (2.9)		4.7 (0.4)						~36.2 (~9.2) [f]	Fruit	2 banana/d (500 g)	~65:21:14		3 mo	
Control	5 H	30 (5.2)	46.9 kg (3.8)	18.4 (1.0)		4.5 (0.6)							Diet alone	No banana	~52:30:19		3 mo	
Cressey et al. 2014 (HCL HD)	15 HCL	43.1 (7.5)			OP, Thailand			-	C	Supp	No					Positive		A
Intervention			59.6 kg (11.8)	24.0 (3.94)		5.7 (0.4)	22.9 (14.6)					~36.2 (~6.3) [f]	Fruit	2 banana/d (500 g)	~57:26:17		12 wk	
Control			59.3 kg (12.1)	24.1 (4.2)		5.1 (0.4)	19.4 (11.1)						Diet alone	No banana	~49:34:17		8 wk	
Cressey et al. 2014 (HCL LD)	15 HCL	44.8 (10.3)			OP, Thailand			-	C	Supp	No					Positive		A
Intervention			61.5 kg (10.9)	24.8 (4.0)		5.5 (0.4)	21.5 (11.1)					~18.1 (~3.5) [f]	Fruit	1 banana/d (250 g)	~56:27:17		12 wk	
Control			61.5 kg (10.7)	24.8 (4.3)		5.1 (0.5)	29.9 (13.9)						Diet alone	No banana	~47:35:17		8 wk	
Ellis et al. 2011	12 OW/OB	50.9 (15.0)	86.6 kg (12.9)	29.2 (2.3)	OP, USA	-	-	-	C	Supp	No				NR	Positive		A, I
Intervention												~5.9 (~1.2) [f]	Fruit	Freeze dried strawberry beverage equivalent to ~100 g/d fresh strawberries			6 wk	
Control													Diet alone	No beverage			7 d	
Mitsou et al. 2011	22 OW/OB (0 M, 22 W)	31	74.2 kg (9.4)	27.6 (2.7)	OP, Greece	5.1 (0.4)	53.8 (14.6)	-	P	Supp	Yes				NR	Positive	60 d	A, I
Intervention	12 OW/OB (0 M, 12 W)		74.6 kg (11.4)	27.6 (2.9)		5.1 (0.5)	53.5 (15.3)					~17.4 (~3.5) [f]	Fruit	240 g/d Dessert Banana				
Control	10 OW/OB 0 M, 10 W)		73.8 kg (6.9)	27.5 (2.5)		5.0 (0.4)	54.2 (14.6)						Water	Water				
Puglisi et al. 2008		56.3 (4.6)	78.6 kg (16.0)	27.7 (3.8)	OP, USA	5.4 (0.6)	-	-	P	Supp	Yes					Positive	6 wk	I
Intervention	10 H (5 M, 5 W)	57.8 (5.2)	78.4 kg (15.9)	27.5 (3.8)		5.22 (0.41)						~49.7 (~9.9) [f]	Fruit	Walking + 1 cup raisins/d	57:29:15			
Control	12 H (6 M, 6 W)	55.0 (3.8)	78.7 kg (16.8)	27.9 (3.9)		5.52 (0.7)							Diet alone	Walking	43:40:16			
Ravn-Haren et al. 2013	23 H (9 M, 14 W)	36.2 (17.9)	-	22.3 (2.6)	OP, Denmark	-	40.6 (28.2)	-	C	Supp	Yes				NR	Positive	4 wk	A
Intervention												~51 (~10) [l]	Fruit	Polyphenolic and pectin restricted diet with whole apples equivalent to ~550 g/d				
Control													Diet alone	Polyphenolic and pectin restricted diet with apple pomace				
Fruit Juice																		
Banini et al. 2006			-		OP, USA				P	Supp	Yes				~50:31:19	Positive	28 d	A, I
Intervention	8 H	50 (13)		29.3 (1.4)		5.0 (0.4)	86.8 (88.4)	5.5 (0.3)				~17[l]	fruit	Muscadine grape juice				
Control	15 H	25 (75)		27.5 (1.4)		4.9 (0.8)	75.7 (43.0)	5.5 (1.2)					Diet alone	No beverage				
Hollis et al. 2009		25 (8.1)	78.3 kg (9.3)	27.2 (1.5)	OP, USA	4.5 (0.6)	81.5 (70.1)	-	P	Supp	Yes					Positive	12 wk	I
Intervention	25 OW	22 (4)	79.0 kg (8.4)	27.0 (1.6)		4.4 (0.6)	83.8 (90.4)					82 (~17)	fruit	Concord grape juice	~50:35:15			
Control	25 OW	28 (10)	77.6 kg (10.3)	27.3 (1.5)		4.7 (0.5)	79.2 (43.0)						Diet alone	No beverage	~50:34:16			

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control[a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Ravn-Haren et al. 2013	23 H (9 M, 14 W)	36.2 (17.9)	-	22.3 (2.6)	OP, Denmark	-	40.6 (28.2)	-	C	Supp	Yes				NR	Positive	4 wk	A
Intervention												~61 (~12.2) [m]	fruit	Polyphenolic and pectin restricted diet with clear or cloudy apple juice (~500 mL/d)				
Control													Diet alone	Polyphenolic and pectin restricted diet				
Fruit Drinks																		
Ellis et al. 2011	12 OW/OB	50.9 (15.0)	86.6 kg (12.9)	29.2 (2.3)	OP, USA	-	-	-	C	Supp	No				NR	Positive		A, I
Intervention												25.9 (~5) total sugar	Sucrose	Strawberry flavored beverage			6 wk	
Control													Diet alone	No beverage			7 d	
Hollis et al. 2009		27 (9)	78.3 kg (10.4)	27.1 (1.5)	OP, USA	4.7 (0.7)	78.9 (36.7)	-	P	Supp	Yes					Positive	12 wk	I
Intervention	26 OW	26 (9)	79.0 kg (10.7)	27.0 (1.5)		4.7 (0.8)	78.6 (30.3)					82 (~17)	sucrose	Grape flavored drink	~48:36:16			
Control	25 OW	28 (10)	77.6 kg (10.3)	27.3 (1.5)		4.7 (0.5)	79.2 (43.0)						Diet alone	No beverage	~50:34:16			
Mitsou et al. 2011	20 OW/OB (0 M, 22 W)	31	71.3 kg (7.6)	26.7 (2.3)	OP, Greece	5.0 (0.3)	48.7 (20.3)	-	P	Supp	Yes				NR	Positive	60 d	A, I
Intervention	10 OW/OB (0 M, 10 W)		68.8 kg (7.7)	25.8 (1.8)		5.0 (0.3)	43.1 (24.3)					50.6 (~10)	Sucrose	Banana flavored drink				
Control	10 OW/OB (0 M, 10 W)		73.8 kg (6.9)	27.5 (2.5)		5.0 (0.4)	54.2 (14.6)						Water	Water				
SSBs																		
Abdel-Sayed et al. 2008	6 H (6 M, 0 W)	24.7 (3.1)	78.3 kg (7.4)	23.1 (2.2)	OP, Switzerland	-	-	-	C	Met	Yes	234 (~47)				Positive	7 d	A
Intervention													Fructose	Fructose dissolved in water	67:22:11			
Control													Diet alone	No beverage	55:30:15			
Beck-Nielsen et al. 1980	10 H	(21-35)		-	OP, Denmark	5.2	21.2	-	P	Supp	Yes				44:38:18	Positive	7 d	A, I
Intervention	8 H		61.5 kg (9.9)			5.2 (0.6)	27.8 (19.6)					250 (~33)	Fructose	Fructose SSB				
Control	2 H		57 kg			5.4	34.7						Diet alone	No beverage				
Koopman et al. 2014		22.2 (2.7)	78.6 kg (8.0)	22.3 (1.7)	OP, Netherlands	4.8 (0.2)	48.0 (24.1)	-	P	Supp	Yes					Positive	6 wk	A
Intervention	15 H (15 M , 0 W)	21.9 (2.6)	79.9 kg (8.3)	22.2 (1.5)		4.8 (0.2)	48.0 (24.1)					~237 (~27)	Sucrose	Sucrose SSB	~57:28:12			
Control	5 H (5 M, 0 W)	23.0 (3.1)	76.6 kg (7.7)	22.6 (2.3)		4.8 (0.4)	45.0 (13.4)						Diet alone	No beverage				
Lê et al. 2006	7 H (7 M, 0 W)	24.7 (3.4)	69.3 kg (6.9)	(19-25)	OP, Switzerland	4.9 (0.3)	50.4 (9.5)	-	C	Supp	No				55:30:15	Positive	4 wk	A
Intervention												~104 (18)	Fructose	20% fructose solution				
Control												<20	Diet alone	No beverage				
Lê et al. 2009 (ODM2)	16 ODM2 (16 M, 0 W)	24.7 (5.2)	-	-	OP, Switzerland	-	-	-	C	Met	Yes	~220 (35)			55:30:15	Positive	7 d	A
Intervention													Fructose	20% fructose solution				
Control													Diet alone	No beverage				
Maersk et al. 2012	35 OW/OB (14 M, 21 W)	39 (7)	97.3 kg (16.5)	32.1 (3.8)	OP, Denmark	5.4 (0.6)	72.5 (42.5)	-	P	Supp	Yes				NR	Positive	6 mo	A, I
Intervention	10 OW/OB (6 M, 4 W)	39 (6)	97.8 kg (12.5)	31.3 (2.9)		5.4 (0.6)	54.3 (26.7)					~106 (~21)	Sucrose	Cola				
Control	25 OW/ OB (8 M, 17 W)	39 (8)	97.1 kg (18.1)	32.5 (4.2)		5.4 (0.6)	79.8 (45.8)						Sweetener, Water	Diet beverage, water				
Majid et al. 2013		20.1 (0.8)	-	-	IP, Pakistan	5.0 (0.3)	-	-	P	Met	Yes				NR	Positive	4 wk	A
Intervention	32 H (32 M, 0 W)	20.1 (0.1)				5.0 (0.1)						70 (~11)	Honey	Honey dissolved in tap water				
Control	31 H (31 M, 0 W)	20.0 (0.2)				4.9 (0.1)							Diet Alone	No beverage				
Silbernagel et al. 2011	10 (7 M, 3 W)	32.8 (9.3)	80.3 kg (9.1)	25.5 (2.2)	OP, Germany	4.8 (0.3)	45.4 (36.7)	-	C	Supp	Yes				50:35:15	Positive		A
Intervention												150 (~22)	Fructose	Fructose dissolved in water			4 wk	
Control													Diet alone	No beverage			2 wk	
Sobrecases et al. 2010 (XX)	8 H (8 M, 0 W)	24.8 (3.2)	-	(19-25)	OP, Switzerland	-	-	-	C	Supp	No				55:30:15	Positive	7 d	A
Intervention												~214 (35)	Fructose	Fructose SSB				
Control													Diet alone	No beverage				
Stanhope et al. 2011 (AJCN)	17 OW/ OB (9 M, 8 W)	52.5 (9.3)	85.8 kg (10.7)	29.3 (2.6)	IP/ OP, USA	4.9 (0.2)	99.2 (45.0)	-	C	Met/ Supp	No				~55:30:15	Positive		A
Intervention												158 (25)	Fructose	Fructose SSB			8 wk	
Control													Diet alone	No beverage			2 wk	
Stanhope et al. 2011 (JCEM FRU)	16 (9 M, 7 W)	28.0 (6.8)	76.8 kg (10.6)	25.4 (3.8)	IP/OP, USA	4.9 (0.4)	102.8 (86.4)	-	C	Met/ Supp	No	~125 (25)			55:30:15	Positive	2 wk	A
Intervention													Fructose	Fructose SSB				
Control													Diet alone	No Beverage				

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control [a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet [c]	Energy Balance [d]	Follow-Up	Funding Sources [e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Stanhope et al. 2011 (JCEM HFCS)	16 (9 M, 7 W)	27.8 (7.60	74.3 kg (14.9)	24.9 (4.8)	IP/OP, USA	4.9 (0.4)	89.1 (31.6)	-	C	Met/ Supp	No	~125 (25)			55:30:15	Positive	2 wk	A
Intervention													HFCS	HFCS SSB				
Control													Diet alone	No Beverage				
Sweetened Chocolate																		
Njike et al. 2011	39 OW (6 M, 33 W)	52.2 (10.6)			OP, USA		-	-	C	Supp	Yes			Sucrose		Positive	6 wk	A, I
Intervention			81.7 kg (10.7)	30.4 (3.4)		5.1 (0.5)						Sugar-sweetened cocoa, 91 (~18) ; Placebo, 110 (~26) [n]	Sucrose	Sugar-sweetened hot cocoa beverage, placebo beverage	~55:30:15			
Control			81.3 kg (10.9)	30.2 (3.4)		5.1 (0.4)							Sweetener	Sugar-free hot cocoa beverage	~47:35:17			
Baked Goods and Sweets																		
Schwingshandl et al. 1994	24 DM1 (11 M, 13 W)	15.5 (5.5)	-		OP, Australia	-	-	8.7 (1.5)	P	DA	No			Sucrose		Positive		NR
Intervention	11 DM1 (8 M, 3 W)	15.0 (5.4)		20.2 (2.7)				8.5 (1.4)				~25 (5)	Sucrose	≤ 5% E as sucrose incorporated into cakes, ice-cream and snacks	49:36:16		83 d (42-127)	
Control	13 DM1 (3 M, 10 W)	16.0 (5.7)		21.2 (4.5)				8.8 (1.8)					Diet alone	Sucrose free diet	48:35:16		77 d (41-103)	
Added Sweeteners																		
Bahrami et al. 2009	48 DM2 (13 M, 35 W)	57.2 (8.4)	70.8 kg (10.6)	-	OP, Iran	8.0 (2.5)	-	7.1 (1.2)	P	Supp	Yes	~125 (~33)				Positive	8 wk	A
Intervention	25 DM2		71.3 kg (12.7)			8.5 (2.4)		7.1 (1.2)					Honey	Honey added to diet	64:23:15			
Control	23 DM2		70.3 kg (8.1)			7.5 (2.5)		7.1 (1.3)					Diet alone	Regular diet	60:22:15			
Colagiuri et al. 1989	9 DM2 (8 M, 1 W)	66 (5)	70.3 kg (8.1)	26.4 (2.1)	OP, Australia	5.7 (3.3)	-	7.2 (1.1)	C	Supp	No				NR	Positive	6 wk	A, I
Intervention												45 (~9)	Sucrose	Sucrose sachets added to beverages and meals				
Control													Sweetener	Aspartame sachets added to beverages and meals				
Enginyurt et al. 2017 (DM)	32 DM2 (16 M, 16 W)	(18-80)	-	-	OP, Turkey	-	-		P	Supp	Yes				NR	Positive	4 mo	NR
Intervention								6.6 (0.8)				5,10,15	Honey	Honey added to diet at 5,15, 25 g				
Control								7.09 (0.91)					Diet alone	Regular diet				
Enginyurt et al. 2017 (H)	32 H (16 M, 16 W)	(18-80)	-	-	OP, Turkey	-	-		P	Supp	Yes				NR	Positive	4 mo	NR
Intervention								5.4 (0.3)				5,10,15	Honey	Honey added to diet at 5,15, 25 g				
Control								5.15 (0.35)					Diet alone	Regular diet				
Mixed Sources																		
Raben et al. 2011		35.4 (10.6)	82.4 kg (9.0)	28.2 (2.5)	OP, Denmark	4.7 (0.3)	39.5 (17.7)	-	P	Supp	Yes					Positive	10 wk	A, I
Intervention	12 OW	35.3 (9.7)	84.5 kg (8.3)	28.7 (2.4)		4.7 (0.4)	41.8 (18.4)					180 (27)	Sucrose	Sucrose containing food and beverages	56:29:11			
Control	11 OW	35.5 (11.9)	80.1 kg (9.6)	27.6 (2.7)		4.8 (0.3)	37.0 (17.6)					27 (5)	Sweetener	Artificially sweetened food and beverages	47:32:15			
Subtraction Studies (Hypocaloric comparison)																		
SSBs																		
Campos et al. 2015 (G1)	12 OW/OB (3 M, 9 W)	28.3 (6.5)	-	-	OP, Switzerland	5.1 (0.5)	85.8 (40.6)	-	P	Supp	Yes					Negative	12 wk	A
Intervention	6 OW/OB					4.9 (0.5)	104.9 (42.5)						Sweetener Sucrose, HFCS	Replace SSB with ASB Habitual SSB consumption (≥ 2 SSB/d)	~46:38:16			
Control	6 OW/OB					5.2 (0.5)	66.7 (30.6)					86.8 (~15)			~51:34:15			

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control [a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet[c]	Energy Balance [d]	Follow-Up	Funding Sources [e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Campos et al. 2015 (G2)	15 OW/OB (11 M, 4 W)	29.1 (6.9)	-	-	OP, Switzerland	5.5 (0.6)	133.7 (54.5)	-	P	Supp	Yes					Negative	12 wk	A
Intervention	7 OW/OB					5.2 (0.5)	127.1 (60.6)						Sweetener	Replace SSB with ASB	~46:38:16			
Control	8 OW/OB					5.7 (0.5)	140.3 (51.4)					86.8 (~15)	Sucrose, HFCS	Habitual SSB consumption (≥ 2 SSB/d)	~51:34:15			
Hernandez-Cordero et al. 2014	240 OW/OB (0 M, 240 W)				OP, Mexico	5.0 (0.2)	-	5.8 (0.1)	P	Supp	Yes				NR	Negative	9 mo	I
Intervention	120 OW/OB (0 M, 120 W)	33.5 (6.7)	76.9 kg (3.3)	31.0 (1.1)		5.0 (0.2)		5.8 (0.1)					Water	Substitute water for SSBs, general recommendations for healthy eating				
Control	120 OW/OB (0 M, 120 W)	33.4 (6.7)	76.0 kg (3.3)	31.0 (1.1)		5.0 (0.2)		5.8 (0.1)				~73 (19.3)	Sucrose, HFCS	Habitual SSB consumption (≥250 kcal/d), general recommendations for healthy eating				
Tate et al. 2012					OP, USA	5.1 (0.9)			P	Supp, DA	Yes				NR	Negative	6 mo	I
Intervention	213 OW/ OB (35 M, 178 W)	42.2 (10.9)	99.6 kg (18.5)	35.9 (5.7)		5.1 (1.0)	-	-				~33.7 (~8.7)	Sweetener, water	Diet beverage, Water				
Control	105 OW/OB (15 M, 90 W)	41.6 (10.4)	102.6 kg (18.3)	36.8 (6.2)		4.9 (0.6)	-	-				~55.7 (~13.8)	Sucrose, HFCS	Habitual SSB consumption (≥280 kcal/d)				
Mixed Sources																		
Friedman et al. 1970	6 HTG (6 M, 0 W)	45 (4.2)	103.2 kg (16.7)	-	OP, USA	-	-	-	C	DA	No					Negative		A
Intervention												~24 (~6) [m]	No sucrose	Avoid sucrose containing foods from habitual diet	25:45:30		60 d	
Control												~58 (~10) [m]	Sucrose	Habitual diet	29:39:32		7 d	
Ad Libitum Studies (Free feeding comparison)																		
Baked Goods and Sweets																		
Chantelau et al. 1985	10 DM1 (2 M, 8 W)	(25-43)	66.7 kg (7.6)	26.4 (2.1)	OP, Germany	-	-	7.6 (0.4)	C		Yes				52:26:22	Positive	4 wk	NR
Intervention										DA		24 (~5)	Sucrose	Ad libitum sucrose-containing food consumption; sucrose-containing soft drinks discouraged				
Control										Supp			Sweetener	Ad libitum sodium cyclamate tablets and liquids				
Mixed Sources																		
Huttunen et al. 1976	127 H	(13-55)	-	-	OP, Finland	-	-	-	P	Supp	Partial [n]				-	Neutral	18 mo	NR
Intervention	68 H											~72 (~14)	Fructose, sucrose	Ad libitum fructose and sucrose containing foods				
Control	48 H												Sweetener	Ad libitum xylitol containing foods with avoidance of sweet fruits and sucrose containing products				
Markey et al. 2015	50 H (16 M, 34 W)	31.3 (9.6)	69.8 kg (11.4)	24.0 (3.3)	OP, UK	4.9 (0.4)	31.0 (14.3)	-	C	Supp	Yes					Neutral	8 wk	I
Intervention	22 H (7 M, 15 W)	31.6 (10.2)	70.5 kg (13.1)	24.2 (3.3)		5.0 (0.5)	34.0 (16.9)					62 (~12) [o]	Sucose	Exchange ≥1 food portion and ≥1 beverage per day from habitual diet with sugar containing products	54:30:14			
Control	28 (9 M, 19 W)	31.1 (9.2)	69.3 kg (10.1)	23.9 (3.4)		4.8 (0.4)	29.4 (14.7)						Sweetener	Exchange ≥1 food portion and ≥1 beverage per day from habitual diet with sugar reformulated products	48:33:15			
Poppitt et al. 2002					OP, UK	5.7 (0.6)	-	-	P	Partial Met	Yes					Neutral	6 mo	A, I
Intervention	14 MetS (6 M, 8 W)	45.9 (5.0)	89.3 kg (15.7)	30.9 (3.0)		5.6 (0.5)						~165.4 (29) [p]	Sucrose	Ad libitum low-fat SCHO diet	~59:20:22			
Control	25 MetS (6 M, 19 W)	46.1 (5.4)	91.3 kg (9.2)	32.7 (35.2)		5.7 (0.7)							Starch, Mixed comparator	Ad libitum low fat CCHO diet, ad libitum habitual diet	Starch, ~50:26:24; Mixed, ~48:31:21			

Supplementary Table 2. (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Baseline			Design	Feeding Control [a]	Randomization	Fructose-Containing Sugars Dosage, g/d (% E)[b]	Intervention or comparator	Food source	Diet [c]	Energy Balance [d]	Follow-Up	Funding Sources [e]
						FBG, mmol/L (SD or range)	FBI, pmol/L (SD or range)	HbA1c, % (SD)										
Raben et al. 2000 (PO)	8 PO (0 M, 8 W)	40 (11.3)	65.4 kg (3.4)	23.5 (1.4)	OP, Denmark			-	C	Met	Yes					Neutral	2 wk	A, I
Intervention						4.6 (0.2)	33 (18)					~156.7 (23)	Sucrose	Ad libitum sucrose diet	59:28:13			
Control						4.8 (0.3)	32 (21)						Starch, fat	Ad libitum starch diet, ad libitum fat diet	Starch, 59:28:13; Fat, 41:46:13			
Raben et al. 2000 (C)	10 H (0 M, 10 W)	38 (9.5)	62.1 kg (4.1)	22.9 (0.9)	OP, Denmark			-	C	Met	Yes					Neutral	2 wk	A, I
Intervention						4.9 (0.1)	32 (13)					~141.6 (23)	Sucrose	Ad libitum sucrose diet	59:28:13			
Control						4.8 (0.4)	34 (23)						Starch, fat	Ad libitum starch diet, ad libitum fat diet	Starch, 59:28:13; Fat, 41:46:13			
Saris et al. 2000					OP, Netherlands	5.4 (0.8)	84.5 (35.2)	-	P	Partial Met	Yes					Neutral	6 mo	A, I
Intervention	76 OW/OB (36 M, 40 W)	41 (9)	90.7 kg (12.7)	30.9 (2.8)								~183 (~29.5) [p]	Sucrose	Ad libitum Low-fat high SCHO diet	~56:26:16			
Control	160 OW/OB (80 M, 80 W)	38 (9)	88.7 kg (12.3)	30.3 (2.7)								Starch, ~ 105.7 (~18.8); Mixed, ~132.5 (~21.4) [p]	Starch, Mixed comparator	Ad libitum low-fat high CCHO diet, Ad libitum control diet	Starch, ~52:28:18 ; Mixed, ~46:37:18			

FBG=fasting blood glucose; FBI=fasting blood insulin; A= agency; AD=Adolescent; ADA= American Diabetes Association; ASB= artificially sweetened beverage; BB=blueberries; bw=body weight; C= controls; CAD= coronary artery disease; cal=calories; CCHO= complex carbohydrate; CG= control group; CHO=carbohydrate; CKD= chronic kidney disease; CND= chronic neurological disease; d=days; DBW= desirable body weight; DM1= Diabetes Mellitus Type 1; DA= dietary advice; DM2=Diabetes Mellitus Type 2; E=energy; EXP 1= experiment 1; EXP 2= experiment 2; G1=group 1; G2=group2; HCL= hypercholesterolemic; HD=high dose; HFCS= high fructose corn syrup; HI=hyperinsulinemic; HLP= hyperlipidemia; HTG = hypertriglyceridemia; HTN=hypertension; I= industry; IBW= ideal body weight; IGT= impaired glucose tolerance; kg=kilograms; M=men; mo=months; MD=moderate dose; OP=outpatient; Met=metabolic; MetS=metabolic syndrome criteria; MRW= mean relative weight; NGT=normal glucose tolerance; NR= not reported; OB= obese; OC= oral contraceptive users; ODM2 = offspring of parent with Type 2 Diabetes; OW= overweight; P1= protocol 1; P2= protocol 2; PCOS= polycystic ovarian syndrome; PO= post-obese; PP=pre-pubertal; RBW= relative body weight; SB= strawberries; SCHO=simple carbohydrates; SG= study group; SSB=sugars-sweetened beverage; Supp=supplemented; TEI= total energy intake; W= women; wk=weeks

[a] Metabolic feeding control included provision of all study foods, supplement feeding control included provision of study supplements only, and dietary advice included dietary counseling without the provision of any dietary foods or supplements.

[b] Doses preceded by "~" represent approximate amounts calculated on the basis of average body weight or energy intake reported by participants. In the absence of this data, an average of 70 kg body weight or 2000 kcal/d was assumed.

[c] Total energy intake in the form of carbohydrate:fat:protein

[d] Positive energy balance included interventions designed to consume excess calories on top of a baseline diet. Negative energy balance included interventions designed to create a caloric deficit compared to the baseline diet. Neutral energy balance included interventions designed to continue habitual caloric intake.

[e] Agency funding included government, not-for profit health agencies or University sources.

[f] Fructose-containing sugars dose estimated based on data from United States Department of Agriculture (USDA) nutrient database

[g] Fructose-containing sugars dose estimated based on data from Finland National Food Composition Database

[h] Fructose-containing sugars was given at 2 different doses.

[i] Although honey roasted peanuts were provided as the intervention, sucrose was the main sugar used to sweeten the study products.

[j] Represents estimated sugar intake excluding underreporters

[k] Values reported as medians and inter-quartile ranges (IQR)

[l] Fructose-containing sugars dose estimated based on the carbohydrate difference between the control diet (no juice) and the treatment diet (muscadine grape juice).

[m] Fructose-containing sugars dose estimated from total sugars used in study products

[n] Half of the participants were assigned to groups according to personal preference, while the other half of the participants were randomly allocated

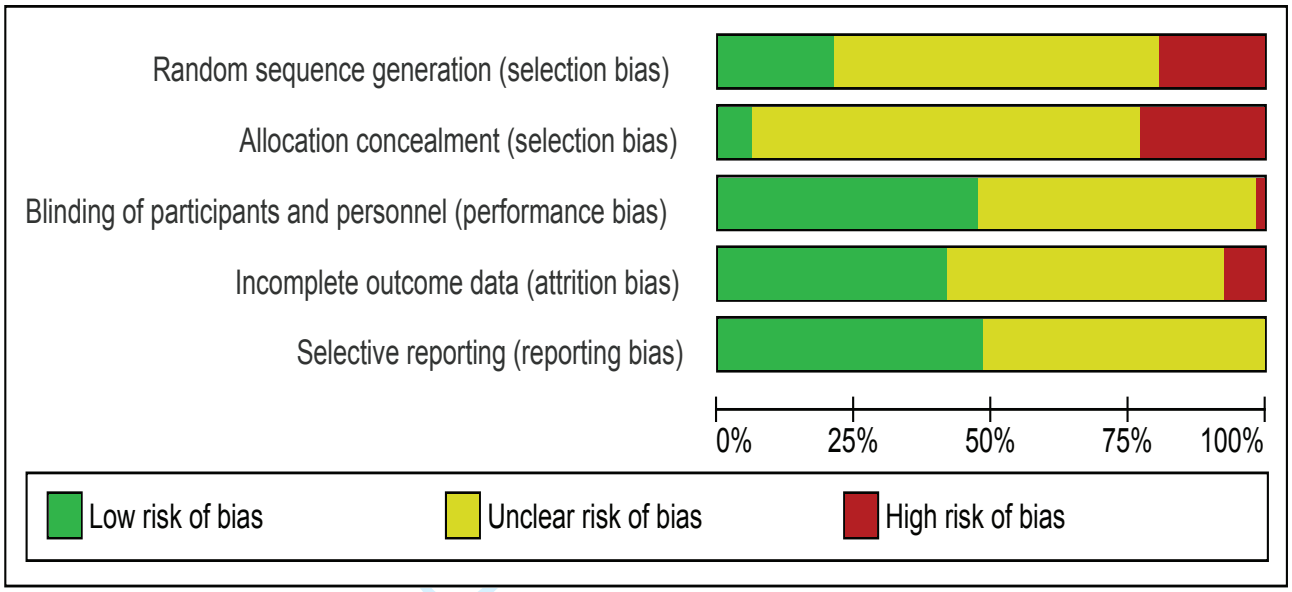
[o] Fructose-containing sugars dose estimated from non-milk extrinsic sugar intake

[p] Fructose-containing sugars dose estimated from simple carbohydrate intake

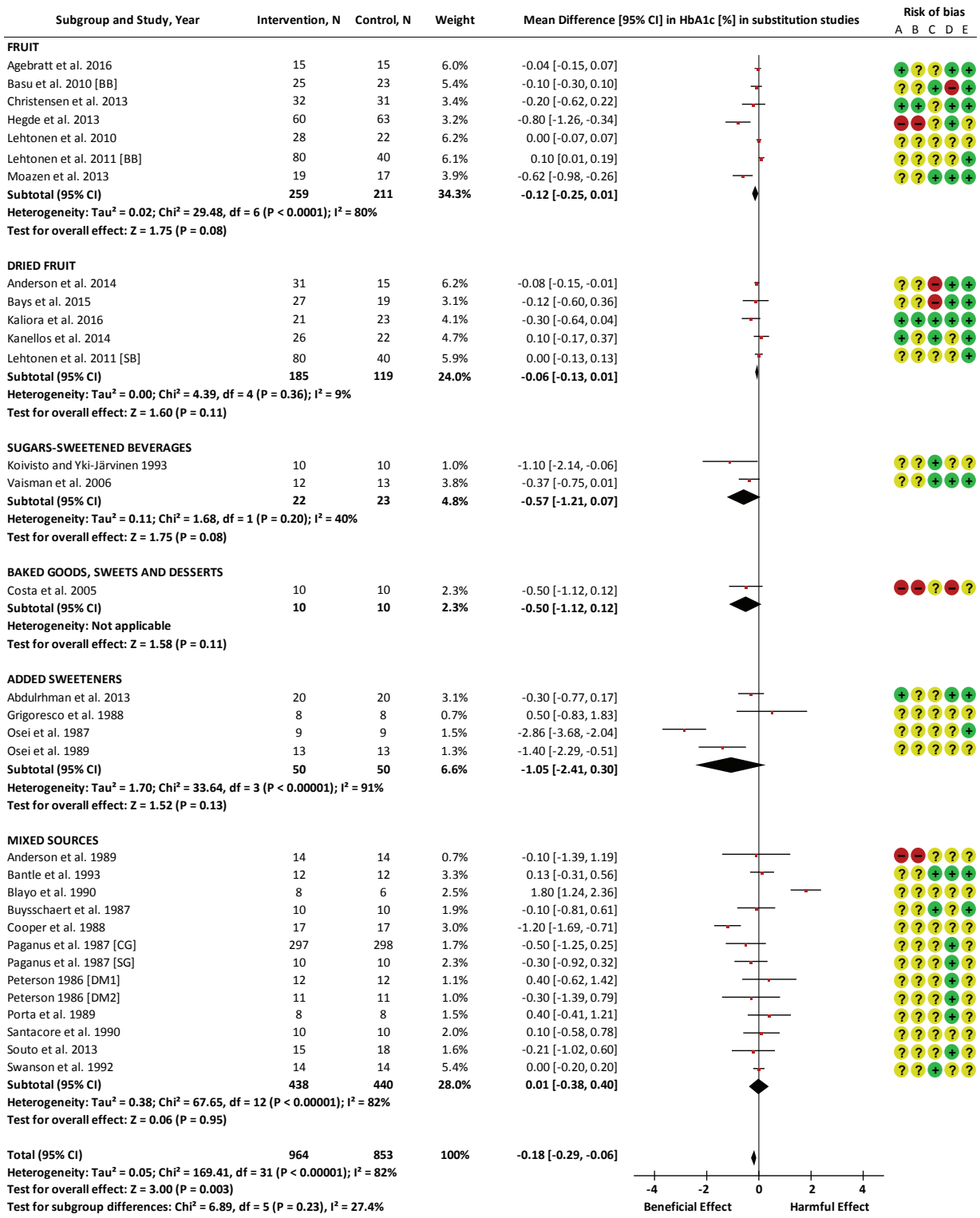
Supplementary Table 3. Select sensitivity analyses in which the systematic removal of an individual study altered the significance of the effect estimate or the evidence for heterogeneity.

Removal of	Intervention N	Control N	Mean Difference MD	95% CI	*P*-value	Heterogeneity I^2	*P*-value
Fasting Blood Glucose							
Addition Studies							
Puglisi et al. 2008	10	12	0.08	[0.00, 0.15]	0.04	71%	<0.0001
Ellis et al. 2011	12	12	0.08	[0.00, 0.15]	0.04	71%	<0.0001
Abdel-Sayed et al. 2008	6	6	0.08	[0.00, 0.15]	0.04	71%	<0.0001
Njike et al. 20011	39	39	0.08	[0.01, 0.16]	0.03	69%	<0.0001
Bahrami et al. 2009	25	23	0.08	[0.01, 0.15]	0.03	69%	<0.0001
Majid et al. 2013	32	31	0.09	[0.02, 0.16]	0.02	67%	<0.0001
Subtraction Studies							
Campos et al. 2015 [G2]	7	8	-0.02	[-0.11, 0.07]	0.63	0%	0.78
Tate et al. 2012	213	105	0.20	[0.00, 0.40]	0.05	32%	0.23
Fasting Blood Insulin							
Substitution studies							
Beck-Nielsen et al. 1980	15	15	2.60	[0.09, 5.11]	0.04	59%	<0.0001
Maersk et al. 2012	10	12	2.83	[0.35, 5.31]	0.03	57%	<0.0001
Koh et al. 1988 - NGT	9	9	2.63	[0.24, 5.03]	0.03	55%	<0.0001
Subtraction Studies							
Campos et al. 2015 (G2)	7	8	-39.54	[-75.02, -4.06]	0.03	1%	0.31
Ad Libitum Studies							
Raben et al. 2000 (c)	8	8	5.72	[-1.55. 12.99]	0.12	0 %	0.51

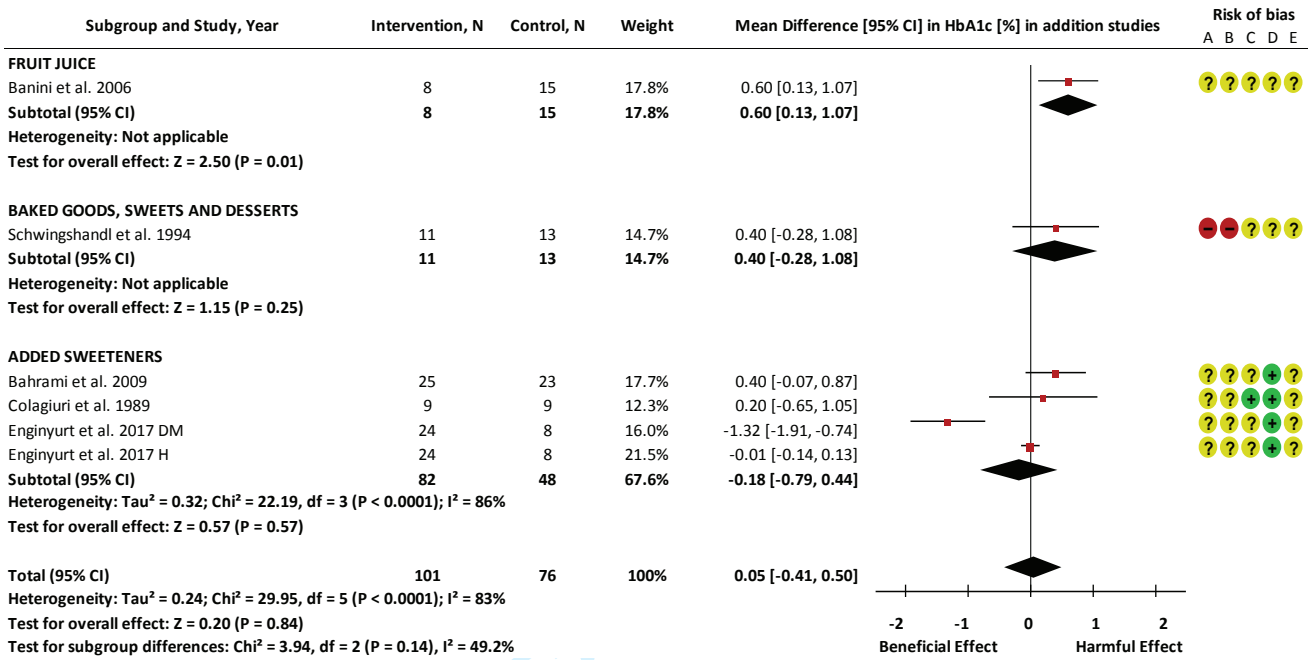
DM= diabetes mellitus; G2= Group 2; ODM2=offspring of people with type 2 diabetes. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ and quantified by I^2, levels ≥ 50 % represent substantial heterogeneity. The residual I^2 value indicates the interstudy heterogeneity unexplained by the removal of each study.



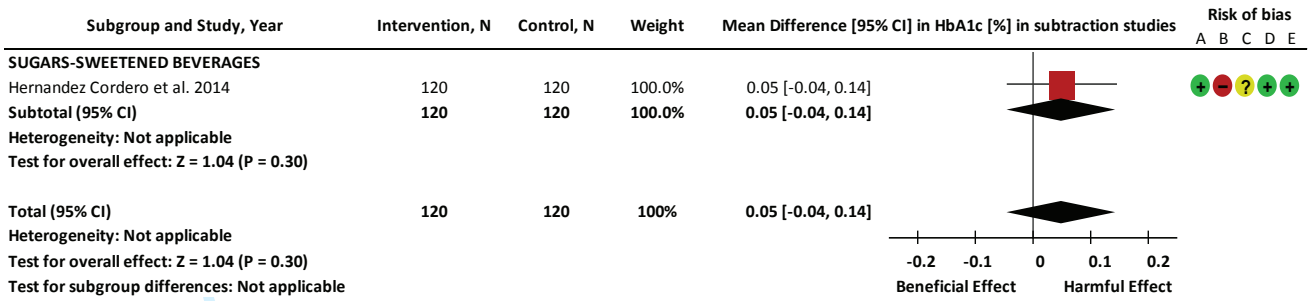
Supplementary Figure 1. Risk of bias summary for the effect of food sources of fructose-containing sugars on glycemic control. Colored bars represent the proportion of studies assessed as low (green), unclear (yellow) or high (red) risk of bias for the 5 domains of bias above according to criteria set by the Cochrane Risk of Bias tool in the 117 included unique studies.



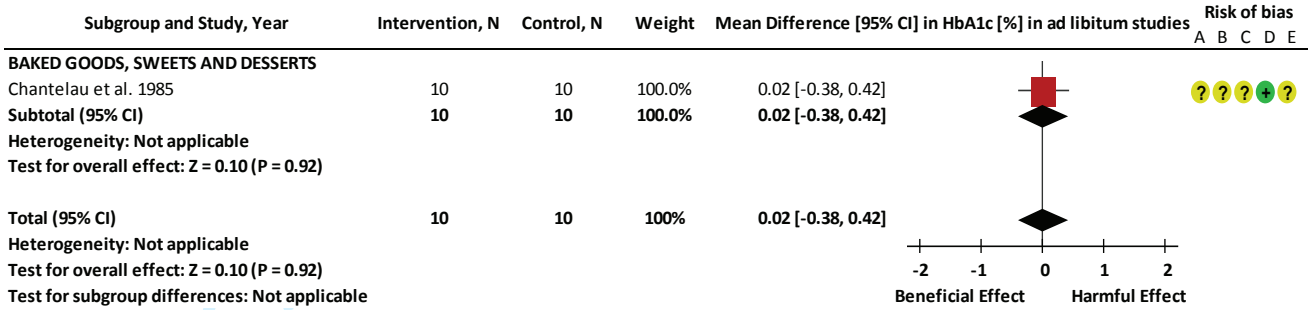
Supplementary Figure 2. Forest plot for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on HbA1c. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. CG= control group; SG= study group; df= degrees of freedom; DM1= type 1 diabetes mellitus; DM2= type 2 diabetes mellitus; EXP=experiment; HbA1c= hemoglobin A1c; N= number of participants. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with random effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represented substantial heterogeneity.



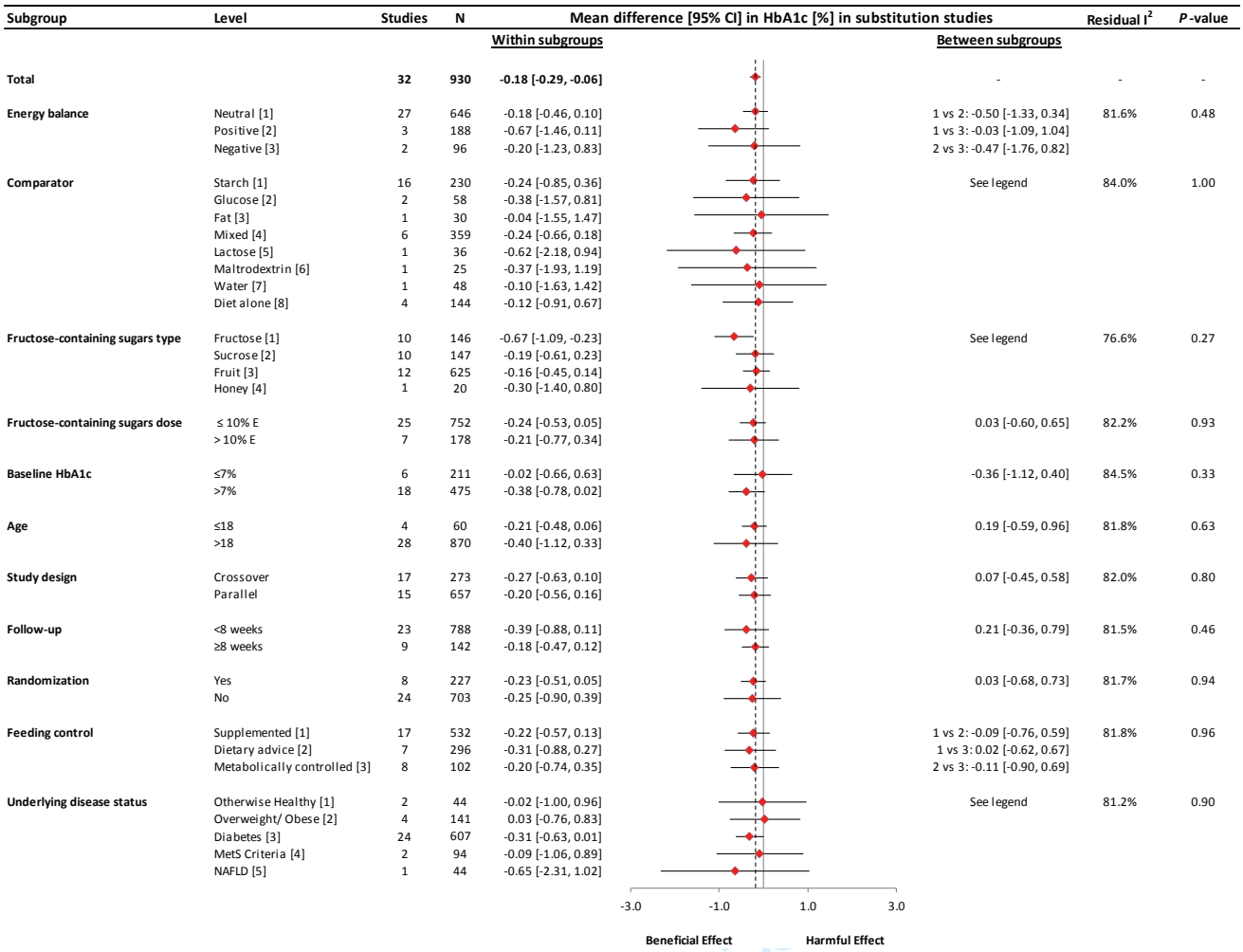
Supplementary Figure 3. Forest plot for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on HbA1c. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. BB= blueberries; HbA1c= hemoglobin A1c; N= number of participants; DM=diabetes mellitus; H=healthy. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with random effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represented substantial heterogeneity.



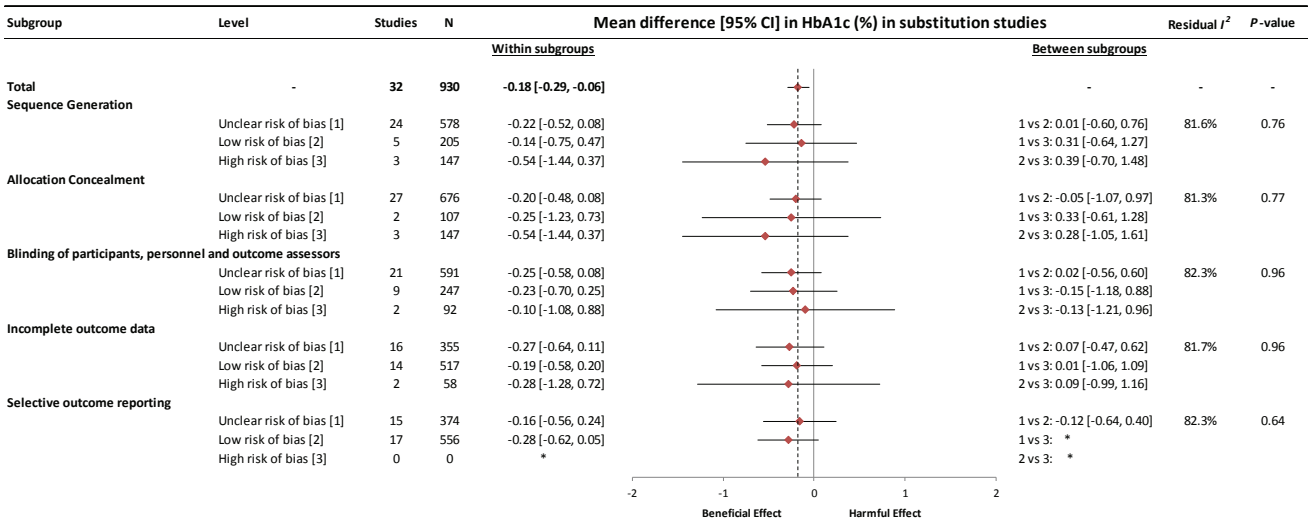
Supplementary Figure 4. Forest plot for subtraction studies investigating the effect of removing calories from the diet in the form of food sources of fructose-containing sugars on HbA1c. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. HbA1c= hemoglobin A1c; N= number of participants. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with fixed effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represented substantial heterogeneity.



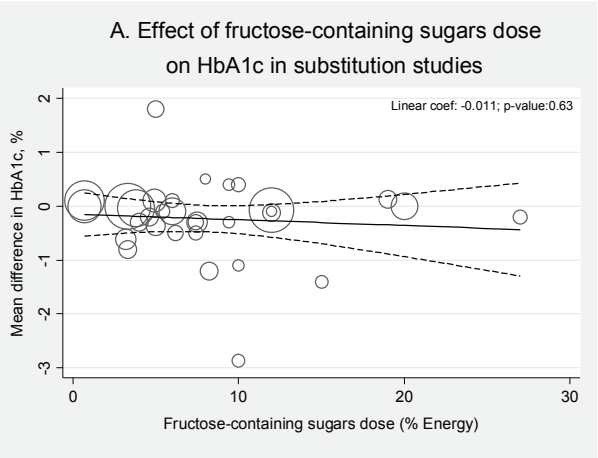
Supplementary Figure 5. Forest plot for ad libitum studies investigating the effect of freely replacing calories from food sources of fructose-containing sugars with other dietary sources on HbA1c. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. HbA1c= hemoglobin A1c; N= number of participants. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with fixed effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represented substantial heterogeneity.

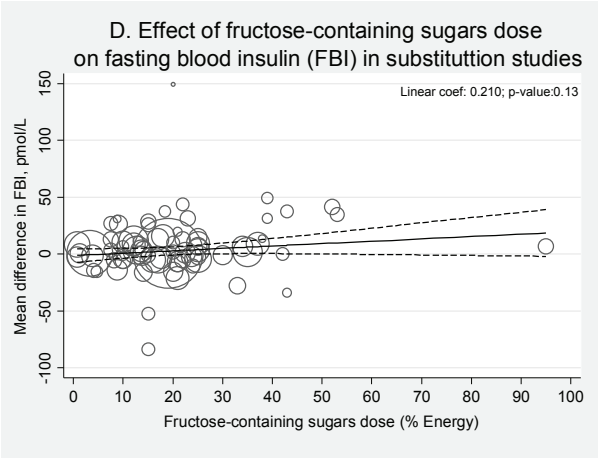


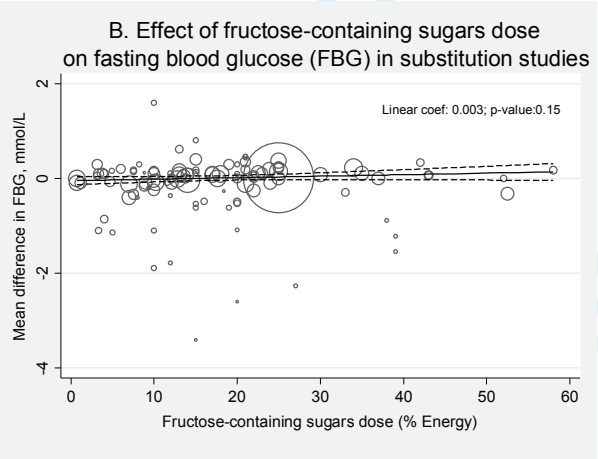
Supplementary Figure 6. Subgroup analyses for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on HbA1c. E= energy; HbA1c=hemoglobin A1C; MetS= metabolic syndrome; N= number of participants. Pooled effect estimates for each subgroup are represented by the diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value represents unexplained heterogeneity for each subgroup. Pairwise between-subgroup mean differences (95% CI) for comparator are as follows: 1 vs 2: -1.14 [-1.48, 1.20]; 1 vs 3: 0.20 [-1.43, 1.83]; 1 vs 4: 0.00 [-0.71, 0.72]; 1 vs 5: -0.38 [-2.05, 1.30]; 1 vs 6: -0.13 [-1.80, 1.55]; 1 vs 7: 0.14 [-1.50, 1.78]; 1 vs 8: 0.12 [-0.79, 1.03]; 2 vs 3: -0.34 [-2.27, 1.58]; 2 vs 4: -0.14 [-1.41, 1.12]; 2 vs 5: 0.24 [-1.72, 2.20]; 2 vs 6: -0.01 [-1.98, 1.95]; 2 vs 7: -0.28 [-2.21, 1.65]; 2 vs 8: -0.26 [-1.69, 1.16]; 3 vs 4: 0.20 [-1.37, 1.77]; 3 vs 5: 0.58 [-1.59, 2.75]; 3 vs 6: 0.33 [-1.85, 2.51]; 3 vs 7: 0.06 [-2.09, 2.21]; 3 vs 8: 0.08 [-1.63, 1.79]; 4 vs 5: 0.38 [-1.24, 2.00]; 4 vs 6: 0.13 [-1.50, 1.75]; 4 vs 7: -0.14 [-1.72, 1.44]; 4 vs 8: -0.12 [-1.06, 0.82]; 5 vs 6: -0.25 [-2.46, 1.96]; 5 vs 7: -0.52 [-2.70, 1.66]; 5 vs 8: -0.50 [-2.25, 1.25]; 6 vs 7: -0.27 [-2.45, 1.91]; 6 vs 8: -0.25 [-2.00, 1.50]; 7 vs 8: 0.02 [-1.70, 1.74]. Pairwise between-subgroup mean differences (95% CI) for fructose-containing sugars type are as follows: 1 vs 2: 0.47 [-0.13, 1.07]; 1 vs 3: 0.50 [-0.02, 1.02]; 1 vs 4: 0.36 [-0.83, 1.54]; 2 vs 3: -0.03 [-0.54, 0.48]; 2 vs 4: 0.11 [-1.07, 1.30]; 3 vs 4: 0.15 [-1.00, 1.29]. Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: -0.02 [-1.92 to 1.88]; 1 vs 3: 0.28 [-0.88 to 1.44]; 1 vs 4: 0.06 [-1.84 to 1.96]; 2 vs 3: 0.30 [-1.28 to 1.89]; 2 vs 4: 0.08 [-2.11 to 2.27]; 3 vs 4: 0.22 [-1.37 to 1.81].

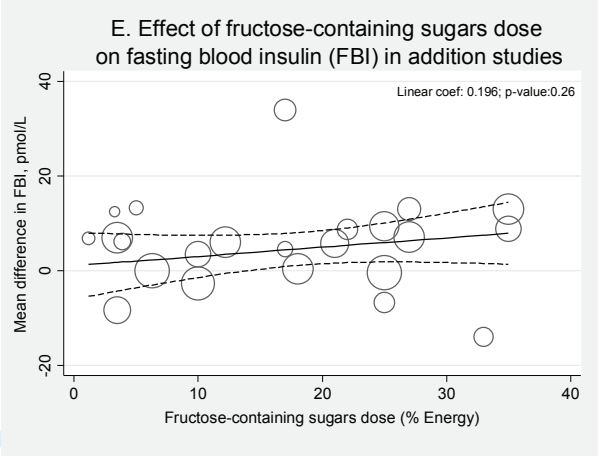


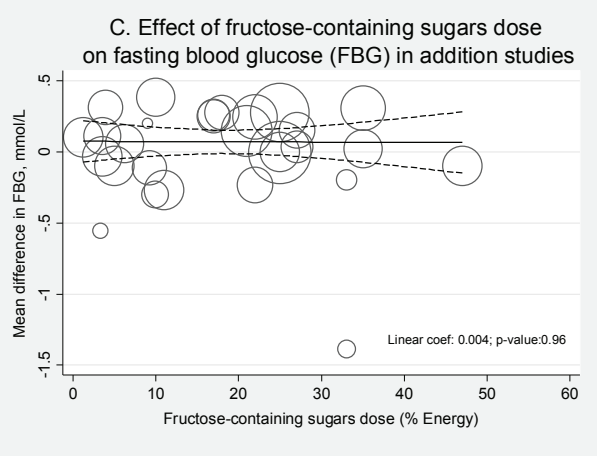
Supplementary Figure 7. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on HbA1c. Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The residual I^2 value represents unexplained heterogeneity for each subgroup. HRB=High Risk of Bias, LRB=Low Risk of Bias, URB= Unclear Risk of Bias. *Within and/or between subgroup analysis could not be performed since no values were available for respective HRB/URB/LRB subgroups. Statistically significant pairwise subgroup effect modification by meta-regression analysis (P< 0.05).



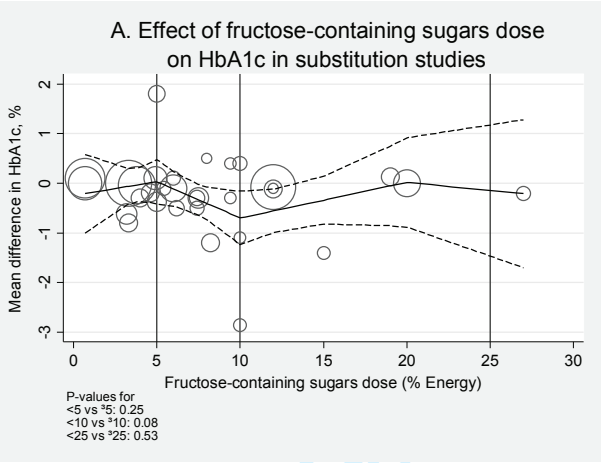


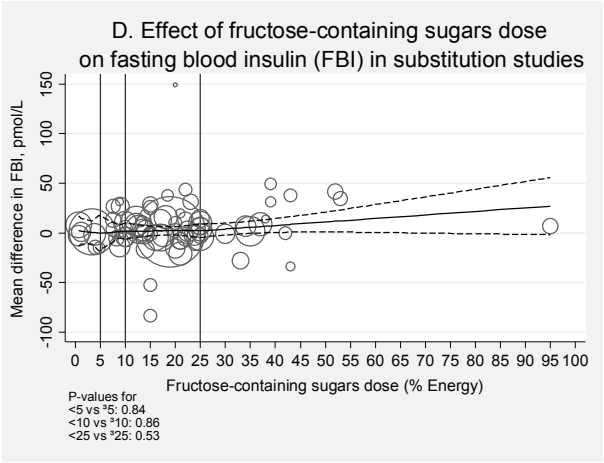


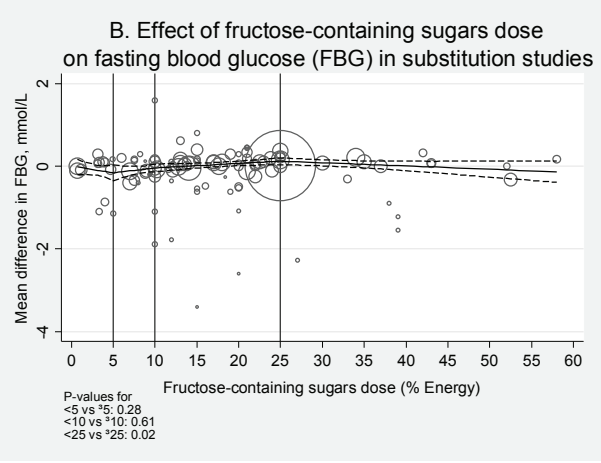


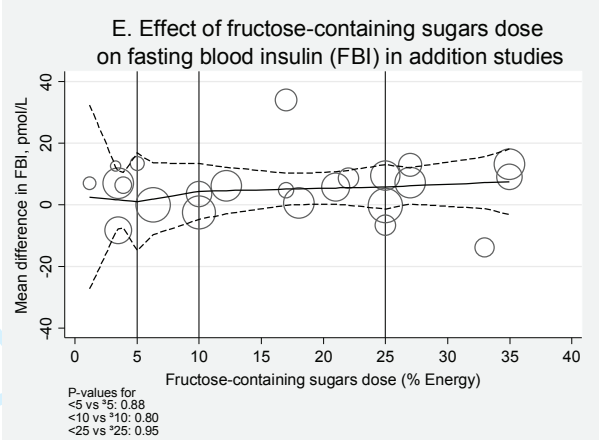


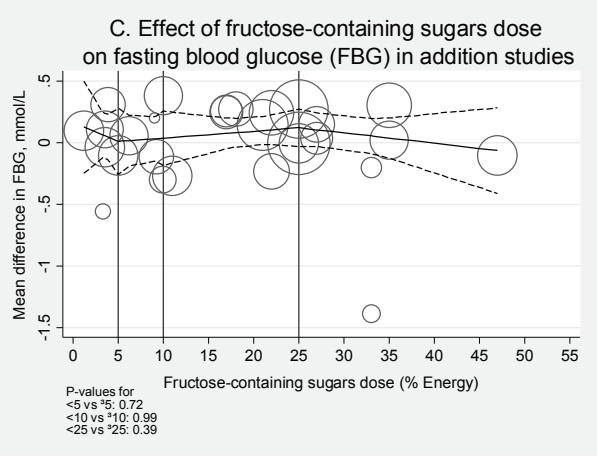
Supplementary Figure 8. Linear meta-regression analyses for the effect of fructose-containing sugars dose (%E) on glycemic control in substitution and addition studies. Individual studies are represented by the circles, with their weight in the overall analysis represented by the size of the circles. The straight line represents the estimate dose response for amount of fructose-containing sugars consumed (% of total energy intake) and the dashed lines represent the upper and lower 95% Confidence Intervals.



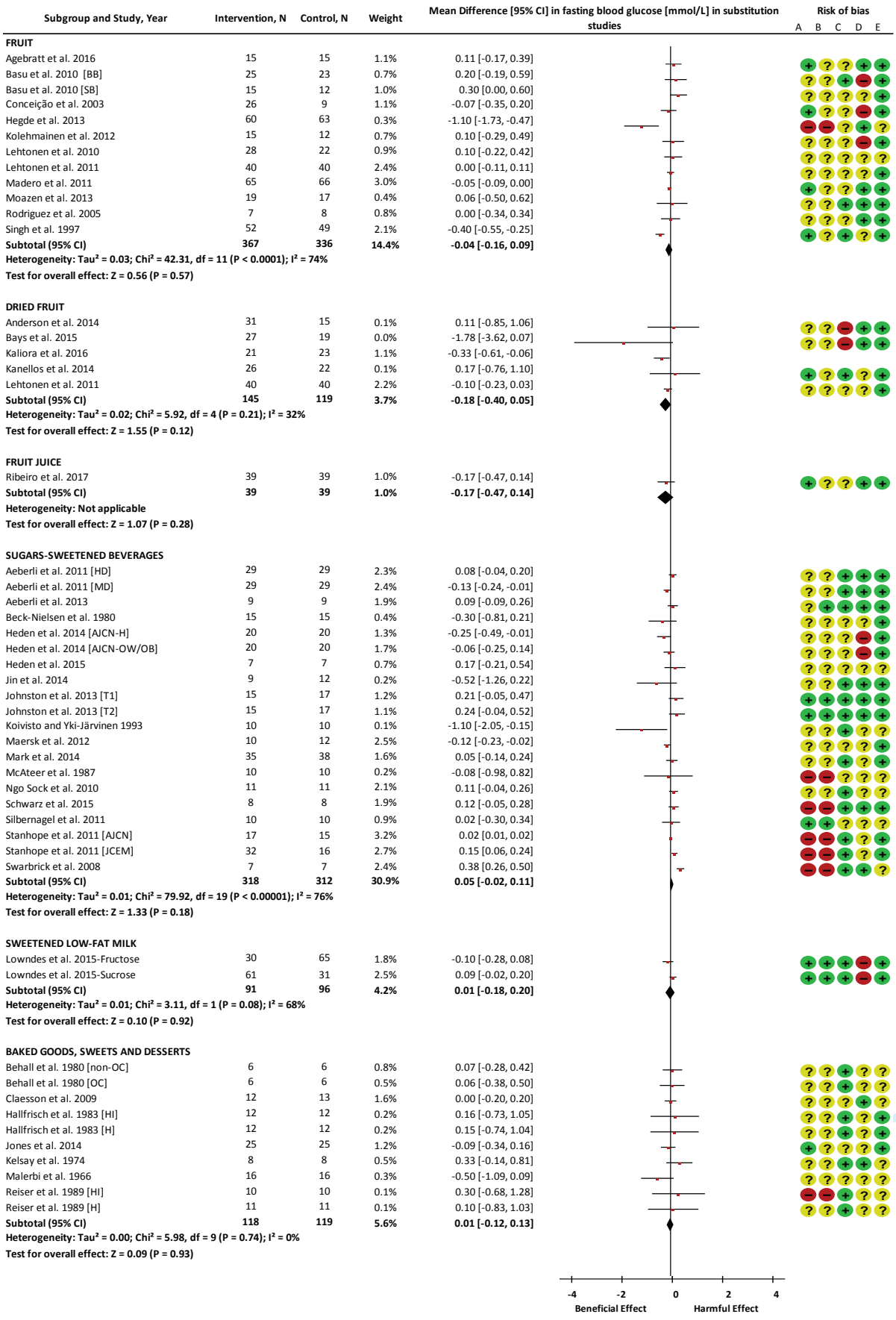




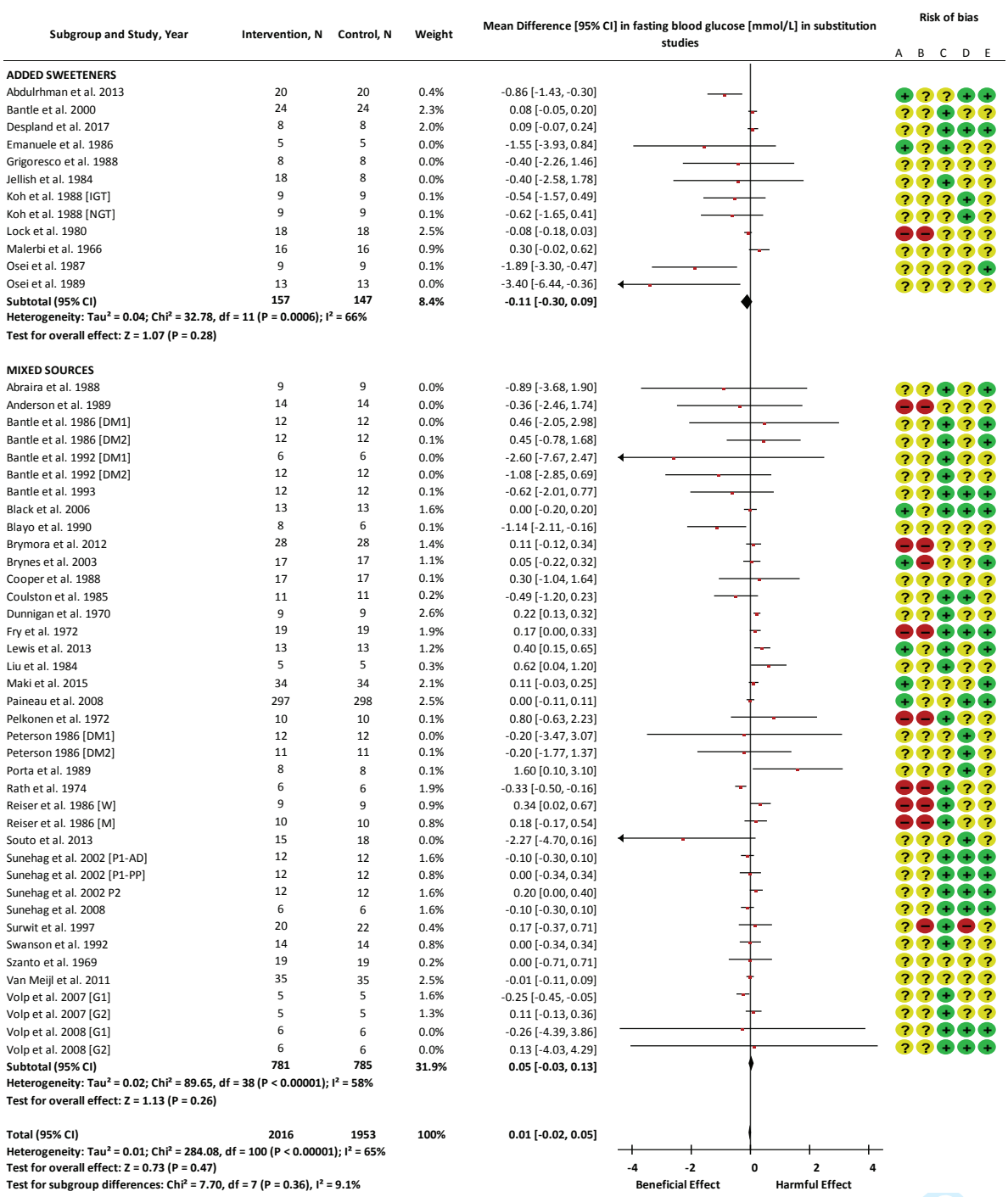




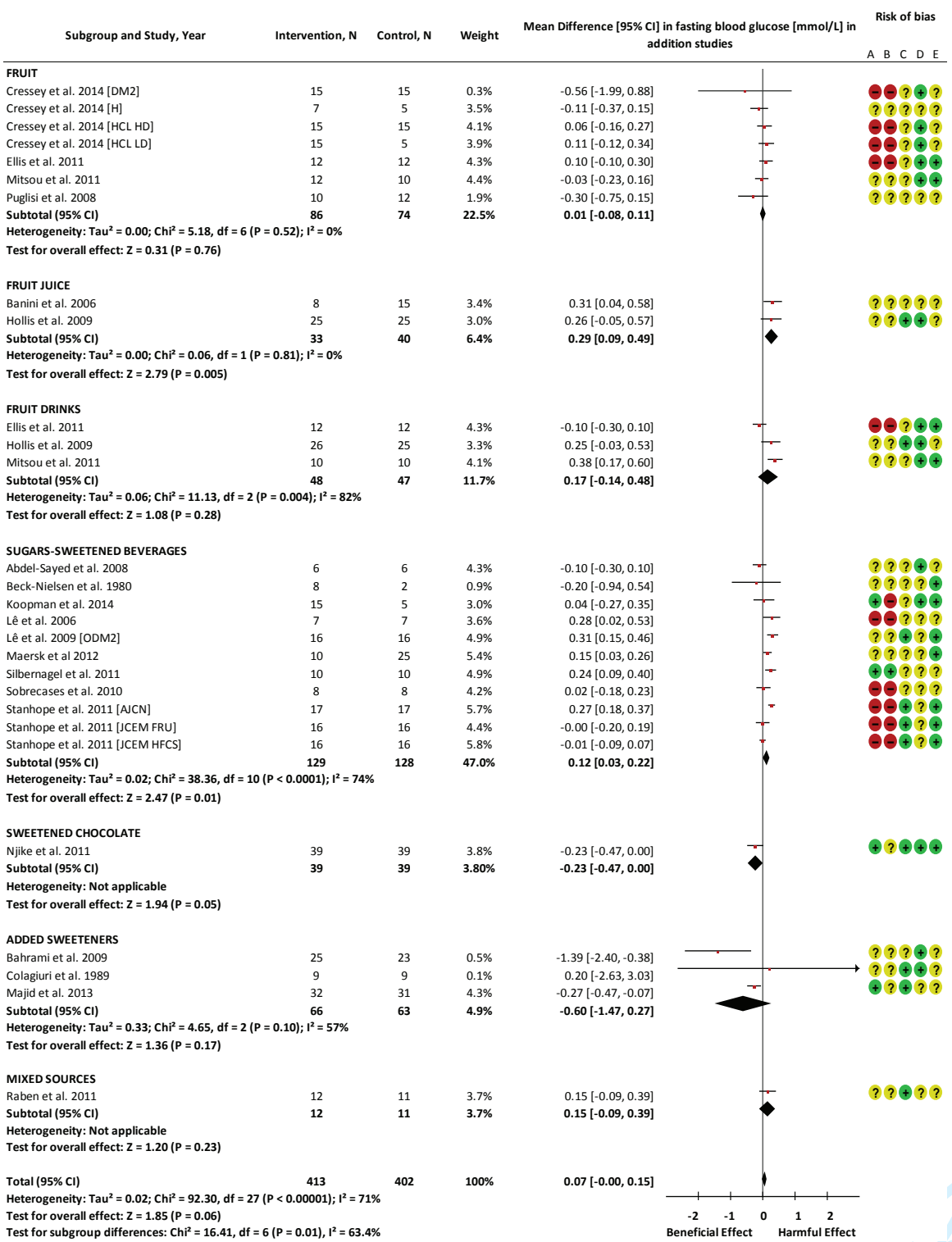
Supplementary Figure 9. Non-linear meta-regression analyses for the effect of fructose-containing sugars dose (%E) on glycemic control in substitution and addition studies. Individual studies are represented by the circles, with their weight in the overall analysis represented by the size of the circles. The horizontal straight line represents the estimate dose response for amount of fructose-containing sugars consumed (% of total energy intake), and the dashed lines represent the upper and lower 95% Confidence Intervals. The vertical straight lines represent the threshold knots.



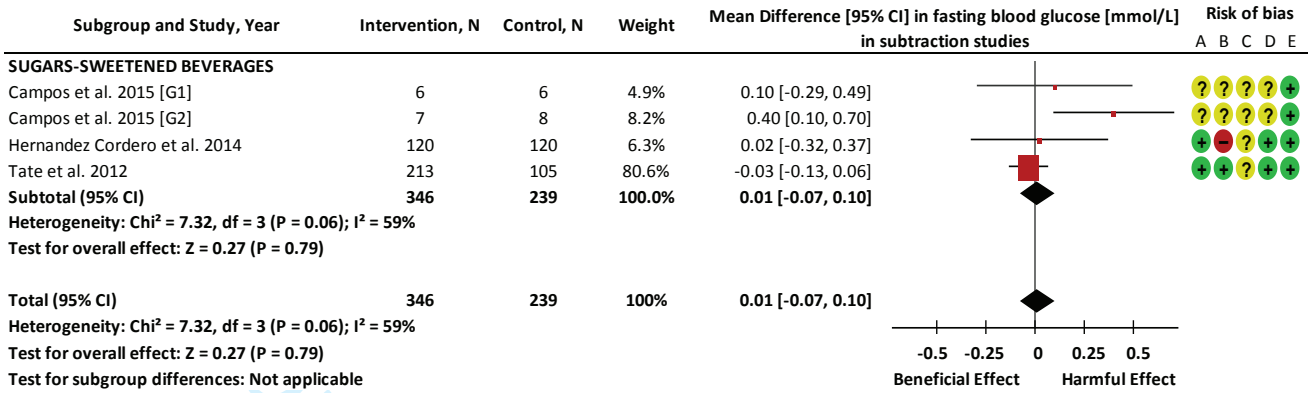
Supplementary Figure 10. Forest plot for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose (continues next page).



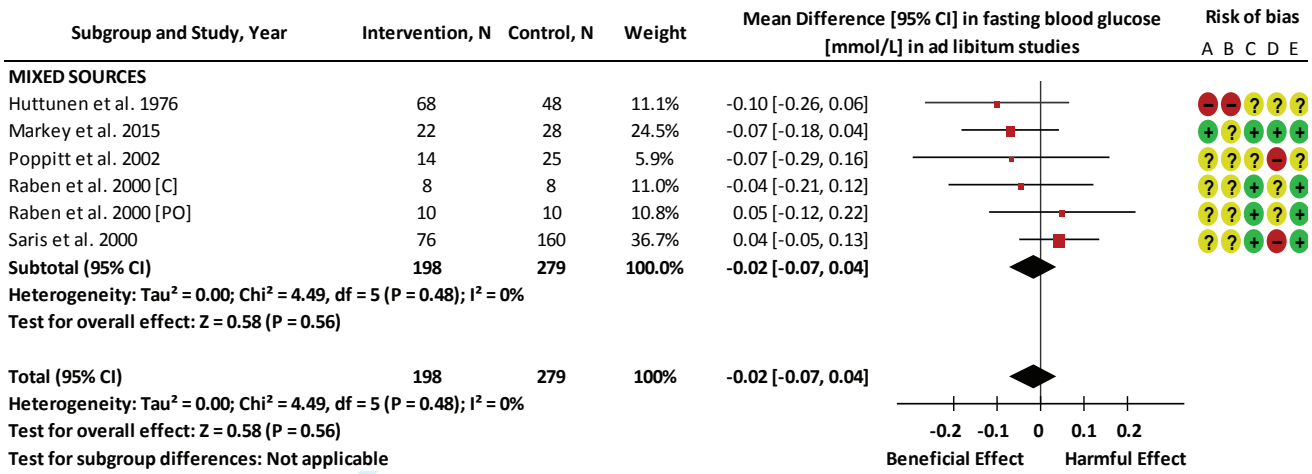
Supplementary Figure 10. (continued). Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. AJCN = American Journal of Clinical Nutrition; DM= diabetes mellitus; EXP1= experiment 1; EXP2= experiment 2; H=healthy; HC= high carbohydrate; HD= high dose; HI=hyperinsulinemic; JPAH= Journal of Physical Activity and Health; JCEM= Journal of Clinical Endocrinology and Metabolism; LC= low carbohydrate; MD= moderate dose; N= number of participants; OC= oral contraceptive users; OW/OB= overweight/obese participants; T1= trial 1; T2=Trial 2. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with random effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represents substantial heterogeneity.



Supplementary Figure 11. Forest plot for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood glucose. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. AJCN = American Journal of Clinical Nutrition; BB= blueberries; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructose; H=healthy; HCL= hypercholesterolemic; HD= high dose; HFCS= high fructose corn syrup; JCEM= Journal of Clinical Endocrinology and Metabolism; LD= low dose; N= number of participants; ODM2= offspring of people with type 2 diabetes; SB= strawberries. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with random effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represents substantial heterogeneity.

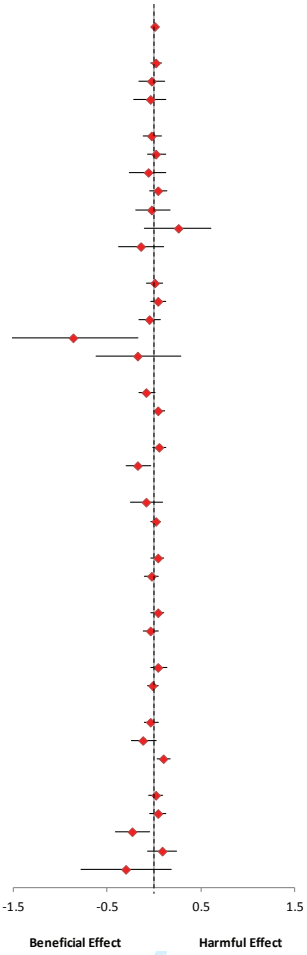


Supplementary Figure 12. Forest plot for subtraction studies investigating the effect of removing calories from the diet in the form of food sources of fructose-containing sugars on fasting blood glucose. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. G1= group 1; G2= group 2; N= number of participants. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with fixed effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represents substantial heterogeneity.

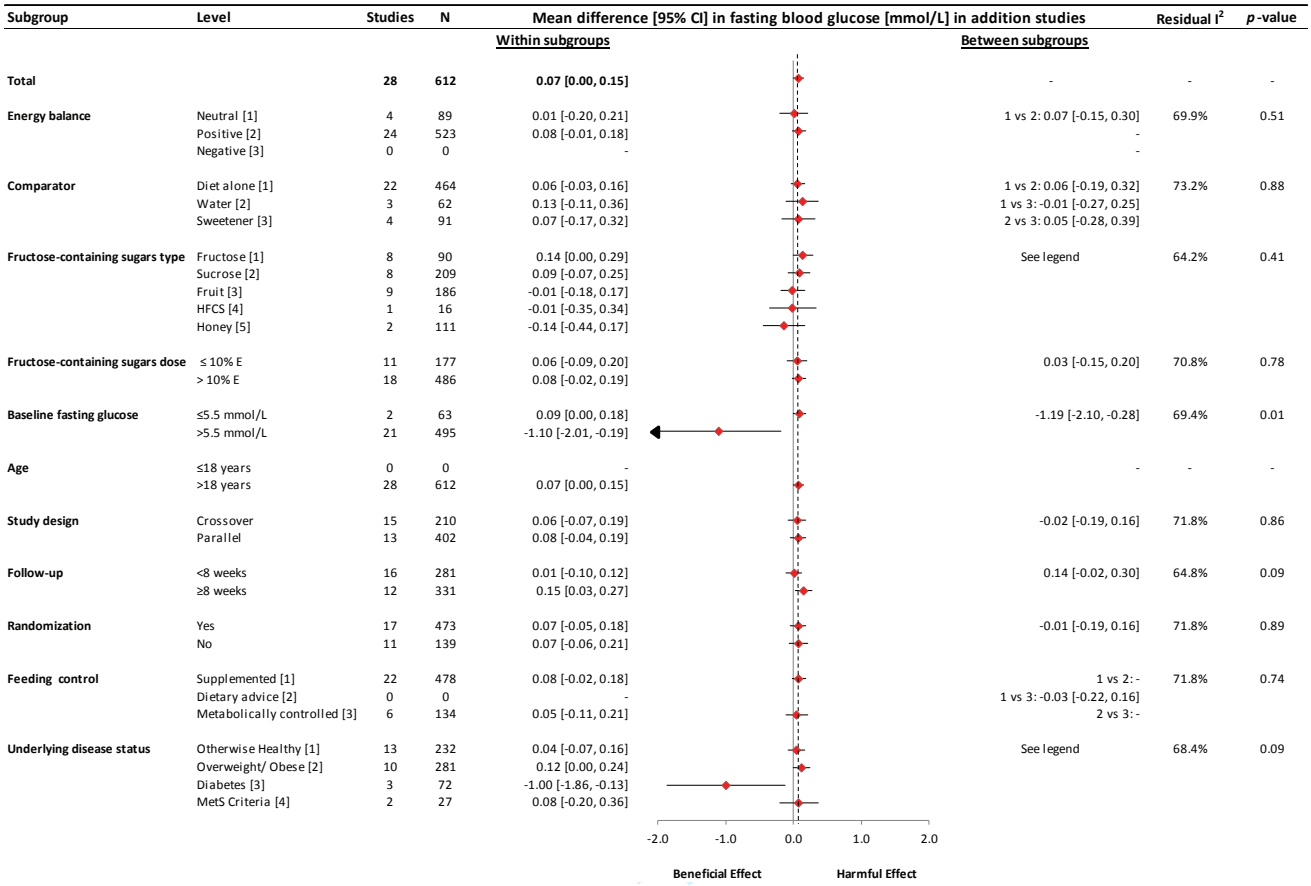


Supplementary Figure 13. Forest plot for ad libitum studies investigating the effect of freely replacing calories from food sources of fructose-containing sugars with other dietary sources on fasting blood glucose. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. C= controls; N= number of participants; PO= post-obese. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with random effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represents substantial heterogeneity.

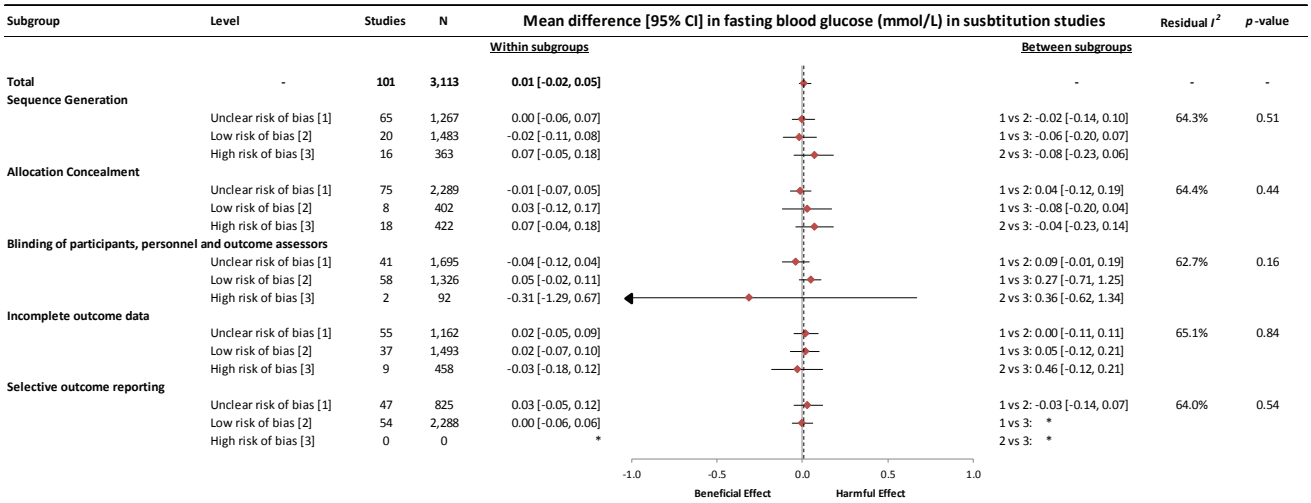
Subgroup	Level	Studies	N	Mean difference [95% CI] in fasting blood glucose [mmol/L] in substitution studies Within subgroups	Between subgroups	Residual I^2	*p*-value
Total		**101**	**3,113**	**0.01 [-0.02, 0.05]**	-	-	-
Energy balance	Neutral [1]	83	1,863	0.02 [-0.03, 0.08]	1 vs 2: -0.05 [-0.19, 0.10]	64.1%	0.67
	Positive [2]	11	322	-0.02 [-0.16, 0.11]	1 vs 3: -0.07 [-0.25, 0.11]		
	Negative [3]	7	928	-0.04 [-0.22, 0.13]	2 vs 3: 0.02 [-0.20, 0.24]		
Comparator	Starch [1]	46	1,345	-0.02 [-0.12, 0.08]	See legend	64.4%	0.54
	Glucose [2]	23	590	0.02 [-0.07, 0.12]			
	Fat [3]	8	154	-0.06 [-0.26, 0.13]			
	Mixed [4]	15	630	0.05 [-0.05, 0.14]			
	Lactose [5]	5	219	-0.02 [-0.20, 0.17]			
	Water [6]	2	77	0.26 [-0.10, 0.61]			
	Diet alone [7]	3	100	-0.14 [-0.38, 0.10]			
Fructose-containing sugars type	Fructose [1]	42	764	0.01 [-0.08, 0.09]	See legend	62.9%	0.08
	Sucrose [2]	44	1,427	0.05 [-0.03, 0.13]			
	Fruit [3]	18	976	-0.05 [-0.16, 0.07]			
	Honey [4]	2	28	-0.86 [-1.56, -0.17]			
	HFCS [5]	3	148	-0.17 [-0.62, 0.29]			
Fructose-containing sugars dose	≤ 10% E	35	1,182	-0.08 [-0.16, 0.01]	0.13 [0.03, 0.23]	61.3%	0.01
	> 10% E	69	1,955	0.05 [0.00, 0.11]			
Baseline fasting glucose	≤5.5 mmol/L	37	1,261	0.06 [-0.01, 0.13]	-0.23 [-0.37, -0.09]	64.8%	<0.01
	>5.5 mmol/L	32	862	-0.17 [-0.30, -0.04]			
Age	≤18 years	7	103	-0.08 [-0.25, 0.09]	0.10 [-0.08, 0.28]	64.6%	0.27
	>18 years	93	3,010	0.02 [-0.03, 0.07]			
Study design	Crossover	61	862	0.04 [-0.03, 0.10]	-0.06 [-0.16, 0.04]	64.2%	0.25
	Parallel	40	2,251	-0.02 [-0.10, 0.05]			
Follow-up	<8 weeks	69	1,277	0.04 [-0.03, 0.10]	-0.07 [-0.18, 0.03]	64.8%	0.16
	≥8 weeks	32	1,836	-0.04 [-0.12, 0.05]			
Randomization	Yes	72	2,543	0.05 [-0.04, 0.14]	-0.06 [-0.16, 0.05]	63.8%	0.30
	No	29	570	-0.01 [-0.07, 0.05]			
Feeding control	Supplemented [1]	43	1,446	-0.03 [-0.10, 0.04]	1 vs 2: -0.08 [-0.23, 0.07]	62.0%	<0.01
	Dietary advice [2]	15	1,063	-0.11 [-0.24, 0.02]	1 vs 3: 0.13 [0.03, 0.23]		
	Metabolically controlled [3]	43	604	0.10 [0.03, 0.17]	2 vs 3: -0.21 [-0.36, -0.06]		
Underlying disease status	Otherwise Healthy [1]	34	1,133	0.02 [-0.06, 0.09]	See legend	65.0%	0.05
	Overweight/ Obese [2]	25	961	0.04 [-0.05, 0.12]			
	Diabetes [3]	30	645	-0.23 [-0.41, -0.05]			
	MetS Criteria [4]	11	330	0.09 [-0.07, 0.24]			
	NAFLD [5]	1	44	-0.30 [-0.78, 0.18]			



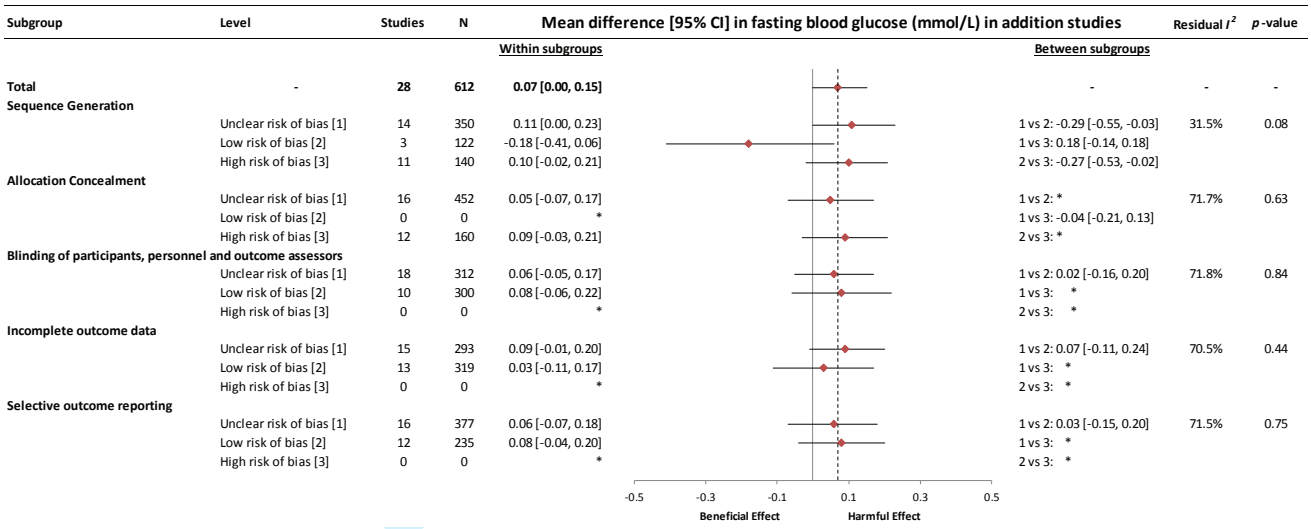
Supplementary Figure 14. Subgroup analyses for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. Pooled effect estimates for each subgroup are represented by the diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value represents unexplained heterogeneity for each subgroup. Pairwise between-subgroup mean differences (95% CI) for comparator are as follows: 1 vs 2: 0.05 [-0.09, 0.18]; 1 vs 3: -0.04 [-0.24, 0.16]; 1 vs 4: 0.06 [-0.06, 0.19]; 1 vs 5: 0.01 [-0.18, 0.20]; 1 vs 6: 0.28 [-0.09, 0.65]; 1 vs 7: -0.02[-0.12, 0.08]; 2 vs 3: 0.09 [-0.13, 0.30]; 2 vs 4: -0.02 [-0.16, 0.12]; 2 vs 5: 0.04 [-0.16, 0.24]; 2 vs 6: -0.23 [-0.60, 0.13]; 2 vs 7: 0.16 [-0.09, 0.42]; 3 vs 4: -0.11 [-0.34, 0.12]; 3 vs 5: -0.05 [-0.30, 0.21]; 3 vs 6: -0.32 [-0.72, 0.09]; 3 vs 7: 0.08 [-0.23, 0.39]; 4 vs 5: 0.06 [-0.316, 0.28]; 4 vs 6: -0.21 [-0.58, 0.16]; 4 vs 7: 0.19 [-0.07, 0.44]; 5 vs 6: -0.27 [-0.67, 0.13]; 5 vs 7: 0.13 [-0.17, 0.42]; 6 vs 7: 0.40 [-0.03, 0.83]. Pairwise between-subgroup mean differences (95% CI) for fructose-containing sugars type are as follows: 1 vs 2: -0.04 [-0.16, 0.08]; 1 vs 3: 0.05 [-0.09, 0.20]; 1 vs 4: 0.87 [0.17, 1.56]; 1 vs 5: 0.17 [-0.29, 0.64]; 2 vs 3: 0.09 [-0.05, 0.24]; 2 vs 4: 0.91 [0.21, 1.61]; 2 vs 5: 0.21 [-0.25, 0.68]; 3 vs 4: 0.82 [0.11, 1.52]; 3 vs 5: 0.12 [-0.35, 0.59]; 4 vs 5: -0.17 [-0.62, 0.29]. Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: -0.02 [-0.13, 0.09]; 1 vs 3: 0.24 [0.05, 0.44]; 1 vs 4: -0.07 [-0.24, 0.10]; 1 vs 5: 0.32 [-0.17, 0.80]; 2 vs 3: 0.26 [0.07, 0.46]; 2 vs 4: -0.07 [-0.25, 0.10]; 2 vs 5: -0.05 [-0.23, 0.13]; 3 vs 4: 0.31 [0.07, 0.55]; 3 vs 5: -0.07 [-0.59, 0.44]; 4 vs 5: 0.39 [-0.12, 0.89].



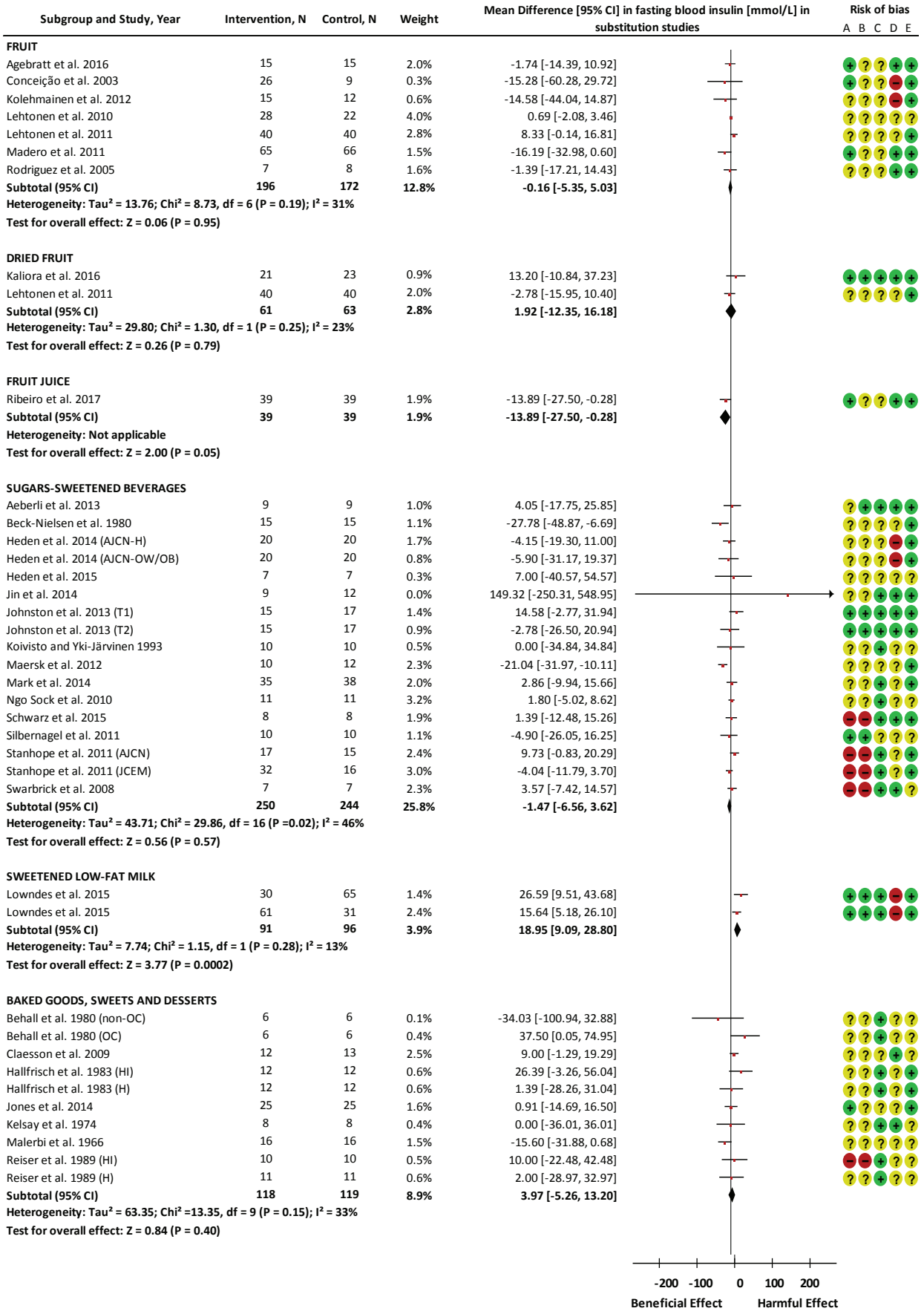
Supplementary Figure 15. Subgroup analyses for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood glucose. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. Pooled effect estimates for each subgroup are represented by the diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value represents unexplained heterogeneity for each subgroup. Pairwise between-subgroup mean differences (95% CI) for fructose-containing sugars type are as follows: 1 vs 2: 0.05 [-0.17, 0.27]; 1 vs 3: 0.15 [-0.08, 0.38]; 1 vs 4: 0.15 [-0.23, 0.53]; 1 vs 5: 0.28 [-0.06, 0.62]; 2 vs 3: 0.10 [-0.14, 0.34]; 2 vs 4: 0.10 [-0.29, 0.48]; 2 vs 5: 0.23 [-0.11, 0.57]; 3 vs 4: 0.00 [-0.39, 0.39]; 3 vs 5: 0.13 [-0.22, 0.48]; 4 vs 5: 0.13 [-0.33, 0.59]. Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: -0.08 [-0.24, 0.09]; 1 vs 3: 1.04 [0.17, 1.91]; 1 vs 4: -0.04 [-0.134, 0.26]; 2 vs 3: 1.11 [0.24, 1.99]; 2 vs 4: 0.04 [-0.27, 0.34]; 3 vs 4: 1.08 [0.17, 1.99].



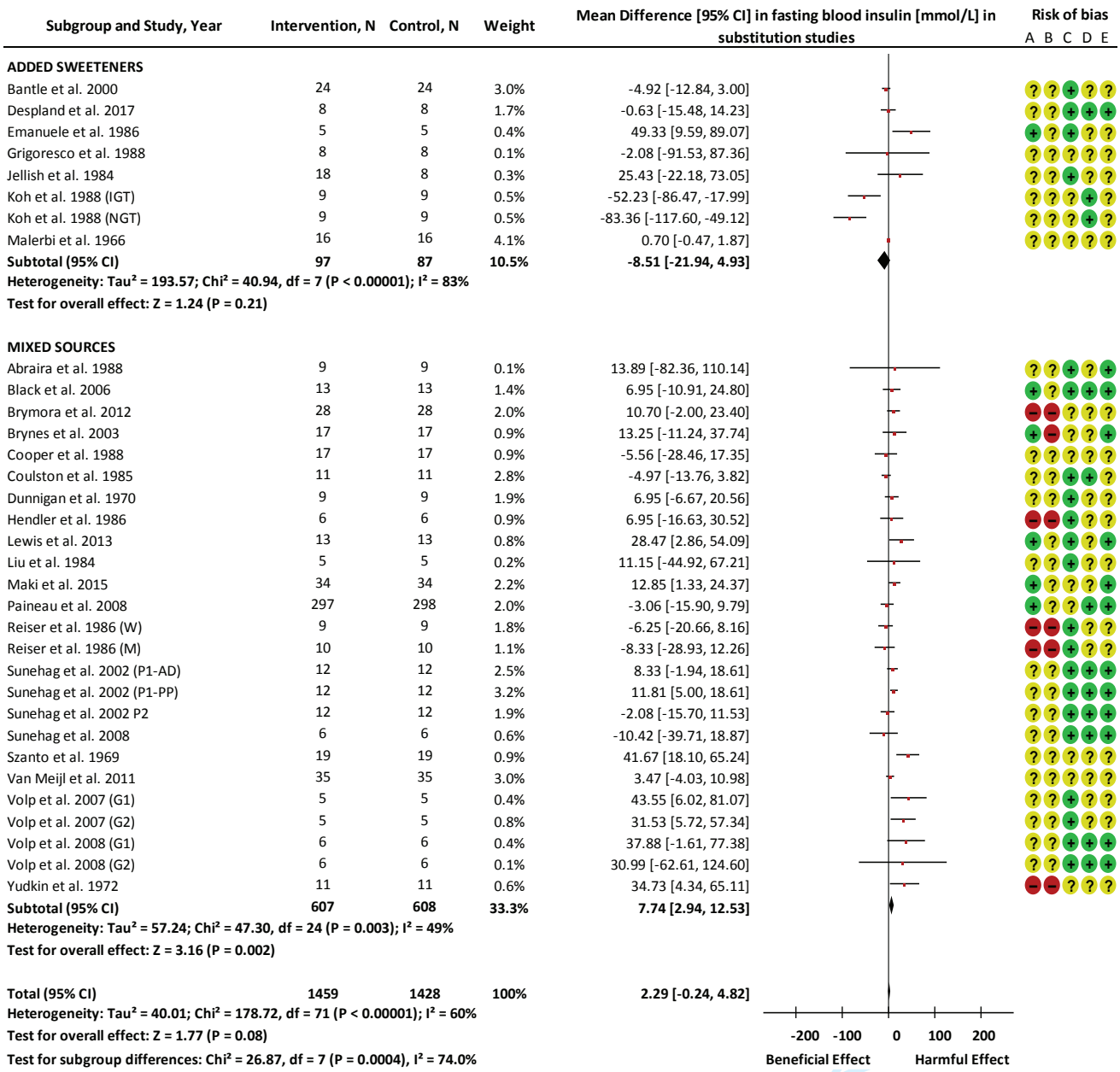
Supplementary Figure 16. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose. Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The residual I^2 value represents unexplained heterogeneity for each subgroup. HRB=High Risk of Bias, LRB=Low Risk of Bias, URB= Unclear Risk of Bias. *Within and/or between subgroup analysis could not be performed since no values were available for respective HRB/URB/LRB subgroups. Statistically significant pairwise subgroup effect modification by meta-regression analysis (P< 0.05).



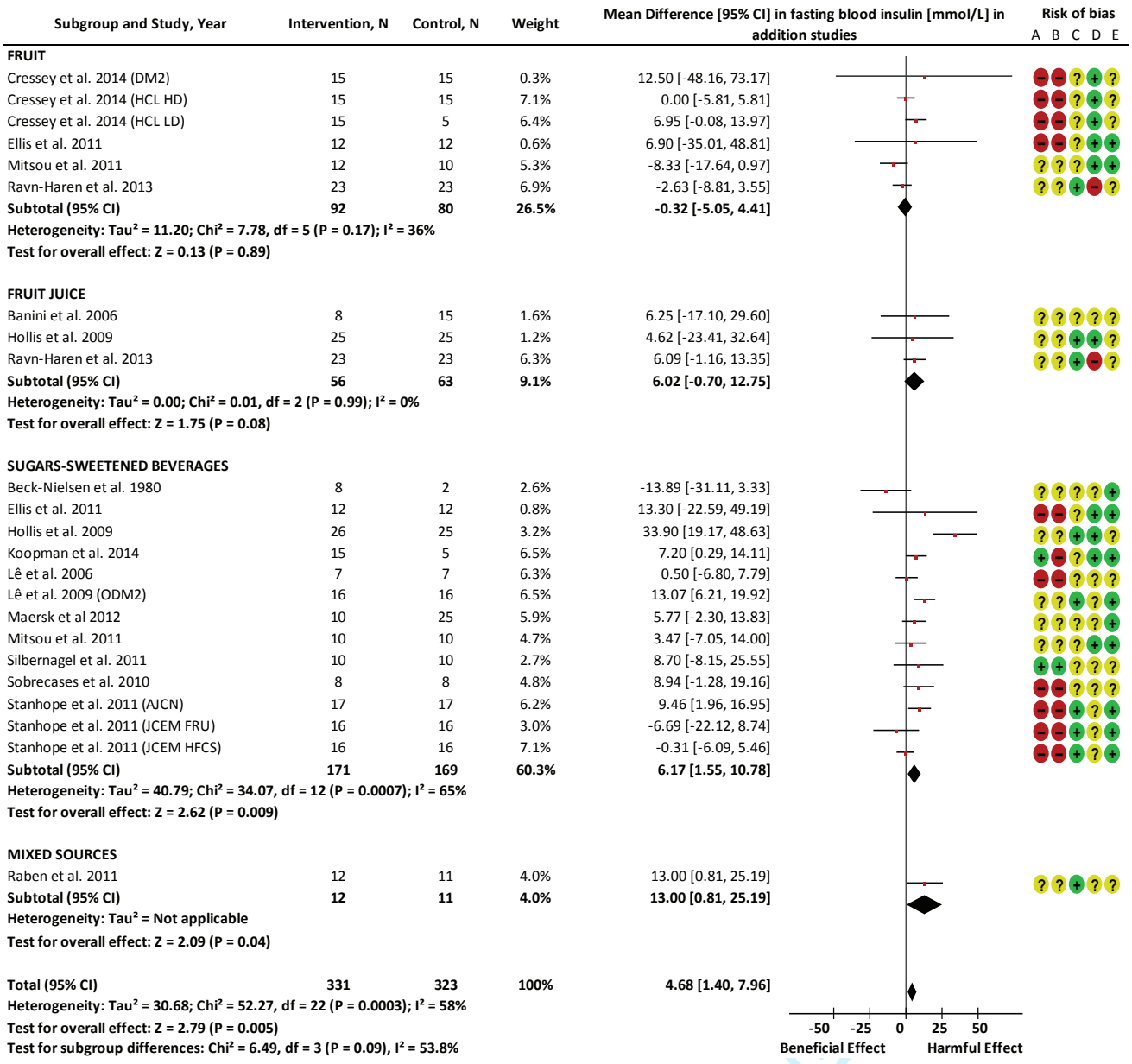
Supplementary Figure 17. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for addition studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose. Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The residual I^2 value represents unexplained heterogeneity for each subgroup. HRB=High Risk of Bias, LRB=Low Risk of Bias, URB= Unclear Risk of Bias. *Within and/or between subgroup analysis could not be performed since no values were available for respective HRB/URB/LRB subgroups. Statistically significant pairwise subgroup effect modification by meta-regression analysis (P< 0.05).



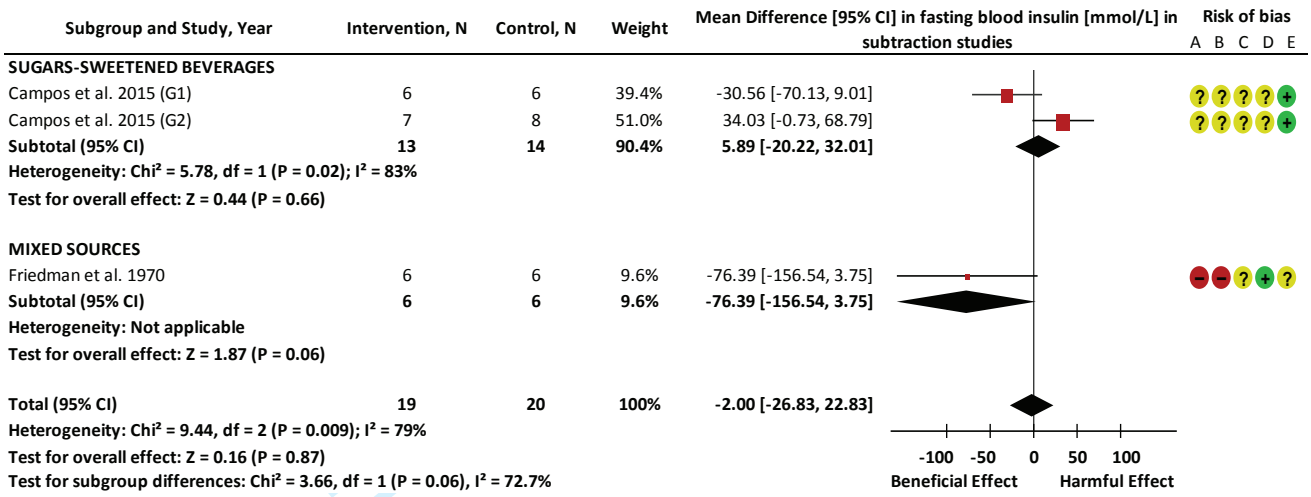
Supplementary Figure 18. Forest plot for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood insulin (Continues next page).



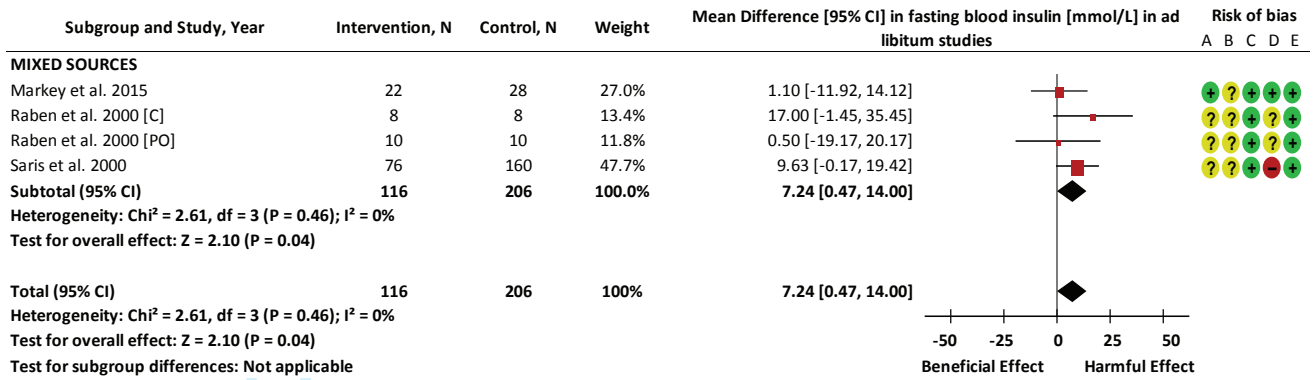
Supplementary Figure 18. (continued). Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting.AD= adolescent; AJCN = American Journal of Clinical Nutrition; DM= diabetes mellitus; EXP1= experiment 1; EXP2= experiment 2; G1= group 1; G2= group 2; H=healthy; HC= high carbohydrate; HI=hyperinsulinemic; IGT= impaired glucose tolerance; JPAH= Journal of Physical Activity and Health; JCEM= Journal of Clinical Endocrinology and Metabolism; LC= low carbohydrate; M=men; N= number of participants; NGT= normal glucose tolerance; OC= oral contraceptive users; OW/OB= overweight/obese participants; PP=pre-pubertal; P1= protocol 1; P2= protocol 2; T1= trial 1; T2=Trial 2; W= women. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with random effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represents substantial heterogeneity.



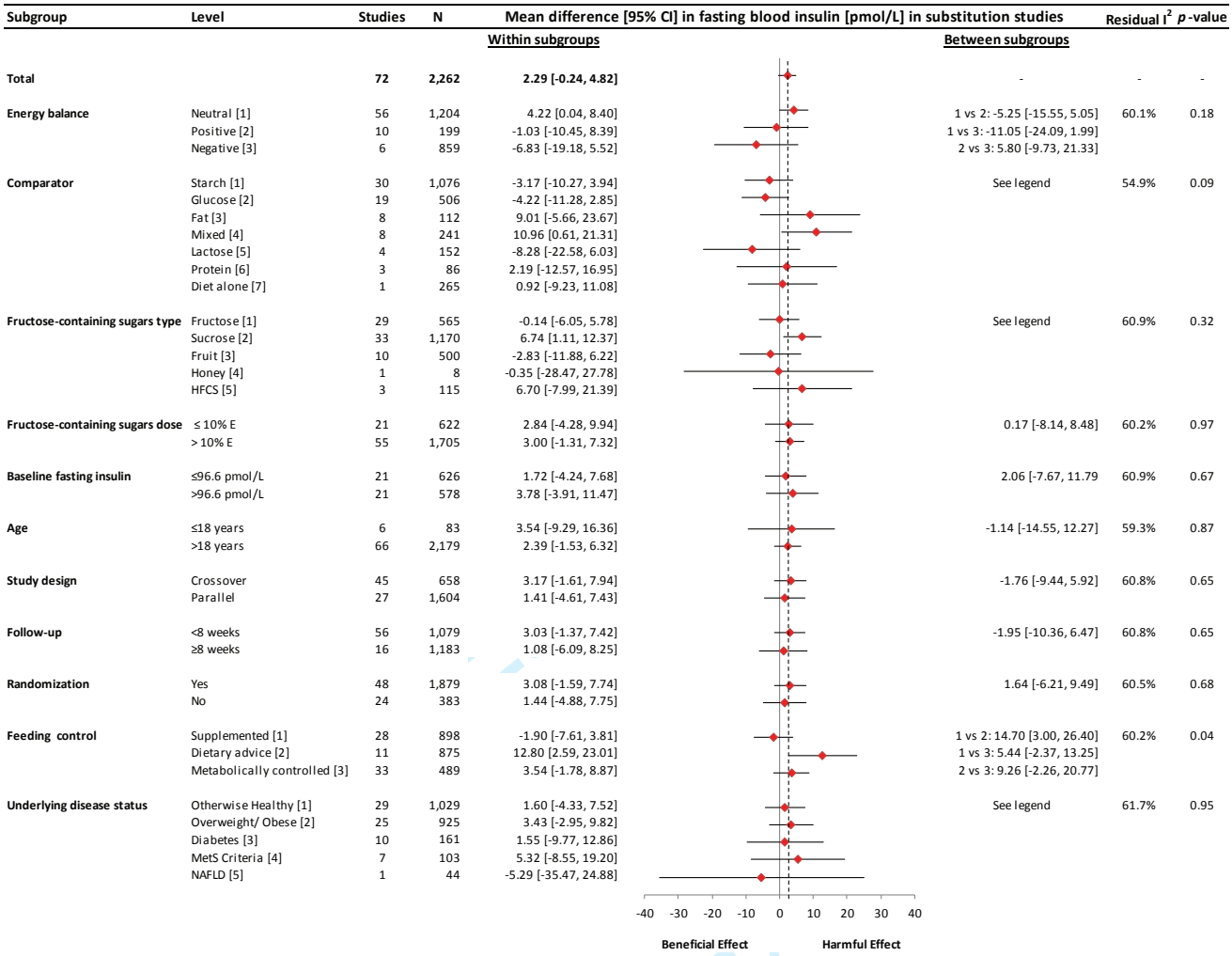
Supplementary Figure 19. Forest plot for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood insulin. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. AJCN = American Journal of Clinical Nutrition; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructose; HCL= hypercholesterolemic; HD= high dose; HFCS= high fructose corn syrup; JCEM= Journal of Clinical Endocrinology and Metabolism; LD= low dose; N= number of participants; ODM2= offspring of people with type 2 diabetes. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with random effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represents substantial heterogeneity.



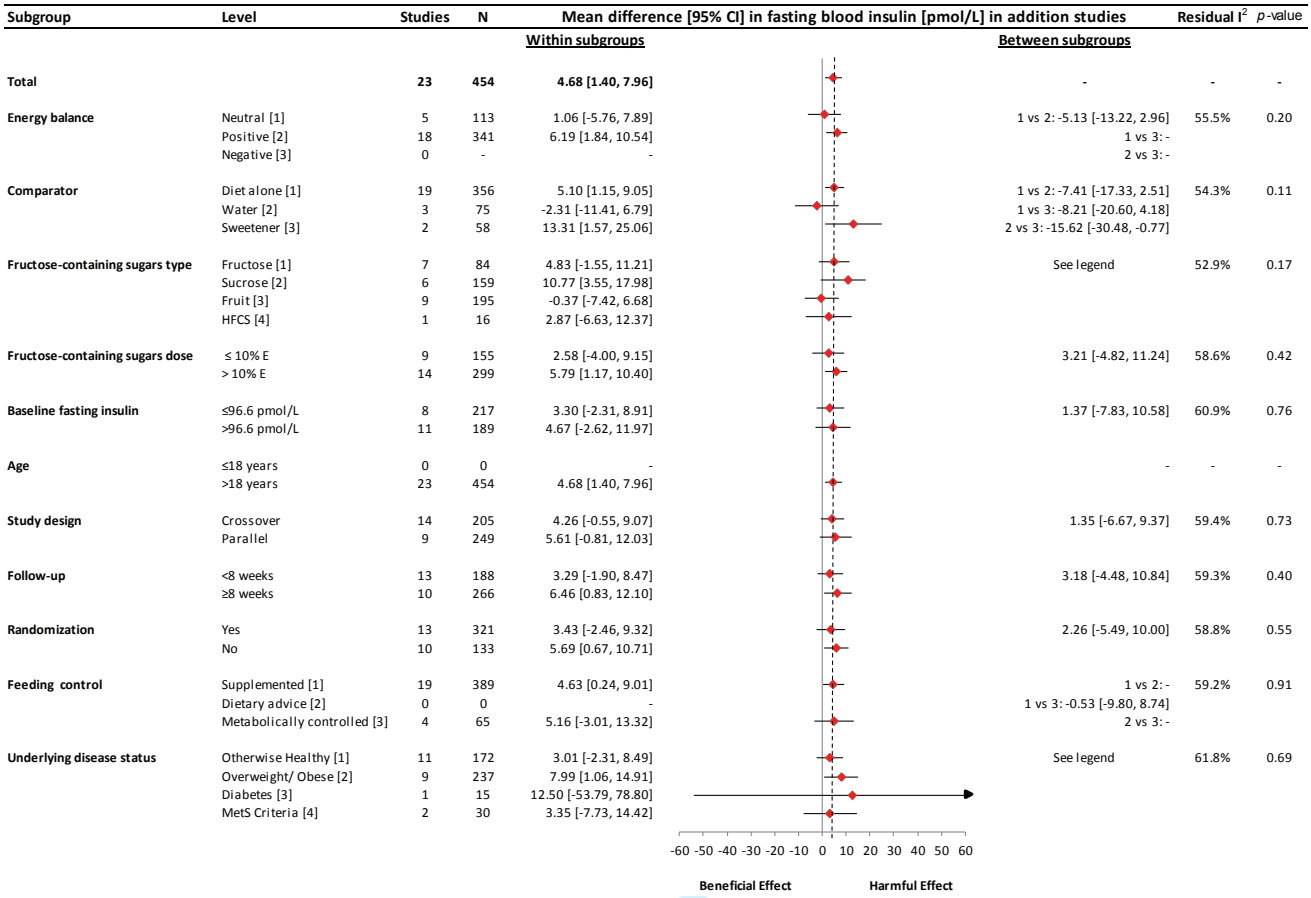
Supplementary Figure 20. Forest plot for subtraction studies investigating the effect of removing calories from the diet in the form of food sources of fructose-containing sugars on fasting blood insulin. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. G1= group 1; G2= group 2; N= number of participants. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with fixed effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represents substantial heterogeneity.



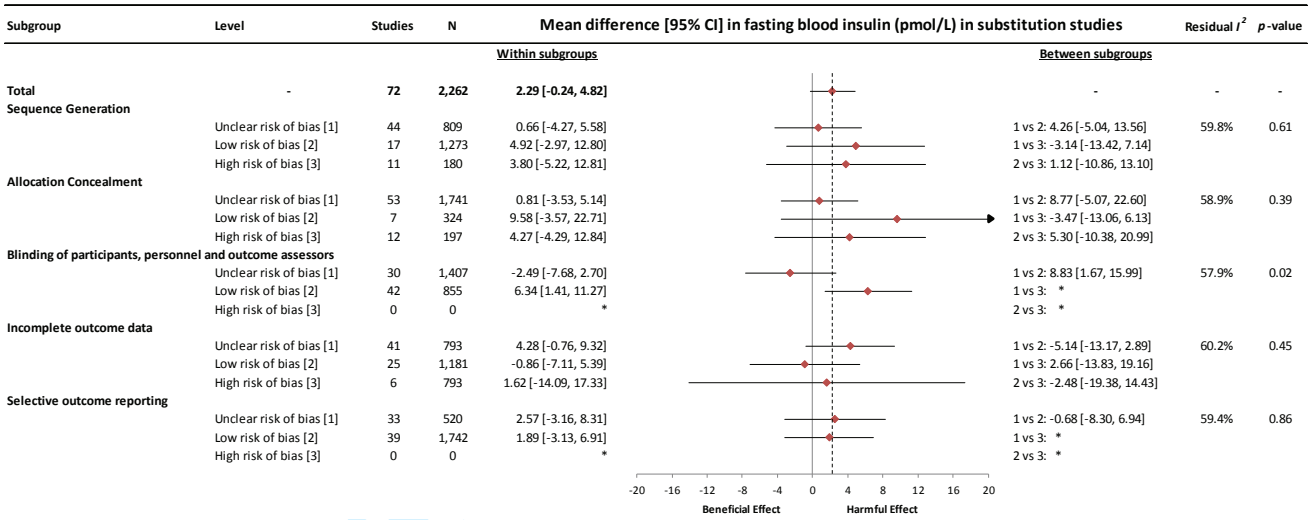
Supplementary Figure 21. Forest plot for ad libitum studies investigating the effect of freely replacing calories from food sources of fructose-containing sugars with other dietary sources on fasting blood insulin. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. C=control; N= number of participants; PO= post-obese. Pooled effect estimates for each subgroup and overall effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the generic inverse-variance method with fixed effects models. Paired analyses were applied to all crossover studies. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, level of ≥ 50 % represents substantial heterogeneity.



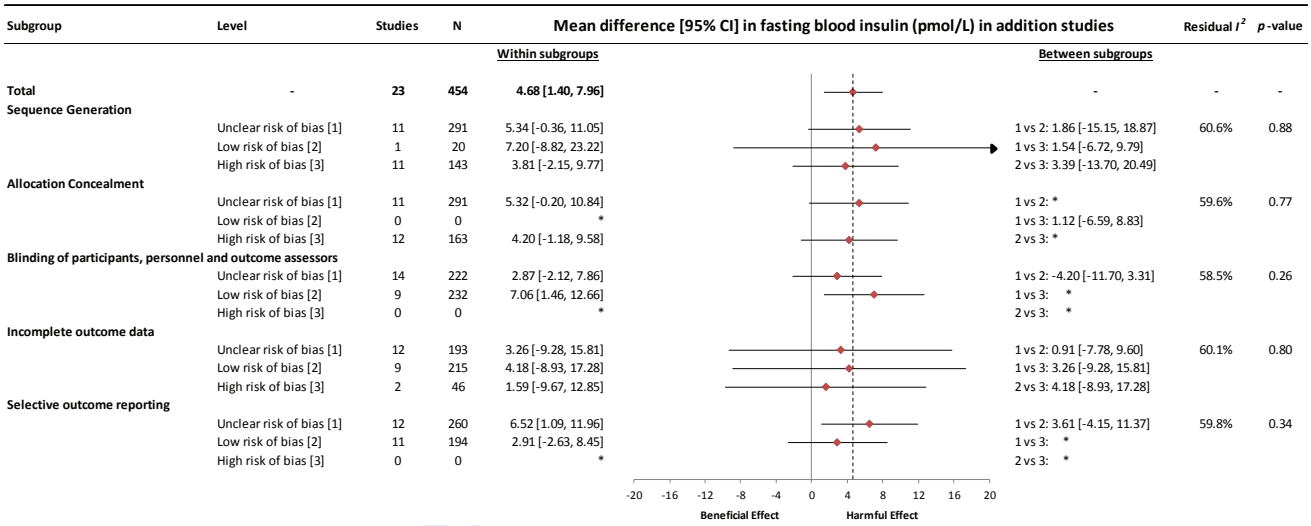
Supplementary Figure 22. Subgroup analyses for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood insulin. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. Pooled effect estimates for each subgroup are represented by the diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value represents unexplained heterogeneity for each subgroup. Pairwise between-subgroup mean differences [95% CI] for comparator are as follows: 1 vs 2: 1.05 [-8.97, 11.07]; 1 vs 3: -12.17 [-27.64, 3.30]; 1 vs 4: -14.13 [-28.13, -0.13]; 1 vs 5: 5.11 [-9.22, 19.44]; 1 vs 6: -5.36 [-21.30, 10.59]; 1 vs 7: -4.09 [-15.01, 6.83]; 2 vs 3: -13.22 [-29.49, 3.05]; 2 vs 4: -15.18 [-27.71, -2.65]; 2 vs 5: 4.06 [-11.89, 20.02]; 2 vs 6: -6.41 [-22.77, 9.96]; 2 vs 7: -5.14 [-17.51, 7.23]; 3 vs 4: -1.96 [-20.66, 16.74]; 3 vs 5: 17.28 [-2.31, 36.88]; 3 vs 6: 6.82 [-13.74, 27.38]; 3 vs 7: 8.08 [-9.05, 25.21]; 4 vs 5: 19.24 [0.16, 38.33]; 4 vs 6: 8.77 [-9.66, 27.21]; 4 vs 7: 10.04 [1.51, 18.58]; 5 vs 6: -10.47 [-30.55, 9.61]; 5 vs 7: -9.20 [-25.35, 6.95]; 6 vs 7: 1.27 [-16.27, 18.81]. Pairwise between-subgroup mean differences (95% CI) for fructose-containing sugars type are as follows: 1 vs 2: -6.80 [-37.30, 23.70]; 1 vs 3: -16.37 [-47.68, 14.94]; 1 vs 4: -13.89 [-54.99, 27.22]; 1 vs 5: -6.84 [-22.68, 9.00]; 2 vs 3: -9.50 [-40.76, 21.76]; 2 vs 4: -7.01 [-48.08, 21.77]; 2 vs 5: 0.04 [-15.70, 15.77]; 3 vs 4: -9.53 [-26.79, 7.73]; 3 vs 5: -9.53 [-26.79, 7.73]; 4 vs 5: -7.05 [-38.78, 24.68]. Pairwise between-subgroup mean differences [95% CI] for underlying disease status are as follows: 1 vs 2: -1.84 [-10.54, 6.87]; 1 vs 3: 0.05 [-12.72, 12.82]; 1 vs 4: -3.73 [-18.81, 11.36]; 1 vs 5: 6.89 [-23.86, 37.64];2 vs 3: 1.89 [-11.11, 14.88]; 2 vs 4: -1.89 [-17.16, 13.38]; 2 vs 5: 8.73 [-22.12, 39.57]; 3 vs 4: ; 3 vs 5: 6.84 [-24.11, 37.79]; 4 vs 5: 10.62 [-20.68, 41.91].



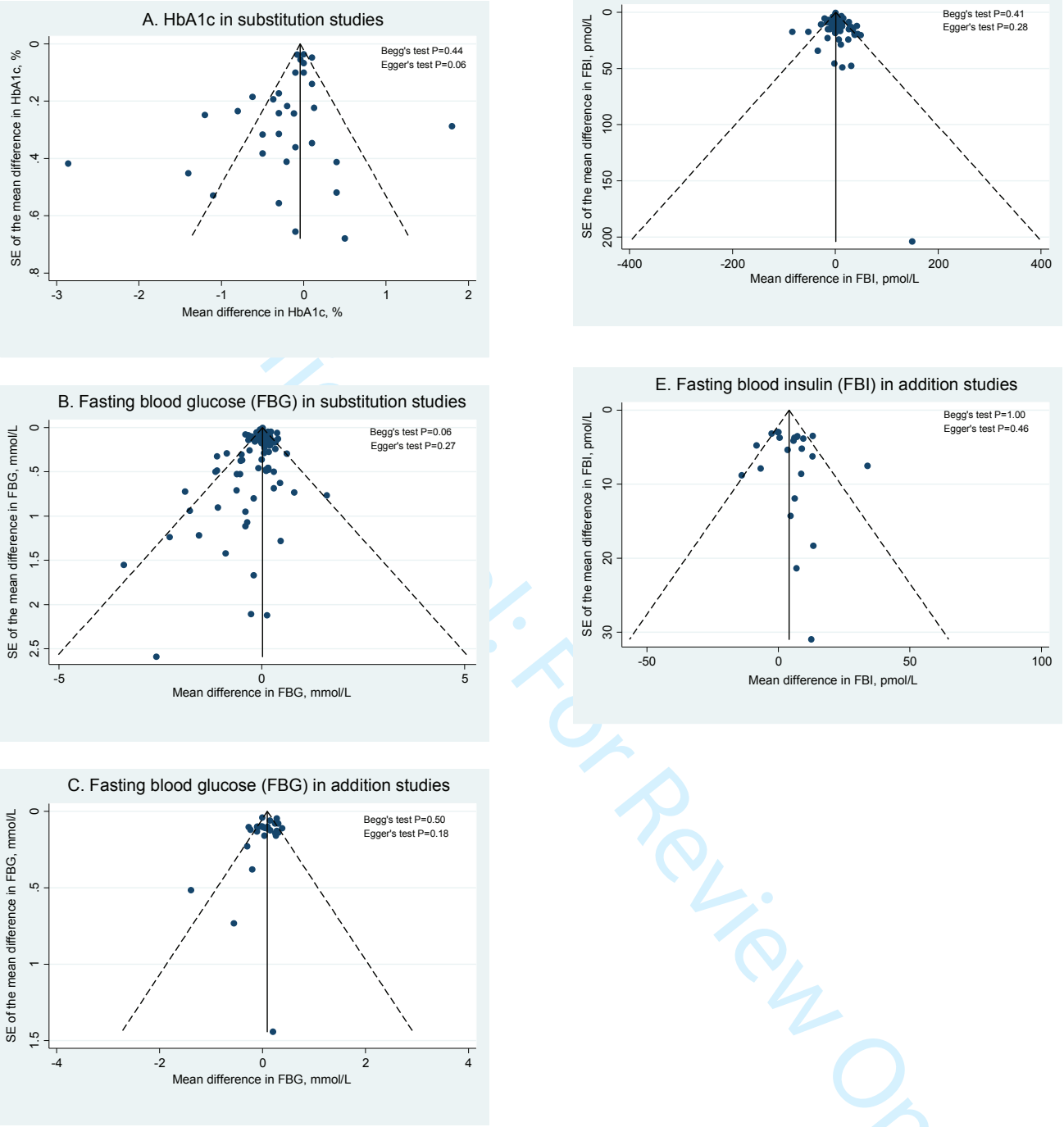
Supplementary Figure 23. Subgroup analyses for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood insulin. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. Pooled effect estimates for each subgroup are represented by the diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value represents unexplained heterogeneity for each subgroup. Pairwise between-subgroup mean differences (95% CI) for fructose-containing sugars type are as follows: 1 vs 2: -5.94 [-15.56, 3.69]; 1 vs 3: 5.20 [-4.31, 14.70]; 1 vs 4: 1.96 [-9.48, 13.40]; 2 vs 3: 11.13 [1.05, 21.22]; 2 vs 4: 7.90 [-4.03, 19.82]; 3 vs 4: -3.24 [-15.06, 8.59]. Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: 4.90 [-3.88, 13.67]; 1 vs 3: 9.41 [-57.10, 75.92]; 1 vs 4: 0.26 [-12.06, 12.57]; 2 vs 3: -4.52 [-71.17, 62.14]; 2 vs 4: 4.64 [-8.42, 17.70]; 3 vs 4: 9.16 [-58.06, 76.37].



Supplementary Figure 24. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood insulin. Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The residual I^2 value represents unexplained heterogeneity for each subgroup. HRB=High Risk of Bias, LRB=Low Risk of Bias, URB= Unclear Risk of Bias. *Within and/or between subgroup analysis could not be performed since no values were available for respective HRB/URB/LRB subgroups. Statistically significant pairwise subgroup effect modification by meta-regression analysis (P< 0.05).



Supplementary Figure 25. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood insulin. Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The residual I^2 value represents unexplained heterogeneity for each subgroup. HRB=High Risk of Bias, LRB=Low Risk of Bias, URB= Unclear Risk of Bias. *Within and/or between subgroup analysis could not be performed since no values were available for respective HRB/URB/LRB subgroups. Statistically significant pairwise subgroup effect modification by meta-regression analysis (P< 0.05).



Supplementary Figure 26. Publication bias funnel plots for the effect of food sources of fructose-containing sugars on glycemic control in substitution and addition studies. The solid line represents the pooled effect estimate expressed as the weighted mean difference (MD). The dashed lines represent pseudo-95% confidence limits and the circles represent effect estimates for each included study. P-values were derived from quantitative assessment of publication bias by Egger's and Begg's tests set at a significance level of $p < 0.05$.

Food sources of fructose-containing sugars and glycemic control: A systematic review and meta-analysis of controlled ~~trials~~~~studies~~intervention studies in people with and without diabetes

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Keywords: Fructose, HFCS, sucrose, glycemic control, diabetes, meta-analysis

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Abstract Word Count: ~~387~~4052638648798080143

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Tables: 2

Figures: 4

Supplementary Tables: ~~3~~43

Supplementary Figures: ~~23~~265

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WHAT THIS PAPER ADDS

What is already known

- Current dietary guidelines recommend a reduction to <5-10% ~~of~~ energy ~~of~~in free sugars, especially fructose-containing sugars from sugars-sweetened beverages (SSBs).
- ~~There is evidence that excess energy from fructose independent of food form impairs glycemic control in controlled intervention studies and fructose-containing sugars in the form of SSBs is associated with increased incidence of diabetes in prospective cohort studies.~~Fructose-containing sugars ~~in the form of~~from SSBs have shown an adverse association with diabetes incidence ~~incidence~~ in systematic reviews and meta-analyses of prospective cohort studies and free fructose ~~when~~ adding excess energy to diets has shown an adverse effect on glycemic control in systematic reviews and meta-analyses of controlled intervention studies.
- As dietary guidelines shift from a focus on single nutrients to a focus on ~~foods and~~ dietary patterns, it is unclear whether the evidence for SSBs and excess energy from fructose ~~translates into an adverse effect of~~holds for ~~the~~ other ~~other~~ important ~~important~~ food sources of ~~fructose-containing~~~~these~~fructose-containing sugars at different levels of energy control~~energy control~~. ~~on glycemic control.~~

What this study adds

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~~Most food sources of fructose-containing sugars including fruit and fruit juice in energy-matched substitutions for other macronutrients do not have an adverse effect on glycemic control~~

- Our systematic review and meta-analysis of 152 controlled intervention studies suggests that m~~M~~ost food sources of fructose-containing sugars ~~including fruit and fruit juice in energy-matched substitutions for other macronutrients~~ do not have an adverse effect on glycemic control in energy-matched substitutions for other macronutrients but several food sources do have adverse effects when adding excess energy to the diet, especially SSBs~~Food sources of fructose-containing sugars, especially SSBs, adding excess energy to diets or in free replacement for other macronutrients in the diet, do have adverse effects on glycemic control.~~
- While awaiting further research, public ~~Pending more research to address uncertainties in the evidence, h~~health professionals should be aware that adverse effects of fructose-containing sugars on glycemic control appear~~s~~s to be mediated by energy and food source ~~mediated~~.

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ABSTRACT

Objective: As dietary guidelines move to more dietary pattern-based recommendations, it is unclear whether the ~~public health advice to~~recommendations to ~~reduce free sugars~~the evidence supporting current recommendations to reduce~~a reduction in~~ added or free sugars, especially ~~the free sugars of greatest public health concern, the~~ fructose-containing sugars~~,~~ from sugars-sweetened beverages (SSBs), holds for ~~does donot distinguish between~~ all food sources of these sugars~~, especially the free~~

~~sugars of greatest public health concern, the fructose-containing sugars fructose, sucrose, and high fructose corn syrup (HFCS)~~. We conducted a synthesis of controlled ~~trials~~intervention studies~~,~~ to assess ~~whether the effects on glycemic control are uniform~~ the effect of different food sources of fructose-containing sugars on glycemic control at different levels of energy control.~~across different food sources of fructose-containing sugars.~~

Design: Systematic review and meta-analysis

Data Sources: MEDLINE, EMBASE, and The Cochrane library ~~were searched~~ through May~~Nov~~ 20~~3~~, 2017~~5~~.

Eligibility criteria for selecting studies: We included controlled intervention studies of ~~trials~~ ≥ 7-days duration assessing the effect of food sources of fructose-containing sugars ~~fructose-containing sugars from different food sources~~ on glycemic control in people with and without diabetes. We prespecified 4 study designs based on energy control: substitution studies (sugars in energy matched comparisons with other macronutrients); addition studies (excess energy from sugars added to diets); subtraction studies (energy from sugars subtracted from diets); and *ad libitum* studies (sugars freely replaced by other macronutrients without control for energy). ~~-~~Outcomes ~~of interest were~~ were HbA1c, fasting blood glucose, and fasting blood glucose insulin. ~~and HbA1c.~~

Data extraction and synthesis: Four independent reviewers extracted relevant data and assessed risk of bias. Data were pooled using the inverse variance method and expressed as mean differences with 95% confidence intervals (95% CIs). The overall ~~quality~~ certainty of the evidence was assessed ~~by~~ using ~~the~~ GRADE ~~approach~~.

Results: ~~Eligibility criteria were met by 160~~ 155~~5~~42 controlled intervention ~~trials~~studies (N=~~5,136~~4,979~~9~~) met eligibility criteria ~~including 4 levels of energy control~~intake: ~~104~~ substitution ~~trials (sugars in energy matched comparisons with other macronutrients); 398~~ addition ~~trials (excess energy from sugars supplementing diets); 5~~ subtraction ~~trials (excess energy from sugars reduced from~~ displaced from

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diets); and 7 ad libitum trials (sugars freely replaced by other macronutrients without strict energy controlcontrolling for energy). . Identified food sources of fructose-containing sugars food sources included fruit, sugars-sweetened beverages, fruit juice, dairy, baked goods, mixed sources and added sweeteners. In the substitution trialsstudies, total total food sources of fructose-containing sugars of fructose-containing sugars (-0.18% [-0.30 to -0.06%], p<0.01) and fruit (-0.12% [-0.23 to 0.00], P=0.04), decreased HbA1c (-0.18% [-0.29,30 to -0.06%], (-0.184% [-0.25 30 to -0.064%], p=<0.0104, moderate low quality evidence, p<=0.01107) especially in the form of fruit s (P=0.04) without affecting without affecting fasting blood glucose (moderate low quality evidence) or insulin (moderatelow quality evidence), while individual food sources showed decreasing (fruit juice), null (fruit, SSBs, baked goods, added sweeteners) or increasing (sweetened-milk, mixed sources) effects on fasting blood insulin. fasting blood glucose (high moderate quality evidence) or insulin (moderate quality evidence)), and the effect was stronger for fruit as a food source. In the addition trialsstudies, total food sources increased fasting blood insulintotal total food sources of fructose-containing sugars (4.68 pmol/L [95% CI, 1.40, to 7.96], 4.87pmol/L [1.91 to 7.84], p<0.01) and SSBs (6.17pmol/L [1.55 to 10.78], p<0.01), increased fasting fasting glucose (0.07 mmol/L [0.002 to 0.13], moderate quality evidence, p=0.04) and insulin (5.334.87 pmol/L [1.91 2.26 to 8.417.84], p=<0.001, (moderatelow quality evidence, p=<0.00107) without affecting without affecting HbA1c. (high quality evidence)fasting glucose (moderate quality evidence)(lowhigh quality evidence) or fasting blood glucose (lowmoderate quality evidence), while individual food sources showed increasing effects on both fasting blood glucose (SSBs and fruit juice) and insulin (SSBs, mixed sources). In *ad libitum* studies, total food sources derived exclusively from mixed food sources (inclusive of SSBs) increased fasting blood insulin (7.24pmol/L [0.47, to 14.00], moderatee quality evidence), while neither total nor individual food sources affected HbA1c (low quality evidence) or fasting blood glucose (moderatehigh quality evidence). or fasting glucose (moderate quality evidence)HbA1c (high moderate quality evidence), and the effect was stronger for sugars-

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~~sweetened beverages as a food source.~~ There was no evidence of ~~evidence of an effect~~benefit ~~of total~~ ~~food sources of fructose-containing sugars~~ in ~~the~~ subtraction studies, although the effect was unstable (low to moderate~~high~~ quality evidence) ~~or ad libitum trials (very low to high quality evidence)~~.

Conclusions: Energy control and food source appear to mediate the effect of ~~Pooled analyses showed that f~~Fructose-containing sugars on glycemic control~~food~~. Whereas most food sources of fructose-containing sugars ~~from various food sources, especially fruit, are no worse in their~~do not have an adverse effect~~s on glycemic control~~ in energy-matched ~~comparisons~~ substitutions with other macronutrient~~-containing food~~s, several food sources of ~~. However, total food sources of~~ fructose-containing sugars, especially ~~sugars-sweetened beverages~~SSBs, ~~supplementing diets with~~adding excess energy to diets or in free replacement for other macronutrients ~~in the diet~~ do ~~appear to~~ have adverse effects. ~~Longer, larger, high quality~~More ~~trials~~studies are ~~required~~needed to improve our confidence in the estimates.

~~**Systematic review r**~~**R**egistration: Clinical~~Trials~~Studies.gov identifier, NCT02716870.

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INTRODUCTION

The role of sugars~~- consumption~~ in the development of cardiometabolic disease is actively debated (1, 2). In particular, fructose has recently emerged as a serious public health concern, as ecological parallels have been drawn between the introduction of high fructose corn syrup (HFCS) as a popular sweetener during the 1970s and global rises in obesity and diabetes prevalence (3, 4)~~-~~.

Despite early considerations for the use of fructose as an alternative sweetener in people with diabetes due to its observed potential to lower postprandial glycemic excursions when compared to isocaloric amounts of starch (5), a mounting body of evidence has suggested that fructose may be particularly detrimental to metabolic health, even more so than other sugars (6). This view has received support from ecological evidence(4) as well as animal (7-9) and select human intervention ~~trials~~studies(10-12). However, higher levels of evidence ~~from prospective cohort studies have not shown a clear association between fructose-containing sugars and diabetes risk (13, 14), with the one exception being sugars-sweetened beverages (SSBs)(15, 16).~~from systematic reviews and meta-analyses of controlled human intervention studies have ~~A synthesis of data investigating the role of fructose on glycemic control in people with diabetes also~~ failed to demonstrate adverse glycemic effects unique to fructose, and have even shown a ~~suggested potential~~ benefi~~t~~cial effect on glycated blood proteins ~~when~~ of fructose ~~was~~ in isocaloric~~ally exchanged~~ substitution for other carbohydrates in the diet in people with diabetes (13).

Whether there exists a causal link between fructose and the development of diabetes and related cardiometabolic co-morbidities continues to be contested, though much less appreciated in this debate are the consumption patterns and levels at which fructose is normally consumed in the diet. Fructose is rarely consumed in isolation under real world conditions (14). It is present in a variety of food sources containing comparable amounts of glucose, and the proportion of fructose co-ingested with glucose has

been suggested to influence fructose metabolism (15). In its most commonly consumed form, sucrose (table sugar), fructose is part of a disaccharide with glucose in a 50:50 ratio. HFCS is also a glucose-fructose mix, with varying fructose content (42-55% molecular weight) in a free, ~~n~~ unbound monosaccharide form. Similarly, less refined sources of fructose-containing sugars, including honey, agave and maple syrup, are composed of varying proportions of fructose and glucose, while natural sources of fructose present in various fruit~~s~~ and vegetables also co-exist with glucose ~~in catalytic amounts (≤10 g/meal)~~. These fructose-containing sugars are found in the diet in a variety of food sources, ranging from "nutrient poor" sources of added sugars such as sugars-sweetened beverages (SSBs), to "nutrient dense" sources of bound sugars such as fruit~~s~~. ~~However, despite the high sugar composition of each, c~~Evidence from prospective cohorts on diabetes risk have shown differential associations depending on the food source of the sugars (positive associations with SSBs (16, 17) and inverse association with fruit ~~s~~)(18, 19)).

~~This question has become increasingly important, as~~As dietary guidelines ~~have~~ shifted from nutrient-based recommendations to more food and dietary pattern-based recommendations(20, 21) [Please insert reference for Stevenson E, Swainson MP. Food-based dietary pattern-based recommendations: An overview and a comparison of guidelines for the prevention and management of obesity. Eur J Diabetes 2013 Feb;3(1):51-71.], it is important to understand the role of the food matrix in modifying the effect of fructose-containing sugars. Current recommendations from the WHO, U.S., and England have focussed on the reduction of added or free sugars to <5-10% energy (20, 22, 23)[Please insert reference for Guideline: Sugars intake for Adults and Children: WHO Guidelines Approved by the Guidelines Review Committee. Geneva 2015.] [Please insert reference for Scientific Advisory Committee on Nutrition. Carbohydrates and Health. Public Health England. London 2015. Accessed at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbo

Hydrolase, and Insulin, not on Oct 17, 2017], especially free fructose-containing sugars from sugars-sweetened beverages (SSBs) (20). Whether the evidence for added or free sugars and SSBs can be generalized to all various food sources of fructose-containing sugars differ in relation to their effects on surrogate markers of type 2 diabetes in controlled trials have s not yet been determined. This question has become increasingly important, as dietary guidelines have shifted from nutrient-based recommendations to more food and dietary pattern-based recommendations(24). To help address this gap, wWe conducted a systematic review and meta-analysis of controlled trialsintervention studies to determine the effect of food sources of fructose-containing sugars at different levels of energy control fructose-containing food sources on outcome measures of glycemic control in people with and without diabetes.

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METHODS

This systematic review and meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews and interventions(24), with all results reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (25). The study protocol was registered at ClinicalTrialsStudies.gov, (identification number, NCT02716870).

Data Sources

Medline, EMBASE and the Cochrane Central Register of Controlled TrialsStudies were searched through November May 293, 2015 2017 using the following search terms: fructose OR dietary sucrose, OR HFCS OR sugar OR sugar* sweetened beverage* OR honey AND glyc?em* OR insulin OR HbA1c OR fructosamine OR blood glucose OR gly* albumin (**Supplementary Table 1**). Validated filters from McMaster University Health Information Research Unit were applied to limit the database search to

controlled ~~trials~~studies only (26), and electronic searches were supplemented with manual searches of references from included studies.

Study Selection

~~Inclusion criteria for our analysis~~We included reports of controlled intervention ~~trials~~studies ~~in humans~~ lasting ≥7 days investigating the ~~role~~ effect of diets of ~~-~~fructose-containing sugars (fructose, sucrose, HFCS, honey, syrups~~, honey, or fruit sugars~~) from various food sources compared with control diets free of or lower in fructose-containing sugars on outcome measures of glycemic control (fasting glucose, fasting insulin, and HbA1c) in people with and without diabetes. We excluded reports of studies ~~that used~~~~using~~of meal replacements and ~~-~~studies of interventions ~~or comparators~~ off ~~-~~rare sugars that contained fructose (e.g. isomaltulose or melzitose) or were low-calorie epimers of fructose (~~(e.g. isomaltulose, melzitose,~~ e.g. allulose, tagatose, sorbose) or studies that used these sugars as the comparator ~~as part of the main intervention or comparator~~. Four ~~trial~~ study designs based on the control of energy were prespecified~~identified~~: 1) 'substitution' ~~trials~~studies, in which food sources of fructose-containing sugars ~~fructose-containing sugars added to foods and beverages~~ were compared with ~~-~~food sources of other non-fructose-containing macronutrients ~~t sources~~ under energy matched conditions (isocaloric comparison); (2) 'addition' ~~trials~~studies, in which excess energy from food sources of fructose-containing sugars ~~fructose-containing sugars supplemented a~~ was added to background diets ~~with excess energy~~ compared to the same background diets ~~supplemented with the equivalent amounts of non-caloric food and beverages or the same diet~~ alone without the excess energy from ~~food sources of~~ fructose-containing sugars with or without the use of low-calorie sweeteners to match sweetness~~fructose-containing sugars~~ (hypercaloric comparison); (3) 'subtraction' ~~trials~~studies, in which energy from food sources of fructose-containing sugars ~~fructose-containing sugars~~ was ~~reduced~~subtracted from background diets through displacement by~~with~~ water and/or ~~no-calorie or~~ low-

calorie sweeteners, or by eliminating ~~it~~ the food sources of fructose-containing sugars altogether compared with ~~from~~ the original background diets (hypocaloric comparison); and (4) '~~ad libitum~~*ad libitum*' ~~trials~~studies, in which ~~energy from~~ food sources of fructose-containing sugars ~~fructose-containing sugars were freely replaced~~were compared with ~~with other~~ food ~~and beverages~~sources of other non-fructose-containing macronutrients ~~-~~without any strict control of either the study foods or the background diets to allow for free replacement of the energy from fructose-containing sugars with the energy from other macronutrients (free-feeding comparison). Reports containing b~~B~~oth randomized and non-randomized controlled intervention studies ~~studies~~ were included. ~~only~~ An intervention study was considered non-randomized if the authors~~, where non-randomized studies either~~ explicitly stated that a method of randomization was not used or~~,~~ randomization was not reported in the allocation of participants to the intervention or control treatments in parallel designs or the sequence of the treatments in crossover designs. In reports containing more than one study comparison, we included all available study comparisons. ~~or were conducting using a crossover design where all participants were assigned to the same sequence of treatments.~~

Patient involvement

No patients~~/service users/carers/lay people~~ were involved in the design of this study.

Data Extraction

Data from included reports were individually extracted at least twice by four separate reviewers ~~with all discrepancies resolved through consensus between reviewers~~. Relevant information included number of participants, setting, ~~health~~ underlying disease status of participants, study design, level of feeding control, randomization, comparator ~~form~~, fructose-containing sugars ~~form~~ type, ~~and~~ food sources of fructose-containing sugars~~food source~~, macronutrient profile of the diets, follow-up duration, energy

balance, ~~risk of bias~~ and funding sources. The three o~~O~~utcome ~~measures~~ variables ~~included~~ were HbA1c, fasting blood glucose, and fasting blood insulin. HbA1c was reported instead of total glycated blood proteins as originally indicated in our protocol (identification number, NCT02716870), as mean differences for these values were considered more clinically relevant and did not require the use of standardized mean differences needed to ~~calculate pooled effects for~~the different glycated blood proteins. Authors were contacted for missing outcome data when it was indicated that an outcome was measured but not reported. In the absence of numerical values for outcome measurements and inability to ~~achieve a response from~~ obtain the original data from authors ~~inability to contact authors~~, values were extracted from figures using Plot Digitizer where available(21). All discrepancies between reviewers were resolved through consensus or, where necessary, arbitration by the senior author.

Study quality

Included studies were assessed for risk of bias by at least 2 of the reviewers using the Cochrane Collaboration Risk of bias Tool(27). Final assessments were based on consensus between reviewers.

Data Synthesis and Analysis

We used Review Manager (RevMan) version 5.2 (Copenhagen, Denmark) for primary analyses and Stata (version 12, College Station, TX, USA) for subgroup, dose response, and publication bias analyses. We performed separate analyses for the 4 prespecified study designs based on the control of energy (substitution, addition, subtraction, and *ad libitum* studies) and stratified analyses by food sources of sugars for each of three outcome variables (HbA1c, fasting blood glucose, and fasting blood insulin). The principal effect measure was the mean pair-wise difference (MD) in change from baseline (or, when not available, the post-treatment value) between the food sources of fructose-containing sugars ~~fructose-containing sugar~~ arm and the comparator arm with results reported as mean differences (MD) with

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95% confidence intervals (CI). ~~For each study, w~~We extracted the estimates of the MD and corresponding 95% confidence intervals for each outcome. ~~-~~Change-from-baseline differences were preferred over end differences and paired analyses were applied to all crossover trials with the use of a within-individual correlation coefficient between treatments of 0.5 as described by Elbourne et al.(28)~~-~~. When at least two studies provided data, we performed a DerSimonian and Laird random effects meta-analysis, which yields conservative confidence intervals around effect estimates in the presence of heterogeneity. When ~~four or fewer studies~~less than 5 studies ~~were combined~~were available for analysis, we also considered fixed effect estimates.

Heterogeneity was ~~determined~~ assessed by the~~with~~ Cochran~~'s~~ Q test (significant at P<0.10)~~,~~ and quantified ~~with~~ by the I^2 statistic (range ~~from~~ 0%-100%)(29). The interaction of fructose-containing sugars x food source was assessed using the Chi-square statistic. Other sources of heterogeneity were explored using sensitivity and subgroup analyses. We carried out sensitivity analyses by systematically removing each study from the meta-analyses and recalculating the summary association. A study whose removal explained the heterogeneity, changed the significance of the effect, or altered the ~~magnitude of the nominal~~ effect size by ~~10~~510% or more, was considered an influential study. ~~, and used to assess inconsistency as part of the GRADE assessment of evidence quality. *A priori* subgroup analyses were conducted to explore sources of heterogeneity. Categorical subgroup analyses were conducted for~~If ≥10 studies per outcome were available (30, 31) ~~and heterogeneity was substantial (I^2 >50% or P_Q<0.10)~~(33), then we conducted a priori subgroup and analyses ~~we used~~using meta-regression ~~to explore sources of heterogeneity through a priori subgroup analyses~~. Categorical subgroup analyses were done for ~~included sources of fructose-containing food sources (fruits, fruit juices, sugars-sweetened beverages, dairy products, sweets/desserts/baked goods, and mixed sources),~~ energy balance (positive, neutral, negative), comparator ~~form~~ (~~fill in when subgroup figures made~~starch, glucose, fat, lactose, ~~isomaltulose,~~ maltrodextrin, diet alone, water, non-nutritive sweeteners, protein ~~and~~, ~~-~~mixed sources),

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fructose-containing sugars ~~form~~ type (fruit, sucrose, fructose, HFCS, honey), fructose-containing sugars dose (≤10%, >10% energy (22, 32)~~intake~~), baseline values for HbA1c (≤7%, >7%), fasting glucose (≤5.5, >5.5 mmol/L based on median values)~~,~~ and insulin (≤96.6, >96.6 pmol/L based on median values) ~~and HbA1c (≤7%, >7%)~~, age (≤18, >18), study design (crossover, parallel), follow-up duration (< 8weeks, ≥ 8 weeks) , randomization (yes, no), ~~dietary compliance~~level of feeding control (supplemented, dietary advice and metabolically controlled), underlying ~~health~~ disease status (diabetes, overweight/ obese, metabolic syndrome criteria, otherwise healthy), ~~overall risk of bias,~~ and individual domains of risk of bias (sequence generation, allocation concealment, blinding of participants/ personnel and outcome assessors, incomplete outcome data, selective outcome reporting). ~~*Post-hoc* d~~Continuous d~~D~~ose response analyses were performed using meta-regression to assess linear dose-response gradients and ~~piecewise~~ non-linear meta-regression (MKSPLINE procedure) with knots at the public health thresholds of 5% (22, 23), 10% (22, 33), and 25% (34) energy to assess non-linear dose-threshold effects. ~~for the continuous subgroup of fructose-containing sugars dose (as percentage of total energy intake) on measures of glycemic control. If ≥10 studies were available (34, 35) and heterogeneity was substantial (I^2>50% or P_Q<0.10)~~(33) ~~we used meta-regression to explore heterogeneity by sources of fructose-containing food sources (fruits, fruit juices, sugars-sweetened beverages, liquid meal replacements, dairy products, sweets/desserts/baked goods, and mixed sources).~~

~~Analyses were conducted using Review Manager (RevMan) version 5.2 (Copenhagen, Denmark) and Stata (version 12, College Station, TX, USA) for subgroup analyses. Results were reported as mean differences (MD) with 95% confidence intervals (CI).~~

~~As a sensitivity analysis, we removed each single study from the meta-analyses and recalculated the summary effect (the "leave one out" approach)~~(39). If ≥10 studies per outcome were available(35), then we ~~explored the possibility of~~assessed publication bias by inspection of~~ng~~ funnel plots and formal testing with the ~~conducting~~ Egger~~'s~~ and Begg~~'s~~ tests ~~(each significant at P<0.10)~~. If there was evidence of

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publication bias ~~was suspected~~, then we used the Duval and Tweedie trim and fill method to adjust for funnel plot asymmetry by imputing missing study data, ~~results are shown without imputation and with "missing" studies imputed with Duval and Tweedie's trim and fill method~~(36).

Grading of the evidence

The ~~G~~grading of ~~R~~recommendations ~~A~~assessment, ~~D~~development~~,~~ and ~~E~~evaluation (GRADE) approach was used to assess ~~the confidence in the effect estimates (quality of evidence)~~the certainty in our estimates ~~derived from the body of evidence (quality of evidence) by outcome~~ , and produce evidence profiles (37) using GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University, Canada, 2015). ~~Through E~~this approach, evidence was graded as high, moderate, low or very low quality. Included controlled ~~trials~~studies intervention studies were graded as high quality evidence by default and downgraded based on pre-specified criteria. Criteria to downgrade evidence included risk of bias (assessed through the Cochrane Risk of Bias tool), inconsistency (substantial unexplained ~~interstudy~~ heterogeneity, I^2>50%, P<0.10), indirectness (presence of factors that limited the generalizability of the results), imprecision (the 95% CI for pooled effect estimates ~~were wide or~~ crossed a minimally important difference [MID] for benefit or harm for HbA1c [±0.3%], fasting blood glucose [±0.5 mmo/L], and fasting blood insulin [±10 pmol/L]), and publication bias (significant evidence of ~~small study effects~~publication bias).

RESULTS

Search Results

The systematic search and selection of literature is shown in **Figure 1.** ~~34~~,180~~574~~ reports were identified from database and manual searches, of which 3,~~353~~ 882 were excluded based on title and abstract. ~~221~~ 257 reports were reviewed in full, of which an additional ~~99~~ 1~~37~~40 reports were excluded ~~based on~~for failure to meet the eligibility ~~inclusion~~ criteria. ~~122~~ 1179 reports of controlled intervention

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studies (5, 11, 12, 38-153) including a total of 1524 study comparisons in 4,979 participants were included in the final analysis (5, 11, 12, 43-158).

Study Characteristics

A summary of the mean study characteristics is presented by the 4 prespecified study designs (substitution, addition, subtraction, and *ad libitum* studies) in **Table 1**, with an individual breakdown of individual study characteristics in **Supplementary Table 2**. Study sizes were relatively small, ranging from a median of 15 participants (range 2 to 595) in subtraction studies to 39 (range 8-236) participants in *ad libitum* studies. The majority of studies were performed in an outpatient setting, with almost half of all substitution (44/110), addition (12/3) and subtraction (12/5) studies conducted in the USA, and all *ad libitum* studies conducted in European countries. Participants tended to be middle aged, with approximately equal ratios of males to females in substitution, addition and *ad libitum* studies, but proportionately more females in subtraction studies. Most studies were conducted in those with diabetes (36%) or otherwise healthy participants (37%) in substitution studies; otherwise healthy (38%) or overweight/obese (3%) in addition studies; overweight or obese (80%) in subtractions studies; and otherwise healthy (67%) in *ad libitum* studies. Most studies were randomized (69% of substitution studies, 6% of addition studies, 80% of subtraction studies and 100% of *ad libitum* studies) however. Follow up duration was relatively short, ranging from a median of 5 weeks (range 1 to 52 weeks) in substitution studies to 12 weeks (range 1-36 weeks) in subtraction studies. Fructose-

containing sugars doses ranged from a median of ~~15~~10~~2~~.2% (range 7.7-25.0%) of total energy intake in ~~substitution and subtraction~~addition ~~trials~~studies to 23% (range 13.0-26.0%) of total energy intake in ~~ad libitum~~*ad libitum* ~~trials~~studies, and were mostly in the form of mixed food sources in substitution (~~57~~45~~6~~/110~~410~~) and ~~ad libitum~~*ad libitum* (6/7) ~~trials~~studies while most addition (~~16~~12/35~~98~~) and subtraction (4/5) ~~trials~~studies used sugars-sweetened beverages.~~–~~ Most ~~trials~~studies were funded by agency sources (government, not-for-profit health agency or university sources), except for ~~ad libitum~~*ad libitum* trails which were primarily funded by agency-industry funding.

Study quality

A summary of the r~~R~~isk of bias assessments by the Cochrane Risk of Bias Tool is shown in **Supplementary Figure 1**. Owing to poor reporting standards, most studies were assessed as having unclear risk of bias across the 5 domains of bias. F~~Lastly, very f~~ew ~~trials~~studies ~~(4 /~~were assessed as having high risk of bias ~~that included one to three domains across the 5 domains of bias~~ with only ~~Only~~ 19.3%, 22.7%, 1.7%, 7.6% of studies ~~were~~ assessed as ~~considered at~~ high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and incomplete outcome data, respectively. ~~A priori subgroup analyses by the domains of bias did not shown any evidence of subgroup effect modification with the exception of the blinding of participants and personnel for fasting blood insulin in substitution studies, whereby fructose-containing sugars showed a fasting blood insulin-increasing effect (**Supplementary Figure 23**), as assessed by the Cochrane Risk of Bias Tool (**Supplementary Figure 1**).~~ Overall, no serious risk of bias was detected.

Outcome~~s~~s: HbA1c

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The effect of different food sources of fructose-containing sugars ~~fructose-containing food sources~~ on HbA1c are shown in **Figure 2** and **Supplementary Figures 2-5**. ~~In 32~~ ~~28~~ ~~substitution trials involving 946 839 participants~~Total ~~where food sources of~~ fructose-containing sugars~~fructose-containing sugars were exchanged for other macronutrients of equal energy, a significant reduction in~~independent of food sources showed a significant decreasing effect on HbA1c in substitution studies ~~was observed~~ (~~28~~32 study comparisons, MD=-0.1~~8~~4% [95% CI, ~~=~~ -0.~~30~~29,~~25 to~~, -0.0~~6~~4], p=~~<~~<=0.~~00~~701~~04~~1~~1~~, substantial heterogeneity [I^2=~~81~~8~~23~~%, ~~heterogeneity~~ p <0.00~~00~~0001]~~; moderate low quality evidence~~)~~.~~ ~~No other significant effects were found for total food sources of fructose-containing sugars~~There was no significant effect in addition (~~68 6 trials~~study comparisons, ~~231 295 participants,~~ substantial heterogeneity [I^2=~~75~~83%, p<0.001]~~high quality evidence~~), subtraction (1 ~~trial~~study comparison~~, 240 participants, low~~ ~~medium~~ ~~quality evidence~~) or ~~*ad libitum*~~*ad libitum* ~~trials~~ (1 study comparison~~trial, 10 participants, very low quality evidence~~) studies. There was no fructose-containing sugars x food source interaction in the substitution, addition, subtraction or *ad libitum* studies. ~~Food sources of fructose-containing sugars~~~~Fructose-containing sugars from fruits significantly decreased HbA1c (MD= -0.12% [95% CI= -0.23, -0.003], p=0.04) in substitution trials. No food sources of fructose-containing sugars food sources were significant in addition, subtraction or ad libitum trials.~~

Sensitivity analyses for HbA1c are presented in **Supplementary table 3.** ~~through showed that the r~~RThe removal of each study did not explain ~~the addition study a trial by Enginyurt et al. involving 32~~individual ~~participants with diabetes explained most of~~ the heterogeneity, or ~~in the addition analysis trials did not~~ changed~~ing~~ed the ~~overall significance or direction~~ significance ~~of the effect in any analyses~~~~without changing the lack of significance, but explaining most of the heterogeneity~~ ~~but not the lack of~~ significance of the effect. ~~(**Supplementary table 3**).~~

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A priori subgroup analyses for HbA1c are presented in **supplementary figures 6 and 7**. ~~In substitution trials (**Supplementary Figure 6**), participants with higher baseline levels showed greater improvements in glycemic control on fructose-containing arms relative to controls. Post hoc~~and ~~-~~dose-response analyses for HbA1c are presented in **Supplementary Figure 8 and** ~~**Supplementary table 3**~~**9**. *A priori* subgroup analyses did not reveal~~ed~~ any effect modification ~~under substitution conditions of food sources of fructose-containing sugars intake~~in substitution studies ~~(**Supplementary figures 6 and 7**)~~. ~~Additionally, I~~in substitution ~~trials~~studies~~, we found no significant effect modification by fructose-containing sugars dose~~There was also no evidence of a dose-response gradient ~~(**Supplementary Figure 8A)**~~ or ~~by dose~~ thresholds ~~**(Supplementary table 3A4A)** of food sources of fructose-containing sugars fructose-containing sugars intake~~.

No subgroup or dose-response analyses were conducted for addition, subtraction or ~~ad libitum~~*ad libitum* ~~comparisons~~ studies, as less than 10 ~~trials~~studies were available ~~in each analysis~~for these analyses.

Outcomes: Fasting Blood Glucose

The effect~~s~~ of different food sources of fructose-containing sugars ~~fructose-containing food sources~~ on fasting blood glucose are shown in **Figure 3** and **Supplementary Figures** ~~10-13~~**9-12**. Total ~~In 35 trials involving 985 participants under addition conditions, fructose-containing sugars from all food sources increased fasting blood glucose (MD=0.07 [95% CI=0.002, 0.13], p=0.04, I^2=72%, p heterogeneity<0.0001], moderate quality evidence), but Food sources of~~ fructose-containing sugars independent of food sources had no effect on fasting blood glucose ~~under~~ in substitution studies (~~101~~ ~~95~~101 ~~trials~~study comparisons, ~~2,948 901 participants,~~ substantial heterogeneity [I^2=654, p<0.001]~~moderate quality evidence~~), addition studies (28 study comparisons, substantial heterogeneity

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[I^2=6971, p<0.001]), addition studies (34 trials, 971 participants, moderate quality evidence) subtraction studies (4 (74) trialsstudy comparisons, 585 participants, substantial heterogeneity [I^2=59, p=0.06] high quality evidence) or ad libitumad libitum conditions studies (6 trialsstudy comparisons, 459 participants, no evidence of heterogeneityhigh quality evidence). There was a significant fructose-containing sugars x food source interaction in addition studies (P<0.001): SSBs (11 study comparisons, MD= 0.12 mmol/L [95% CI, 0.03, to 0.22], substantial heterogeneity [I^2=5974], p=0.06<0.001) and fruit juice (2 study comparisons, MD= 0.29 mmol/L [95% CI, 0.09, to 0.49], no evidence of heterogeneity) showed a significant increasing effect, while fruit (7 study comparisons), fruit drinks (3 study comparisons), sweetened chocolate (1 study comparison), added sweeteners (3 study comparisons), and mixed sources (1 study comparison) showed no significant effect on fasting blood glucose. No fructose-containing sugars x food source interactions were seen in the substitution, subtraction or *ad libitum* studies.

Sensitivity analyses for fasting blood glucose are presented in **Supplementary Table 43.** Sensitivity analyses showed that the). Fructose-containing sugars in the form of liquid meal replacements led to a significant increase in fasting blood glucose (0.83 mmol/L [0.28, 1.39], p=<0.0103) when adding excess energy to the diet under addition conditions, although this was only based on one trial. Individual rRemoval of anyone of 9 6 addition studies (38, 46, 72, 105, 114, 123) ((43, 51, 77, 110, 119, 128)38, 46, 72, 105, 114, 123) trials (43, 44, 51, 74, 77, 103, 110, 119, 128) 13 trials (88, 100, 101, 107, 109, 116, 130, 141, 142, 146, 159) from the addition comparisons changed the overall significance from non-significant to non-significant of the effect while keeping direction the samewithout changingbut did not change the magnitude or direction of the effect or the evidence of substantial heterogeneity (**Supplementary Table 43**). Under subtraction conditions, rRemoval of the subtraction a trial study by Campos et al. 2015 (group 2 [(G2])) (60) involving 15 participants over a 12 weeks duration explained all

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of the heterogeneity, ~~reversaltering~~changing~~ed~~ the direction ~~of the effect on fasting blood glucose and explained all of the heterogeneity, but did not modify the overall~~but not the lack of significance of the effect on fasting blood glucose ~~or the evidence of heterogeneity (Supplementary Table 43)~~. Finally, removal of the subtraction study by Tate et al. 2012 (149) involving 318 participants over 6 months explained all of the heterogeneity but did not change the direction~~, and~~or lack of significance~~, and significance~~ of the effect on fasting blood glucose (MD= -0.20 pmol/L [95% CI, -0.040, ~~to~~ 0.4000], p =0.05, no evidence of heterogeneity [I^2=32%, P=0.23]).

A priori subgroup analyses for fasting blood glucose are presented in **Ssupplementary Ffigures 1~~4-17~~3-~~16~~** and -d~~. Post hoc d~~ose-response analyses for fasting blood glucose are presented in **Supplementary Figure 8 and ~~Supplementary Ttable 49 [insert new Figure numbers]~~**. ~~*A priori* subgroup analyses revealed an~~There was significant effect modification by fructose-containing sugars dose, baseline fasting blood glucose, feeding control, and underlying disease status ~~under~~ in ~~by several factors in~~ the substitution studies (P≤0.05) ~~conditions by comparator form, fructose-containing sugars dose, baseline fasting blood glucose, fructose dose, comparator form and dietary compliance (Supplementary Figure 13 and Supplementary Table 4)~~. ~~Significant s~~Subgroup analyses ~~by comparator form showed that all food sources of fructose-containing sugarsdemonstrated had a significant decreasing effect ooin fasting blood glucose withwhen the comparator was mixed macronutrients comparators (P=0.01) and a significantn increasing effecte effect oniin fasting blood glucose when the comparator was in the form of starch (P<0.01). S~~Categorical subgroup analyses by dose showed a greater decreasing effect ~~the effect of fructose-containing sugars was significantly different between the low (≤10% energy) and at high (doses >10% energy) doses~~≤10% energy than >10% energy (P=0.01), although ~~neither dose alone showed a significant effect on fasting blood glucose~~there was no evidence of a continuous linear dose-response gradient by meta-regression or ~~non-linear~~ dose ~~or dose~~ thresholds with knots at 5%, 10%, or 25%

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energy by the MKSPLINE procedure, and there was no evidence of a The difference in fructose-containing sugars dose comparison (≤10% vs >10% of energy) was significant (P=0.02), although a significant response within group or in the continuous linear dose- response gradient in continuous dose-response analyses was not observedthe (**Supplementary figure 8B**). Nonetheless, weWe did, however, observed a significant effect modificationdose-threshold effect by dose-thresholds at higher doses 20, 30 and 40 % of energy using piecewise linear regression (**Supplementary table 4B**), where higher fructose-containing sugars had a doses demonstrated a small decreasing effect on ed in fasting blood glucose when the doses were >20%, >30%, and >40% energy., but not when fructose-containing sugars dose was >50% of energy. such that baselineSubgroup analyses by bBaseline fasting blood glucose showed a greater -decreasing-effect on fasting blood glucose of all food sources of sugars on fasting blood glucose whenat atthe -baseline fasting -blood glucose levels ofwas ≥>6.15.5 mmol/L -than but led to a greater decrease in levels of fasting blood glucosenot -≤5.5mmol/L- (P<=0.014<0.01). Additionally, although -Ffructose dose was not significant at ≤10 or >10% of energy also increased fasting blood glucose (P=0.02), although a significant continuous dose response was not observed. Significant subgroup analyses by comparator form demonstrated a decreasing effect on fasting blood glucose with mixed macronutrient comparators (P=0.09) and an increase in fasting blood glucose when the comparator was in the form of starch (P=0.01). LastlyFinally, significant subgroup effects byFinally, subgroup analyses by dietary complianceLevel of feeding control revealedshowed an greater decreasing effect -increasing effect of thatall food sources of fructose-containing sugars on fasting blood glucose in metabolically controlled studiesstudies using supplementation or dietary advice as the methods of feeding control than in studies using metabolic control (provision of all study foods) as the method of feeding controlbut not in studies in pairwise comparisons -using supplementation or dietary advice lead to a significant increase in fasting plasma glucose (P<0.051). -None of the subgroups explained the substantial heterogeneity in the substitution studies. -(P=0.01) (**Supplementary Figure 8-B**), but this

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~~effect lost significance upon removal of an outlier study using extreme doses of sucrose at 75% of energy(10). Post-hoc dose-threshold analyses also showed significant effect modification by dose at doses >50 % of energy (P<0.05), such that doses >50 % of energy resulted in higher levels of fasting blood glucose (**Supplementary Table 3B**). With the removal of the same outlier study (Hendler et al. 1990(160)), this effect was seen starting at lower doses (>20 % energy [P=0.04]).~~

A s~~S~~ignificant subgroup effect~~s~~ w~~as~~ere also ~~also~~ observed in addition ~~trials~~studies (~~**Supplementary Figure 14**~~). There was significant effect modification by ~~by fructose-containing food source, fructose-containing sugars~~ type~~form, baseline fasting blood glucose, age, dietary compliance, baseline fasting glucose~~feeding control, and underlying disease status (P<0.05). ~~Particularly, fructose-containing sugars~~food sources of fructose-containing sugars in the form of in the form of honey added sweeteners (3 trials~~Subgroup analyses by fructose-containing sugars type showed a greater decreasing effect of) led to greater decreases in fasting blood glucose (P<0.01), Second, and fFfructose-containing sugars in the form of honey than pure led to greater decreases in fasting blood glucose (P<0.01) while fructose, sucrose, fruit, and, HFCS in its pure monomeric form in pairwise comparisons led to an increasing effect oin fasting blood glucose (P<=0.02<0.051). Subgroup analyses by ~~Second, b~~Baseline fasting blood glucose levels showed a greater decreasing effect when the baseline ~~of~~ fasting blood glucose was~~at~~ ≥>5.5 mmol/L than~~also~~ ≤5.5 mmol/L ~~led to greater decreases in levels of fasting blood glucose~~ (P=≤0.01). ~~Subgroup analyses by age showed a greater decreasing effect in children (age ≤18 years) than adults (age >18 years) (P=0.04)Additionally, , whereas fructose in its pure monomeric form (9 trials) lead to increasing effects on fasting blood glucose when adding excess energy to the diet. Second, a~~a greater reduction in levels of fasting blood glucose was observed for children who supplemented the diet with excess calories from food sources of fructose-containing sugars compared to adults, although only one trial study in children was available for analysis. Subgroup analyses by level of feeding control

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showed a greater decreasing effect in studies using Additionally, dDdietary advice asas thea method of dietary compliance than in studies using supplementation and metabolic control as the methods of feeding control in pairwise comparisons led to greater reductions in fasting blood glucose compared to metabolic or supplementation of study foods (P<0.05−0.042). Baseline levels of fasting glucose at ≥5.5 mmol/L also led to greater decreases in levels of fasting blood glucose (P<0.01). FinallyLastly, subgroup analyses by underlying disease status of participants showed a greater decreasing effect participants within diabetes displayed greater improvements in fasting blood glucose on the food sources of fructose-containing sugars interventions (P<0.01)than in overweight/obese, otherwise healthy, or MetS criteria in pairwise comparisons, compared to patients without diabeteswhile participants who were overweight or obese showed a moderate rise (P<=0.0253). ThisNone of the subgroup did nots explained the substantial heterogeneity in in the addition studies in the addition studies.

No subgroup or dose-response analyses were conducted for subtraction or ad libitum*ad libitum* comparisons as less than 10 trialsstudies were available for these analysesin each analysis. No a priori subgroup analyses were conducted in subtraction or ad libitum trials as too few trials were available. Post hoc dose threshold analyses did not show any significant effect modification by dose (**Supplementary Table 3C**).

Outcomes: Fasting Blood Insulin

The effect of different food sources of fructose-containing sugarsfructose-containing food sources on fasting blood insulin are shown in **Figure 4** and **Supplementary Figures 1**8-217 20. In 267 addition trials involving 730 716 participants Total where food sources of fructose-containing sugars supplemented the diet with excess energy compared to the diet alone or non-caloric food sources, anindependent of food

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sources had an increasing effect on fasting blood insulin in addition studies ~~was observed from total food sources~~ (23 study comparisons, MD=~~4.87~~68 ~~5.33~~ pmol/L [95% CI~~=, 2.26, 8.41~~1.9140, ~~to~~ 7.96~~,84~~], p < 0.01~~<0.001~~, substantial heterogeneity [I^2=5~~6~~8%, ~~heterogeneity~~ p<0.001]~~, moderate quality evidence~~) and *ad libitum* studies (4 study comparisons, MD=7.24 pmol/L [95% CI, 0.47, ~~to~~ 14.00], p=0.04, no evidence of heterogeneity [I^2=0%, p=0.46). There was no effect in substitution (72 studies) or subtraction (3 studies, substantial heterogeneity [I^2=79, p=~~0.009~~<0.01]). ~~-~~ There was a significant fructose-containing sugars x food source interaction in substitution studies (P<0.001): fruit juice (1 study comparison, MD=-13.89 pmol/L [95%CI, -27.50, ~~to~~ -0.28], P=0.05) showed a decreasing effect; sweetened low-fat milk (2 study comparisons, MD=18.95 pmol/L [95%CI, 9.09, ~~to~~ 28.80], P<0.001, no evidence of heterogeneity) and mixed sources (25 study comparisons, MD=7.74 pmol/L [95%CI, 2.94, ~~to~~ 12.53], P<0.01, no substantial heterogeneity) showed an increasing effect; and fruit (~~6~~7 study comparisons, no evidence of heterogeneity), dried fruit (2 study comparisons), SSBs (17 study comparisons), baked goods, sweets, and desserts (10 study comparisons, no evidence of heterogeneity), and added sweeteners (8 study comparisons, substantial heterogeneity [I^2=83, p<0.001]) showed no significant effect on fasting blood insulin. There was also a significant fructose-containing sugars x food source interaction in addition studies (P=0.02): ~~Significant food sources of fructose-containing sugars leading to an increase in fasting blood insulin included~~ SSBs (13 study comparisons, MD=6.17 pmol/L [95% CI, ~~=~~1.55, ~~to,~~ 10.78], p <0.001, substantial heterogeneity [I^2=65, p<0.001]~~13 trials~~), ~~dairy products (MD=15.64 pmol/L [95% CI=5.18, 26.10], p=<0.00301, 1 trial)~~ and mixed sources (1 study comparison, MD=13.00 pmol/L [95% CI, ~~=~~0.81, ~~to ,~~ 25.19], p~~=~~0.04~~, 1 trial~~) showed an increasing effect, while fruit (6 study comparisons, no evidence of heterogeneity) and fruit juice (3 study comparisons, no evidence of heterogeneity) showed no significant effect on fasting blood insulin. ~~-~~ No fructose-containing sugars x food source interactions were seen in the *ad libitum* studies (although mixed sources was the exclusive food source of fructose-containing sugars) or subtraction studies. ~~Total food sources of fructose-~~

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containing sugars did not demonstrate any significant effects in substitution (75 69 trials, 2,194 142 participants, moderate quality evidence), subtraction (3 trials, 33 participants, moderate low quality evidence) or ad libitum trials (4 trials, 302 participants, high quality evidence). However, in substitution trials

Sensitivity analyses for fasting blood insulin are presented in **Supplementary table 3.** Removal of anyone of 3 addition studies (52, 91, 104) (52,91,104) changed the significance from non-significant to significant but did not change the magnitude or direction of the effect or the evidence of heterogeneity. , an increase in fasting blood insulin was observed when fructose-containing sugars were in the form of mixed sources (MD=4.717.83 pmol/L [95% CI=3.180.25, 9.1812.48], p<0.01 =0.04, 34 26 trials) as well as dairy products (MD=26.59 [95% CI=9.51, 43.68], p<0.01, 1 trial). Sensitivity analysis through rRemoval of a trialthe subtraction study by Campos et al. (G2) (60) involving 15 iparticipants ndividuals frinom the subtraction analysis explained nearly all of the heterogeneity, changinged the -significance and magnitude but not the direction but notof the effect the direction of the effect and explained 78% of the heterogeneity, while the overall direction of the effect remained the same (MD= -39.54 pmol/L [95% CI, -75.02, -=24.06, 75.02], p =0.0203, no evidence of heterogeneity [I^2=1%, P==insert p-value]]0.31P=]) (**Supplementary Table 43**). Removal of the *ad libitum* study by Raben et al. 2000 (C) (124) involving 16 participants (138)eliminated the evidence for the significance but not the direction of the effect or the evidence for a lack of heterogeneity. Similarly, removal of a trial by Markey et al. involving 50 individuals fromin the ad libitum analysis explained the heterogeneity, changing the significance and magnitude but not the direction of the effect changed the significance of the effect and explained all of the heterogeneity while keeping direction the same (9.51 pmol/L [1.59, 17.42], p-value=0.02, no evidence of heterogeneity [I^2=0%, P=]) (**Supplementary Table 43**).

Significant heterogeneity was present in all analyses except for ad libitum trials.

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A priori subgroup analyses for fasting blood insulin are presented in **supplementary figures 22-25~~1-24~~.** ~~Post-hoc~~ and dose-response analyses for fasting blood insulin are presented in **Supplementary Figure 8 and ~~Supplementary table~~ 49**. There was significant effect modification by level of feeding control and risk of bias for blinding of participants, personnel and outcome assessors in the substitution studies (P<0.05). Subgroup analyses by level of feeding control showed a greater increasing effect in studies using dietary advice as the method of feeding control than in studies using supplementation as the method of feeding control ~~*A priori* subgroup analyses revealed a significant effect modification by fructose-containing sugar dose in addition trials (**Supplementary Figure 21**), where doses greater than 10% of total energy intake lead to larger increases in fasting blood insulin. However, a continuous dose response was not observed (P=0.12) (**Supplementary Figure 12-C**~~food source of fructose-containing ~~sugars in substitution trials, where mixed food sources lead to a significant increase in fasting blood insulin (P<0.01). Significant effect modification by dietary compliance was also observed, where dietary advice showed greater increases in fasting blood insulin (P=~~=~~<0.02~~45~~) (~~**Supplementary Figure 21**~~).~~ Subgroup analyses by risk of bias for blinding of participants, personnel and outcome assessors ~~Lastly, sStudies~~ showed a greater increasing effect in studies ~~that were~~had with a low risk of bias ~~compared to studies that had unclear risk of bias for blinding of participants, personnel and outcome assessorsed demonstrated~~than those with an unclear risk of bias ~~greater improvements in fasting blood insulin compared to unblinded studies~~ (P=0.01) (~~**Supplementary Figure 23**~~). None of the subgroups explained the substantial heterogeneity in the substitution studies.

~~No significant effect modification by *a priori* subgroup analyses on food source of fructose-containing sugars in addition trials was observed.). Although fructose dose was not significant in substitution trials at ≤10 or >10% of energy (**Supplementary Figure 22**), a significant continuous dose response was observed (P=0.04) (**Supplementary Figure 12-B**). However, this effect became non-significant upon~~

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~~removal of two outlier studies using extreme doses of sucrose (75-95% of energy)(10, 11). No subgroup analyses were conducted for subtraction or ad libitum conditions as there were not enough trials available for each analysis.~~ Additionally, in substitution and addition trials, we found no significant effect modification by fructose-containing sugars dose ~~(**Supplementary Figures 8D and 8E**) or by dose-thresholds (**Supplementary table 4D and 4E**).~~ ~~Post-hoc dose-threshold analyses did not show any significant effect modification by~~ fructose-containing sugars dose ~~(**supplementary table 3D**~~**4D**~~)~~ ~~in substitution trials or addition trials (**supplementary table 3E**~~**4E**~~).~~ No subgroup or dose-response analyses were significant in the addition studies, and no subgroup analyses were conducted for the subtraction or ~~ad libitum~~*ad libitum* ~~conditions~~studies, ~~as~~ less than 10 studies were available for these analyses.~~as there were not enough trials available for each analysis.~~

Publication Bias

The publication bias assessment is shown in **Supplementary Figure 2**~~5~~6. There was no evidence ~~for~~ of publication bias through visual inspection of funnel plots or formal testing with the Egger~~'s~~ and Begg~~'s~~ tests for the effect of food sources of fructose containing sugars on HbA1c~~, fasting~~, fasting blood glucose~~,~~ or fasting blood insulin ~~or HbA1c~~ for all analyses where ≥10 ~~trials~~studies were available. ~~(**Supplementary Figure 23**~~**25**~~)~~**.**

GRADE Assessment

A summary of the overall quality of evidence assessment for the effect of total ~~food sources of~~ fructose-containing sugars independent of food source ~~food sources~~ on the outcome measures of glycemic control ~~can be found~~is shown in **Table 2.** ~~In general, t~~The~~The~~ ~~confidence~~ certainty ~~we have~~ in ~~our effect estimates~~the evidence ~~for ranged from the analyses on HbA1c ranged from low to high~~was variable ~~for~~ HbA1c (low, ~~high~~low, ~~moderate~~low, and low), ~~on fasting blood glucose from moderate to high for~~ fasting

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blood glucose (~~moderate~~low, ~~moderate~~low, ~~high~~moderate, and ~~high~~moderate) and ~~on insulin ranged from moderate low to high for~~ fasting blood insulin (~~moderate~~low, low~~moderate~~, ~~low~~low~~moderate~~, and ~~high~~moderate) across substitution, addition, subtraction, and *ad libitum* studies, respectively~~, whereas HbA1c analyses ranged from very low to high~~moderate. Evidence for HbA1c was downgraded for inconsistency in substitution and addition ~~trials~~studies ~~as there was evidence of significant interstudy~~substantial unexplained heterogeneity (I^2=83~~2~~%, p<0.0001) and (I^2=83%, p<0.001) ~~respectively~~, indirectness in subtraction and ~~ad libitum~~*ad libitum* ~~trials~~studies ~~as only 1 trialstudy was available for each of these analyses (240 participants in the subtraction trialstudy and 10 participants in the ad libitum~~*ad libitum* ~~trialstudy)~~, and for imprecision in substitution, addition, subtraction and ad libitum ~~trials~~studies ~~as the 95% CIs (of the MD [0.3029, 0.06 %], [0.41, 0.50%], [0.04, 0.14 %] and [0.38, 0.42%] respectively) crossed the MID included non-clinically important benefit (HbA1c ≥ 0.3%) fasting blood glucose, and insulin and HbA1c in substitution and addition ~~trials~~ as well as HbA1c in substitution ~~trials~~ were downgraded for serious inconsistency due to significant interstudy heterogeneity. Similarly, e~~E~~vidence for fasting blood glucose was downgraded for inconsistency in substitution and addition ~~trials~~studies ~~as there was evidence of substantial significant interstudyunexplained heterogeneity (I^2=645%, p<0.0001) and (I^2=71%, p<0.0001) respectively~~, and for imprecision in substitution, addition, subtraction and ad libitum studies ~~as the 95% CIs ([0.02, 0.05 mmol/L], [0.00, 0.15 mmol/L], [0.07, 0.10 mmol/L] and [0.07, 0.04 mmol/L] respectively) crossed the MID (fasting blood glucose 0.5 mmol/L)~~. Similarly, evidence for fasting blood insulin was downgraded for inconsistency in the ~~substitutio~~substitution, ~~,~~addition, and subtraction ~~n, addition and subtraction trials~~studies ~~as there was evidence of substantial unexplained significant interstudy heterogeneity (I^2=>650%, or p<0.1001)~~, and for imprecision in su~~btraction~~bstitution, addition, subtraction and ad libitum ~~trials~~studies ~~as the 95% CIs (for the effect estimate [22.83, 26.830.24, 4.82 pmol/L], [1.40, 7.96

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~~pmol/L], [-26.83, 22.83] and [0.47, 14.00] respectively) included both clinically important benefitcrossed the MID (<10 pmol/L) and harm (>10 pmol/L).~~

~~insulin in subtraction trials was downgraded for serious imprecision as the 95% CIs for the effect estimate [-22.83, 26.83] included both clinically important benefit (<10 pmol/L) and harm (>10 pmol/L). On the other hand, evidence for HbA1c in subtraction and ad libitum trials were downgraded due to indirectness and imprecision as only 1 trial was available for each of these analyses (240 participants in the subtraction trial and 10 participants in the ad libitum trial). Evidence for HbA1c in substitution and ad libitum trials were also downgraded for imprecision as, and the 95% CI for the effect estimate in substitution trials [-0.30, -0.06] included clinically important benefit (≤-0.3%), and the 95% CI for the effect estimate in ad libitum trials [-0.38, 0.42] included both clinically important benefit (≤-0.3%) and harm (≥0.3%) for the ad libitum trial.~~

DISCUSSION

~~The results from our~~Our systematic review and meta-analysis of ~~160~~ 1554 ~~trials~~studies involving 5,136~~81~~ participants with and without diabetes showed variable effects of food sources of fructose-containing sugars on three outcome measures of glycemic control at median doses ranging from ~~12~~10-23% energy over median follow-up durations of 4-12 weeks. 4Four types of ~~trial~~study designs were identified based on energy control. In substitution ~~trials~~studies, ~~in which food sources of~~total food sources of fructose-containing sugars ~~were~~ in energy matched ~~compared~~ comparisons with ~~other~~ other macronutrient ~~source~~s (mainly refined starches) ~~matched for energy, a decrease in HbA1c for total food sources of fructose-containing sugars, especially from fruit~~showed a beneficial effect on HbA1c~~, was observed~~ with no effects on fasting blood glucose or ~~fasting~~ insulin, while individual food sources showed decreasing (fruit juice), null (fruit, SSBs, baked goods, added sweeteners) or increasing (sweetened-milk, mixed

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sources) effects on fasting blood insulin. In addition ~~trials~~studies, ~~in which~~~~where food sources of~~ total food sources of fructose-containing sugars ~~supplemented~~ supplementing diets with excess energy compared to the same diet alone without the excess energy ~~(with or without the use of non-caloric sweeteners), an adverse effect was observed for total food sources of fructose-containing sugars~~showed a harmful effect on fasting blood insulin without affecting HbA1c or fasting blood glucose, while individual food sources showed harmful effects on both fasting blood glucose (SSBs and fruit juice) and insulin (SSBs, mixed sources)~~, especially fr as well as individual food sources in the form of~~~~om SSBs (813 trials), dairy products (1 trial) and mixed sources (1 trial) on fasting blood insulin.~~ In the *ad libitum* studies, total food sources of fructose-containing sugars freely replacing other macronutrients showed a harmful effect on fasting blood insulin (for which the effect was derived exclusively from mixed food sources inclusive of SSBs) without affecting HbA1c or fasting blood glucose. ~~No significant effects were observed for on fasting blood insulin and glucose but not fasting glucose or HbA1c, although food sources in the form of added sweeteners. showed a significant reduction in fasting glucose (3 trials).~~ No effect of food sources of fructose-containing sugars ~~were~~ was observed ~~on measures of glycemic control~~ in subtraction ~~or ad libitum trials~~studies.

Sources of heterogeneity

M~~Subgroup analyses revealed evidence of some m~~ethodological and clinical sources of heterogeneity ~~influenced~~had an influence on our results. Sensitivity analyses revealed evidence of instability in the significance of our pooled estimates. Removal of anyone of 6 studies (38, 46, 72, 105, 114, 123) changed the significance from non-significant to significant for fasting blood glucose in the addition studies, while the removal of a study by Raben et al. 2000 (C) (124) changed the significance from significant to non-significant for fasting blood insulin in the *ad libitum* studies. None of the studies explained any of the heterogeneity. ~~Sensitivity analyses revealed evidence in the subtraction studies~~Removal of the study

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by ~~Tate el al. (149) and~~ Campos et al. (G2) (60), however, did both ~~and Tate el al.~~ (154) ~~explainined~~ the heterogeneity~~, changing the significance of the and made significant the~~and changing the significance of the effect. This sensitivity analysis revealed a ~~revealed a~~ consistent ~~potential~~ decreasing effect of reducing excess calories from fructose-containing sugars on fasting blood ~~-~~insulin in subtraction studies ~~from nonsignificant to significant for fasting blood insulinthe analysis of (removal of a single study changed the result from a nonsignificant to significant decreasing effect) and ad libitum studies (removal of a sthe study by ingle study changed the result from a non-significant to significant increasing effect in the analysis of *ad libitum* studies)~~. The reason for the strong influence ~~of each individualof this studythis study~~ is unclear. As ~~both~~ Campos et al. (G2) (60) ~~(n=15) and Markey (n=50) were~~ was a small~~er~~ studi~~es y~~ (n=15) ~~-~~that ~~both~~ received most of the weight in ~~their respective~~the analyse~~i~~s (>50%), it is possible that ~~their~~its true within-study variances were seriously underestimated, leading to an important outlier effect~~s~~ on the pooled estimate for fasting blood insulin (154)~~[Borenst ein Alternative Measures of Between-Study Heterogeneity in Meta-Analysis: Reducing the Impact of Outlying Studies. Biometrics. 2017 March; 73(1): 156–166. doi:10.1111/biom.12543.]~~. ~~the large study (n=318)by (149)Markey et al. also used an intervention that may have led to a smaller effect contributing to non-significant result with its inclusion.~~

~~-~~Subgroup analyses also revealed evidence of effect modification under certain conditions. Greater improvements in fasting blood glucose were observed ~~in those studies which enrolled~~ in participants with higher baseline fasting glucose in substitution and addition studies ~~(substitution and addition studies) studies~~, suggesting a regression-to-the-mean phenomenon. ~~-~~These effects were concordant with the observed subgroup modification by underlying disease status in addition studies, demonstrating a greater decreasing effect on fasting blood glucose in patients with ~~and without~~ diabetes ~~than those without in addition studies~~. ~~We also observed a significant subgroup effect by~~

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~~fructose-containing sugars type in addition studies, whereby the addition of honey to the diet led to greater decreases in fasting blood glucose when compared to other fructose-containing sugars types. Although the underlying mechanism and potential use of honey as an alternative antidiabetic sweetener currently remains inconclusive, a few preliminary studies in animals and humans have suggested that honey, through its small but measurable concentration of non-digestible short chain oligosaccharides as well as polyphenols, mineral and other antioxidant components, may exert beneficial metabolic effects including altering glucose metabolism~~(162)~~, lowering insulin resistance~~(163)~~ and reducing hepatic oxidative stress~~(164, 165)~~. Another significant subgroup effect was seen by level of feeding control in substitution studies, whereby fructose-containing sugars only increased fasting blood glucose in metabolically controlled feeding studies and only increased fasting blood insulin in dietary advice studies. Neither of these subgroup analyses explained the substantial heterogeneity and may not be relevant.~~ Although a significant subgroup effect by level of feeding control and age were also observed in addition studies where fasting blood glucose was significantly reduced when dietary advice was the method of feeding control or the age of participants was ≤ 18 years, only one study was available for each of these analyses and neither analysis explained the substantial heterogeneity. The relevance of the subgroup analysis for feeding control is also brought into question by the finding of an opposite result for fasting blood insulin in substitution studies. The categorical subgroup analyses revealed a significant effect modification by dose, whereby fasting blood glucose was lower at doses of ≤10% energy, suggesting that intakes that meet ~~certain~~ current recommendations to consume no more than 10% of energy from sugars (22, 33) may have advantages. These results, however, are difficult to interpret in the absence of a linear dose response gradient or dose threshold effect in continuous analyses at ~~the same~~ this threshold or the other public health thresholds of 5% (22, 23) and 25% (34).

Results in the context of other studies

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These Our findings agree with two other previously conducted systematic reviews and meta-analyses of controlled intervention studies which demonstrated a beneficial effect of the isocaloric substitution ofally exchanging fructose for other carbohydrates on glycated blood proteins in participants with diabetes (SMD = -0.25 [95% CI -0.46 to -0.04], p -value= 0.02; equivalent to ~0.53% reduction in HbA1c)(13), and without diabetes (fructose intake <90 g/d significantly improved HbA1c dependent on dose, study duration and severity of dysglycemia) diabetes (155). Although the modest decrease of -0.14% in HbA1c from our analysis (MD= -0.14% [-0.25 to -0.04]) did not exceed the clinically meaningful threshold of 0.3% proposed by the U.S Food and Drug administration for the development of new drugs for diabetes as observed in the previous meta-analysis (32), our findings suggest that food sources of fructose-containing sugars may have modest benefits for long term glycemic control when they replace other macronutrients on a calorie-for-calorie basis. On the other hand, our results suggest that food sources of fructose-containing sugars providing excess energy to the diet may raise fasting blood glucose and insulin agreeing with the observed findings from the our previous systematic reviews and meta-analyseis on fructose and glycemic controlthat fructose providing excess energy increases insulin resistance (156).

Our data also agree with evidence from prospective cohort studies of the relation of fructose-containing sugars with diabetes risk in prospective cohort studies. While we failed to observe an adverse association of total fructose-containing sugars independent of food source with incident diabetes in an earlier systematic review and meta-analysis of the available prospective cohort studies (157), please reference forTeller CS1, de Souza RJ, Mente SDT, Miocinovic A1, Cozma AI1, Ivanochko VI1, Ha VT, Tawfik B1, Di Buono M1, Jenkins AL1, Leiter LA1, Wolever TM51, Beyene J1, Kraus T1, Kendall CWC1, Jenkins DJA1, Sievenpiper JL2. Relation of total sugars, fructose and sucrose with incident type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. CMAJ. 2017 May 23;189(20):E711-

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[redacted], differential associations have been shown for different food sources of sugars. Systematic reviews and meta-analyses of prospective cohort studies have shown an adverse association with SSBs (16, 17) but a protective association with fruit ~~The adverse effects of SSB consumption are concordant with findings from several large observational studies, showing an increased risk of developing type 2 diabetes with higher SSB consumption(20, 21). Nonetheless, other food sources of fructose-containing sugars, such as fruit intake, seem to differ in their effects on the risk of developing type 2 diabetes and a decreased risk of type 2 diabetes with higher fruit intake~~(18, 19), associations which are consistent with our findings of an increasing effect of SSBs on fasting blood glucose and insulin in addition studies and a non-significant decreasing effect of fruit on HbA1c ~~of fruit~~ in ~~the~~ substitution studies. ~~Although food sources of fructose-containing sugars in the form of dairy products and mixed sources also suggested a signal for harm on fasting blood insulin under substitution and addition conditions, only 1 trial was available for each analysis and additional studies using these food sources are required to confirm these effects. On the other hand, food sources of fructose-containing sugars in the form of added sweeteners (honey or sucrose sachets) demonstrated significant improvements in fasting blood glucose when supplementing the diet with excess energy (3 trials).~~

Potential mechanisms

Several proposed mechanisms may explain the observed beneficial effect of food sources of fructose-containing sugars on HbA1c when substituted for other calories in the diet. Fructose has a relatively low glycemic index (GI) of 16 compared to reference carbohydrates such as starch with a GI of 100 (158). As a majority of the comparators used in substitution ~~trials~~studies were in the form of starch, replacement of these high-GI carbohydrates with fructose may have reduced the overall GI of the diet, leading to long term glycemic improvement through alleviation of pancreatic stress (159, 160). The low GI of fruit may explain why it was the main food source driving of a significant improvement in HbA1c in substitution

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studies, especially when compared to intermediate GI food sources such as SSBs or sweets, which provide calories from sugars in the absence of any nutritional value. The higher fiber content of fruit may contribute to lower postprandial glycemic excursions. Particularly, viscous gels formed by the pectin in fruit may delay gastric emptying and slow down the release of sugars (161). A secondary analysis of a randomized controlled trial of the effect of a 6-month low-GI intervention showed that low-GI fruit intake was the strongest predictor of the reduction in HbA1c in people with type 2 diabetes (162)~~[insert reference for Jenkins DJ, Srichaikul K, Kendall CW, Sievenpiper JL, Abdulnour S, Mirrahimi A, Meneses C, Nishi S, He X, Lee S, So YT, Esfahani A, Mitchell S, Parker TL, Vidgen E, Josse RG, Leiter LA. The relation of low glycaemic index fruit consumption to glycaemic control and risk factors for coronary heart disease in type 2 diabetes. Diabetologia. 2011 Feb;54(2):271-9]~~. Whether or not low-GI food sources of fructose-containing sugars would show similar effects when compared to other low-GI carbohydrate ~~comparators~~foods, including ~~whole grains or~~ legumes or some whole grains, remains to be determined as there ~~was~~is a lack of ~~trials~~studies using high~~her quality carbohydrate~~ quality carbohydrate compar~~isons~~ators. While a low-GI mechanism may have contributed to the observed decrease in HbA1c in the substitution studies ~~(n=32)~~, especially as it relates to fruit, it did not extend to improvements in fasting blood glucose and insulin. Although the summary effects for both endpoints tended to be in the direction of benefit (with the possibility of additional studies providing sufficient power to confirm any beneficial effects), a mechanism that targets postprandial excursions in glucose and insulin would not necessarily be expected to lead to meaningful improvements in these fasting measurements which are more determined by changes in insulin sensitivity (163).

An alternative mechanism accounting for the observed beneficial effects of food sources of fructose-containing sugars on HbA1c in substitution ~~trials~~studies relates to a "catalytic" effect of fructose whereby fructose metabolites have regulatory actions on glucokinase and hepatic glucose uptake.

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~~suggests that~~There is evidence that small catalytic fructose doses of ≤10 g/meal (~~typically found in low GI fruits~~a level obtainable from fruit) may improve glycaemia by the ability of fructose-1-P to up regulate glucokinase activity through the glucokinase regulatory protein, resulting in decreased hepatic glucose production (164) and increased glycogen synthesis(165). The relevance of this mechanism is unclear. It would be expected to have disproportionally greater effect on fasting blood glucose and insulin than HbA1c, the opposite of what we found. The doses of fructose in most of the included studies were also much higher than the catalytic doses (10g/meal) shown to have benefit, although categorical subgroup analyses did show lower fasting blood glucose at doses of ≤10% energy (≤50g/day). How dietary fructose interacts with glucose at the level of hepatic glucose homeostasis remains largely under-explored.~~Additionally, the higher fiber content of fruits may contribute to lowering their glycemic response. Particularly, viscous gels formed by soluble fiber may delay gastric emptying and slow down the release of sugars, while insoluble fiber increases passage through the digestive system, thus decreasing availability of sugars for absorption~~(171)~~. The lower glycemic index (GI) of fruits may explain differences observed between food sources of fructose-containing sugars, especially when compared to high GI SSBs or sweets, which provide calories from sugars in the absence of any nutritional value. While both mechanisms This may explain the decrease in HbA1c observed in substitution trials (n=32) particularly when fruits were compared to other food sources of fructose-containing food sources~~sugars, additional trials are warranted to confirm these effects.. Although the benefit of fruits did not extend to fasting blood glucose and insulin, the summary effects for both endpoints tended to be in the direction of benefit, with the possibility of additional trials allowing sufficient power to confirm any beneficial effects.~~

The increase in insulin in the absence of an adverse effect on HBA1c or fasting blood glucose with sweetened low-fat milk in the substitution studies may relate to an isolated insulinotropic effect of dairy

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proteins. The ability of protein, especially dairy proteins, co-ingested with carbohydrate to stimulate glucose stimulated insulin secretion has been well described (166-168)[please insert references for Lan-Pidhainy X1, Wolever TM. The hypoglycemic effect of fat and protein is not attenuated by insulin resistance. Am J Clin Nutr. 2010 Jan;91(1):98-105. doi: 10.3945/ajcn.2009.28125. Epub 2009 Nov 18.; Wolever TM1, van Klinken BJ2, Bordenave N3, Kaczmarczyk M2, Jenkins AL4, Chu Y2, Harkness L2. Reformulating cereal bars: high resistant starch reduces in vitro digestibility but not in vivo glucose or insulin response; whey protein reduces glucose but disproportionately increases insulin. Am J Clin Nutr. 2016 Oct;104(4):995-1003. Epub 2016 Aug 31; Jakubowicz D1, Froy O, Ahrén B, Boaz M, Landau Z, Bar-Dayan Y, Ganz T, Barnea M, Wainstein J. Incretin, insulinotropic and glucose-lowering effects of whey protein pre-load in type 2 diabetes: a randomised clinical trial. Diabetologia. 2014 Sep;57(9):1807-11. doi: 10.1007/s00125-014-3305-x. Epub 2014 Jul 10.]. This isolated finding does not necessarily imply harm, as sweetened and unsweetened low-fat dairy, especially in the form of yogurt, is associated with decreased risk of weight gain and diabetes incidence (169).

In contrast, the observed adverse effects of food sources of fructose-containing sugars on glycemic control under addition conditionsin addition studies appear to be largely driven by the energy contribution of the sugars. Excess calories in the form of fFructose-containing sugars supplementing the background diets with excess calories may promote ectopic weight gain, contributing to downstream insulin resistance and impaired glycemic control. Related effects have been reported in systematic reviews and meta-analyses of controlled intervention studies of fructose overfeeding for body weight (170), blood pressure(171), uric acid levels (172), markers of Non-Alcoholic Fatty Liver Disease (NAFLD)(173) and postprandial triglycerides (174). Although fructose more than other carbohydrates (because of its ability to enter glycolysis as an unregulated substrate) has been proposed to increase de

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novo lipogenesis (DNL) leading to weight gain and its downstream cardiometabolic disturbances, this mechanism has been shown to be a minor pathway for fructose disposal (175)[please inset van Buul VJ, Tappy L, Brouns FJ. Misconceptions about fructose-containing sugars and their role in the obesity epidemic. Nutr Res Rev. 2014;27:119-30]. ThisIt mechanism is also not unique to fructose-containing sugars per se and weight gain with metabolic disturbances- would be expected for the overconsumption of any food sources of other dietary macronutrients (176)[Please insert Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011;364:2392-2404.Mozaffarian NEJM]. Similar effects have been observed under fructose overfeeding for body weight (180), blood pressure(181), uric acid levels (182), Non-Alcoholic Fatty Liver Disease (NAFLD)(183) and postprandial triglycerides (184).

The lack of a protective anticipated effect of interventions toto reduce excess energy from food sources of fructose-containing sugars in subtraction studies is unclear. It may represent compensation, in which the decrease in energy from food sources of fructose-containing sugars are compensated by replacement with energy from other food sources or spontaneous changes in physical activity that decrease energy expenditure preventing weight loss and its downstream metabolic benefits. Compensation may have been more apparent in these studies as they had the longest median follow-up (12-weeks). It may explain why longer term (median follow-up ~ 1 year) subtraction studies designed to displace excess energy from SSBs have only shown a weight-loss benefit in specific subgroups of overweight or obese individuals (177). The instability in the significance of the pooled effect estimates may have also played a role. Removal of the studiesy by Tate et al. (149) and Campos et al. (G2) (60)[] explained the heterogeneity and Tate et al. (154) made significant therevealing significant decreasing effects on fasting insulinchanged the significance of the decreasing effect on fasting blood insulin from

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nonsignificant to significant, suggesting that this studyit may have masked a true benefit of interventions toto reduce fructose-containing sugarssugars.

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***A priori* and posthoc sSubgroup analyses**

In subgroup analyses, greater improvements in fasting blood glucose were observed in those trials which enrolled participants with higher baseline fasting glucose (substitution and addition trials) and greater improvements HbA1c were observed in those trials enrolling participants with higher baseline HbA1c (substitution trials), suggesting a regression-to-the-mean phenomenon. These effects were concordant with the observed subgroup modification by underlying health disease status demonstrating greatest benefits on fasting blood glucose for patients with diabetes in addition trials, suggesting a potential benefit in using sugars with higher fructose content, particularly in the form of fruit, as an alternative sweetener food source of fructose-containing sugars to replace higher GI sugars-carbohydrates sweetened products in the diet of patients with diabetes. Additionally, a significant subgroup effect by fructose-containing sugars form was observed under addition conditions, whereby the addition of honey to the diet led to greater decreases in fasting blood glucose when compared to other fructose-containing sugars forms. Although the underlying mechanism and potential use of honey as an effective antidiabetic agent currently remains inconclusive, a few preliminary studies in animals and humans have suggested that honey, through its small but measurable concentration of non-digestible short chain oligosaccharides as well as polyphenols, mineral and other antioxidant components, may exert beneficial metabolic effects including altering glucose metabolism(162), lowering insulin resistance (163) and reducing hepatic oxidative stress(164, 165). On the other hand, while subgroup analyses by fructose containing sugars form in addition trials suggested a modest increase in fasting blood glucoseFASTING BLOOD GLUCOSE when fructose was compared to other fructose-containing sugars forms, the supraphysiological doses of fructose used in these addition trials

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(average intake=172.8 ± 57.8 g/d) have been shown to greatly exceed estimated levels of national American dietary intake (average intake=49 ± 1.0 g/d, NHANES 1977-2004)(188). As with the overconsumption of any macronutrient, observed adverse effects may be irrelevant under normal levels of dietary consumption and are likely due to excess calories rather than unique metabolic attributes of fructose per se.

Dietary guidelines informing the consumption of sugars have proposed upper limits of <5-10% based on food modeling patterns as well as the development of dental caries and obesity (26, 174). Significant subgroup effects were also observed in substitution trials on fasting blood glucose, where fasting blood glucosecomparators in the form of starchfasting blood glucose lead to greater increases in fasting blood glucose while mixed sourcesfasting blood glucose led to decreases in fasting blood glucose. A possible mechanism could have been due to the high GI of starch (GI=100) compared to the lower GI of mixed meals(24). In substation trials, dietary compliancefasting blood glucose Through metabolically controlled feeding showed greater increases in FBfasting blood insulinG, while dietary compliance through dietary advice showed greater increases in FB. Although significant subgroup effects were also observed in addition trials where fasting blood glucosefasting blood glucose was significantly reduced by dietary compliance through dietary advice or age of participants ≤ 18 years, only one trial was available for each of these analyses and may not have meaningful effects. Our categorical subgroup analyses revealed a significant effect modification by fructose-containing sugars dose at levels of ≤10% or >10% energy on levels of fasting blood insulin glucosefasting blood glucose in addition substitution trials. However, significant effect modification was not seen for the continuous subgroup analyses, and Ppost-hoc analyses also did not identifiedy a threshold for dose at 20, 30 and 40% of energy (data not shown). However, significant effect modification was not seen for the continuous subgroup analyses. On the other hand, while a categorical dose effect was not observed for the remaining subgroup analyses, continuous subgroup analyses suggested significant dose gradients for the effect of fructose-containing

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~~sugars on fasting blood glucose and fasting blood insulin under substitution conditions. However, removal of a trial by Hendler et al.(10) providing a liquid meal replacement containing 75% of energy as sucrose compared to a liquid meal replacement containing 75% of energy as fat eliminated this dose response in fasting glucose trials. Similarly, removal of two trials by Hendler et al. (10, 11) providing liquid meal replacements containing 75% or 95% of energy as sucrose compared to 75% or 95% of energy as fat or protein respectively also eliminated the observed dose response gradient in fasting insulin trials. Although both trials by Hendler et al. may suggest a potential for harm when substituting sucrose for fat or protein as a primary source of calories in the diet, the dose of sucrose used in these trials were 150-190 grams per day, exceeding estimated levels of average intake from added sugars (approximately 10% energy or ~50 grams/day(189)) by three- to four-fold. Thus, removal of these outlier studies providing extreme doses of sucrose suggested the lack of a true dose response when fructose-containing sugars were isocalorically substituted for other macronutrients in the diet.~~

~~Project~~ **Implications**

~~To our knowledge, this has been the first systematic review and meta-analysis to assess the effect of different food sources of fructose-containing sugars on glycemic control. Various food sources of fructose-containing sugars led to significant differences in glycemic control measurements, however several analyses only had limited number of trials using a particular food source, or lacked robustness in their observed effects. For example, under addition conditions, fructose-containing sugars in the form of liquid meal replacements significantly increased levels of fasting blood glucose, fructose-containing sugars in the form of dairy products and mixed sources increased levels of fasting insulin, and under substitution trials, fructose-containing sugars in the form of dairy products increased fasting blood insulin. However, as only one trial was available for each of these analyses, additional trials are warranted to determine any meaningful effects. Furthermore, although fructose-containing sugars in the form of mixed dietary sources (food and beverages) led to a modest increase in levels of fasting~~

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~~blood insulin in substitution trials, this effect was bordering significance (p=0.04), and individual removal of 18 of the 34 trials~~ (12, 61-63, 76, 78, 90, 104, 111, 112, 149, 156, 158)~~, led to non-significant results. Additionally, while fructose-containing sugars in the form of fruits showed a modest decrease in levels of HbA1c in substitution trials, individual removal of 5 of the 8 trials~~ (50, 56, 67, 86, 117)~~ eliminated the significance of the effect although direction remained the same. On the other hand, combined pooled analyses from 13 trials of fructose-containing sugars in the form of SSBs lead to significant increases in fasting insulin when providing excess energy to the diet (6.17 pmol/L [1.55, 10.78], p=<0.00901), and these results were not sensitive to removal of any individual trial.~~

~~Taken together, a~~As dietary guidelines ~~have~~ shift from a focus on individual nutrients ~~ed~~ towards a focus on foods and ~~food~~dietary patterns~~-based approach~~, our findings may have implications for guiding recommendations on important food sources of fructose-containing sugars ~~towards~~ in the prevention and management of diabetes. ~~Particularly, as~~As various food sources of fructose-containing sugars, ~~,~~ especially ~~in the form of fruits,~~ tended to demonstrate improvements on HbA1c, encouraging ~~fruit~~ the consumption food sources of sugars such as fruit, yogurt, and whole grain cereals to replace foods high in refined starches ~~as an alternative to other food sources of dietary sweetenersfructose-containing sugars~~ within the recommendation to consume no more than 10% of energy from free sugars ~~[~~(22, 32) ~~please insert 24 and WHO reference]~~ may be an effective strategy for improving glycemic control, especially in people with diabetes. ~~Additionally, a~~As SSBs tended to impair fasting blood glucose ~~and glucose and~~ insulin when adding excess energy to the diet, public health strategies to reduce consumption of this food source of fructose-containing ~~food source~~sugars may be useful, especially as SSBs ~~have recently come under scrutiny for providing~~provide empty calories in absence of any nutritional "value". While these findings highlight the role of food sources of fructose-containing ~~food sources~~sugars on glycemic control, other important cardiometabolic parameters should also be taken

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into consideration in future syntheses. ~~when creating guidelines on fructose-containing sugars consumption.~~

Strengths and Limitations

Our systematic review and meta-analysis has ~~presented~~ several strengths, including: 1) a comprehensive and reproducible~~rigorous~~ search and selection process of the ~~available~~ literature examining the effect of food sources of fructose-containing ~~food sources~~ sugars on glycemic control, 2) collation and synthesis ~~inclusion~~ of the totality of the available evidence from a large body (1524 studies, n=~~5,173~~4,979) of controlled intervention ~~trials~~studies -which give the greatest protection against bias (noting that results did not differ between randomized and ~~non-randomized~~non-randomized ~~trials~~studies), and ~~3) the collation and synthesis of data from 160~~ 1554 ~~controlled trials involving 5181~~ 5,~~136~~ ~~human participants, and 43~~) an assessment of overall quality of evidence using the GRADE assessment ~~tool~~approach.

-Several of our analyses ~~also~~ presented limitations. ~~In particular~~First, despite the inclusion of a large number of studies, there was a limited number of studies using particular food sources. For example, there were no study comparisons available for sweetened breakfast cereals or yogurt and only one study comparison was available for sweetened chocolate and two study comparisons for sweetened low-fat milk for any of the analyses. Many analyses also had only one or two study comparisons available for inclusion: baked goods, sweets and desserts for HbA1c in substitution and addition studies (1 study); fruit juice for fasting blood glucose and insulin in substitution studies (1 study); mixed sources for fasting blood glucose and insulin in addition studies (1 study); SSBs for HbA1c in substitution studies (2 studies); and fruit juice for fasting blood glucose in additions studies (2 studies). As a result, we elected only to do GRADE assessments for total food sources. Second, substantial~~ignificant~~ unexplained heterogeneity was present ~~for~~ in all analyses for the substitution studies~~analyses~~, as well as the addition

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analyses studies for HbA1c, and fasting blood glucose, and fasting blood insulin and fasting blood insulin. Although there was also substantial heterogeneity present in the addition studies for HbA1cfasting blood insulin, the subtraction studies for HbA1c, fasting blood glucose and insulin, and *ad libitum* studies for HbA1cfasting blood insulin, the removal of individual studies during sensitivity analyses explained this heterogeneity, and so we did not downgrade for inconsistency. ThirdSecond, serious indirectness was suggested forpresent in several some analyses as only one trial in 240 overweight and obese women was available in the HbA1c subtraction analysis, and similarly, one trial in 10 patients with diabetes was available in the HbA1c ad libitum*ad libitum* analysis. Although the small sample sizes of the included studies (median sample sizes ranged from 145 participants in substitutiontraction studies to 39 participants in *ad libitum* studies) are another potential source of indirectness, we did not downgrade the evidence for indirectness owing to the very large number of included studies (1524 study comparisonsies) representing a diverse range of study conditions and range of metabolic phenotypes with and without diabetes across a large total number involvingof participantsparticipants (n=51734,979) participants. WWe also did not downgrade for indirectness based on thise relatively short duration of follow-up (median follow-up, 4.5-12 weeks), as in the included studies. Although the median follow-up was 4.5-12 weeks, we felt that it was sufficient to assess the question of harm (a decision sharedin keepingshared with thean earlier WHO commissioned review of the evidence for sugars and body weight (178)[insert TeMorenga BMJ 2013 reference]). ThirdFinally, there was evidence of serious imprecision in twoall of the analyses. As tas the 95% CIis for HbA1ceffect estimates in the *ad libitum*studiescrossed the MI-Ds for HbA1c, fasting blood glucose and fasting blood insulinfor benefit and the 95% CIs(0.3% for HbA1c, 0.5 mmo/L for FBIglucose and 10 pmol/L for fasting blood) in thesubtraction trialsstudies on fasting insulin as well as subtraction and ad libitum trials on HbA1c crossed the minimally important difference forcontained both important benefit or harm, these analyses were downgraded for serious imprecision. imprecision in these results reduced

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confidence in the overall effect. Fourth, the inclusion of non-randomized trials may have added a potential for bias, although our subgroup analyses did not reveal any significant differences between randomized and non-randomized trials. LastlyAdditionally, a majority of the trials were small and short in duration, with a median follow-up of less than 8 weeks for substitution and addition trials and a median trial size ranging from 14 participants in substitution trials to 39 participants in ad libitum trials. AdditionallyLastly, as Hba1c reflects average blood glucose levels over 8-12 weeks, our ability to determine longer term effects on glycemic control may be limited.

Based onWeighing the strengths and limitations, our GRADE assessmentwe graded the certainty in the evidence using GRADE as from very low to high quality for HbA1c, and moderatelow to high moderate quality for fasting blood glucoseFBGfasting blood glucose and low to moderate quality for fasting blood insulinFBIfasting blood insulin across the four study designs based on energy control.

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CONCLUSION

In conclusion, the effects of food sources of fructose-containing sugars on glycemic control are appear to be both energy and food source dependent. Most food sources of fFructose-containing sugars form from various food sources, especially from fruit, exchangedsubstituted for equal amounts of calories from other macronutrient sources (mainly refined starches) led to improvements in HbA1c without adversely affecting fasting blood glucose or insulin. However, when several food sources of fructose-containing sugars added excess energy to the diet, particularly in theespecially form of SSBs, a significant increases in fasting blood glucose and insulin and fasting blood glucose wereas observed. The same was also seen for the effect of mixed food sources (inclusive of SSBs) of fructose-containing sugars freely

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replacing other macronutrients on fasting blood insulin without an adverse effect on HbA1c or fasting blood glucose. The anticipated benefit of interventions to reduce the excess energy from sugars ~~No significant effects were observed under subtraction or ad libitum conditions~~, however, was not seen reliably, suggesting that compensatory behaviours may ~~influence outcomes~~be an important consideration~~, however, both trial designs had fewer than 10 trials per outcome and limited strength of evidence~~. The lack of any harm and even advantages were most pronounced in those with higher HbA1c and fasting blood glucose baseline levels or who had diabetes. While our findings may suggest that common ~~important~~ food sources of fructose-containing sugars do not have adverse effects on glycemic control in energy matched replacement ~~or even free replacement~~ of other less sugary foods, our GRADE assessment suggests that more research is likely to have an important influence on many of our estimates. More ~~l~~Longer~~, larger~~, high quality ~~trials~~studies using a greater variety of food sources of fructose-containing ~~food sources~~ sugars are required to assess the durability of these effects under free living conditions ~~under real-world conditions~~. ~~While awaiting this evidence~~While awaiting these data, ~~the results of this synthesis should inform~~policy and guidelines makers ~~the transition to food and dietary pattern based dietary guidelines~~should consider the influence of ~~e~~Energy control and food source in the development recommendations to reduce sugars for the prevention and management of diabetes.

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CONTRIBUTIONS~~ORS~~

VLC, SBM and JLS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: VLC, JLS and DJAJ. Acquisition, analysis and interpretation of data: VLC, EV, SBM, AIC, VH, LAL, TMSW, TAK, DJAJ and JLS. Drafting of the manuscript: VLC. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: VLC and SBM. Study supervision: JLS and DJAJ.

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COMPETING INTERESTS

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; Thomas M S Wolever is a part owner and the President of Glycemic Index Laboratories, Inc, Toronto, Canada, and has authored several popular diet books on the glycemic index for which he has received royalties from Phillipa Sandall Publishing Services and CABI Publishers. He has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for CIHR, CDA, Dairy Farmers of Canada, McCain Foods, Temasek Polytechnic, Northwestern University, Royal Society of London, Glycemic Index Symbol program, CreaNutrition AG, McMaster University, Canadian Society for Nutritional Sciences, National Sports and Conditioning Association, Faculty of Public Health and Nutrition—Autonomous University of Nuevo Leon, Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD). Cyril WC Kendall has received research support from the Advanced Foods and Material Network, Agrifoods and Agriculture Canada, the Almond Board of California, the American Pistachio Growers, Barilla, the California Strawberry Commission, the Calorie Control Council, CIHR, the Canola Council of Canada, the Coca-Cola Company (investigator initiated, unrestricted grant), Hain Celestial, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Kraft, Loblaw Companies Ltd., Orafti, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. He has received travel funding, consultant fees and/or honoraria from Abbott Laboratories, the Almond Board of California, the American Peanut Council, the American Pistachio Growers, Barilla, Bayer, the Canola Council of Canada, the Coca-Cola Company, Danone, General Mills, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Loblaw Companies Ltd., the Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms, the Peanut Institute, PepsiCo, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate and Lyle, and Unilever. He is on the Dietary Guidelines Committee for the Diabetes Nutrition Study Group of the European Association for the Study of Diabetes and has served on the

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EXCLUSIVE LICENCE

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TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ETHICS APPROVAL

Not required.

DATA SHARING STATEMENT

No additional data are available.

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Figures and Tables

Figure 1. Flow of literature for the effect of food sources of ~~F~~fructose-containing sugars on glycemic control.

Figure 2. Summary super-plot for the effect of food sources of fructose-containing sugars on HbA1c. N= Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for summary effects of individual food sources and total ~~food sources of fructose-containing sugars~~ on HbA1c. Analyses were conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using the Cochran's Q statistic (chi-square) at a significance level of P<0.10.

Figure 3. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood glucose. N= Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for summary effects of individual food sources and total ~~food sources of fructose-containing sugars~~ on fasting blood glucose. Analyses were conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using the Cochran's Q statistic (chi-square) at a significance level of P<0.10.

Figure 4. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood insulin. N= Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for summary effects of individual food sources and total ~~food sources of fructose-containing sugars~~ on fasting blood insulin. Analyses were conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of P<0.10.

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Table 1. Summary of ~~Trial~~ Study Characteristics

~~Trial~~ Study Characteristics	Substitution ~~Trials~~Studies	Addition Studies~~Trials~~	Subtraction ~~Trials~~Studies	~~Ad Libitum~~*Ad libitum* ~~Trials~~Studies
~~Trial~~ Study Comparisons~~Number~~ (N)	1100~~410~~	3~~598~~	5	7
~~Trial~~ Study Size (participants)[~~31~~1]	16~~145~~ (5~~42~~-595)	~~22~~120 (6~~6~~-6~~38092~~)	15 (~~12-31~~86-318)	39 (8-236)
Male: ~~Female~~ [~~3~~] Female [~~2~~]	4~~05~~4: 60~~55~~6	4~~63~~89: ~~62~~541	12: 88	41: 59
Age (years)[~~13~~]	~~40.1~~38.~~1~~40.0 (25.1~~23.2~~-53.8~~53.89~~)	3~~6.25.8~~ (~~25.5.0-50.1~~)27.4-49.4~~46.7~~)	33.5 (29.1-4~~2.2~~1.9)	~~37.4~~38 (34-39.8)
Setting (Inpatient: Outpatient: Inpatient/outpatient)[~~32~~2]	~~25~~13: ~~75~~8710: 75: 15	~~10~~:3: ~~97~~89: 9~~0~~	0: 100: 0	0: 100: 0
Baseline Fasting Glucose (mmol/L)[~~13~~3]	5.0~~5~~4 (4.84.9-5.38.50)	5.1 (4.9-5.4)	5.1 (5.1-5.2)	4.9 (4.9-5.4)
Baseline Fasting Insulin (pmol/L)[~~13~~3]	~~89~~89.6~~96.6~~ (56.7~~57.9~~-126.81~~30~~1.6)	52.0~~3~~.50.4 (40.6-81.40.0~~1.5~~)	109.8 (97.8-121.7)	32.8~~5~~ (32.11.8-45.9)
Baseline HbA1c (%)[~~13~~3]	7.5~~3~~ (~~6.7~~6.8-8.5~~8.5~~4)	~~7.2~~6.8 (5.5~~7.21~~-7.16~~2~~)	N/A [4]	N/A [4]
Study Design (Crossover: Parallel)[~~32~~2]	~~6~~62~~2~~: 38~~38~~	~~50~~49: 5~~10~~	20: 80	57: 43
Feeding Control (Met: Supp: DA)[~~32~~2]	4~~35~~9: 4~~23~~9: 15~~64~~	~~15~~136: ~~839~~280: ~~2~~73	0: ~~67~~70: 3~~03~~	50~~14~~: 37.5~~57~~: 12.5~~29~~
Randomization (Yes: No)[~~32~~2]	~~69~~71: 29~~31~~	6~~67~~6: 34~~34~~	80: 20	~~88~~100: 0~~12~~
Fructose~~-~~Containing Sugars Dosage (%E)[~~13~~3]	~~15.0~~14.5 (8.99.~~96~~-22.0~~22~~3.~~6~~)	~~11.6~~10.0~~1~~2.2 (7.7~~5.03.8~~-25.0~~25.0~~23.5)	15.0 (~~13.8-15.0~~11.3-15.0)	23.0 (13.0-26.0)
Follow-Up Duration (Weeks)[~~31~~1]	~~4~~.55 (~~11~~-52)	6~~87~~ (1-24~~86~~)	12 (~~8.6~~1-~~39.1~~6)	8 (2-7~~6~~8)
Funding Sources (A: I: AI: NR)[~~32~~2]	3~~21~~: ~~178~~27: 29~~719~~: ~~232~~25	~~484~~96: ~~151~~93: 3~~43031~~: 9~~107~~	60: 40: 0: 0	0: 17: 50: 33
Fructose-Containing Sugars ~~Form~~ Type (N)	Fructose=~~52~~47; Fruit=1~~3~~; HFCS=~~31~~; Sucrose=48; Honey=~~250~~ ~~D-maltose=3;~~ Fat=~~7~~9; ~~Galactose=2~~ Glucose=2~~35~~; ~~Isomaltulose=2;~~ Lactose=~~45~~; Maltodextrin=1; Mixed Comparator=~~13~~14; Protein=1; Starch=~~55~~53; Diet alone=5; Water=1	Fructose=~~10~~8; Fruit=1~~3~~7; HFCS=~~12~~; Honey=~~4~~3; Sucrose=9 Diet alone=~~28~~27; Sweetener=4; Water=~~5~~8	Sucrose= 5; HFCS=4 Water=2; Sweetener=3; No sucrose=1	Fructose=1; Sucrose=7 Fat=2; Mixed comparator=2; Starch=4; Sweetener=3
Food Sources of Fructose-Containing Sugars	Fruit=13; Dried Fruit=5; Fruit Juice=1; SSBs=21; Sweetened Low-Fat Milk=2; Baked Goods, Sweets and Desserts=11; Added Sweeteners=12; ~~Dairy=1; Fruit=13; LMRs=7;~~ Mixed Sources= ~~57~~45; ~~SSBs=21~~	Fruits=10; Fruit Juice=3; Fruit Drink=3; SSBs=12; Sweetened Chocolate=1; Baked Goods, Sweets and Desserts=1; Added Sweeteners=4~~Dairy=1~~; ~~Fruits=12; Fruit Juice=3; LMRs=1 SSBs=16;~~ Mixed Sources=14	Mixed Sources=1; SSBs=4	Baked Goods, Sweets and Desserts=1; Mixed Sources=6

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A=agency; AI=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; ~~LMRs=liquid meal replacements;~~ Met=metabolic; N=number of ~~trials~~studies; NR=not reported; SSBs=sugars-sweetened beverages; Supp=supplemented

[1,2,3]Values are reported as Medians and ranges[1] ~~Interquartile Ranges (IQR)~~[1], percent ratios ~~ranges~~[2] or Interquartile Ranges (IQR) ~~percent ratios~~[3].

[4]Baseline data were only reported for one ~~trial~~study.

Table 2. GRADE Quality of Evidence Assessment

Quality assessment							
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
HbA1c in Substitution ~~Trials~~Studies							
2~~8~~32	randomized and non-randomized ~~studies~~trials	no serious risk of bias	serious [1]	no serious indirectness	serious [2]	none	⊕⊕OO LOW
HbA1c in Addition ~~Trials~~Studies							
~~8~~6	randomized and non-randomized ~~trials~~ studies	no serious risk of bias	serious [3]	no serious indirectness	serious [4]	none	⊕⊕OO LOW
HbA1c in Subtraction ~~Trials~~ Studies							
1	randomized and non-randomized ~~trials~~studies	no serious risk of bias	no serious inconsistency [5]	serious [6]	serious [7]	none [8]	⊕⊕OO ~~MEDIUM~~MODERATE~~LOW~~
HbA1c in ~~Ad Libitum~~*Ad libitum* ~~Trials~~Studies							
1	randomized and non-randomized ~~trials~~studies	no serious risk of bias	no serious inconsistency [5]	serious [9]	~~very~~ serious [10]	none [8]	⊕⊕OO ~~LOW⊕⊕OO~~ ~~VERY LOW~~
Fasting Blood Glucose in Substitution ~~Trials~~Studies							
~~10195~~1014	randomized and non-randomized ~~trials~~studies	no serious risk of bias	~~serious~~ [1] serious [11]	no serious indirectness	~~no~~ serious ~~imprecision~~ [12]	none	⊕⊕OO~~⊕⊕⊕O~~ ~~MODERATE~~LOW
Fasting Blood Glucose in Addition ~~Trials~~Studies							
~~35~~30428	randomized and non-randomized ~~trials~~studies	no serious risk of bias	~~serious~~ [2] serious [13]	no serious indirectness	~~no~~ serious [14] ~~imprecision~~	none	⊕⊕OO~~⊕⊕⊕O~~ MODERATE~~LOW~~
Fasting Blood Glucose in Subtraction Studies~~Trials~~							
4	randomized and non-randomized ~~trials~~studies	no serious risk of bias	~~no Sno~~ serious inconsistency~~inconsistency~~ [3] ~~inconsistency~~ [15]	no serious indirectness	~~none serious~~ ~~serious~~ [16] [4] imprecision	~~none~~ [5] none [8]	⊕⊕⊕O ~~MODERATE⊕⊕⊕⊕~~ ~~HIGH~~
Fasting Blood Glucose in ~~Ad Libitum~~*Ad libitum* Studies~~Trials~~							
6	randomized and non-randomized ~~trials~~studies	no serious risk of bias	no serious inconsistency	no serious indirectness	~~no~~ serious [17] ~~imprecision~~	~~none~~ [5] none [8]	⊕⊕⊕O~~⊕⊕⊕⊕~~ ~~HIGH~~MODERATE
Fasting Blood Insulin in Substitution Studies~~Trials~~							

69

6897275	randomized and non-randomized trialsstudies	no serious risk of bias	serious[6] serious[18]	no serious indirectness	no serious[19] imprecision	none	⊕⊕OO⊕⊕⊕O MODERATELOW
Fasting Blood Insulin in Addition StudiesTrials							
216237	randomized and non-randomized trialsstudies	no serious risk of bias	no serious[7] serious inconsistency[20]	no serious indirectness	no serious[21] imprecision	none	⊕⊕⊕OO MODERATELOW
Fasting Blood Insulin in Subtraction StudiesTrials							
3	randomized and non-randomized trialsstudies	no serious risk of bias	no no serious inconsistency[22] inconsistency	no serious indirectness	serious[6] serious[23]	none[5] none[8]	⊕⊕⊕OO LOW ⊕⊕⊕⊕ MODERATE⊕⊕⊕⊕ MODERATE
Fasting Blood Insulin in Ad LibitumAd libitum StudiesTrials							
4	randomized and non-randomized trialsstudies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious[1524] imprecision	none[5] none[8]	⊕⊕⊕O MODERATE⊕⊕⊕⊕ HIGH
HbA1c in Substitution Trials							
3228	randomized and non-randomized trials	no serious risk of bias	serious[10]	no serious indirectness	no serious imprecisionserious[11]	none	⊕⊕OO⊕⊕⊕O MODERATELOW
HbA1c in Addition Trials							
68	randomized and non-randomized trials	no serious risk of bias	no serious inconsistencyserious[12]	no serious indirectness	no serious imprecision	none	⊕⊕⊕O⊕⊕⊕⊕ HIGHMODERATE
HbA1c in Subtraction Trials							
1	randomized and non-randomized trials	no serious risk of bias	no serious inconsistency	Serious[1311]	no serious imprecision	none[5]	⊕⊕⊕O MODERATE
HbA1c in Ad Libitum Trials							
1	randomized and non-randomized trials	no serious risk of bias	no serious inconsistency	Serious[1311]	very serious[1412]	none[5]	⊕OOO VERY LOW

[1] Serious inconsistency for the effect of fructose-containing sugars on HbA1c in substitution trialsstudies, as there was evidence of significant interstudy heterogeneity (I^2=82%, p<0.0001).

[2] Serious imprecision for the effect of fructose-containing sugars on HbA1c in substitution trialsstudies, as the 95% CIs of the MD [-0.29, to -0.06 %] overlaps the minimally important difference (MID) for HbA1c (±0.3%), includinges non- clinically -unimportant benefit (HbA1c ≥ -0.3%).

[3] Serious inconsistency for the effect of fructose-containing sugars on HbA1c in addition trialsstudies, as there was evidence of significant interstudy heterogeneity (I^2=83%, p<0.0001).. Althoughthe explained most of the interstudy heterogeneity (I^2=75%, p<0.001), it did not change the lack of significance of the results

[4]Serious imprecision for the effect of fructose-containing sugars on HbA1c in addition studies, as the 95% CI [-0.41, 0.50 %] overlaps the MID for HbA1c (±0.3%), including includes both clinically -important benefit (HbA1c ≤ -0.3%) and harm (HbA1c ≥0.3%).

[5]Inconsistency cannot be exlcluded since we were not able to test for heterogeneity due to lack of trialsstudies (only 1 trialstudy included in the analysis).

[6]Serious indirectness for the effect of fructose-containing sugars on HbA1c in subtraction trialsstudies, as only 1 trialstudy in 240 overweight/ obese females was available for analysis.

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studies.[7] Serious imprecision for the effect of fructose-containing sugars on HbA1c in subtraction studies, as the 95% CI [-0.04, 0.14 %] overlaps the MID for HbA1c (±0.3%), including clinically unimportant benefit (≥ -0.3%). includes non-clinically important benefit (HbA1c ≥ -0.3%).

[8] Bias cannot be excluded since we were unable to test for funnel plot asymmetry due to lack of power (<10 studies included in the analysis).

[9] Serious indirectness for the effect of fructose-containing sugars on HbA1c in ad libitum *ad libitum* trialsstudies, as only 1 trialstudy in 10 participants with type 1 diabetes mellitus was available for analysis.

[§10] Very sSerious imprecision for the effect of fructose-containing sugars on HbA1c in ad libitum *ad libitum* trialsstudies, as the 95% CIs of the MD [-0.38, to 0.42 %] overlaps the MID for HbA1c (±0.3%), including includes both clinically important benefit (HbA1c ≤ -0.3%) and harm (HbA1c ≥0.3%). Bias cannot be excluded since we were unable to test for funnel plot asymmetry due to lack of power (<10 trials included in the analysis).

[11] Serious inconsistency for the effect of fructose-containing sugars on fasting blood glucose in substitution trialsstudies, as there was evidence of significant interstudy heterogeneity (I^2=65%, p<0.0001).

[14] [12] Serious imprecision for the effect of fructose-containing sugars on fasting blood glucose in substitution studies, as the 95% CI [-0.02, 0.05 mmol/L] overlaps the MID for fasting blood glucose (±0.5 mmol/L), including clinically unimportant includes non-clinically important benefit (fasting blood glucose ≥ -0.5 mmol/L).

[13] Serious inconsistency for the effect of fructose-containing sugars on fasting blood glucose in addition trialsstudies, as there was evidence of significant intersudy heterogeneity (I^2=71%, p<0.0001).

[14] Serious imprecision for the effect of fructose-containing sugars on fasting blood glucose in addition studies, as the 95% CI [-0.00, 0.15 mmol/L] overlaps the MID for fasting blood glucose (±0.5 mmol/L), including clinically unimportant benefit includes non-clinically important benefit (fasting blood glucose ≥ -0.5 mmol/L).

[15] No Very serious imprecision for the effect of fructose-containing sugars on HbA1c, as the 95% CIs of the MD [-0.38, 0.42] includes both clinically important benefit (HbA1c ≤-0.3%) and harm (HbA1c≥0.3%). Only 1 trail in 10 participants was available for analysis. [1] Serious inconsistency for the effect of fructose-containing sugars on fasting blood glucose, as there was evidence of significant interstudy heterogeneity (I^2=647%, p<0.0001).

[2] Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin, as there was evidence of significant intersudy heterogeneity (I^2=712%, p<0.0001).

[3] No sSerious inconsistency for the effect of fructose-containing sugars on fasting plasma blood glucose in subtraction studies, as. Even though tAlthough the removal of Tate et al. 2012 here was explained most of theevidence of significant interstudy heterogeneity (I^2=5932%, p=0.0623), removal of a trial by Campos et al. (G2) explained all of the heterogeneity (I^2=0%, p=0.78) , itwithout changinged theWhile removal of this trial changed the direction of the effect, overall results remained non-significant.direction or , magnitude, and significance of the effect on fasting blood glucose (MD= -0.20 mmol/L [95% CI, -0.040, 0.400 mmol/L], p =0.05) and . Although the removal of Campost et al. 2015 (G2) explained all the heterogeneity (I^2=0%, p=0.78), it changinged the direction, but not the magnitude, and lack of significance of the effect on fasting blood glucose (MD=-0.02 mmol/L [95% CI, -0.11, 0.07mmol/L], p=0.63).

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[16] Serious imprecision for the effect of fructose-containing sugars on fasting blood glucose in subtraction studies, as the 95% CI [-0.07, 0.10 mmol/L] overlaps the MID for fasting blood glucose (±0.5 mmol/L), including clinically unimportant ~~includes non-clinically important~~ benefit (~~fasting blood glucose~~ ≥ -0.5 mmol/L).

[17] Serious imprecision for the effect of fructose-containing sugars on fasting blood glucose in ad libitum studies, as the 95% CI [-0.07, 0.04 mmol/L] overlaps the MID for fasting blood glucose (±0.5 mmol/L), including clinically unimportant benefit ~~includes non-clinically important benefit~~ (~~fasting blood glucose~~ ≥ -0.5 mmol/L).

[18] Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin in substitution ~~trials~~studies, as there was evidence of significant interstudy heterogeneity (I^2=60%, p<0.001).

[19] Serious imprecision for the effect of fructose-containing sugars on fasting blood insulin in substitution studies, as the 95% CI [-0.24, 4.82 pmol/L] overlaps the MID for fasting blood insulin (±10 mmol/L), including clinically unimportant benefit ~~includes non-clinically important benefit~~ (~~fasting blood insulin~~ ≥ -10 pmol/L).

[20] ~~SNo s~~erious inconsistency for the effect of fructose-containing sugars on fasting blood insulin in addition ~~trials~~studies, as ~~. Although~~ there was evidence of significant interstudy heterogeneity (I^2=58%, p<0.001)~~., the removal of Hollis et al. 2009 explained some of the heterogeneity (I^2=42%, p=0.02), without changing the overall significance and the direction of the effect.~~

[21] Serious imprecision for the effect of fructose-containing sugars on fasting blood insulin in addition studies, as the 95% CI [-1.40, 7.96 pmol/L] overlaps the MID for fasting blood insulin (±10 mmol/L), including clinically unimportant benefit (≥ -10 pmol/L).
~~includes non-clinically important benefit (fasting blood insulin ≥ -10 pmol/L).~~

[22] ~~SNo s~~erious inconsistency for the effect of fructose-containing sugars on fasting plasma insulin in subtraction ~~trials~~studies. Although ~~the~~re ~~was~~ evidence of significant interstudy heterogeneity (I^2=79%, p<0.01) was explained by ~~, Although~~the removal of ~~the~~a ~~trial~~study by Campos et al. 2015 (G2) (I^2=1%, p=0.31), the conclusion changed for ~~explained the heterogeneity (I^2=1%, p=0.31)~~the significance (from non-significant to significant) and magnitude (from smaller to larger) of the effect ~~, increased the magnitud effect without the removal of this trialitchanging the overall significance and the direction of the effect~~ on fasting blood insulin~~n~~ (MD=-39.54 pmol/L [95% CI, -75.02, -4.06 pmol/L], p=0.03).

[23] Serious imprecision for the effect of fructose-containing sugars on fasting plasma insulin in subtraction studies, as the 95% CI~~s~~ [-22.83, ~~to~~ 26.83 pmol/L] overlaps the MID for fasting blood insulin (±10 mmol/L), including ~~includes~~ both clinically important benefit (<10 pmol/L) and harm (>10 pmol/L). Only 3 ~~trials~~studies involving 33 participants were available for analysis.

~~[4] No serious imprecision for the effect of fructose-containing sugars on fasting blood glucose as 585 participants were included in the analysis although only 4 trials were available.~~

~~[5] Bias cannot be excluded since we were unable to test for funnel plot asymmetry due to lack of power (<10 trials included in the analysis).~~

~~[6] Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin, as there was evidence of significant interstudy heterogeneity (I^2=6057%, p<0.0001).~~

~~[7] Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin, as there was evidence of significant interstudy heterogeneity (I^2=56%, p<0.0002).~~

~~[8] No serious inconsistency for the effect of fructose-containing sugars on fasting plasma insulin. Even though was evidence of significant interstudy heterogeneity (I^2=79%, p=0.009), removal of a trial by Campos et al. 2015 (G2) explained 78% of the heterogeneity. While removal of~~

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~~this trial changed the overall significance, the direction of effect remained the same.~~

~~9~~

~~16~~24 Serious imprecision for the effect of fructose-containing sugars on fasting plasma insulin in *ad libitum* studies, as the 95% CI [0.47 to 14.00] overlaps the MID for fasting blood insulin (±10 mmol/L), including clinically unimportant ~~includes clinically important~~ harm (>10 pmol/L).

~~Serious imprecision for the effect of fructose-containing sugars on fasting plasma insulin, as the 95% CIs [-22.83, 26.83] includes both clinically important benefit (<10 pmol/L) and harm (>10 pmol/L). Only 3 trials involving 33 participants were available for analysis.~~

~~10~~ ~~Serious inconsistency for the effect of fructose-containing sugars on HbA1c, as there was evidence of significant interstudy heterogeneity (I^2=831%, p<0.00001).~~

~~11~~ ~~Serious inconsistency for the effect of fructose-containing sugars on HbA1c, as there was evidence of significant interstudy heterogeneity (I^2=75%, p<0.001).~~

~~12~~ ~~Serious imprecision for the effect of fructose-containing sugars on HbA1c, as the 95% CIs of the MD [-0.30, 0.06] includes clinically important benefit (HbA1c ≤ 0.3%).~~

~~11~~ ~~13~~ ~~Serious indirectness for the effect of fructose-containing sugars on HbA1c as only 1 trial in 240 overweight/ obese females was available for analysis.~~

~~12~~ ~~14~~ ~~Very serious imprecision for the effect of fructose-containing sugars on HbA1c, as the 95% CIs of the MD [-0.38, 0.42] includes both clinically important benefit (HbA1c ≤ 0.3%) and harm (HbA1c≥0.3%). Only 1 trail in 10 participants was available for analysis.~~

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Figure 1. Flow of literature for the effect of food sources of fructose-containing sugars on glycemic control.

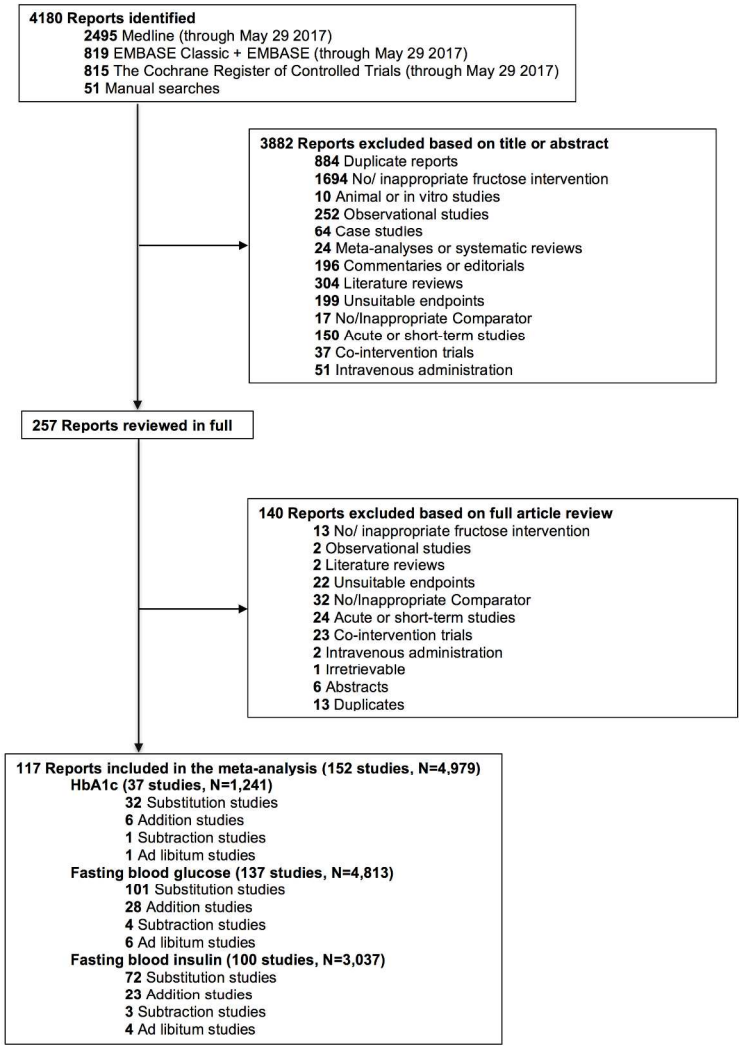

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Figure 2. Summary super-plot for the effect of food sources of fructose-containing sugars on HbA1c.

Comparison	Studies	Intervention, N	Control, N	Weight	MD [95% CI]	Heterogeneity I^2	Heterogeneity *P*-value	*P*-value
SUBSTITUTION STUDIES								
Fruit	7	259	211	34.3%	-0.12 [-0.25, 0.01]	80%	<0.001	0.08
Dried Fruit	5	185	119	24.0%	-0.06 [-0.13, 0.01]	9%	0.36	0.11
Sugars-Sweetened Beverages	2	22	23	4.8%	-0.57 [-1.21, 0.07]	40%	0.20	0.08
Baked Goods, Sweets and Desserts	1	10	10	2.3%	-0.50 [-1.12, 0.12]	-	-	0.11
Added Sweeteners	4	50	50	6.6%	-1.05 [-2.41, 0.30]	91%	<0.001	0.13
Mixed Sources	13	438	440	28.0%	0.01 [-0.38, 0.40]	82%	<0.001	0.95
Total	**32**	**964**	**853**	**100%**	**-0.18 [-0.29, -0.06]**	**82%**	**<0.001**	**<0.01**
ADDITION STUDIES								
Fruit juice	1	8	15	17.8%	0.60 [0.13, 1.07]	-	-	0.01
Baked Goods, Sweets and Desserts	1	11	13	14.7%	0.40 [-0.28, 1.08]	-	-	0.25
Added Sweeteners	4	82	48	67.6%	-0.18 [-0.79, 0.44]	86%	<0.001	0.84
Total	**6**	**101**	**76**	**100%**	**0.05 [-0.41, 0.50]**	**83%**	**<0.001**	**0.84**
SUBTRACTION STUDIES								
Sugars-Sweetened Beverages	1	120	120	100.0%	0.05 [-0.04, 0.14]	-	-	0.30
Total	**1**	**120**	**120**	**100%**	**0.05 [-0.04, 0.14]**	**-**	**-**	**0.30**
AD LIBITUM STUDIES								
Baked Goods, Sweets and Desserts	1	10	10	100.0%	0.02 [-0.38, 0.42]	-	-	0.92
Total	**1**	**10**	**10**	**100%**	**0.02 [-0.38, 0.42]**	**-**	**-**	**0.92**

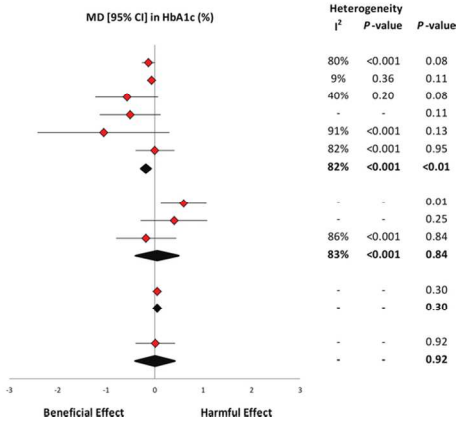

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Figure 3. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood glucose.

Comparison	Studies	Intervention, N	Control, N	Weight	MD [95% CI]	Heterogeneity I^2	Heterogeneity *P*-value	*P*-value
SUBSTITUTION STUDIES								
Fruit	12	367	336	14.4%	-0.04 [-0.16, 0.09]	74%	<0.001	0.57
Dried Fruit	5	145	119	3.7%	-0.18 [-0.40, 0.05]	32%	0.21	0.12
Fruit Juice	1	39	39	1.0%	-0.17 [-0.47, 0.14]	-	-	0.28
Sugars-Sweetened Beverages	20	318	312	30.9%	0.05 [-0.02, 0.11]	76%	<0.001	0.18
Sweetened Low-Fat Milk	2	91	96	4.2%	0.01 [-0.18, 0.20]	68%	0.08	0.92
Baked Goods, Sweets and Desserts	10	118	119	5.6%	0.01 [-0.12, 0.13]	0%	0.74	0.93
Added Sweeteners	12	157	147	8.4%	-0.11 [-0.30, 0.09]	66%	<0.001	0.28
Mixed Sources	39	781	785	31.9%	0.05 [-0.03, 0.13]	58%	<0.001	0.26
Total	**101**	**2,016**	**1,953**	**100%**	**0.01 [-0.02, 0.05]**	**65%**	**<0.001**	**0.47**
ADDITION STUDIES								
Fruit	7	86	74	22.5%	0.01 [-0.08, 0.11]	0%	0.52	0.76
Fruit Juice	2	33	40	6.4%	0.29 [0.09, 0.49]	0%	0.81	<0.01
Fruit Drinks	3	48	47	11.7%	0.17 [-0.14, 0.48]	82%	<0.01	0.28
Sugars-Sweetened Beverages	11	129	128	47.0%	0.12 [0.03, 0.22]	74%	<0.001	0.01
Sweetened Chocolate	1	39	39	3.8%	-0.23 [-0.47, 0.00]	-	-	0.05
Added Sweeteners	3	66	63	4.9%	-0.60 [-1.47, 0.27]	57%	0.10	0.17
Mixed Sources	1	12	11	3.7%	0.15 [-0.09, 0.39]	-	-	0.23
Total	**28**	**413**	**402**	**100%**	**0.07 [-0.00, 0.15]**	**71%**	**<0.001**	**0.06**
SUBTRACTION STUDIES								
Sugars-Sweetened Beverages	4	346	239	100.0%	0.01 [-0.07, 0.10]	59%	0.06	0.79
Total	**4**	**346**	**239**	**100%**	**0.01 [-0.07, 0.10]**	**59%**	**0.06**	**0.79**
AD LIBITUM STUDIES								
Mixed Sources	6	198	279	100.0%	-0.02 [-0.07, 0.04]	0%	0.48	0.56
Total	**6**	**198**	**279**	**100%**	**-0.02 [-0.07, 0.04]**	**0%**	**0.48**	**0.56**

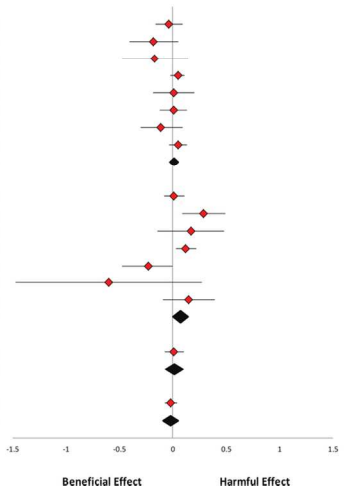

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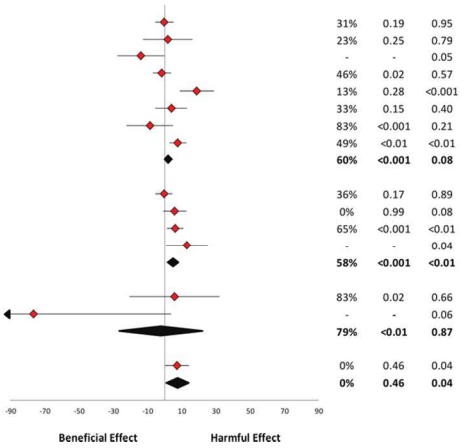
Figure 4. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood insulin.

Comparison	Studies	Intervention, N	Control, N	Weight	MD [95% CI]	Heterogeneity I^2	Heterogeneity *P*-value	*P*-value
SUBSTITUTION STUDIES								
Fruit	7	196	172	12.8%	-0.16 [-5.35, 5.03]	31%	0.19	0.95
Dried Fruit	2	61	63	2.8%	1.92 [-12.35, 16.18]	23%	0.25	0.79
Fruit Juice	1	39	39	1.9%	-13.89 [-27.50, -0.28]	-	-	0.05
Sugars-Sweetened Beverages	17	250	244	25.8%	-1.47 [-6.56, 3.62]	46%	0.02	0.57
Sweetened Low-Fat Milk	2	91	96	3.9%	18.95 [9.09, 28.80]	13%	0.28	<0.001
Baked Goods, Sweets and Desserts	10	118	119	8.9%	3.97 [-5.26, 13.20]	33%	0.15	0.40
Added Sweeteners	8	97	87	10.5%	-8.51 [-21.94, 4.93]	83%	<0.001	0.21
Mixed Sources	25	607	608	33.3%	7.74 [2.94, 12.53]	49%	<0.01	<0.01
Total	**72**	**1,459**	**1,428**	**100%**	**2.29 [-0.24, 4.82]**	**60%**	**<0.001**	**0.08**
ADDITION STUDIES								
Fruit	6	92	80	26.5%	-0.32 [-5.05, 4.41]	36%	0.17	0.89
Fruit Juice	3	56	63	9.1%	6.02 [-0.70, 12.75]	0%	0.99	0.08
Sugars-Sweetened Beverages	13	171	169	60.3%	6.17 [1.55, 10.78]	65%	<0.001	<0.01
Mixed Sources	1	12	11	4.0%	13.00 [0.81, 25.19]	-	-	0.04
Total	**23**	**331**	**323**	**100%**	**4.68 [1.40, 7.96]**	**58%**	**<0.001**	**<0.01**
SUBTRACTION STUDIES								
Sugars-Sweetened Beverages	2	13	14	90.4%	5.89 [-20.22, 32.01]	83%	0.02	0.66
Mixed Sources	1	6	6	9.6%	-76.39 [-156.54, 3.75]	-	-	0.06
Total	**3**	**19**	**20**	**100%**	**-2.00 [-26.83, 22.83]**	**79%**	**<0.01**	**0.87**
AD LIBITUM STUDIES								
Mixed Sources	4	116	206	100.0%	7.24 [0.47, 14.00]	0%	0.46	0.04
Total	**4**	**116**	**206**	**100%**	**7.24 [0.47, 14.00]**	**0%**	**0.46**	**0.04**



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APPENDIX 3: PRINT ABSTRACT

Study question: Does the the evidence supporting current recommendations to reduce free sugars, especially fructose-containing sugars from sugars-sweetened beverages (SSBs), hold for all food sources of these sugars in relation to glycemic control?

Methods: We conducted a systematic review and meta-analysis. We searched MEDLINE, EMBASE, and The Cochrane library through May 29, 2017. We included controlled intervention studies of ≥7-days in people with and without diabetes assessing the effect of different food sources of fructose-containing sugars on glycemic control at anyone of 4 levels of energy control: substitution (sugars in energy matched comparisons); addition (excess energy from sugars added to diet); subtraction (energy from sugars subtracted from diet); or *ad libitum* (sugars freely replaced). Outcomes were HbA1c and fasting blood glucose and insulin. Four independent reviewers extracted data and assessed risk of bias. Data were pooled using the inverse variance method. The certainty of the evidence was assessed by GRADE.

Study Answer and limitations: We included 152 controlled intervention studies (N=4,979). Whereas total fructose containing sugars decreased HbA1c (mean difference, -0.18% [95% confidence interval, -0.29, -0.06%]) in substitution studies and had no adverse effect on any outcome in substitution or subtraction studies, there was an increasing-effect on fasting blood insulin (4.68pmol/L [1.40, 7.96] and 7.24pmol/L [0.47, 14.00]) in addition and *ad libitum* studies, respectively. There was an interaction by food source with different food sources showing increasing effects on fasting blood insulin (sweetened-milk, mixed sources) in substitution studies and fasting blood glucose (SSBs, fruit juice) and insulin (SSBs, mixed sources) in addition studies. The majority of the evidence was low quality.

What this study adds: Energy control and food source appear to mediate the effect of fructose-containing sugars on glycemic control with adverse effects seen when fructose-containing sugars, especially SSBs, contribute excess energy to the diet.

Registration: ClinicalStudies.gov identifier, NCT02716870.