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

Journal:	*BMJ*
Manuscript ID	BMJ.2017.038661.R2
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	29-Aug-2018
Complete List of Authors:	Choo, Vivian; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto Viguiliouk, Effie; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto Blanco Mejia, Sonia; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto Cozma, Adrian; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto Khan, Tauseef; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto Ha, Vanessa; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Clinical Epidemiology & Biostatistics, McMaster University Wolever, Thomas; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto Leiter, Lawrence; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Li Ka Shing Knowledge Institute, St. Michael's Hospital Vuksan, Vladimir; Toronto 3D (Diet, Digestive Tract and Disease)

	Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto Kendall, Cyril; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto de Souza, Russell; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Clinical Epidemiology & Biostatistics, McMaster University Jenkins, David; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto Sievenpiper, John; Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto
Keywords:	fructose, HFCS, sucrose, glycemic control, diabetes, meta-analysis

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

Vivian L Choo[1,2], Effie Viguiliouk[1,2], Sonia Blanco Mejia[1,2], Adrian I Cozma[1,2], Tauseef A Khan[1,2], Vanessa Ha[1,3], Thomas MS Wolever[1,2,4,5], Lawrence A Leiter[1,4,5], Vladimir Vuksan,[1,2,4] Cyril WC Kendall[1,2,6], Russell J de Souza[1,3], David JA Jenkins[1,2,4,5] and John L Sievenpiper[1,2,4]

[1]Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, ON, Canada; [2] Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [3]Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada and [4]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; [5]Division of Endocrinology, St. Michael's Hospital, Toronto, ON, Canada; [6]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada

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

Corresponding Author:

John L Sievenpiper MD, PhD, FRCPC

Toronto 3D Knowledge Synthesis and Clinical Trials Unit

Clinical Nutrition and Risk Factor Modification Centre,

St. Michael's Hospital

61 Queen Street East, Toronto, ON, M5C 2T2, CANADA

Tel: 416 867 7475

Fax: 416 867 7495

Email: john.sievenpiper@medportal.ca

Abstract Word Count: 415

Text Word Count: 6888

Tables: 2

Figures: 4

Supplementary Tables: 3

Supplementary Figures: 27

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 April 25, 2018.

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: We included 155 study comparisons (N=5,086). Whereas total fructose containing sugars had no adverse effect on any outcome in substitution or subtraction studies with a decrease in HbA1c (mean difference, -0.22% [95% CI, -0.35, -0.08%], -25.9mmol/mol [95% CI, -27.3, -24.4mmol/mol]) in substitution studies, there was an increasing-effect on fasting insulin in addition (4.68pmol/L [1.40, 7.96]) and *ad libitum* (7.24pmol/L [0.47, 14.00]) studies. There was an interaction by food source with

specific food sources showing decreasing-effects (fruit and fruit juice) or increasing-effects (sweetened-milk and mixed sources) in substitution studies and increasing-effects (SSBs and fruit juice) in addition studies on glycemic control outcomes. The majority of the evidence was low quality.

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 (especially fruit), 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. Our certainty in these estimates is low. More large, high quality randomized controlled trials are needed.

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 (added sugars plus sugars contained in fruit juices) 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 April 25, 2018 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(1). 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. 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.** 4,442 reports were identified from database and manual searches, of which 4,157 were excluded based on title and abstract. 285 reports were reviewed in full, of which an additional 164 reports were excluded for failure to meet the eligibility criteria. 118 reports of controlled intervention studies (5, 11, 12, 38-152) including a total of 155 study comparisons in 5,086 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 (43/108), 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 (37%) or otherwise healthy participants (28%) 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 (72% 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 4.5 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 (45/108) 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 (30 study comparisons, MD=-0.22% [95% CI, -0.35, -0.08], -25.9mmol/mol [95% CI, -27.3, -24.4mmol/mol], 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 interaction by food source in the substitution, addition, subtraction or *ad libitum* studies, although fruit was the only food source that showed a significant decreasing effect on HbA1c accounting for 30% of the weighted benefit in the substitution studies and only one food source category was assessed in the subtraction studies (SSBs) and *ad libitum* studies (baked goods, sweets and desserts). .

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 evidence of a dose threshold seen at 10% energy by MKSPLINE procedure with the largest decreases seen only at doses ≤10% energy (P=0.04). No subgroup or dose-response analyses were conducted for addition, subtraction or *ad libitum* studies, as less than 10 studies were available for 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 (99 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 interaction by food source 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 interaction by food source was seen in the substitution, subtraction or *ad libitum* studies, although only one food source category was assessed in the subtraction studies (SSBs) and *ad libitum* studies (mixed sources).

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) 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 (148) explained most of the heterogeneity (I^2=32%, P=0.23) but did not change the direction or lack of significance of the effect on fasting blood glucose..

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 (≤10% energy or >10mmol/L) with a further threshold effect (25% energy) identified by the MKSPLINE procedure, comparator (starch, glucose, fat, mixed, lactose, dairy), baseline fasting blood glucose (≤5.5mmol/L or >5.5mmol/L), feeding control (dietary advice, supplementation, or metabolic), or underlying disease status (otherwise healthy, overweight/obese, diabetes, Metabolic syndrome, or NAFLD) in the substitution studies (P<0.05). A significant subgroup effect was alsoobserved by baseline fasting blood glucose (≤5.5mmol/L or >5.5mmol/L) in addition studies (P=0.01). None of the subgroup or dose-response analyses explained the substantial heterogeneity in the substitution and addition studies. No subgroup or dose-response analyses were conducted for subtraction or *ad libitum* comparisons as less than 10 studies were available for 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 (70 studies, substantial heterogeneity [I^2=62%, p<0.001]) or subtraction (3 studies, substantial heterogeneity [I^2=79%, p<0.01]). There was a significant interaction by food source 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 (6 study comparisons, no evidence of heterogeneity), dried fruit (1 study comparison), 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. No interaction by food source was seen in the addition, *ad libitum* , or subtraction studies, although SSBs accounted for >50% of the weighted harm in addition studies and mixed sources was the exclusive food source of fructose containings sugars in the ad libitum studies.

Sensitivity analyses for fasting blood insulin are presented in **Supplementary table 3.** Removal of the addition study by Hollis et al. 2009 (83)explained some of the heterogeneity (I^2=42%, P=0.02), without changing the significance, magnitude, or direction of the effect. Removal of either one of two substitution studies (92, 104) changed the evidence of significance from non-significant to significant without changing the magnitude or direction of the effect or the evidence of substantial heterogeneity.

Removal of the subtraction study by Campos et al. (G2) (60) explained nearly all of the heterogeneity (I^2=1%, P=0.31) and changing the significance and magnitude but not the direction of the effect. Removal of the *ad libitum* study by Raben et al. 2000 (C) (124) eliminated the evidence for the significance but not the direction of the effect or evidence of no substantial 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 in substitution studies by level of feeding control (dietary advice, supplementation, or metabolic) or risk of bias for blinding of participants, personnel and outcome assessors (low, high, or unclear) in the substitution studies (P<0.05). None of the subgroup or dose-response analyses explained the substantial heterogeneity in the substitution studies. No subgroup or dose-response analyses were significant in the addition studies. No subgroup analyses were conducted for the subtraction or *ad libitum* studies, as less than 10 studies were available for analyses.

Publication Bias

The publication bias assessment is shown in **Supplementary Figures 26 and 27** for all analyses where ≥10 studies were available. There was no evidence of publication bias for the effect of food sources of fructose containing sugars on HbA1c, fasting blood glucose, or fasting blood insulin. Although the Begg test was significant (P=0.04), visual inspection of funnel plots and the Egger test did not show evidence of publication bias for the effect of food sources of fructose containing sugars on fasting blood glucose in substitution studies. Adjustment for funnel plot asymmetry by the Duval and Tweedie method also did not alter the results.

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 152 studies involving 4,979 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 (153).

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 free or added 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% free sugars (22, 23) and 25% added sugars (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 (154). 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 (155).

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 (156), 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 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 (157). 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 (158) through alleviation of beta-cell stress (159, 160). There is also evidence that high-GI diets are associated with reliable clinical markers of insulin resistance such as

higher triglycerides and lower HDL-C (161, 162) . The low GI of fruit may explain why it was the main food source driving 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 (163). 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 (164). 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 effect estimatesfor both outcomes 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 (158).

An alternative mechanism accounting for the observed beneficial effects of food sources of fructose-containing sugars on HbA1c in substitution studies relates to a so called “catalytic“effect of fructose whereby fructose metabolites have regulatory actions on glucokinase and hepatic glucose uptake. There is evidence that fructose, especially at small 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 (165) and increased glycogen synthesis(166). The relevance of this mechanism is unclear. It has not been reliably shown(167, 168) under different experimental conditions and would be expected to have disproportionally greater effect on fasting blood glucose and insulin than HbA1c, the opposite of what we found. 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 (169-171). This isolated finding does not necessarily imply harm, as fasting glucose was not increased and sweetened and unsweetened low-fat dairy, especially in the form of yogurt, is associated with decreased risk of weight gain and diabetes incidence (172).

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 (173), blood pressure(174), uric acid levels (175), markers of Non-Alcoholic Fatty Liver Disease (NAFLD)(176) and postprandial triglycerides (177). 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 (178). 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 (179).

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 (180). 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 in 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 (181). 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. Food sources of fructose-containing sugars, especially fruit, 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 large, high quality studies using a greater variety of food sources of fructose-containing sugars are required to assess the durability of these effects and understand whether certain food sources with an apparent signal for benefit, such as fruit, may even have advantages for glycemic control under free living conditions over the longer term (≥ 6 months). 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.

ACKNOWLEDGEMENTS

The authors thank Zujaja-Tul-Noor for her help in the creation of some figures. Aspects of this work were presented at the 34th International Symposium on Diabetes and Nutrition (ISDN), Diabetes and Nutrition Study Group (DNSG) of the European Association of the Study of Diabetes (EASD), Prague, Czech Republic, June 29-July 1, 2016.

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.

FUNDING STATEMENT

This work was funded by Diabetes Canada (grant # CS-5-15-4771-JS). The Diet, Digestive tract, and Disease (3-D) Centre, funded through the Canada Foundation for Innovation (CFI) and the Ministry of Research and Innovation's Ontario Research Fund (ORF), provided the infrastructure for the conduct of this work. David JA Jenkins was funded by the Government of Canada through the Canada Research Chair Endowment. John L Sievenpiper was funded by a PSI Graham Farquharson Knowledge Translation Fellowship, Diabetes Canada Clinician Scientist award, CIHR INMD/CNS New Investigator Partnership Prize, and Banting & Best Diabetes Centre Sun Life Financial New Investigator Award. None of the sponsors had a role in any aspect of the present study, including design and conduct of the study;

collection, management, analysis, and interpretation of the data; and preparation, review, approval of the manuscript or decision to publish.

COMPETING INTERESTS

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 scientific advisory board for the Almond Board of California, the International Tree Nut Council, Oldways Preservation Trust, Paramount Farms and Pulse Canada. Russell J de Souza was previously funded by a CIHR Postdoctoral Fellowship Award and has received research support from the CIHR, the Calorie Control Council, the Canadian Foundation for Dietetic Research and the Coca-Cola Company (investigator initiated, unrestricted grant) and travel support from the World Health Organization (WHO) to attend group meetings. He has served as an external resource person to WHO's Nutrition Guidelines Advisory Group and is the lead author of 2 systematic reviews and meta-analyses commissioned by WHO of the relation of saturated fatty acids and trans fatty acids with health outcomes. David J.A. Jenkins has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies Ltd., Unilever, Barilla, the Almond Board of California, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the Calorie Control Council, the CIHR, the Canada Foundation for Innovation and the Ontario Research Fund. He has received an honorarium from the United States Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013 Award for Excellence in Research from the International Nut and Dried Fruit Council. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association. He has been on the speaker's panel, served on the scientific advisory board, and/or received travel support and/or honoraria from the Almond Board of

California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd, the Griffin Hospital (for the development of the NuVal scoring system), the Coca- Cola Company, Saskatchewan Pulse Growers, Sanitarium Company, Orafti, the Almond Board of California, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter and Gamble, the Coca-Cola Company, the Griffin Hospital, Abbott Laboratories, the Canola Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi- Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, the Nutritional Fundamentals for Health, AgriCulture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Saskatchewan Pulse Growers, the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. John L Sievenpiper has received research support from the Canadian Institutes of health Research (CIHR), Canadian Diabetes Association (CDA), PSI Foundation, Calorie Control Council, Banting and Best Diabetes Centre (BBDC), American Society for Nutrition (ASN), Dr. Pepper Snapple Group (investigator initiated, unrestricted donation), INC International Nut and Dried Fruit Council, and The Tate and Lyle Nutritional Research Fund at the University of Toronto. He has received speaker fees and/or honoraria from the Canadian Diabetes Association (CDA), Canadian Nutrition Society (CNS), University of Alabama at Birmingham, Abbott Laboratories, Canadian Sugar Institute, Dr. Pepper Snapple Group, The Coca-Cola Company, Dairy Farmers of Canada, Nutrition

Foundation of Italy (NFI), C3 Collaborating for Health, WhiteWave Foods, Rippe Lifestyle, mdBriefcase, Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, and Pulse Canada. He has ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines Expert Committees of the Canadian Diabetes Association (CDA), European Association for the study of Diabetes (EASD), and Canadian Cardiovascular Society (CCS), as well as an expert writing panel of the American Society for Nutrition (ASN). He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Studies foundation. His wife is an employee of Unilever Canada. No competing interests were declared by Vivian L Choo, Effie Viguiliouk, Sonia Blanco Mejia, Adrian I Cozma, Tauseef A Khan, Vanessa Ha, and Lawrence A Leiter. There are no patents, products in development or marketed products to declare.

EXCLUSIVE LICENCE

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license (http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%20March%202013.doc) to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution and convert or allow conversion into any format including without limitation audio, iii) create any other derivative work(s) based in

whole or part on the on the Contribution, iv) to exploit all subsidiary rights to exploit all subsidiary rights that currently exist or as may exist in the future in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) license any third party to do any or all of the above.

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.

References

1. Bray GA, Popkin BM. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes?: health be damned! Pour on the sugar. Diabetes care. 2014;37(4):950-6.
2. Kahn R, Sievenpiper JL. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes?: we have, but the pox on sugar is overwrought and overworked. Diabetes care. 2014;37(4):957-62.
3. Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. The American journal of clinical nutrition. 2004;79(5):774-9.
4. Goran MI, Ulijaszek SJ, Ventura EE. High fructose corn syrup and diabetes prevalence: a global perspective. Global public health. 2013;8(1):55-64.
5. Bantle JP, Laine DC, Thomas JW. Metabolic effects of dietary fructose and sucrose in types I and II diabetic subjects. Jama. 1986;256(23):3241-6.
6. Lustig RH. Fructose: it's "alcohol without the buzz". Advances in nutrition. 2013;4(2):226-35.
7. Huang BW, Chiang MT, Yao HT, Chiang W. The effect of high-fat and high-fructose diets on glucose tolerance and plasma lipid and leptin levels in rats. Diabetes, obesity & metabolism. 2004;6(2):120-6.
8. de Moura RF, Ribeiro C, de Oliveira JA, Stevanato E, de Mello MA. Metabolic syndrome signs in Wistar rats submitted to different high-fructose ingestion protocols. The British journal of nutrition. 2009;101(8):1178-84.
9. Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. Hypertension. 1987;10(5):512-6.
10. Hendler R, Bonde AA. Effects of sucrose on resting metabolic rate, nitrogen balance, leucine turnover and oxidation during weight loss with low calorie diets. International journal of obesity. 1990;14(11):927-38.
11. Hendler RG, Walesky M, Sherwin RS. Sucrose substitution in prevention and reversal of the fall in metabolic rate accompanying hypocaloric diets. The American journal of medicine. 1986;81(2):280-4.
12. Yudkin J, Szanto S. Increased levels of plasma insulin and eleven hydroxycorticosteroid induced by sucrose, and their reduction by phenformin. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 1972;4(6):417-20.
13. Cozma AI, Sievenpiper JL, de Souza RJ, Chiavaroli L, Ha V, Wang DD, et al. Effect of fructose on glycemic control in diabetes: a systematic review and meta-analysis of controlled feeding trials. Diabetes care. 2012;35(7):1611-20.
14. White JS. Challenging the fructose hypothesis: new perspectives on fructose consumption and metabolism. Advances in nutrition. 2013;4(2):246-56.
15. Theytaz F, de Giorgi S, Hodson L, Stefanoni N, Rey V, Schneiter P, et al. Metabolic fate of fructose ingested with and without glucose in a mixed meal. Nutrients. 2014;6(7):2632-49.
16. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. BMJ. 2015;351:h3576.
17. Greenwood DC, Threapleton DE, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, et al. Association between sugar-sweetened and artificially sweetened soft drinks and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. The British journal of nutrition. 2014;112(5):725-34.

18. Li S, Miao S, Huang Y, Liu Z, Tian H, Yin X, et al. Fruit intake decreases risk of incident type 2 diabetes: an updated meta-analysis. Endocrine. 2015;48(2):454-60.
19. Muraki I, Imamura F, Manson JE, Hu FB, Willett WC, van Dam RM, et al. Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. BMJ. 2013;347:f5001.
20. Manios Y, Moschonis G, Mavrogianni C, Tsoutsoulopoulou K, Kogkas S, Lambrinou CP, et al. Postprandial glucose and insulin levels in type 2 diabetes mellitus patients after consumption of ready-to-eat mixed meals. European journal of nutrition. 2017;56(3):1359-67.
21. Sievenpiper JL, Dworatzek PD. Food and dietary pattern-based recommendations: an emerging approach to clinical practice guidelines for nutrition therapy in diabetes. Canadian journal of diabetes. 2013;37(1):51-7.
22. Guideline: Sugars Intake for Adults and Children. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2015.
23. Scientific Advisory Committe on Nutrition. Carbohydrates and Health. The Stationery Office. Access date Nov 27 2017. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf; 2015.
24. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane collaboration Available from wwwcochrane-handbookorg. 2011.
25. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery. 2010;8(5):336-41.
26. Wilczynski NL, Morgan D, Haynes RB, Hedges T. An overview of the design and methods for retrieving high-quality studies for clinical care. BMC medical informatics and decision making. 2005;5:20.
27. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
28. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. International journal of epidemiology. 2002;31(1):140-9.
29. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
30. Borenstein M, Hedges LV, Higgins JP, H.R. R. Introduction to meta-analysis. Wiley J, editor2008.
31. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-73.
32. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at http://health.gov/dietaryguidelines/2015/guidelines/.
33. USDA. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. In: DGAC-USDA, editor. 2015. https://health.gov/dietaryguidelines/2015-scientific-report/pdfs/scientific-report-of-the-2015-dietary-guidelines-advisory-committee.pdf.
34. Medicine Io. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: The National Academies Press; 2005. 1358 p.
35. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000;53(11):1119-29.
36. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455-63.
37. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
38. Abdel-Sayed A, Binnert C, Le KA, Bortolotti M, Schneiter P, Tappy L. A high-fructose diet impairs basal and stress-mediated lipid metabolism in healthy male subjects. The British journal of nutrition. 2008;100(2):393-9.

39. Abdulrhman MM, El-Hefnawy MH, Aly RH, Shatla RH, Mamdouh RM, Mahmoud DM, et al. Metabolic effects of honey in type 1 diabetes mellitus: a randomized crossover pilot study. Journal of medicinal food. 2013;16(1):66-72.
40. Abraira C, Derler J. Large variations of sucrose in constant carbohydrate diets in type II diabetes. The American journal of medicine. 1988;84(2):193-200.
41. Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I, et al. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. The American journal of clinical nutrition. 2011;94(2):479-85.
42. Aeberli I, Hochuli M, Berneis K. Response to Comment on: Aeberli et al. Moderate amounts of fructose consumption impair insulin sensitivity in healthy young men: a randomized controlled trial. Diabetes Care 2013;36:150-156. Diabetes care. 2013;36(7):e105.
43. Agebratt C, Strom E, Romu T, Dahlqvist-Leinhard O, Borga M, Leandersson P, et al. A Randomized Study of the Effects of Additional Fruit and Nuts Consumption on Hepatic Fat Content, Cardiovascular Risk Factors and Basal Metabolic Rate. PLoS One. 2016;11(1):e0147149.
44. Anderson JW, Story LJ, Zettwoch NC, Gustafson NJ, Jefferson BS. Metabolic effects of fructose supplementation in diabetic individuals. Diabetes care. 1989;12(5):337-44.
45. Anderson JW, Weiter KM, Christian AL, Ritchey MB, Bays HE. Raisins compared with other snack effects on glycemia and blood pressure: a randomized, controlled trial. Postgraduate medicine. 2014;126(1):37-43.
46. Bahrami M, Ataie-Jafari A, Hosseini S, Foruzanfar MH, Rahmani M, Pajouhi M. Effects of natural honey consumption in diabetic patients: an 8-week randomized clinical trial. International journal of food sciences and nutrition. 2009;60(7):618-26.
47. Banini AE, Boyd LC, Allen JC, Allen HG, Sauls DL. Muscadine grape products intake, diet and blood constituents of non-diabetic and type 2 diabetic subjects. Nutrition. 2006;22(11-12):1137-45.
48. Bantle JP, Raatz SK, Thomas W, Georgopoulos A. Effects of dietary fructose on plasma lipids in healthy subjects. The American journal of clinical nutrition. 2000;72(5):1128-34.
49. Bantle JP, Swanson JE, Thomas W, Laine DC. Metabolic effects of dietary fructose in diabetic subjects. Diabetes care. 1992;15(11):1468-76.
50. Bantle JP, Swanson JE, Thomas W, Laine DC. Metabolic effects of dietary sucrose in type II diabetic subjects. Diabetes care. 1993;16(9):1301-5.
51. Basu A, Du M, Leyva MJ, Sanchez K, Betts NM, Wu M, et al. Blueberries decrease cardiovascular risk factors in obese men and women with metabolic syndrome. The Journal of nutrition. 2010;140(9):1582-7.
52. Bays H, Weiter K, Anderson J. A randomized study of raisins versus alternative snacks on glycemic control and other cardiovascular risk factors in patients with type 2 diabetes mellitus. The Physician and sportsmedicine. 2015;43(1):37-43.
53. Beck-Nielsen H, Pedersen O, Lindskov HO. Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects. The American journal of clinical nutrition. 1980;33(2):273-8.
54. Behall KM, Moser PB, Kelsay JL, Prather ES. The effect of kind of carbohydrate in the diet and use of oral contraceptives on metabolism of young women. III. Serum glucose, insulin, and glucagon. The American journal of clinical nutrition. 1980;33(5):1041-8.
55. Black RN, Spence M, McMahon RO, Cuskelly GJ, Ennis CN, McCance DR, et al. Effect of eucaloric high- and low-sucrose diets with identical macronutrient profile on insulin resistance and vascular risk: a randomized controlled trial. Diabetes. 2006;55(12):3566-72.

56. Blayo A, Fontevieille S, Rizkalla S, Bruzzo F, Slama G. Effets métaboliques de la consommation quotidienne pendant un an de saccharose ou de fructose par des diabétiques. Médecine et Nutrition. 1990;26(1):11-4.
57. Brymora A, Flisinski M, Johnson RJ, Goszka G, Stefanska A, Manitius J. Low-fructose diet lowers blood pressure and inflammation in patients with chronic kidney disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2012;27(2):608-12.
58. Brynes AE, Mark Edwards C, Ghatei MA, Dornhorst A, Morgan LM, Bloom SR, et al. A randomised four-intervention crossover study investigating the effect of carbohydrates on daytime profiles of insulin, glucose, non-esterified fatty acids and triacylglycerols in middle-aged men. The British journal of nutrition. 2003;89(2):207-18.
59. Buysschaert M, Sory R, Mpoy M, Lambert AE. Effect of the addition of simple sugars to mixed meals on the glycemic control of insulin treated diabetic patients. Diabete & metabolisme. 1987;13(6):625-9.
60. Campos V, Despland C, Brandejsky V, Kreis R, Schneiter P, Chiolero A, et al. Sugar- and artificially sweetened beverages and intrahepatic fat: A randomized controlled trial. Obesity. 2015;23(12):2335-9.
61. Chantelau EA, Gosseringer G, Sonnenberg GE, Berger M. Moderate intake of sucrose does not impair metabolic control in pump-treated diabetic out-patients. Diabetologia. 1985;28(4):204-7.
62. Christensen AS, Viggers L, Hasselstrom K, Gregersen S. Effect of fruit restriction on glycemic control in patients with type 2 diabetes--a randomized trial. Nutrition journal. 2013;12:29.
63. Claesson AL, Holm G, Ernersson A, Lindstrom T, Nystrom FH. Two weeks of overfeeding with candy, but not peanuts, increases insulin levels and body weight. Scandinavian journal of clinical and laboratory investigation. 2009;69(5):598-605.
64. Colagiuri S, Miller JJ, Edwards RA. Metabolic effects of adding sucrose and aspartame to the diet of subjects with noninsulin-dependent diabetes mellitus. The American journal of clinical nutrition. 1989;50(3):474-8.
65. Conceicao de Oliveira M, Sichieri R, Sanchez Moura A. Weight loss associated with a daily intake of three apples or three pears among overweight women. Nutrition. 2003;19(3):253-6.
66. Cooper PL, Wahlqvist ML, Simpson RW. Sucrose versus saccharin as an added sweetener in non-insulin-dependent diabetes: short- and medium-term metabolic effects. Diabetic medicine : a journal of the British Diabetic Association. 1988;5(7):676-80.
67. Costa PC, Franco LJ. [Introduction of sucrose in the diet plan of persons with type 1 diabetes: its influence in the glycemic control]. Arquivos brasileiros de endocrinologia e metabologia. 2005;49(3):403-9.
68. Coulston AM, Hollenbeck CB, Donner CC, Williams R, Chiou YA, Reaven GM. Metabolic effects of added dietary sucrose in individuals with noninsulin-dependent diabetes mellitus (NIDDM). Metabolism. 1985;34(10):962-6.
69. Cressey R, Kumsaiyai W, Mangklabruks A. Daily consumption of banana marginally improves blood glucose and lipid profile in hypercholesterolemic subjects and increases serum adiponectin in type 2 diabetic patients. Indian journal of experimental biology. 2014;52(12):1173-81.
70. Despland C, Walther B, Kast C, Campos V, Rey V, Stefanoni N, et al. A randomized-controlled clinical trial of high fructose diets from either Robinia honey or free fructose and glucose in healthy normal weight males. Clinical Nutrition ESPEN. 2017;19:16-22.
71. Dunnigan MG, Fyfe T, McKiddie MT, Crosbie SM. The effects of isocaloric exchange of dietary starch and sucrose on glucose tolerance, plasma insulin and serum lipids in man. Clinical science. 1970;38(1):1-9.
72. Ellis CL, Edirisinghe I, Kappagoda T, Burton-Freeman B. Attenuation of meal-induced inflammatory and thrombotic responses in overweight men and women after 6-week daily strawberry

(Fragaria) intake. A randomized placebo-controlled trial. Journal of atherosclerosis and thrombosis. 2011;18(4):318-27.

73. Emanuele MA, Abraira C, Jellish WS, DeBartolo M. A crossover trial of high and low sucrose-carbohydrate diets in type II diabetics with hypertriglyceridemia. Journal of the American College of Nutrition. 1986;5(5):429-37.

74. Enginyurt O, Cakir L, Karatas A, Cankaya S, Kaya Y, Handan Tugcu H, et al. The role of pure honey in the treatment of diabetes mellitus. Biomedical Research (India). 2017;28(7):3305-12.

75. Friedman M, Rosenman RH, Byers SO, Elevitch FR. Effect of low sugar intake upon blood lipids and insulin levels of hyperlipemic subjects. Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine. 1970;135(3):785-91.

76. Fry AJ. The effect of a 'sucrose-free' diet on oral glucose tolerance in man. Nutrition and metabolism. 1972;14(5):313-23.

77. Grigoresco C, Rizkalla SW, Halfon P, Bornet F, Fontvieille AM, Bros M, et al. Lack of detectable deleterious effects on metabolic control of daily fructose ingestion for 2 mo in NIDDM patients. Diabetes care. 1988;11(7):546-50.

78. Hallfrisch J, Ellwood KC, Michaelis OEt, Reiser S, O'Dorisio TM, Prather ES. Effects of dietary fructose on plasma glucose and hormone responses in normal and hyperinsulinemic men. The Journal of nutrition. 1983;113(9):1819-26.

79. Heden TD, Liu Y, Park YM, Nyhoff LM, Winn NC, Kanaley JA. Moderate amounts of fructose- or glucose-sweetened beverages do not differentially alter metabolic health in male and female adolescents. The American journal of clinical nutrition. 2014;100(3):796-805.

80. Heden TD, Liu Y, Park YM, Winn NC, Kanaley JA. Walking Reduces Postprandial Insulin Secretion in Obese Adolescents Consuming a High-Fructose or High-Glucose Diet. Journal of physical activity & health. 2015;12(8):1153-61.

81. Hegde SV, Adhikari P, M N, D'Souza V. Effect of daily supplementation of fruits on oxidative stress indices and glycaemic status in type 2 diabetes mellitus. Complementary therapies in clinical practice. 2013;19(2):97-100.

82. Hernandez-Cordero S, Barquera S, Rodriguez-Ramirez S, Villanueva-Borbolla MA, Gonzalez de Cossio T, Dommarco JR, et al. Substituting water for sugar-sweetened beverages reduces circulating triglycerides and the prevalence of metabolic syndrome in obese but not in overweight Mexican women in a randomized controlled trial. The Journal of nutrition. 2014;144(11):1742-52.

83. Hollis JH, Houchins JA, Blumberg JB, Mattes RD. Effects of concord grape juice on appetite, diet, body weight, lipid profile, and antioxidant status of adults. Journal of the American College of Nutrition. 2009;28(5):574-82.

84. Huttunen JK, Makinen KK, Scheinin A. Turku sugar studies XI. Effects of sucrose, fructose and xylitol diets on glucose, lipid and urate metabolism. Acta odontologica Scandinavica. 1976;34(6):345-51.

85. Jellish WS, Emanuele MA, Abraira C. Graded sucrose/carbohydrate diets in overtly hypertriglyceridemic diabetic patients. The American journal of medicine. 1984;77(6):1015-22.

86. Jin R, Welsh JA, Le NA, Holzberg J, Sharma P, Martin DR, et al. Dietary fructose reduction improves markers of cardiovascular disease risk in Hispanic-American adolescents with NAFLD. Nutrients. 2014;6(8):3187-201.

87. Jones JB, Provost M, Keaver L, Breen C, Ludy MJ, Mattes RD. A randomized trial on the effects of flavorings on the health benefits of daily peanut consumption. The American journal of clinical nutrition. 2014;99(3):490-6.

88. Johnston RD, Stephenson MC, Crossland H, Cordon SM, Palcidi E, Cox EF, et al. No difference between high-fructose and high-glucose diets on liver triacylglycerol or biochemistry in healthy overweight men. Gastroenterology. 2013;145(5):1016-25 e2.

89. Kaliora AC, Kokkinos A, Diolintzi A, Stoupaki M, Gioxari A, Kanellos PT, et al. The effect of minimal dietary changes with raisins in NAFLD patients with non-significant fibrosis: a randomized controlled intervention. Food Funct. 2016;7(11):4533-44.
90. Kanellos PT, Kaliora AC, Tentolouris NK, Argiana V, Perrea D, Kalogeropoulos N, et al. A pilot, randomized controlled trial to examine the health outcomes of raisin consumption in patients with diabetes. Nutrition. 2014;30(3):358-64.
91. Kelsay JL, Behall KM, Holden JM, Prather ES. Diets high in glucose or sucrose and young women. The American journal of clinical nutrition. 1974;27(9):926-36.
92. Koh ET, Ard NF, Mendoza F. Effects of fructose feeding on blood parameters and blood pressure in impaired glucose-tolerant subjects. Journal of the American Dietetic Association. 1988;88(8):932-8.
93. Koivisto VA, Yki-Jarvinen H. Fructose and insulin sensitivity in patients with type 2 diabetes. Journal of internal medicine. 1993;233(2):145-53.
94. Kolehmainen M, Mykkanen O, Kirjavainen PV, Leppanen T, Moilanen E, Adriaens M, et al. Bilberries reduce low-grade inflammation in individuals with features of metabolic syndrome. Molecular nutrition & food research. 2012;56(10):1501-10.
95. Koopman KE, Caan MW, Nederveen AJ, Pels A, Ackermans MT, Fliers E, et al. Hypercaloric diets with increased meal frequency, but not meal size, increase intrahepatic triglycerides: a randomized controlled trial. Hepatology. 2014;60(2):545-53.
96. Le KA, Faeh D, Stettler R, Ith M, Kreis R, Vermathen P, et al. A 4-wk high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans. The American journal of clinical nutrition. 2006;84(6):1374-9.
97. Le KA, Ith M, Kreis R, Faeh D, Bortolotti M, Tran C, et al. Fructose overconsumption causes dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes. The American journal of clinical nutrition. 2009;89(6):1760-5.
98. Lehtonen HM, Suomela JP, Tahvonen R, Vaarno J, Venojarvi M, Viikari J, et al. Berry meals and risk factors associated with metabolic syndrome. European journal of clinical nutrition. 2010;64(6):614-21.
99. Lewis AS, McCourt HJ, Ennis CN, Bell PM, Courtney CH, McKinley MC, et al. Comparison of 5% versus 15% sucrose intakes as part of a eucaloric diet in overweight and obese subjects: effects on insulin sensitivity, glucose metabolism, vascular compliance, body composition and lipid profile. A randomised controlled trial. Metabolism. 2013;62(5):694-702.
100. Liu G, Coulston A, Hollenbeck C, Reaven G. The effect of sucrose content in high and low carbohydrate diets on plasma glucose, insulin, and lipid responses in hypertriglyceridemic humans. The Journal of clinical endocrinology and metabolism. 1984;59(4):636-42.
101. Lock S, Ford MA, Bagley R, Green LF. The effect on plasma lipids of the isoenergetic replacement of table sucrose by dried glucose syrup (maize-syrup solids) in the normal diet of adult men over a period of 1 year. The British journal of nutrition. 1980;43(2):251-6.
102. Lowndes J, Sinnett SS, Rippe JM. No Effect of Added Sugar Consumed at Median American Intake Level on Glucose Tolerance or Insulin Resistance. Nutrients. 2015;7(10):8830-45.
103. Madero M, Arriaga JC, Jalal D, Rivard C, McFann K, Perez-Mendez O, et al. The effect of two energy-restricted diets, a low-fructose diet versus a moderate natural fructose diet, on weight loss and metabolic syndrome parameters: a randomized controlled trial. Metabolism. 2011;60(11):1551-9.
104. Maersk M, Belza A, Stodkilde-Jorgensen H, Ringgaard S, Chabanova E, Thomsen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. The American journal of clinical nutrition. 2012;95(2):283-9.
105. Majid M, Younis MA, Naveed AK, Shah MU, Azeem Z, Tirmizi SH. Effects of natural honey on blood glucose and lipid profile in young healthy Pakistani males. Journal of Ayub Medical College, Abbottabad : JAMC. 2013;25(3-4):44-7.

106. Maki KC, Nieman KM, Schild AL, Kaden VN, Lawless AL, Kelley KM, et al. Sugar-sweetened product consumption alters glucose homeostasis compared with dairy product consumption in men and women at risk of type 2 diabetes mellitus. The Journal of nutrition. 2015;145(3):459-66.
107. Malerbi DA, Paiva ES, Duarte AL, Wajchenberg BL. Metabolic effects of dietary sucrose and fructose in type II diabetic subjects. Diabetes care. 1996;19(11):1249-56.
108. Mark AB, Poulsen MW, Andersen S, Andersen JM, Bak MJ, Ritz C, et al. Consumption of a diet low in advanced glycation end products for 4 weeks improves insulin sensitivity in overweight women. Diabetes care. 2014;37(1):88-95.
109. Markey O, Le Jeune J, Lovegrove JA. Energy compensation following consumption of sugar-reduced products: a randomized controlled trial. European journal of nutrition. 2015.
110. McAteer EJ, O'Reilly G, Hadden DR. The effects of one month high fructose intake on plasma glucose and lipid levels in non-insulin-dependent diabetes. Diabetic medicine : a journal of the British Diabetic Association. 1987;4(1):62-4.
111. Mitsou EK, Kougia E, Nomikos T, Yannakoulia M, Mountzouris KC, Kyriacou A. Effect of banana consumption on faecal microbiota: a randomised, controlled trial. Anaerobe. 2011;17(6):384-7.
112. Moazen S, Amani R, Homayouni Rad A, Shahbazian H, Ahmadi K, Taha Jalali M. Effects of freeze-dried strawberry supplementation on metabolic biomarkers of atherosclerosis in subjects with type 2 diabetes: a randomized double-blind controlled trial. Annals of nutrition & metabolism. 2013;63(3):256-64.
113. Ngo Sock ET, Le KA, Ith M, Kreis R, Boesch C, Tappy L. Effects of a short-term overfeeding with fructose or glucose in healthy young males. The British journal of nutrition. 2010;103(7):939-43.
114. Njike VY, Faridi Z, Shuval K, Dutta S, Kay CD, West SG, et al. Effects of sugar-sweetened and sugar-free cocoa on endothelial function in overweight adults. International journal of cardiology. 2011;149(1):83-8.
115. Osei K, Bossetti B. Dietary fructose as a natural sweetener in poorly controlled type 2 diabetes: a 12-month crossover study of effects on glucose, lipoprotein and apolipoprotein metabolism. Diabetic medicine : a journal of the British Diabetic Association. 1989;6(6):506-11.
116. Osei K, Falko J, Bossetti BM, Holland GC. Metabolic effects of fructose as a natural sweetener in the physiologic meals of ambulatory obese patients with type II diabetes. The American journal of medicine. 1987;83(2):249-55.
117. Paganus A, Maenpaa J, Akerblom HK, Stenman UH, Knip M, Simell O. Beneficial effects of palatable guar and guar plus fructose diets in diabetic children. Acta paediatrica Scandinavica. 1987;76(1):76-81.
118. Paineau DL, Beaufils F, Boulier A, Cassuto DA, Chwalow J, Combris P, et al. Family dietary coaching to improve nutritional intakes and body weight control: a randomized controlled trial. Archives of pediatrics & adolescent medicine. 2008;162(1):34-43.
119. Pelkonen R, Aro A, Nikkila EA. Metabolic effects of dietary fructose in insulin dependent diabetes of adults. Acta medica Scandinavica Supplementum. 1972;542:187-93.
120. Peterson DB, Lambert J, Gerring S, Darling P, Carter RD, Jelfs R, et al. Sucrose in the diet of diabetic patients--just another carbohydrate? Diabetologia. 1986;29(4):216-20.
121. Poppitt SD, Keogh GF, Prentice AM, Williams DE, Sonnemans HM, Valk EE, et al. Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. The American journal of clinical nutrition. 2002;75(1):11-20.
122. Porta M, Pigino M, Minonne A, Morisio Guidetti L. Moderate Amounts of Sucrose with Mixed Meals do not Impair Metabolic Control in Patients with Type II (Non-Insulin Dependent) Diabetes. Diabetes, Nutrition & Metabolism. 1989;2(2):133-7.

123. Puglisi MJ, Vaishnav U, Shrestha S, Torres-Gonzalez M, Wood RJ, Volek JS, et al. Raisins and additional walking have distinct effects on plasma lipids and inflammatory cytokines. Lipids in health and disease. 2008;7:14.
124. Raben A, Astrup A. Leptin is influenced both by predisposition to obesity and diet composition. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2000;24(4):450-9.
125. Raben A, Moller BK, Flint A, Vasilaris TH, Christina Moller A, Juul Holst J, et al. Increased postprandial glycaemia, insulinemia, and lipidemia after 10 weeks' sucrose-rich diet compared to an artificially sweetened diet: a randomised controlled trial. Food & nutrition research. 2011;55.
126. Rath R, Masek J, Kujalova V, Slabochova Z. Effect of a high sugar intake on some metabolic and regulatory indicators in young men. Die Nahrung. 1974;18(4):343-53.
127. Ravn-Haren G, Dragsted LO, Buch-Andersen T, Jensen EN, Jensen RI, Nemeth-Balogh M, et al. Intake of whole apples or clear apple juice has contrasting effects on plasma lipids in healthy volunteers. European journal of nutrition. 2013;52(8):1875-89.
128. Reiser S, Hallfrisch J, Fields M, Powell A, Mertz W, Prather ES, et al. Effects of sugars on indices of glucose tolerance in humans. The American journal of clinical nutrition. 1986;43(1):151-9.
129. Reiser S, Powell AS, Scholfield DJ, Panda P, Fields M, Canary JJ. Day-long glucose, insulin, and fructose responses of hyperinsulinemic and nonhyperinsulinemic men adapted to diets containing either fructose or high-amylose cornstarch. The American journal of clinical nutrition. 1989;50(5):1008-14.
130. Ribeiro C, Dourado G, Cesar T. Orange juice allied to a reduced-calorie diet results in weight loss and ameliorates obesity-related biomarkers: A randomized controlled trial. Nutrition. 2017;38:13-9.
131. Rodriguez MC, Parra MD, Marques-Lopes I, De Morentin BE, Gonzalez A, Martinez JA. Effects of two energy-restricted diets containing different fruit amounts on body weight loss and macronutrient oxidation. Plant foods for human nutrition. 2005;60(4):219-24.
132. Santacroce G, Forlani G, Giangiulio S, Galuppi V, Pagani M, Vannini P. Long-term effects of eating sucrose on metabolic control of type 1 (insulin-dependent) diabetic outpatients. Acta diabetologica latina. 1990;27(4):365-70.
133. Saris WH, Astrup A, Prentice AM, Zunft HJ, Formiguera X, Verboeket-van de Venne WP, et al. Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs complex carbohydrates on body weight and blood lipids: the CARMEN study. The Carbohydrate Ratio Management in European National diets. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2000;24(10):1310-8.
134. Schwarz JM, Noworolski SM, Wen MJ, Dyachenko A, Prior JL, Weinberg ME, et al. Effect of a High-Fructose Weight-Maintaining Diet on Lipogenesis and Liver Fat. The Journal of clinical endocrinology and metabolism. 2015;100(6):2434-42.
135. Schwingshandl J, Rippel S, Unterluggauer M, Borkenstein M. Effect of the introduction of dietary sucrose on metabolic control in children and adolescents with type I diabetes. Acta diabetologica. 1994;31(4):205-9.
136. Silbernagel G, Machann J, Unmuth S, Schick F, Stefan N, Haring HU, et al. Effects of 4-week very-high-fructose/glucose diets on insulin sensitivity, visceral fat and intrahepatic lipids: an exploratory trial. The British journal of nutrition. 2011;106(1):79-86.
137. Singh RB, Rastogi SS, Singh R, Niaz MA, Singh NK, Madhu SV. Effects on Plasma Ascorbic Acid and Coronary Risk Factors of Adding Guava Fruit to the Usual Diet in Hypertensives with Mild to Moderate Hypercholesterolaemia. Journal of Nutritional & Environmental Medicine. 1997;7:5-14.
138. Sobrecases H, Le KA, Bortolotti M, Schneiter P, Ith M, Kreis R, et al. Effects of short-term overfeeding with fructose, fat and fructose plus fat on plasma and hepatic lipids in healthy men. Diabetes & metabolism. 2010;36(3):244-6.

139. Souto DL, Zajdenverg L, Rodacki M, Rosado EL. Does sucrose intake affect antropometric variables, glycemia, lipemia and C-reactive protein in subjects with type 1 diabetes?: a controlled-trial. Diabetology & metabolic syndrome. 2013;5(1):67.
140. Stanhope KL, Griffen SC, Bremer AA, Vink RG, Schaefer EJ, Nakajima K, et al. Metabolic responses to prolonged consumption of glucose- and fructose-sweetened beverages are not associated with postprandial or 24-h glucose and insulin excursions. The American journal of clinical nutrition. 2011;94(1):112-9.
141. Stanhope KL, Bremer AA, Medici V, Nakajima K, Ito Y, Nakano T, et al. Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women. The Journal of clinical endocrinology and metabolism. 2011;96(10):E1596-605.
142. Sunehag AL, Toffolo G, Campioni M, Bier DM, Haymond MW. Short-term high dietary fructose intake had no effects on insulin sensitivity and secretion or glucose and lipid metabolism in healthy, obese adolescents. Journal of pediatric endocrinology & metabolism : JPEM. 2008;21(3):225-35.
143. Sunehag AL, Toffolo G, Treuth MS, Butte NF, Cobelli C, Bier DM, et al. Effects of dietary macronutrient content on glucose metabolism in children. The Journal of clinical endocrinology and metabolism. 2002;87(11):5168-78.
144. Surwit RS, Feinglos MN, McCaskill CC, Clay SL, Babyak MA, Brownlow BS, et al. Metabolic and behavioral effects of a high-sucrose diet during weight loss. The American journal of clinical nutrition. 1997;65(4):908-15.
145. Swanson JE, Laine DC, Thomas W, Bantle JP. Metabolic effects of dietary fructose in healthy subjects. The American journal of clinical nutrition. 1992;55(4):851-6.
146. Swarbrick MM, Stanhope KL, Elliott SS, Graham JL, Krauss RM, Christiansen MP, et al. Consumption of fructose-sweetened beverages for 10 weeks increases postprandial triacylglycerol and apolipoprotein-B concentrations in overweight and obese women. The British journal of nutrition. 2008;100(5):947-52.
147. Szanto S, Yudkin J. The effect of dietary sucrose on blood lipids, serum insulin, platelet adhesiveness and body weight in human volunteers. Postgraduate medical journal. 1969;45(527):602-7.
148. Tate DF, Turner-McGrievy G, Lyons E, Stevens J, Erickson K, Polzien K, et al. Replacing caloric beverages with water or diet beverages for weight loss in adults: main results of the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial. The American journal of clinical nutrition. 2012;95(3):555-63.
149. Vaisman N, Niv E, Izkhakov Y. Catalytic amounts of fructose may improve glucose tolerance in subjects with uncontrolled non-insulin-dependent diabetes. Clinical nutrition. 2006;25(4):617-21.
150. van Meijl LE, Mensink RP. Low-fat dairy consumption reduces systolic blood pressure, but does not improve other metabolic risk parameters in overweight and obese subjects. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2011;21(5):355-61.
151. Volp AC, Hermsdorff HH, Bressan J. Glycemia and insulinemia evaluation after high-sucrose and high-fat diets in lean and overweight/obese women. Journal of physiology and biochemistry. 2008;64(2):103-13.
152. Volp AC, Hermsdorff HM, Bressan J. [Effect of high sucrose- and high-fat diets ingested under free-living conditions in insulin resistance in normal weight and overweight women]. Nutricion hospitalaria. 2007;22(1):46-60.
153. Lin L, Chu H, Hodges JS. Alternative measures of between-study heterogeneity in meta-analysis: Reducing the impact of outlying studies. Biometrics. 2017;73(1):156-66.
154. Livesey G, Taylor R. Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies. The American journal of clinical nutrition. 2008;88(5):1419-37.

155. Sievenpiper JL. Sickeningly Sweet: Does Sugar Cause Chronic Disease? No. Canadian journal of diabetes. 2016;40(4):287-95.
156. Tsilas CS, de Souza RJ, Mejia SB, Mirrahimi A, Cozma AI, Jayalath VH, et al. Relation of total sugars, fructose and sucrose with incident type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2017;189(20):E711-E20.
157. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. Diabetes care. 2008;31(12):2281-3.
158. Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health--a systematic review and meta-analysis: relations between dietary glycemic properties and health outcomes. The American journal of clinical nutrition. 2008;87(1):258S-68S.
159. Brand-Miller JC, Petocz P, Colagiuri S. Meta-analysis of low-glycemic index diets in the management of diabetes: response to Franz. Diabetes care. 2003;26(12):3363-4; author reply 4-5.
160. Jenkins DJ, Wolever TM, Collier GR, Ocana A, Rao AV, Buckley G, et al. Metabolic effects of a low-glycemic-index diet. The American journal of clinical nutrition. 1987;46(6):968-75.
161. Ford ES, Liu S. Glycemic index and serum high-density lipoprotein cholesterol concentration among us adults. Arch Intern Med. 2001;161(4):572-6.
162. Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, et al. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. The American journal of clinical nutrition. 2001;73(3):560-6.
163. Lattimer JM, Haub MD. Effects of dietary fiber and its components on metabolic health. Nutrients. 2010;2(12):1266-89.
164. Jenkins DJ, Srichaikul K, Kendall CW, Sievenpiper JL, Abdulnour S, Mirrahimi A, et al. The relation of low glycaemic index fruit consumption to glycaemic control and risk factors for coronary heart disease in type 2 diabetes. Diabetologia. 2011;54(2):271-9.
165. Hawkins M, Gabriely I, Wozniak R, Vilcu C, Shamoon H, Rossetti L. Fructose improves the ability of hyperglycemia per se to regulate glucose production in type 2 diabetes. Diabetes. 2002;51(3):606-14.
166. Petersen KF, Laurent D, Yu C, Cline GW, Shulman GI. Stimulating effects of low-dose fructose on insulin-stimulated hepatic glycogen synthesis in humans. Diabetes. 2001;50(6):1263-8.
167. Braunstein CR, Noronha JC, Glenn AJ, Viguiliouk E, Noseworthy R, Khan TA, et al. A Double-Blind, Randomized Controlled, Acute Feeding Equivalence Trial of Small, Catalytic Doses of Fructose and Allulose on Postprandial Blood Glucose Metabolism in Healthy Participants: The Fructose and Allulose Catalytic Effects (FACE) Trial. Nutrients. 2018;10(6).
168. Noronha JC, Braunstein CR, Glenn AJ, Khan TA, Viguiliouk E, Noseworthy R, et al. The effect of small doses of fructose and allulose on postprandial glucose metabolism in type 2 diabetes: A double-blind, randomized, controlled, acute feeding, equivalence trial. Diabetes, obesity & metabolism. 2018.
169. Lan-Pidhainy X, Wolever TM. The hypoglycemic effect of fat and protein is not attenuated by insulin resistance. The American journal of clinical nutrition. 2010;91(1):98-105.
170. Wolever TM, van Klinken BJ, Bordenave N, Kaczmarczyk M, Jenkins AL, Chu Y, et al. 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. The American journal of clinical nutrition. 2016;104(4):995-1003.
171. Jakubowicz D, Froy O, Ahren B, Boaz M, Landau Z, Bar-Dayan Y, et al. Incretin, insulinotropic and glucose-lowering effects of whey protein pre-load in type 2 diabetes: a randomised clinical trial. Diabetologia. 2014;57(9):1807-11.
172. Mozaffarian D. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. Circulation. 2016;133(2):187-225.

173. Sievenpiper JL, de Souza RJ, Mirrahimi A, Yu ME, Carleton AJ, Beyene J, et al. Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis. Annals of internal medicine. 2012;156(4):291-304.
174. Silbernagel G, Kovarova M, Cegan A, Machann J, Schick F, Lehmann R, et al. High hepatic SCD1 activity is associated with low liver fat content in healthy subjects under a lipogenic diet. The Journal of clinical endocrinology and metabolism. 2012;97(12):E2288-92.
175. Wang DD, Sievenpiper JL, de Souza RJ, Chiavaroli L, Ha V, Cozma AI, et al. The effects of fructose intake on serum uric acid vary among controlled dietary trials. The Journal of nutrition. 2012;142(5):916-23.
176. Chiu S, Sievenpiper JL, de Souza RJ, Cozma AI, Mirrahimi A, Carleton AJ, et al. Effect of fructose on markers of non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of controlled feeding trials. European journal of clinical nutrition. 2014;68(4):416-23.
177. David Wang D, Sievenpiper JL, de Souza RJ, Cozma AI, Chiavaroli L, Ha V, et al. Effect of fructose on postprandial triglycerides: a systematic review and meta-analysis of controlled feeding trials. Atherosclerosis. 2014;232(1):125-33.
178. van Buul VJ, Tappy L, Brouns FJ. Misconceptions about fructose-containing sugars and their role in the obesity epidemic. Nutrition research reviews. 2014;27(1):119-30.
179. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. The New England journal of medicine. 2011;364(25):2392-404.
180. Kaiser KA, Shikany JM, Keating KD, Allison DB. Will reducing sugar-sweetened beverage consumption reduce obesity? Evidence supporting conjecture is strong, but evidence when testing effect is weak. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2013;14(8):620-33.
181. Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ. 2012;346:e7492.

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)	108	35	5	7
Study Size (participants)[1]	15 (5-595)	20 (6-63)	15 (6-318)	39 (8-236)
Male: Female[2]	42: 58	46: 54	12: 88	41: 59
Age (years)[3]	39.8 (24.7-53.8)	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]	5.4 (4.9-8.5)	5.1 (4.9-5.4)	5.1 (5.1-5.2)	4.9 (4.9-5.4)
Baseline Fasting Insulin (pmol/L)[3]	96.6 (57.9-128.5)	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]	61: 39	49: 51	20: 80	57: 43
Feeding Control (Met: Supp: DA)[2]	44: 41: 16	13: 80: 7	0: 70: 30	50: 37.5: 12.5
Randomization (Yes: No)[2]	72: 28	66: 34	80: 20	100: 0
Fructose-Containing Sugars Dosage (%E)[3]	15.0 (9.3-22.1)	12.2 (7.7-25.0)	15.0 (11.3-15.0)	23.0 (13.0-26.0)
Follow-Up Duration (Weeks)[1]	4.5 (1-52)	6 (1-24)	12 (1-36)	8 (2-76)
Funding Sources (A: I: AI: NR)[2]	32: 18: 28: 22	49: 9: 34: 9	60: 40: 0: 0	0: 17: 50: 33
Fructose-Containing Sugars Type (N)	Fructose=47; Fruit=17; 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=3; 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=12; Dried Fruit=4; 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).

Figure1. Flow of the literature for the effect of food sources of fructose-containing sugars on glycemic control.

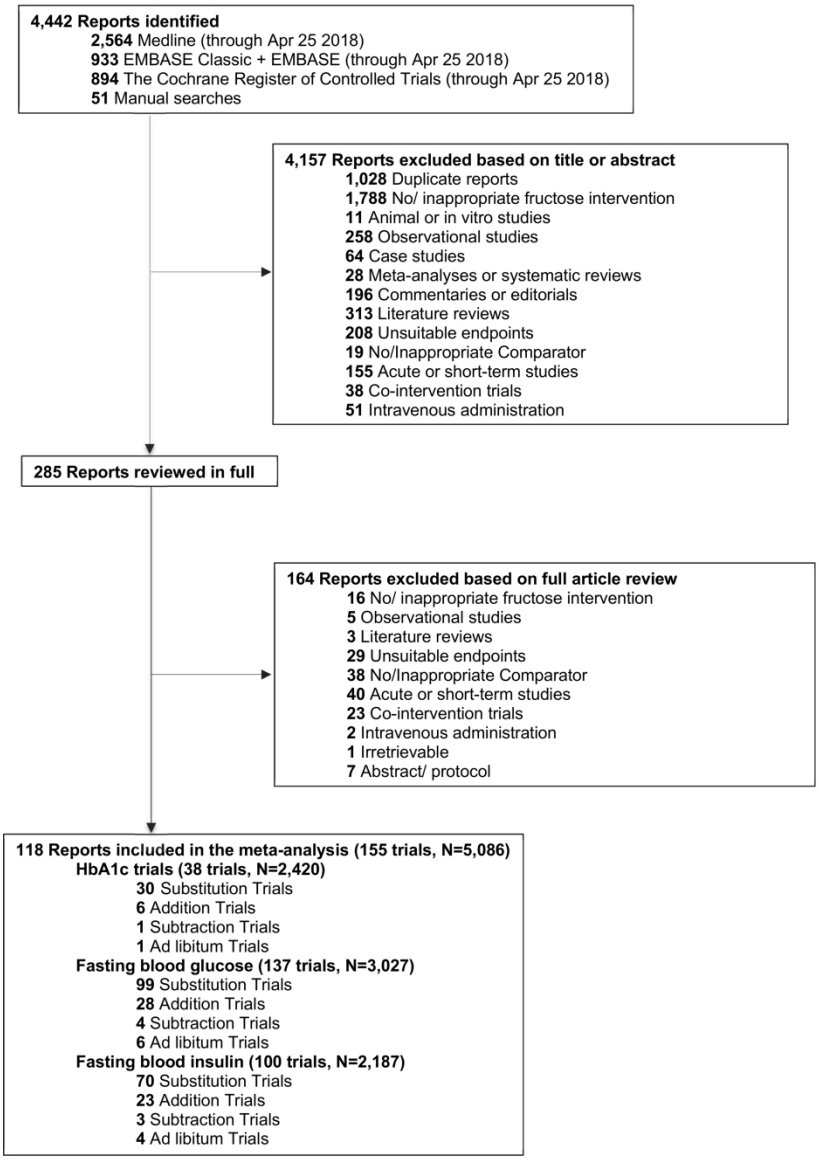


Figure1. Flow of the literature for the effect of food sources of fructose-containing sugars on glycemic control

118x173mm (600 x 600 DPI)

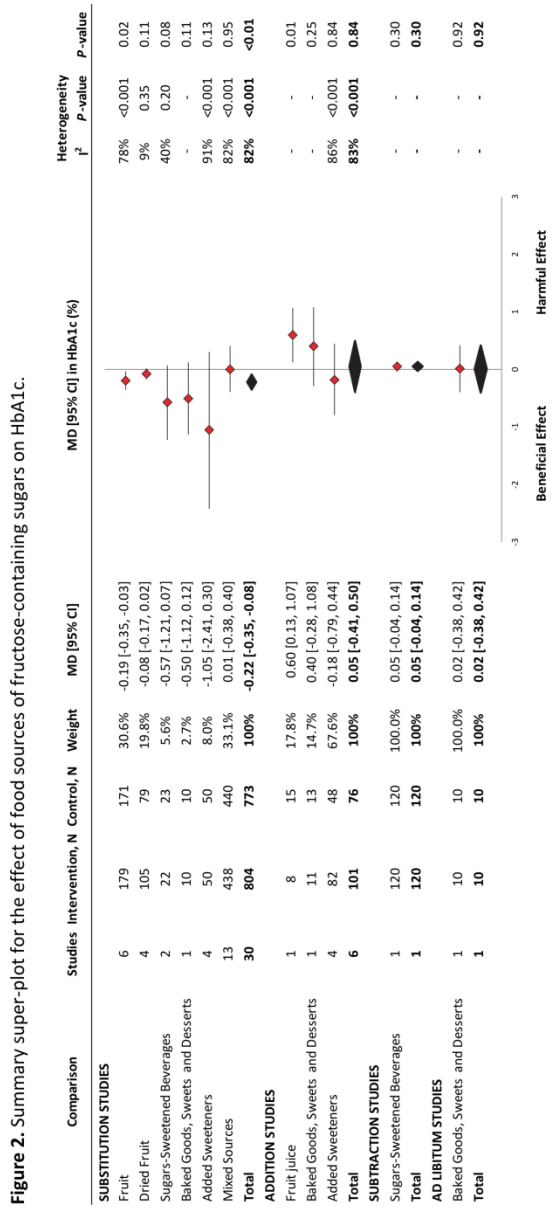


Figure 2. Summary super-plot for the effect of food sources of fructose-containing sugars on HbA1c.

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

168x377mm (300 x 300 DPI)

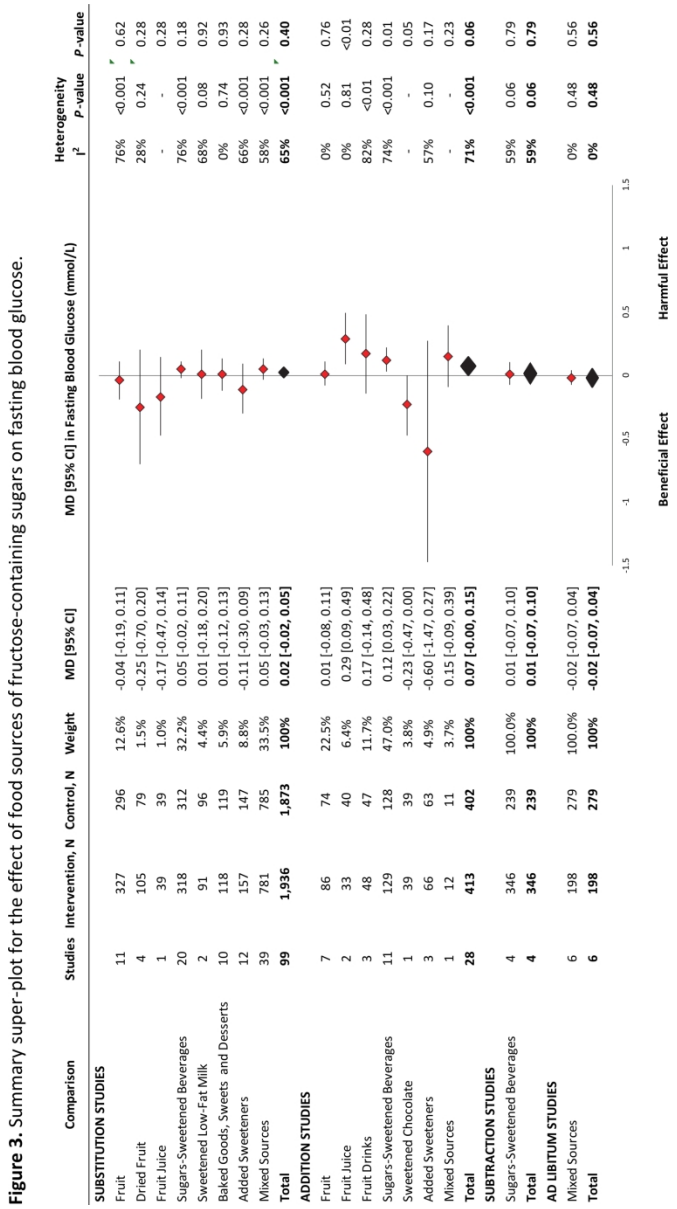


Figure 3. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood glucose.

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

146x265mm (600 x 600 DPI)

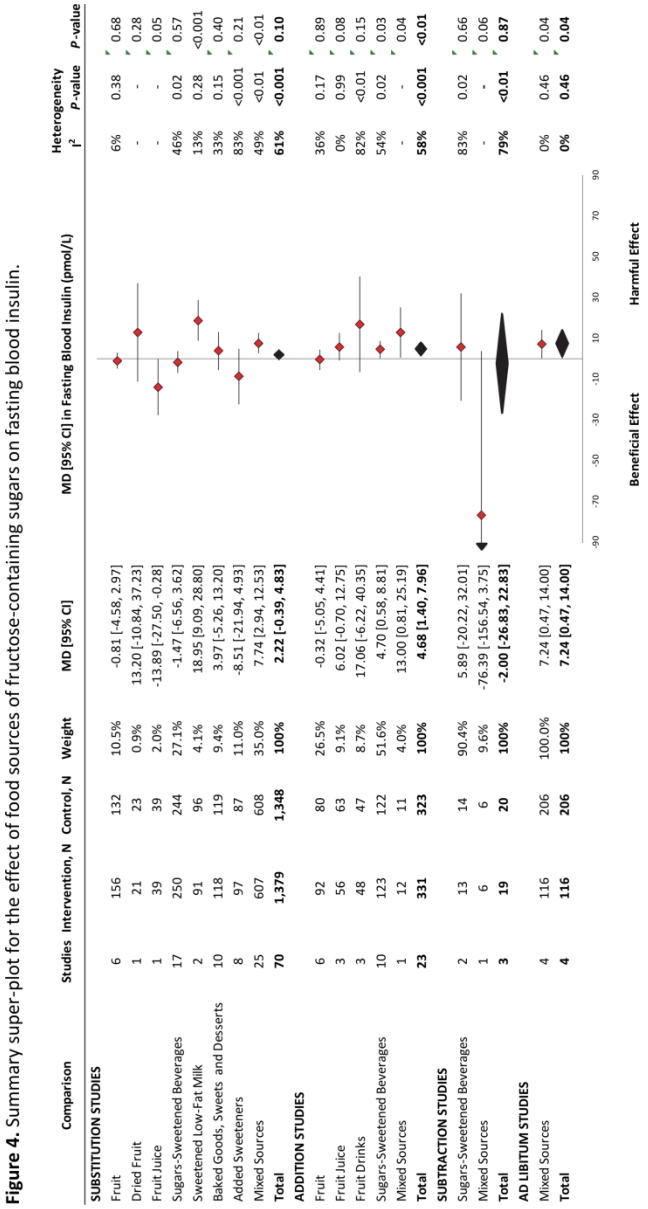


Figure 4. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood insulin.

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

151x285mm (600 x 600 DPI)

Supplementary Tables and Figures

SUPPLEMENTARY TABLES

SUPPLEMENTARY FIGURES

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 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 searches were performed on May 29th 2017 and April 25th 2018 .

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 de Oliveira 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
Interventiengin on	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			
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)			6.2 (0.7)							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				
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)		5.0 (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				
Santacroce 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				
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				
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				

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)										
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)[h]	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				
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				
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	Replace SSB with ASB	~46:38:16			
Control	6 OW/OB					5.2 (0.5)	66.7 (30.6)					86.8 (~15)	Sucrose, HFCS	Habitual SSB consumption (≥ 2 SSB/d)	~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)											
Control	8 OW/OB					5.7 (0.5)	140.3 (51.4)					86.8 (~15)	Sweetener Sucrose, HFCS	Replace SSB with ASB Habitual SSB consumption (≥ 2 SSB/d)	~46:38:16 ~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

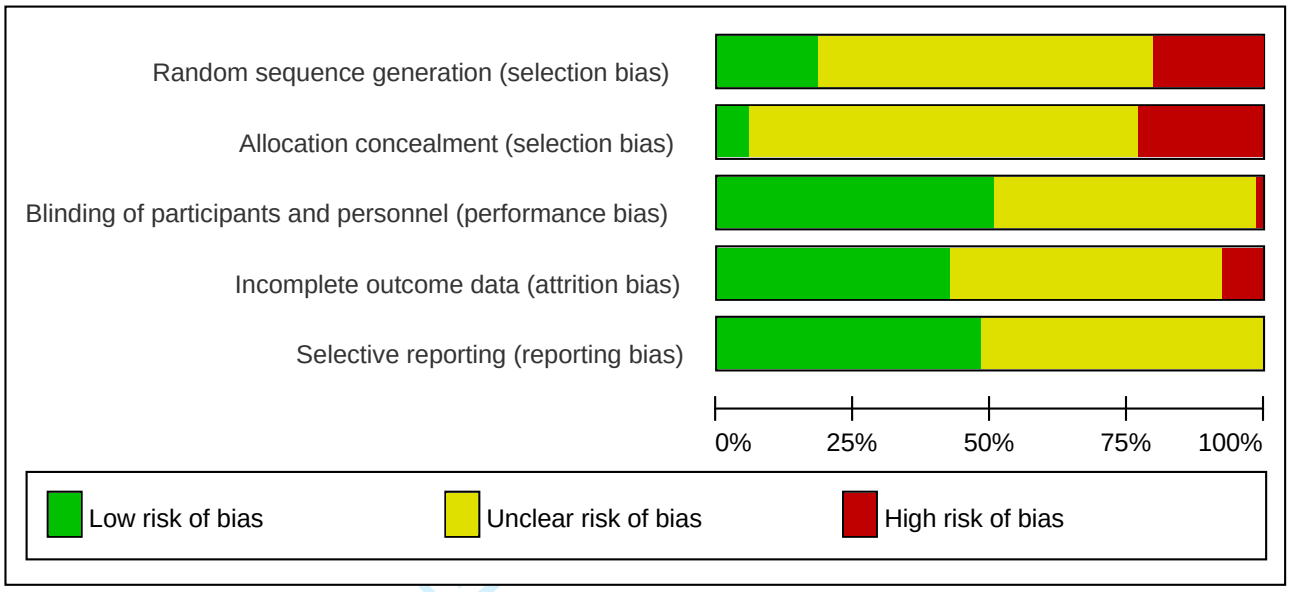
[o] Fructose-containing sugars dose estimated from non-milk extrinsic sugar intake

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

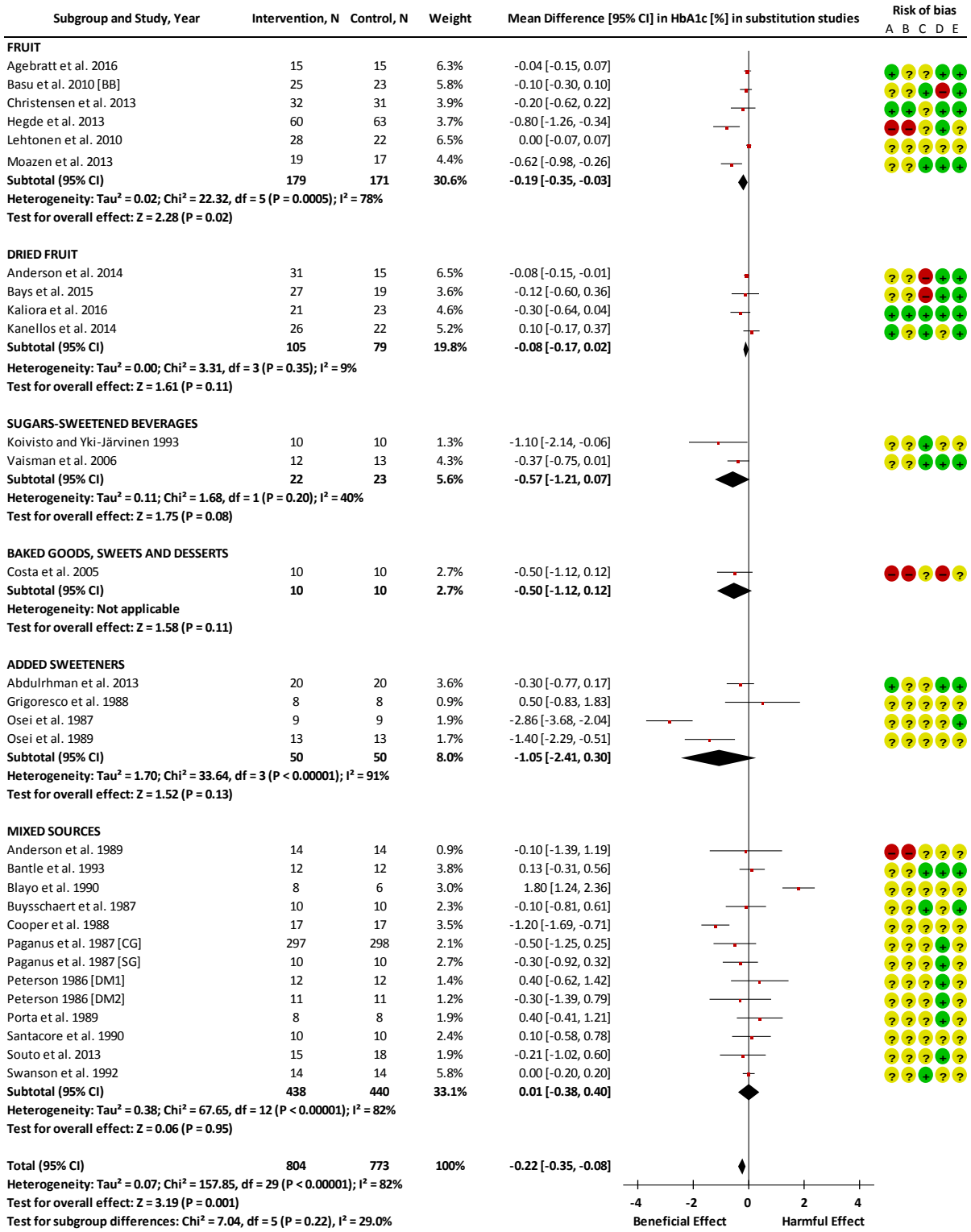
Supplementary Table 3. Select sensitivity analyses in which the systematic removal of an individual study altered the significance of the effect estimate or the evidence for substantial heterogeneity.

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							
Addition Studies							
Hollis et al. 2009	25	25	3.71	[0.94. 6.49]	<0.01	42%	0.02
Substitution studies							
Maersk et al. 2012	10	12	2.78	[0.22, 5.34]	0.03	57%	<0.0001
Koh et al. 1988 - NGT	9	9	2.58	[0.10, 5.05]	0.04	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

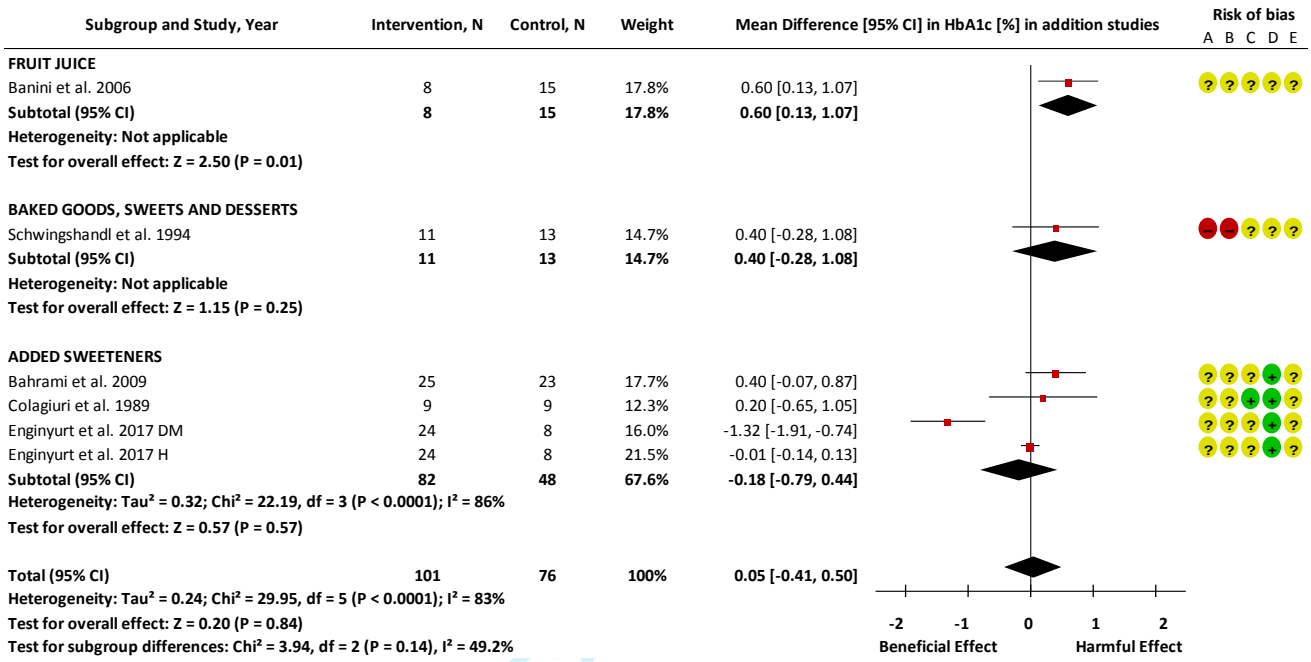
DM= diabetes mellitus; G2= Group 2; ODM2=offspring of people with type 2 diabetes. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ 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.



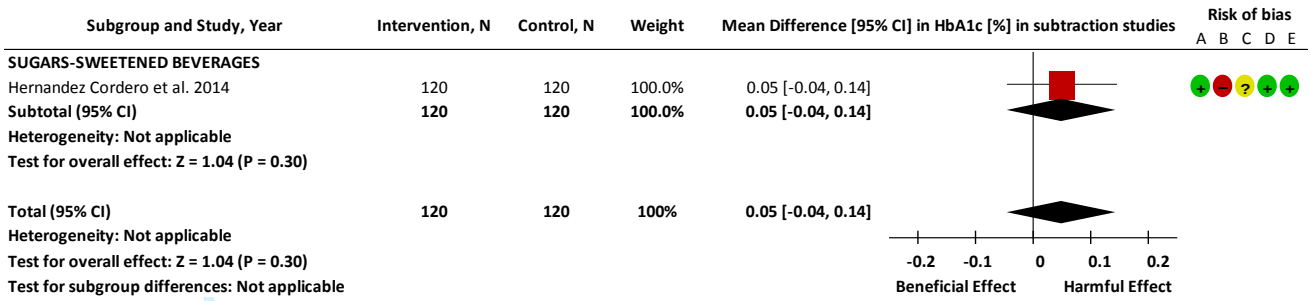
Supplementary Figure 1. Risk of bias summary for the effect of food sources of fructose-containing sugars on glycemic control. Colored bars represent the proportion of studies assessed as low (green), unclear (yellow) or high (red) risk of bias for the 5 domains of bias above according to criteria set by the Cochrane Risk of Bias tool in the 118 included unique studies.



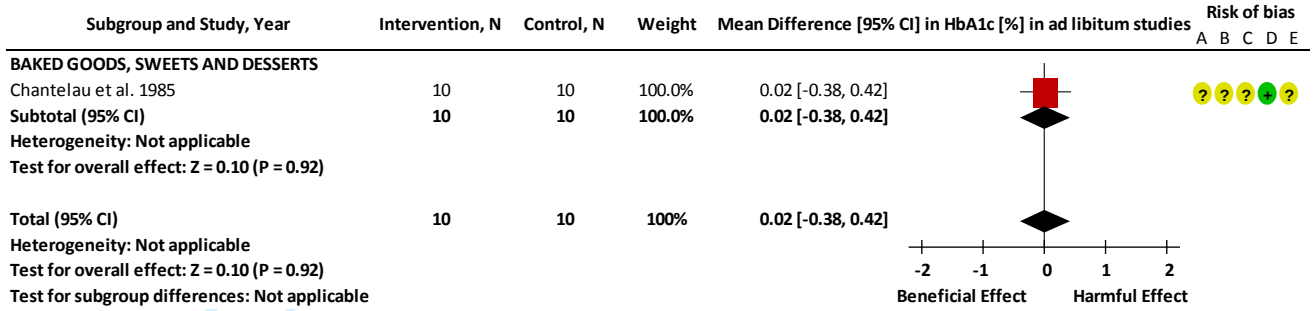
Supplementary Figure 2. Forest plot for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on HbA1c. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; 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.



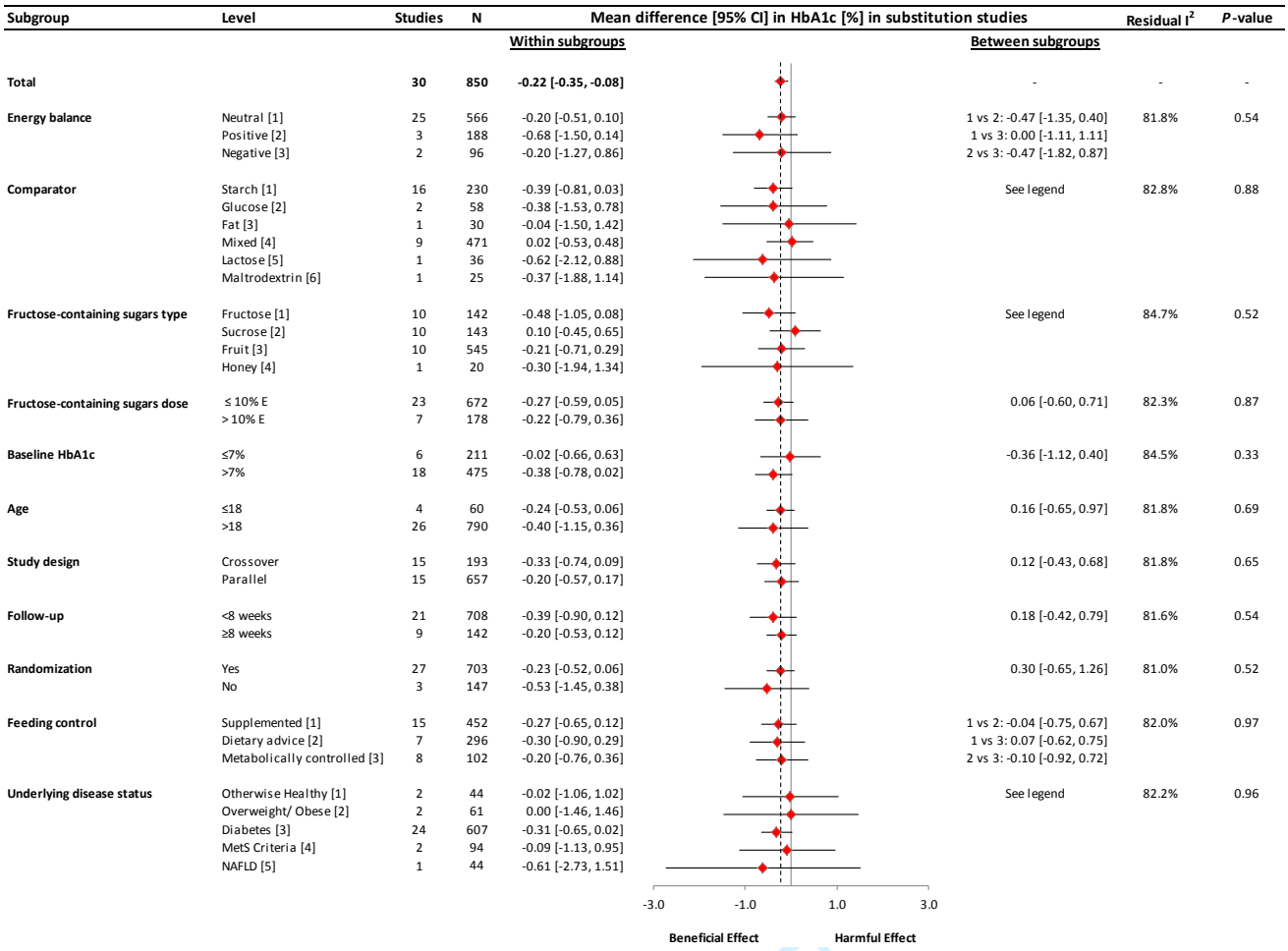
Supplementary Figure 3. Forest plot for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on HbA1c. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete 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.



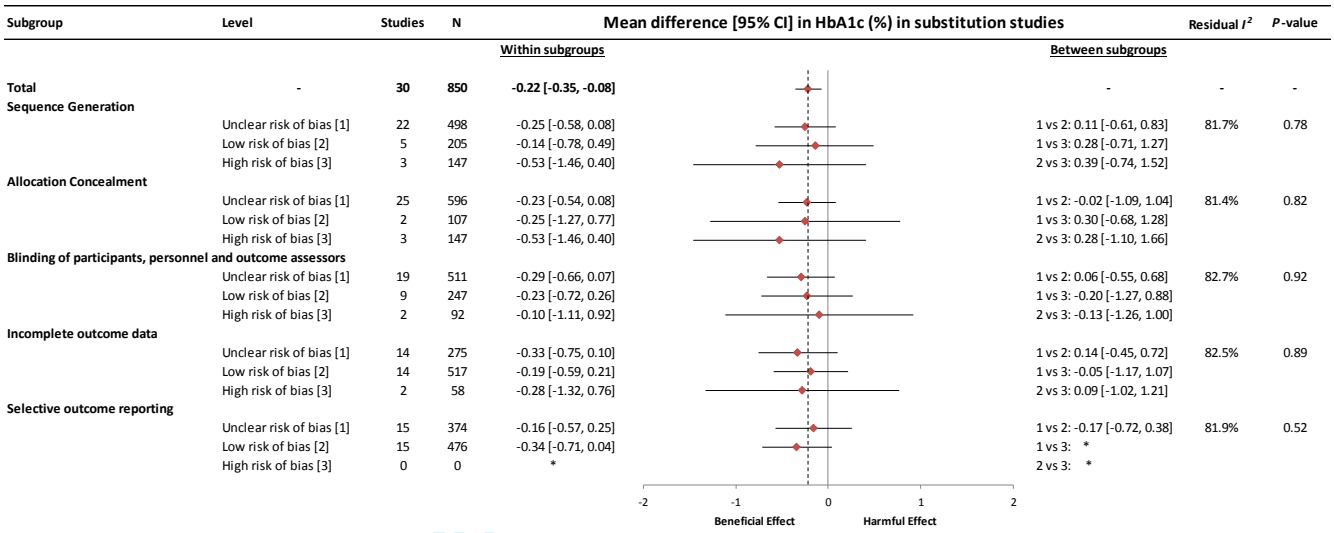
Supplementary Figure 4. Forest plot for subtraction studies investigating the effect of removing calories from the diet in the form of food sources of fructose-containing sugars on HbA1c. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete 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.



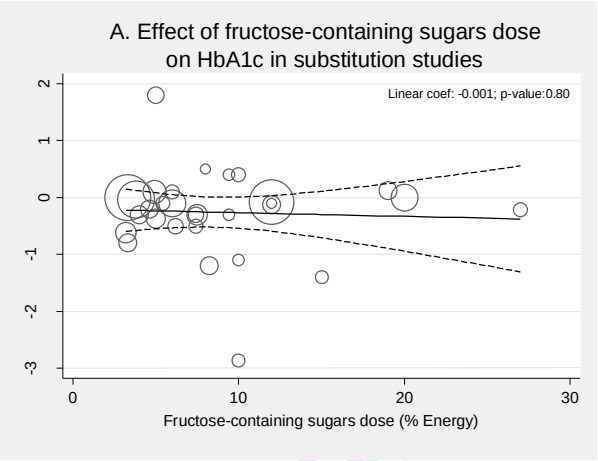
Supplementary Figure 5. Forest plot for ad libitum studies investigating the effect of freely replacing calories from food sources of fructose-containing sugars with other dietary sources on HbA1c. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; 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.

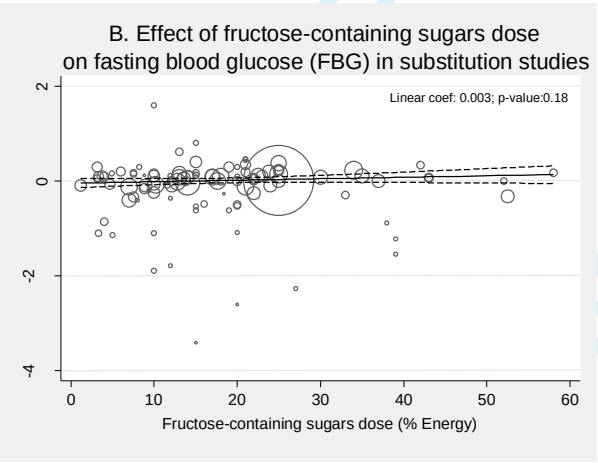


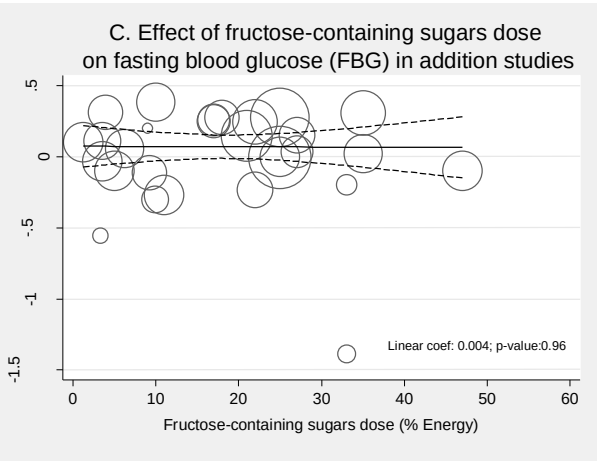
Supplementary Figure 6. Subgroup analyses for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on HbA1c. E= energy; HbA1c=hemoglobin A1C; MetS= metabolic syndrome; N= number of participants. Pooled effect estimates 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: 0.01 [-1.21, 1.24]; 1 vs 3: 0.35 [-1.17, 1.86]; 1 vs 4: 0.37 [-0.29, 1.02]; 1 vs 5: -0.23 [-1.79, 1.33]; 1 vs 6: 0.02 [-1.55, 1.58]; 2 vs 3: -0.34 [-2.19, 1.52]; 2 vs 4: -0.35 [-1.61, 0.91]; 2 vs 5: 0.25 [-1.65, 2.14]; 2 vs 6: -0.01 [-1.90, 1.89]; 3 vs 4: -0.02 [-1.56, 1.52]; 3 vs 5: 0.58 [-1.51, 2.67]; 3 vs 6: 0.33 [-1.77, 2.43]; 4 vs 5: 0.60 [-0.99, 2.18]; 4 vs 6: 0.35 [-1.24, 1.93]; 5 vs 6: -0.25 [-2.38, 1.88]. Pairwise between-subgroup mean differences (95% CI) for fructose-containing sugars type are as follows: 1 vs 2: 0.58 [-0.21, 1.37]; 1 vs 3: 0.27 [-0.48, 1.03]; 1 vs 4: 0.18 [-1.55, 1.92]; 2 vs 3: 0.31 [-0.44, 1.06]; 2 vs 4: 0.40 [-1.33, 2.13]; 3 vs 4: 0.09 [-1.62, 1.80]. Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: -0.02 [-1.81, 1.77]; 1 vs 3: 0.29 [-0.80, 1.38]; 1 vs 4: 0.07 [-1.40, 1.53]; 1 vs 5: 0.59 [-1.77, 2.95]; 2 vs 3: 0.31 [-1.18, 1.81]; 2 vs 4: 0.09 [-1.70, 1.88]; 2 vs 5: 0.61 [-2.68, 3.91]; 3 vs 4: 0.22 [-0.87, 1.31]; 3 vs 5: -0.30 [-2.39, 1.79]; 4 vs 5: 0.52 [-1.83, 2.88].

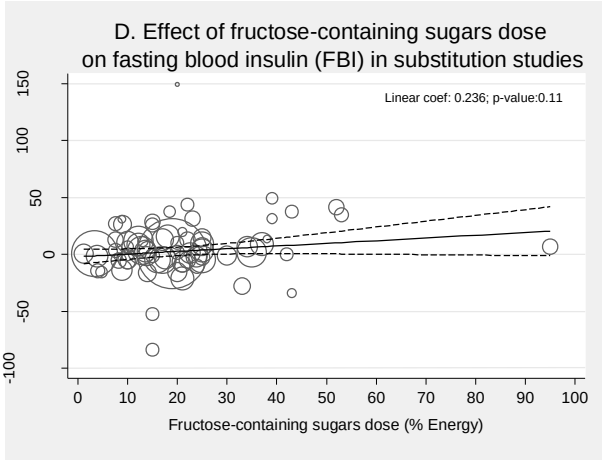


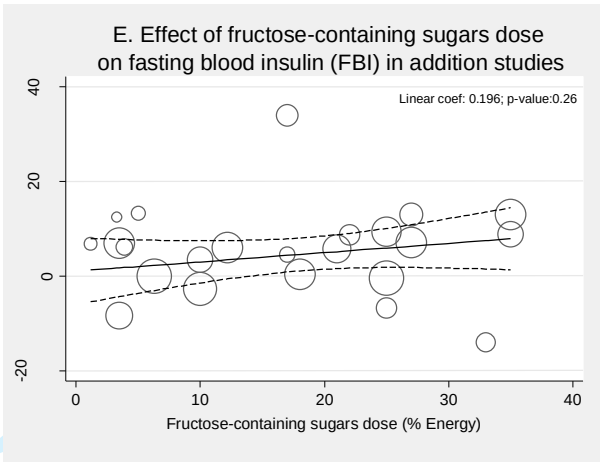
Supplementary Figure 7. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on HbA1c. Point estimates for each subgroup level are the pooled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



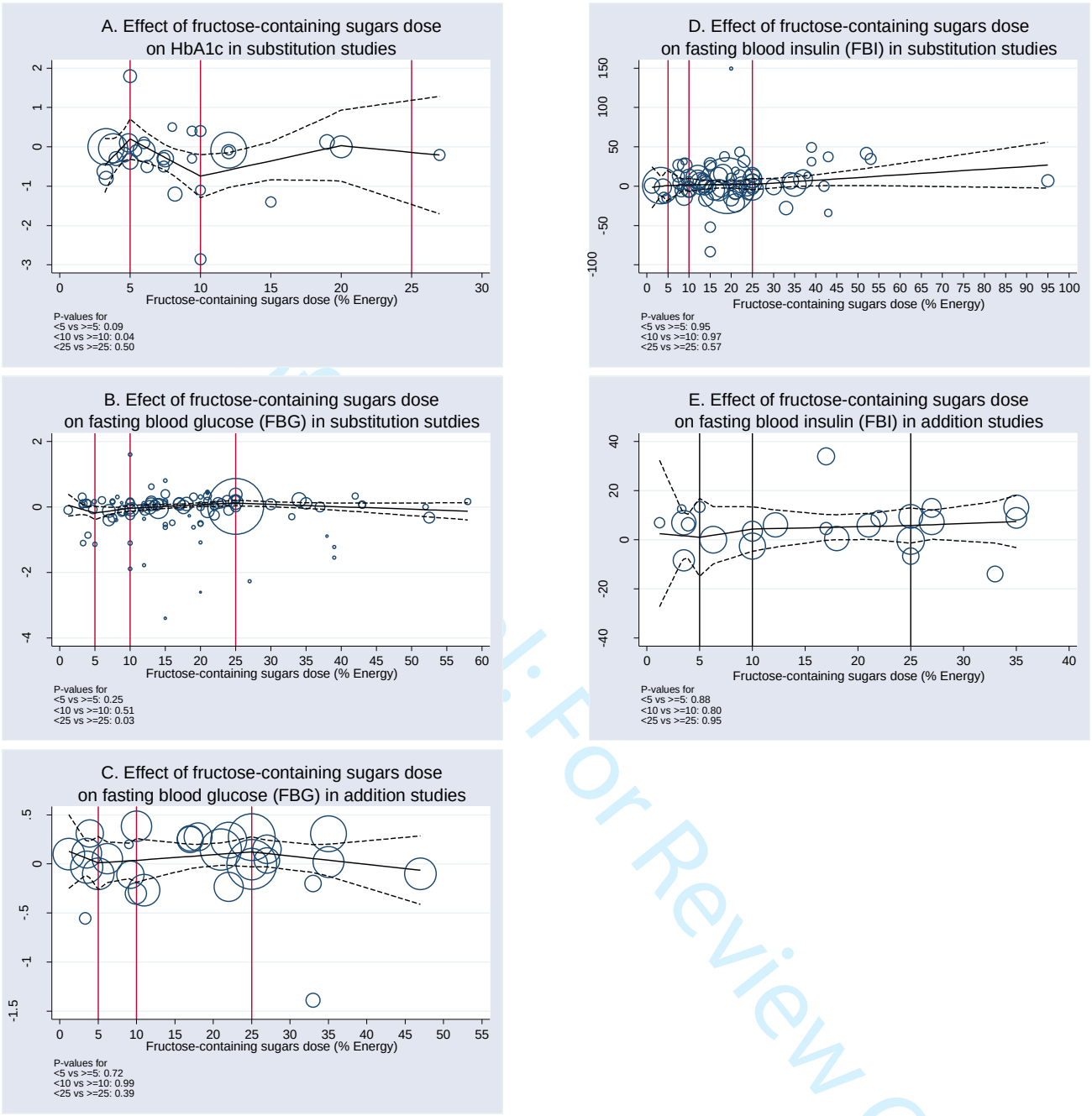




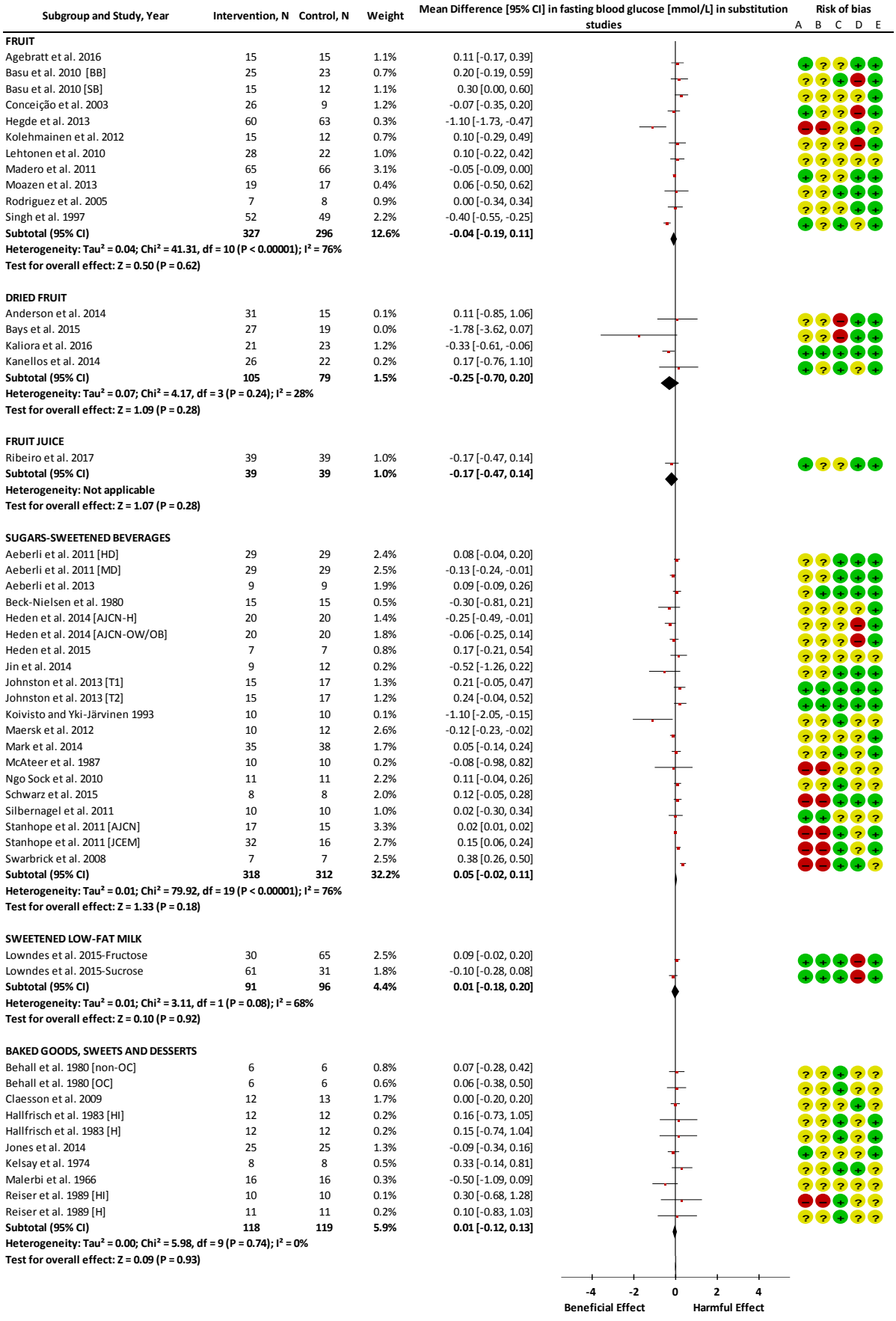




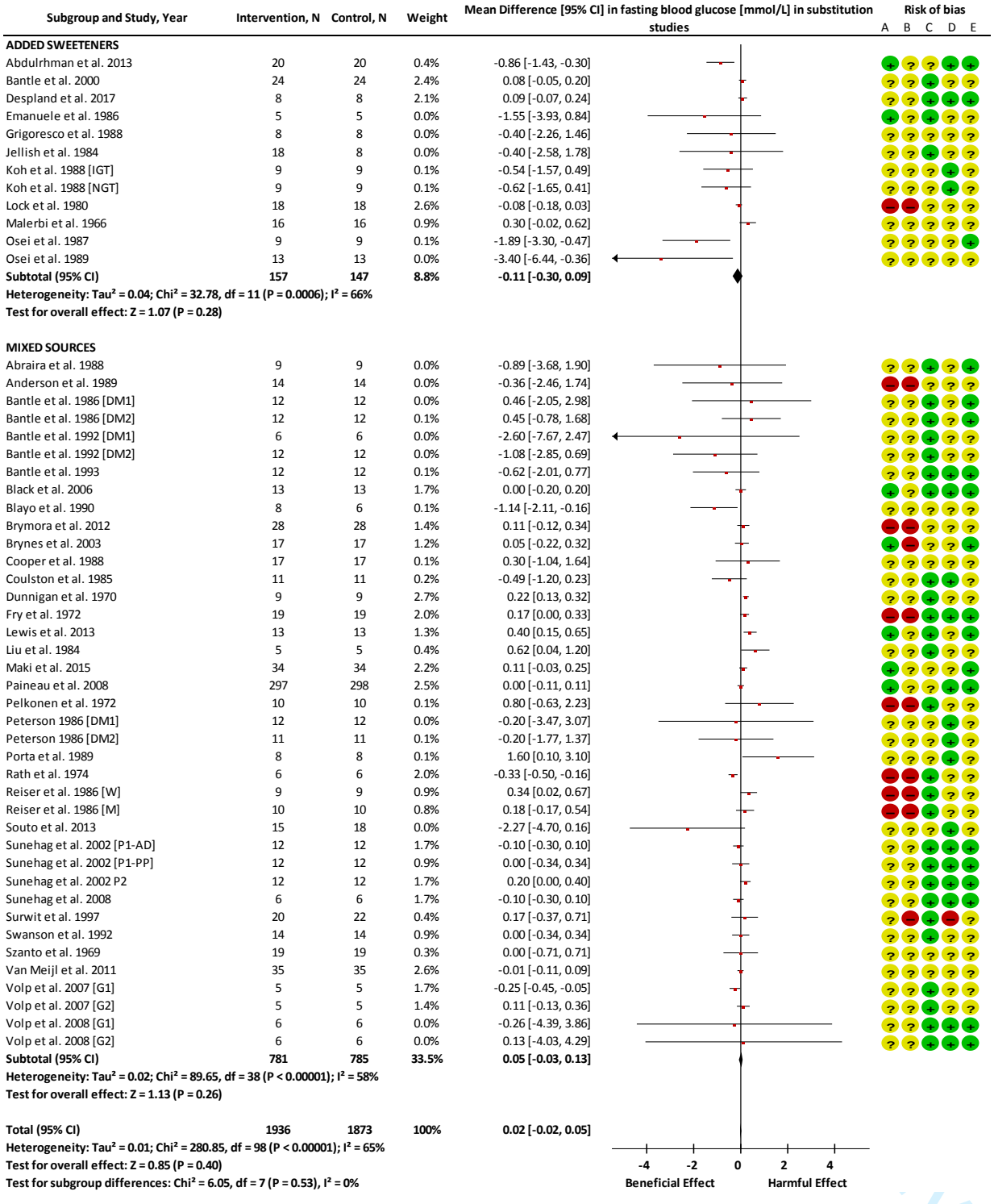
Supplementary Figure 8. Linear meta-regression analyses for the effect of fructose-containing sugars dose (%E) on glycemic control in substitution and addition studies. Individual studies are represented by the circles, with their weight in the overall analysis represented by the size of the circles. 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.



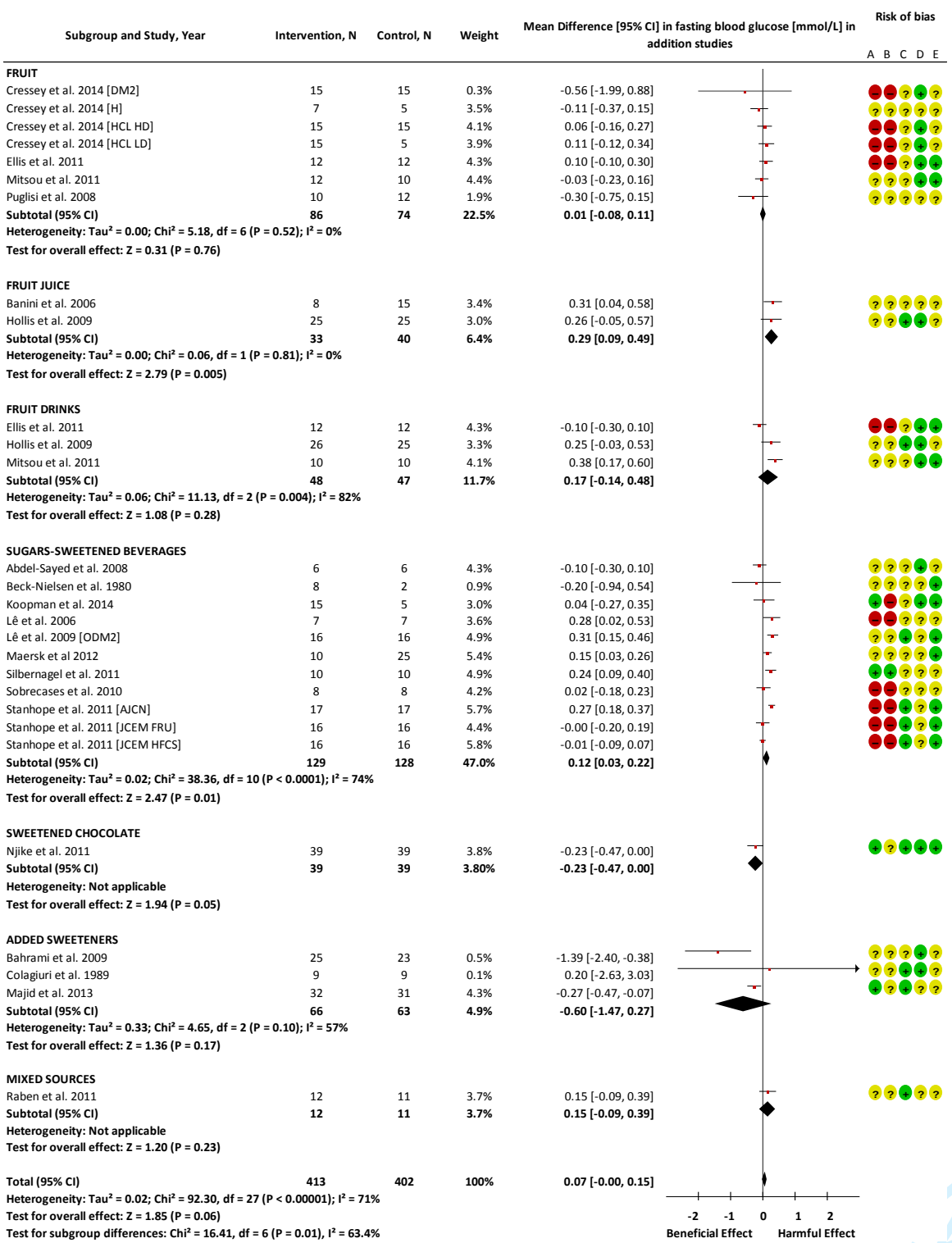
Supplementary Figure 9. Non-linear meta-regression analyses for the effect of fructose-containing sugars dose (% Energy) on glycemic control in substitution and addition studies. Individual studies are represented by the circles, with their weight in the overall analysis represented by the size of the 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.



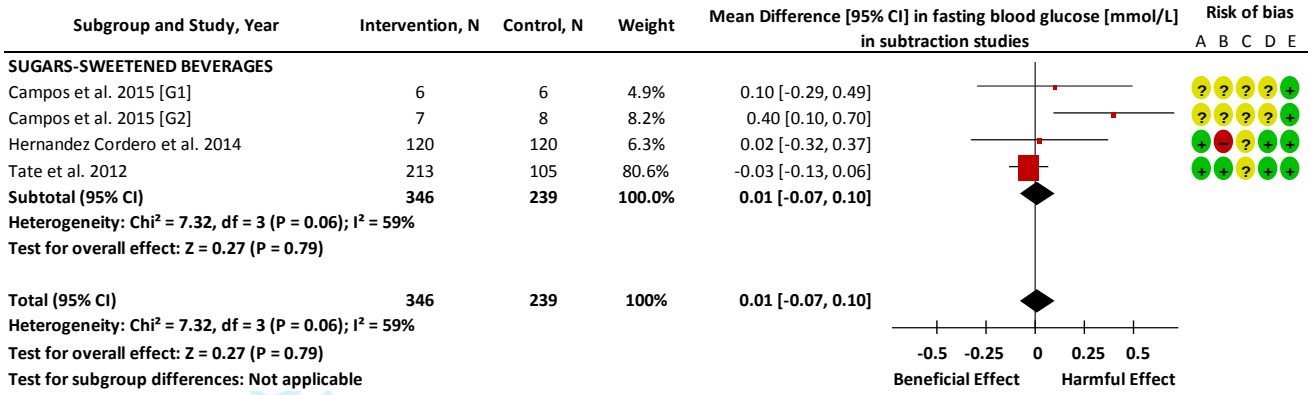
Supplementary Figure 10. Forest plot for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose (continues next page).



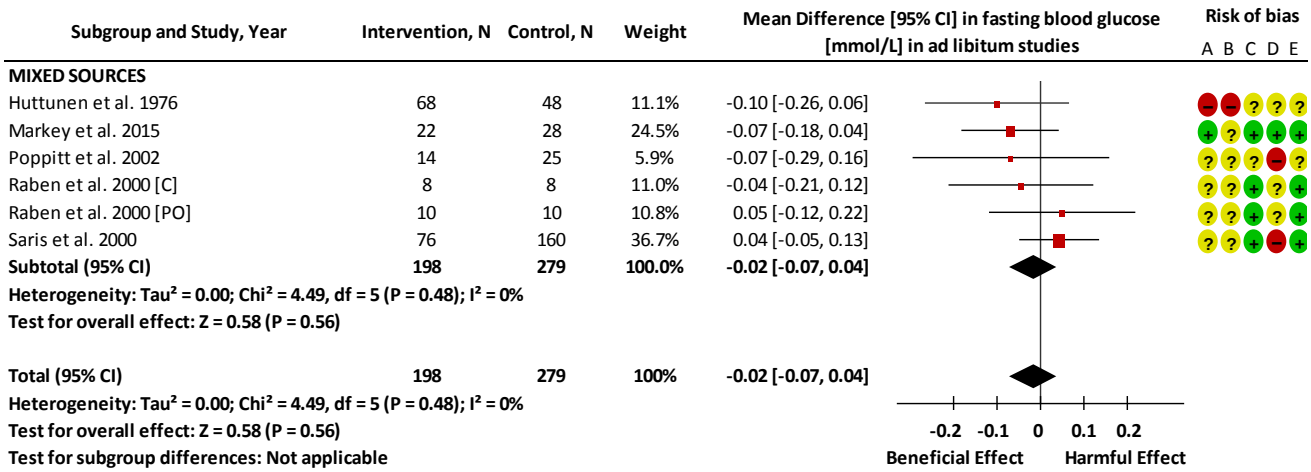
Supplementary Figure 10. (continued). Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting. AJCN = American Journal of Clinical Nutrition; DM= diabetes mellitus; EXP1= experiment 1; EXP2= experiment 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.

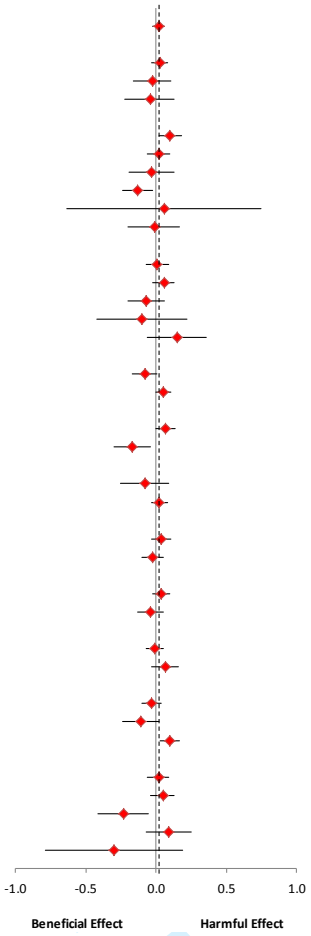


Supplementary Figure 12. Forest plot for subtraction studies investigating the effect of removing calories from the diet in the form of food sources of fructose-containing sugars on fasting blood glucose. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants 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.

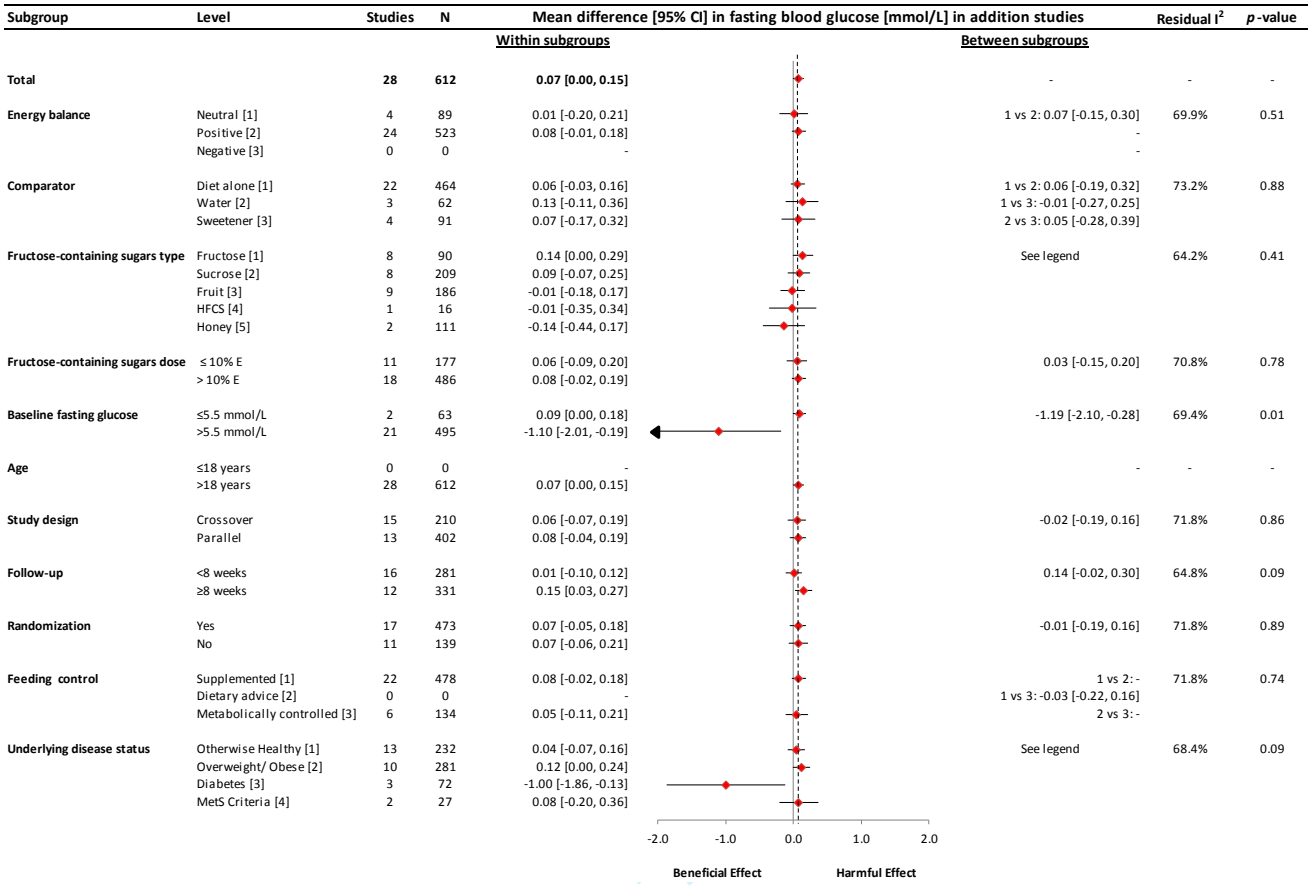


Supplementary Figure 13. Forest plot for ad libitum studies investigating the effect of freely replacing calories from food sources of fructose-containing sugars with other dietary sources on fasting blood glucose. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants 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.

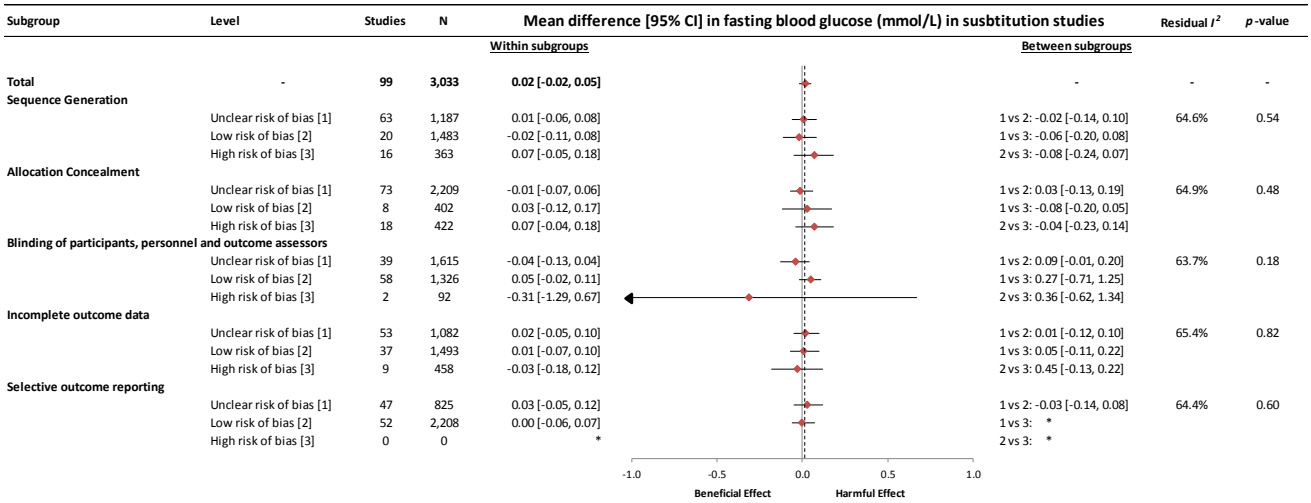
Subgroup	Level	Studies	N	Mean difference [95% CI] in fasting blood glucose [mmol/L] in substitution studies	Residual I^2	*p*-value
				Within subgroups	Between subgroups	
Total		**99**	**3,033**	**0.02 [-0.02, 0.05]**	-	-	-
Energy balance	Neutral [1]	81	1,783	0.03 [-0.03, 0.08]	1 vs 2: -0.05 [-0.20, 0.10]	64.2%	0.64
	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	0.10 [0.02, 0.18]	See legend	63.4%	<0.05
	Glucose [2]	23	590	0.02 [-0.06, 0.10]			
	Fat [3]	8	154	-0.03 [-0.19, 0.13]			
	Mixed [4]	20	863	-0.13 [-0.24, -0.02]			
	Lactose [5]	1	36	0.06 [-0.63, 0.75]			
	Dairy [6]	3	91	-0.01 [-0.20, 0.17]			
Fructose-containing sugars type	Fructose [1]	42	758	0.01 [-0.07, 0.09]	See legend	62.7%	0.32
	Sucrose [2]	44	1,364	0.06 [-0.02, 0.13]			
	Fruit [3]	16	896	-0.07 [-0.20, 0.06]			
	Honey [4]	2	28	-0.10 [-0.42, 0.22]			
	HFCS [5]	3	96	0.15 [-0.06, 0.36]			
Fructose-containing sugars dose	≤ 10% E	33	1,102	-0.08 [-0.17, 0.01]	0.13 [0.03, 0.24]	61.7%	0.02
	> 10% E	69	1,955	0.05 [0.00, 0.11]			
Baseline fasting glucose	≤5.5 mmol/L	35	1,181	0.07 [0.00, 0.14]	-0.24 [-0.39, -0.09]	65.3%	<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]	64.9%	0.26
	>18 years	92	2,930	0.02 [-0.03, 0.08]			
Study design	Crossover	59	782	0.04 [-0.03, 0.11]	-0.06 [-0.17, 0.04]	64.2%	0.21
	Parallel	40	2,251	-0.02 [-0.10, 0.05]			
Follow-up	<8 weeks	67	1,197	0.04 [-0.02, 0.10]	-0.08 [-0.19, 0.03]	65.0%	0.14
	≥8 weeks	32	1,836	-0.04 [-0.13, 0.05]			
Randomization	Yes	72	2,543	-0.01 [-0.07, 0.05]	-0.07 [-0.19, 0.04]	64.1%	0.21
	No	27	490	0.07 [-0.03, 0.16]			
Feeding control	Supplemented [1]	41	1,366	-0.03 [-0.10, 0.04]	1 vs 2: -0.08 [-0.23, 0.07]	62.6%	<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	65.3%	0.04
	Overweight/ Obese [2]	23	881	0.05 [-0.04, 0.13]			
	Diabetes [3]	30	645	-0.23 [-0.41, -0.05]			
	MetS Criteria [4]	11	330	0.09 [-0.07, 0.25]			
	NAFLD [5]	1	44	-0.30 [-0.79, 0.19]			



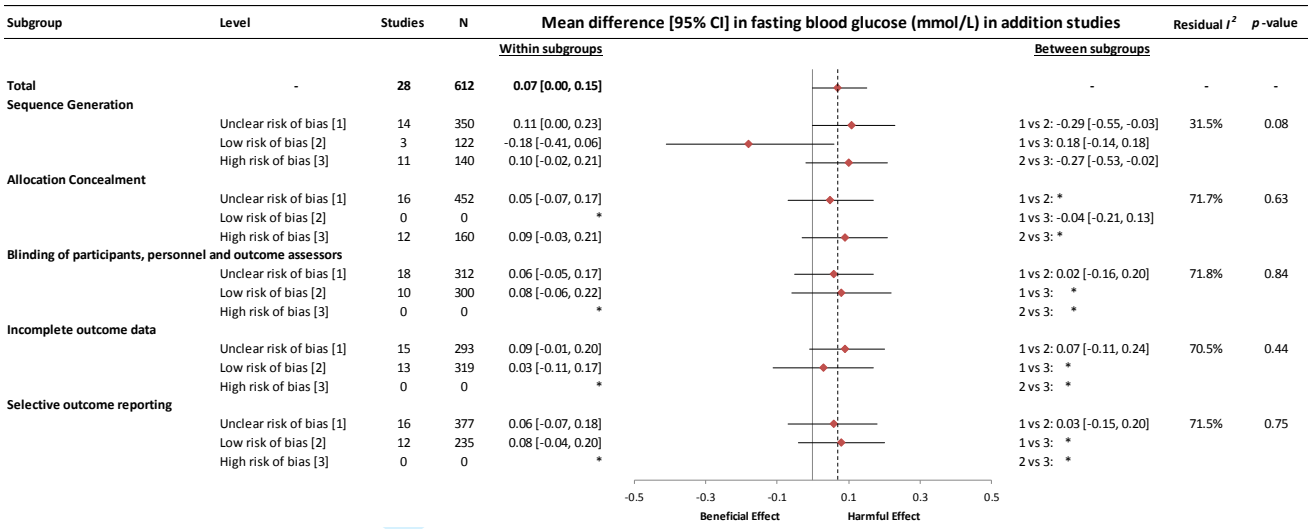
Supplementary Figure 14. Subgroup analyses for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. 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: -0.07 [-0.19, 0.04]; 1 vs 3: -0.13 [-0.31, 0.06]; 1 vs 4: -0.23 [-0.37, -0.09]; 1 vs 5: -0.04 [-0.73, 0.66]; 1 vs 6: 0.11 [-0.31, 0.09]; 2 vs 3: 0.05 [-0.13, 0.24]; 2 vs 4: 0.16 [0.02, 0.29]; 2 vs 5: -0.04 [-0.73, 0.66]; 2 vs 6: 0.4 [-0.17, 0.24]; 3 vs 4: 0.10 [-0.09, 0.30]; 3 vs 5: -0.09 [-0.80, 0.62]; 3 vs 6: -0.02 [-0.26, 0.23]; 4 vs 5: -0.19 [-0.89, -0.50]; 4 vs 6: -0.12 [-0.34, 0.09]; 5 vs 6: 0.07 [-0.64, 0.78]. Pairwise between-subgroup mean differences (95% CI) for fructose-containing sugars type are as follows: 1 vs 2: -0.04 [-0.16, 0.07]; 1 vs 3: 0.08 [-0.07, 0.24]; 1 vs 4: 0.11 [-0.22, 0.44]; 1 vs 5: -0.13 [-0.36, 0.09]; 2 vs 3: 0.13 [-0.02, 0.28]; 2 vs 4: 0.15 [-0.18, 0.49]; 2 vs 5: -0.09 [-0.31, 0.13]; 3 vs 4: 0.03 [-0.32, 0.38]; 3 vs 5: -0.22 [-0.46, 0.03]; 4 vs 5: -0.25 [-0.63, 0.14]. Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: -0.03 [-0.15, 0.08]; 1 vs 3: 0.25 [0.05, 0.44]; 1 vs 4: -0.07 [-0.25, 0.11]; 1 vs 5: 0.32 [-0.17, 0.81]; 2 vs 3: 0.28 [0.08, 0.48]; 2 vs 4: -0.04 [-0.22, 0.14]; 2 vs 5: 0.35 [-0.15, 0.84]; 3 vs 4: 0.32 [0.08, 0.56]; 3 vs 5: -0.07 [-0.59, 0.45]; 4 vs 5: 0.39 [-0.12, 0.90].



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].

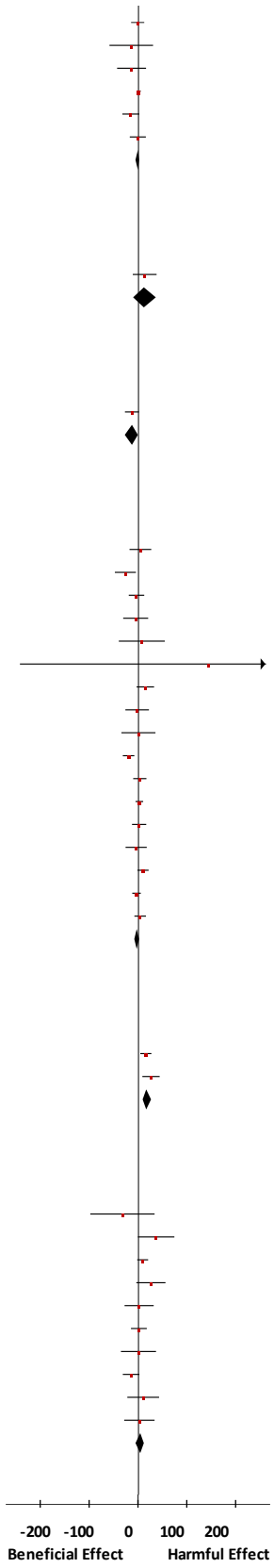


Supplementary Figure 16. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose. Point estimates for each subgroup level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

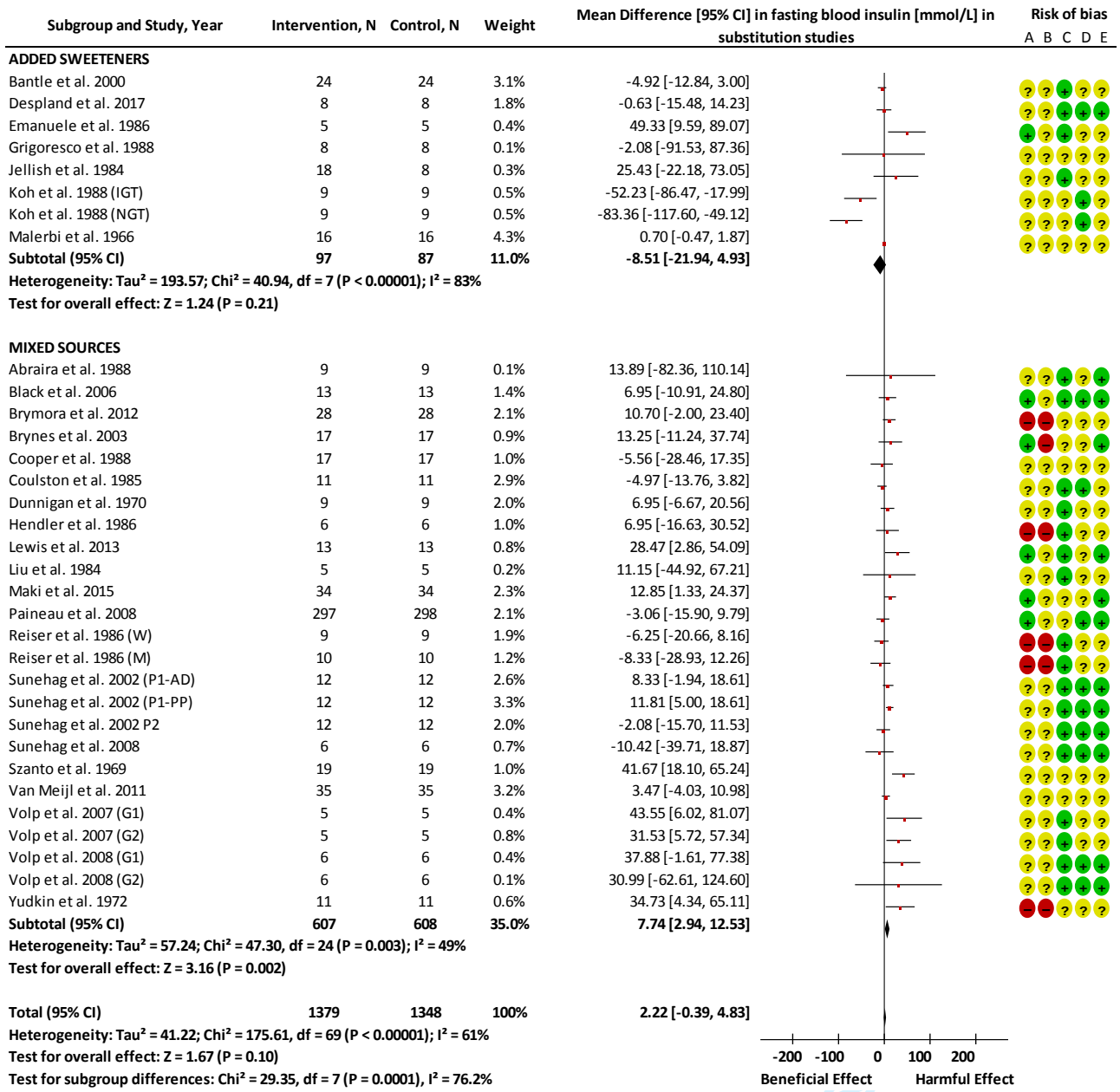


Supplementary Figure 17. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for addition studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood glucose. Point estimates for each subgroup level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

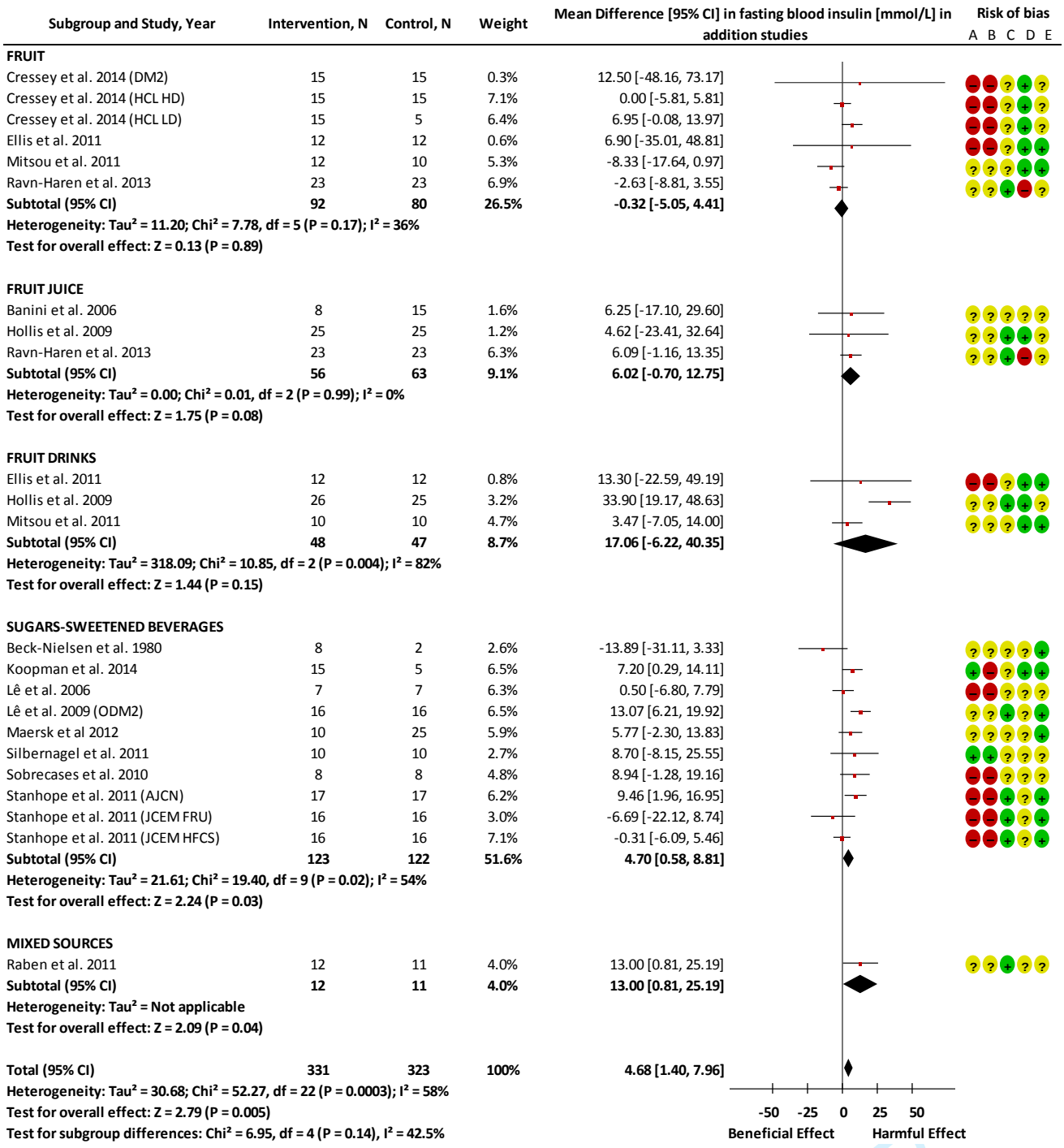
Subgroup and Study, Year	Intervention, N	Control, N	Weight	Mean Difference [95% CI] in fasting blood insulin [mmol/L] in substitution studies	Risk of bias A B C D E
FRUIT					
Agebratt et al. 2016	15	15	2.1%	-1.74 [-14.39, 10.92]	+ ? ? + +
Conceição et al. 2003	26	9	0.3%	-15.28 [-60.28, 29.72]	+ ? ? − +
Kolehmainen et al. 2012	15	12	0.7%	-14.58 [-44.04, 14.87]	? ? ? − +
Lehtonen et al. 2010	28	22	4.1%	0.69 [-2.08, 3.46]	? ? ? ? ?
Madero et al. 2011	65	66	1.6%	-16.19 [-32.98, 0.60]	+ ? ? + +
Rodriguez et al. 2005	7	8	1.7%	-1.39 [-17.21, 14.43]	? ? ? + +
Subtotal (95% CI)	**156**	**132**	**10.5%**	**-0.81 [-4.58, 2.97]**	
Heterogeneity: Tau² = 2.70; Chi² = 5.30, df = 5 (P = 0.38); I² = 6%					
Test for overall effect: Z = 0.42 (P = 0.68)					
DRIED FRUIT					
Kaliora et al. 2016	21	23	0.9%	13.20 [-10.84, 37.23]	+ + + + +
Subtotal (95% CI)	**21**	**23**	**0.9%**	**13.20 [-10.84, 37.23]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 1.08 (P = 0.28)					
FRUIT JUICE					
Ribeiro et al. 2017	39	39	2.0%	-13.89 [-27.50, -0.28]	+ ? ? + +
Subtotal (95% CI)	**39**	**39**	**2.0%**	**-13.89 [-27.50, -0.28]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 2.00 (P = 0.05)					
SUGARS-SWEETENED BEVERAGES					
Aeberli et al. 2013	9	9	1.1%	4.05 [-17.75, 25.85]	? + + + +
Beck-Nielsen et al. 1980	15	15	1.1%	-27.78 [-48.87, -6.69]	? ? ? ? +
Heden et al. 2014 (AJCN-H)	20	20	1.8%	-4.15 [-19.30, 11.00]	? ? ? − +
Heden et al. 2014 (AJCN-OW/OB)	20	20	0.9%	-5.90 [-31.17, 19.37]	? ? ? − +
Heden et al. 2015	7	7	0.3%	7.00 [-40.57, 54.57]	? ? ? ? ?
Jin et al. 2014	9	12	0.0%	149.32 [-250.31, 548.95]	? ? + + +
Johnston et al. 2013 (T1)	15	17	1.5%	14.58 [-2.77, 31.94]	+ + + + +
Johnston et al. 2013 (T2)	15	17	0.9%	-2.78 [-26.50, 20.94]	+ + + + +
Koivisto and Yki-Järvinen 1993	10	10	0.5%	0.00 [-34.84, 34.84]	? ? + ? ?
Maersk et al. 2012	10	12	2.5%	-21.04 [-31.97, -10.11]	? ? ? ? +
Mark et al. 2014	35	38	2.1%	2.86 [-9.94, 15.66]	? ? + ? +
Ngo Sock et al. 2010	11	11	3.3%	1.80 [-5.02, 8.62]	? ? + ? ?
Schwarz et al. 2015	8	8	1.9%	1.39 [-12.48, 15.26]	− − + + +
Silbernagel et al. 2011	10	10	1.1%	-4.90 [-26.05, 16.25]	+ + ? ? ?
Stanhope et al. 2011 (AJCN)	17	15	2.5%	9.73 [-0.83, 20.29]	− − + ? +
Stanhope et al. 2011 (JCEM)	32	16	3.1%	-4.04 [-11.79, 3.70]	− − + ? +
Swarbrick et al. 2008	7	7	2.4%	3.57 [-7.42, 14.57]	− − + + ?
Subtotal (95% CI)	**250**	**244**	**27.1%**	**-1.47 [-6.56, 3.62]**	
Heterogeneity: Tau² = 43.71; Chi² = 29.86, df = 16 (P = 0.02); I² = 46%					
Test for overall effect: Z = 0.56 (P = 0.57)					
SWEETENED LOW-FAT MILK					
Lowndes et al. 2015-Fructose	30	65	2.6%	26.59 [9.51, 43.68]	+ + + − +
Lowndes et al. 2015-Sucrose	61	31	1.5%	15.64 [5.18, 26.10]	+ + + − +
Subtotal (95% CI)	**91**	**96**	**4.1%**	**18.95 [9.09, 28.80]**	
Heterogeneity: Tau² = 7.74; Chi² = 1.15, df = 1 (P = 0.28); I² = 13%					
Test for overall effect: Z = 3.77 (P = 0.0002)					
BAKED GOODS, SWEETS AND DESSERTS					
Behall et al. 1980 (non-OC)	6	6	0.1%	-34.03 [-100.94, 32.88]	? ? + ? ?
Behall et al. 1980 (OC)	6	6	0.4%	37.50 [0.05, 74.95]	? ? + ? ?
Claesson et al. 2009	12	13	2.6%	9.00 [-1.29, 19.29]	? ? ? + ?
Hallfrisch et al. 1983 (HI)	12	12	0.7%	26.39 [-3.26, 56.04]	? ? + ? +
Hallfrisch et al. 1983 (H)	12	12	0.7%	1.39 [-28.26, 31.04]	? ? + ? +
Jones et al. 2014	25	25	1.7%	0.91 [-14.69, 16.50]	+ ? ? ? +
Kelsay et al. 1974	8	8	0.5%	0.00 [-36.01, 36.01]	? ? + + ?
Malerbi et al. 1966	16	16	1.6%	-15.60 [-31.88, 0.68]	? ? ? ? ?
Reiser et al. 1989 (HI)	10	10	0.6%	10.00 [-22.48, 42.48]	− − + ? ?
Reiser et al. 1989 (H)	11	11	0.6%	2.00 [-28.97, 32.97]	? ? + ? ?
Subtotal (95% CI)	**118**	**119**	**9.4%**	**3.97 [-5.26, 13.20]**	
Heterogeneity: Tau² = 63.35; Chi² =13.35, df = 9 (P = 0.15); I² = 33%					
Test for overall effect: Z = 0.84 (P = 0.40)					



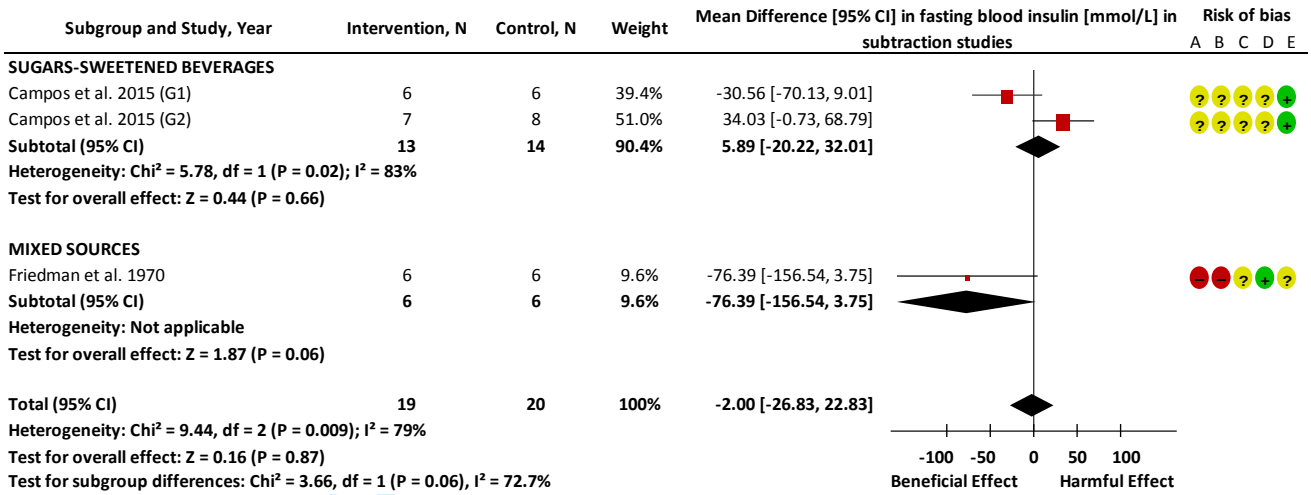
Supplementary Figure 18. Forest plot for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood insulin (Continues next page).



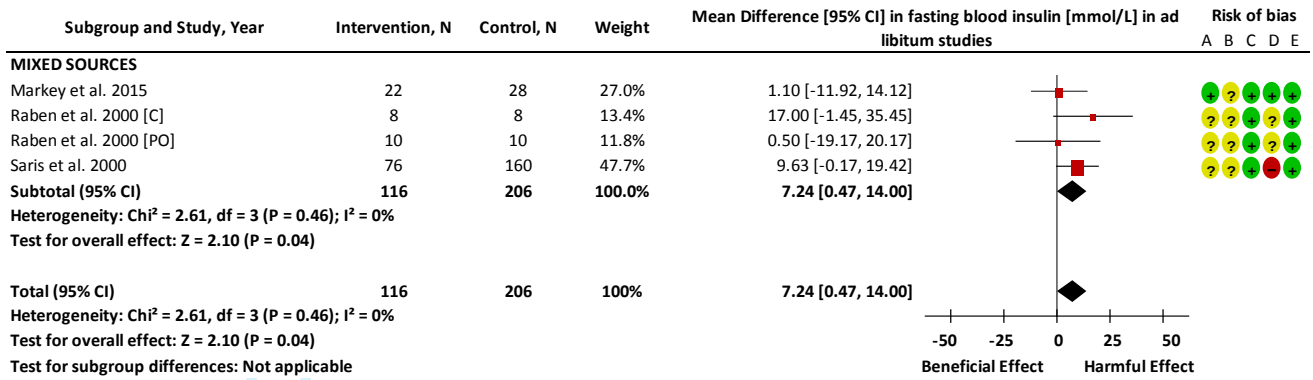
Supplementary Figure 18. (continued). Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants and personnel; D=incomplete outcome data; E=selective reporting.AD= adolescent; AJCN = American Journal of Clinical Nutrition; DM= diabetes mellitus; EXP1= experiment 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.



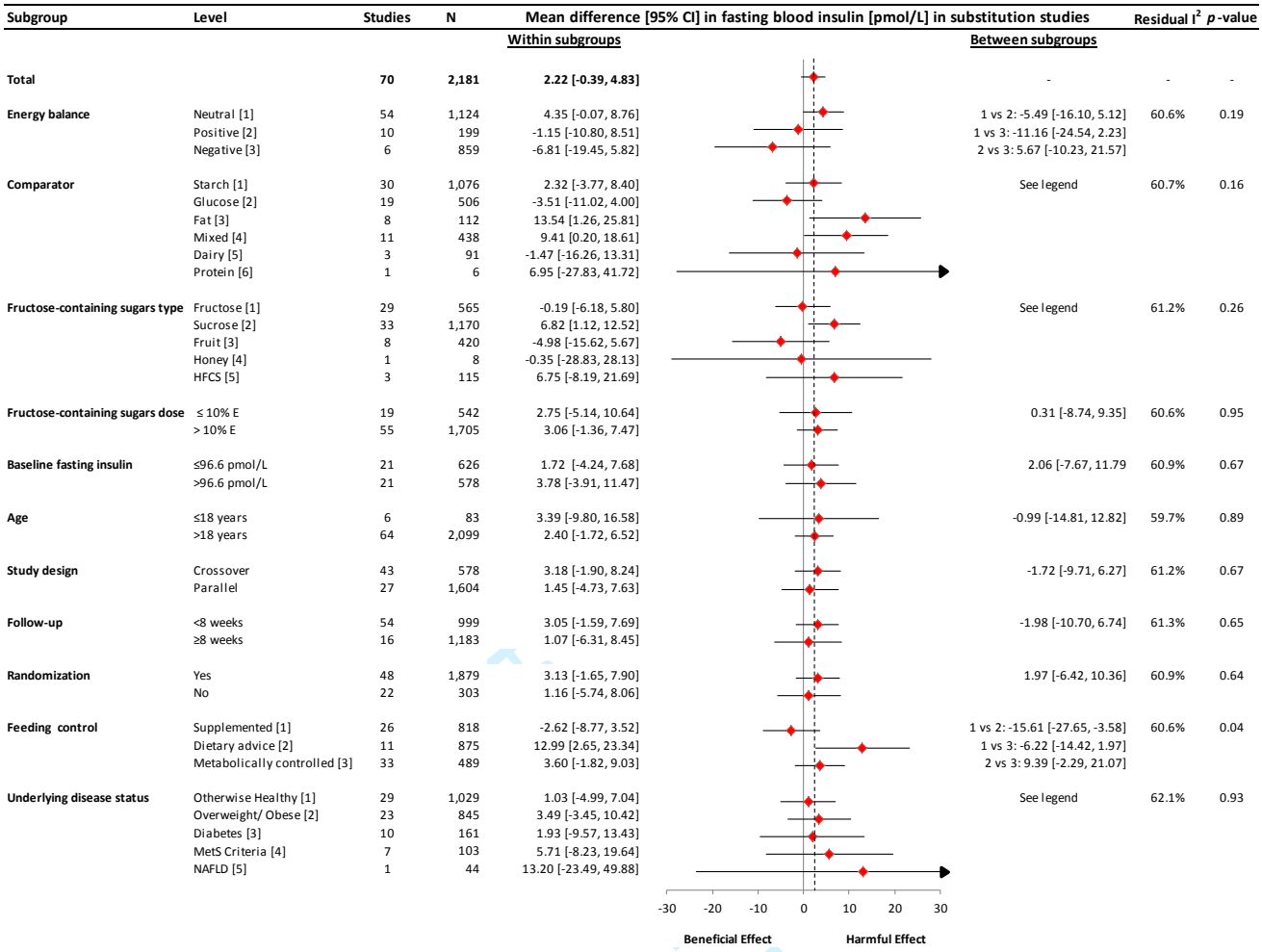
Supplementary Figure 19. Forest plot for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood insulin. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants 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.



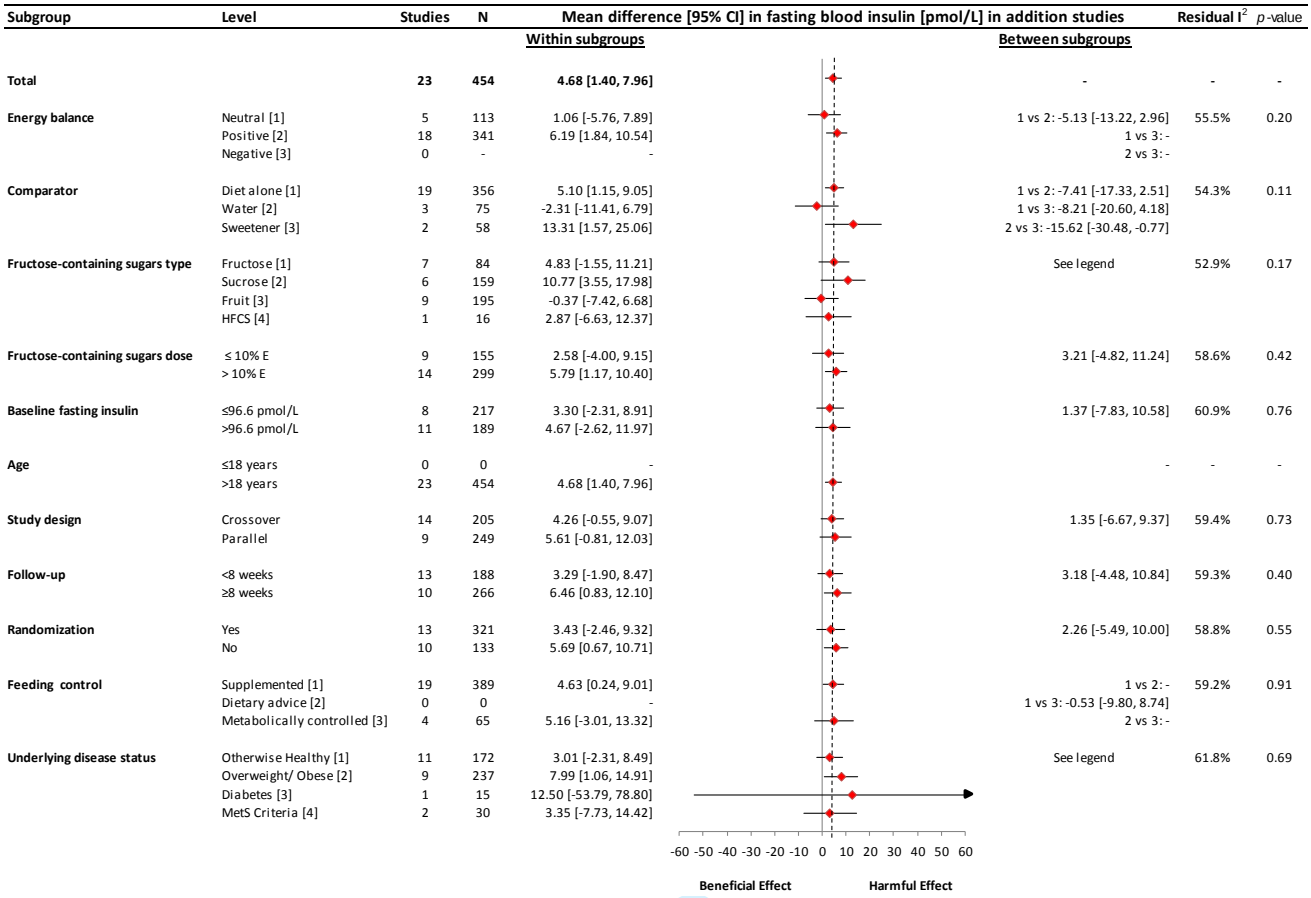
Supplementary Figure 20. Forest plot for subtraction studies investigating the effect of removing calories from the diet in the form of food sources of fructose-containing sugars on fasting blood insulin. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants 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.



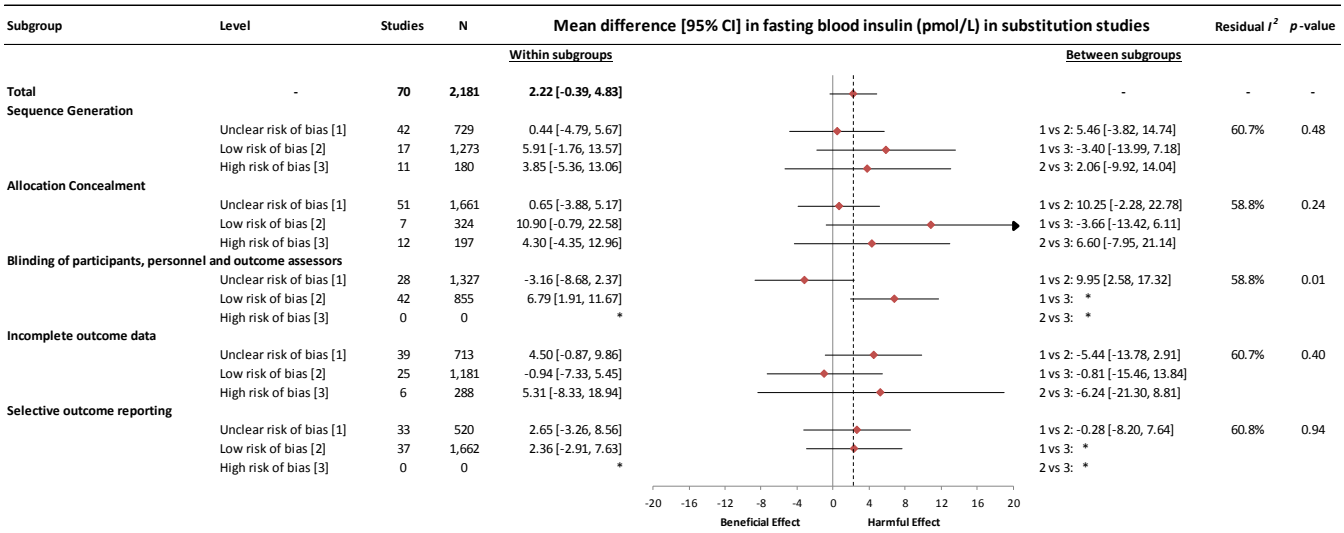
Supplementary Figure 21. Forest plot for ad libitum studies investigating the effect of freely replacing calories from food sources of fructose-containing sugars with other dietary sources on fasting blood insulin. Risk of bias: A=random sequence generation; B=allocation concealment; C=blinding of participants 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.



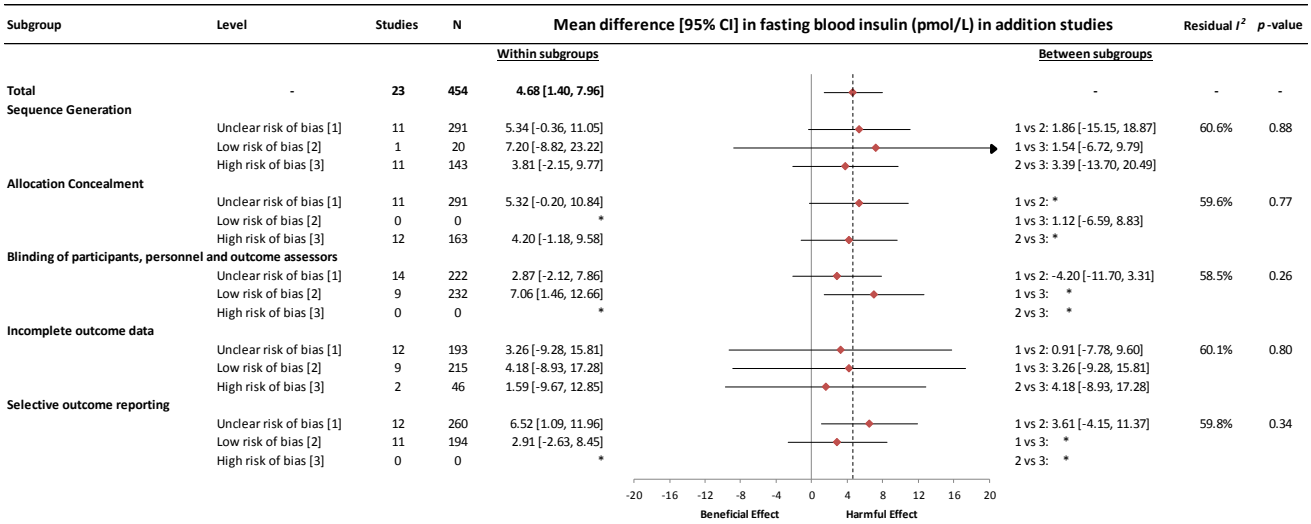
Supplementary Figure 22. Subgroup analyses for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood insulin. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. 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: -5.83 [-15.50, 3.84]; 1 vs 3: 11.22 [-2.48, 24.91]; 1 vs 4: 7.09 [-3.95, 18.13]; 1 vs 5: -3.79 [-19.78, 12.20]; 1 vs 6: 4.63 [-30.68, 39.93]; 2 vs 3: -17.05 [-31.44, -2.66]; 2 vs 4: -12.92 [-24.80, -1.04]; 2 vs 5: -2.04 [-18.62, 14.55]; 2 vs 6: -10.46 [-46.03, 25.12]; 3 vs 4: 4.13 [-11.21, 19.47]; 3 vs 5: 15.01 [-4.21, 34.22]; 3 vs 6: 6.59 [-30.29, 43.47]; 4 vs 5: 10.88 [-6.54, 28.30]; 4 vs 6: 2.46 [-33.51, 38.44]; 5 vs 6: -8.42 [-46.21, 29.37]. Pairwise between-subgroup mean differences (95% CI) for fructose-containing sugars type are as follows: 1 vs 2: -7.01 [-15.28, 1.26]; 1 vs 3: 4.79 [-7.42, 17.00]; 1 vs 4: 0.16 [-28.94, 29.26]; 1 vs 5: -6.94 [-23.03, 9.16]; 2 vs 3: -11.80 [-23.87, 0.28]; 2 vs 4: -7.17 [-36.21, 21.88]; 2 vs 5: -0.07 [-16.06, 15.92]; 3 vs 4: -4.63 [-35.03, 25.77]; 3 vs 5: -11.73 [-30.06, 6.61]; 4 vs 5: -7.10 [-39.25, 25.06]. Pairwise between-subgroup mean differences [95% CI] for underlying disease status are as follows: 1 vs 2: 2.46 [-6.71, 11.64]; 1 vs 3: 0.90 [-11.95, 13.75]; 1 vs 4: 4.68 [-10.33, 19.69]; 1 vs 5: 12.17 [-25.01, 49.35]; 2 vs 3: 1.56 [-11.87, 14.99]; 2 vs 4: -2.22 [-17.78, 13.35]; 2 vs 5: -9.71 [-47.04, 27.63]; 3 vs 4: -3.78 [-22.37, 14.81]; 3 vs 5: -11.27 [-49.72, 27.18]; 4 vs 5: -7.49 [-46.73, 41.76].



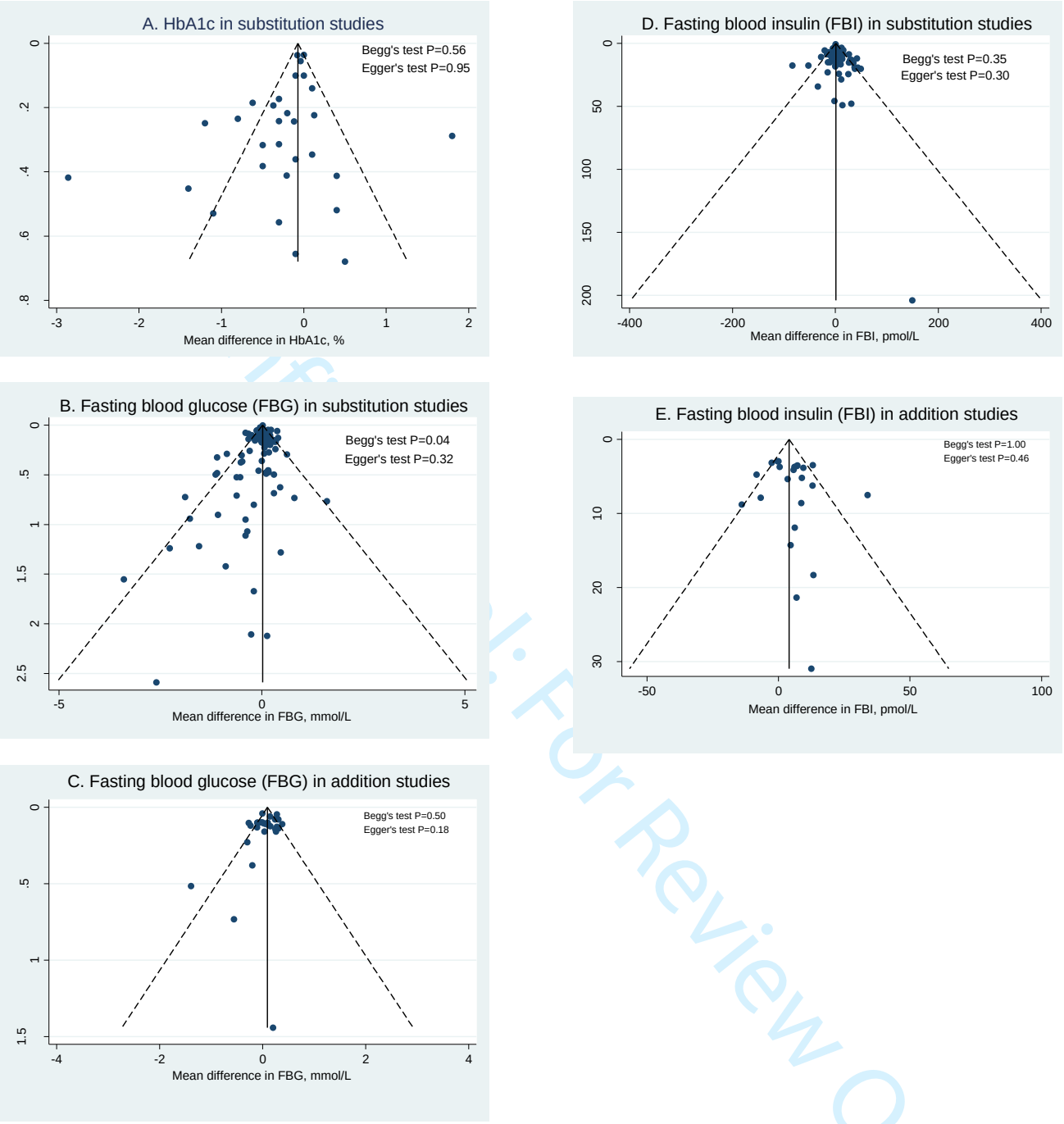
Supplementary Figure 23. Subgroup analyses for addition studies investigating the effect of adding excess calories to the diet in the form of food sources of fructose-containing sugars on fasting blood insulin. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. 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].



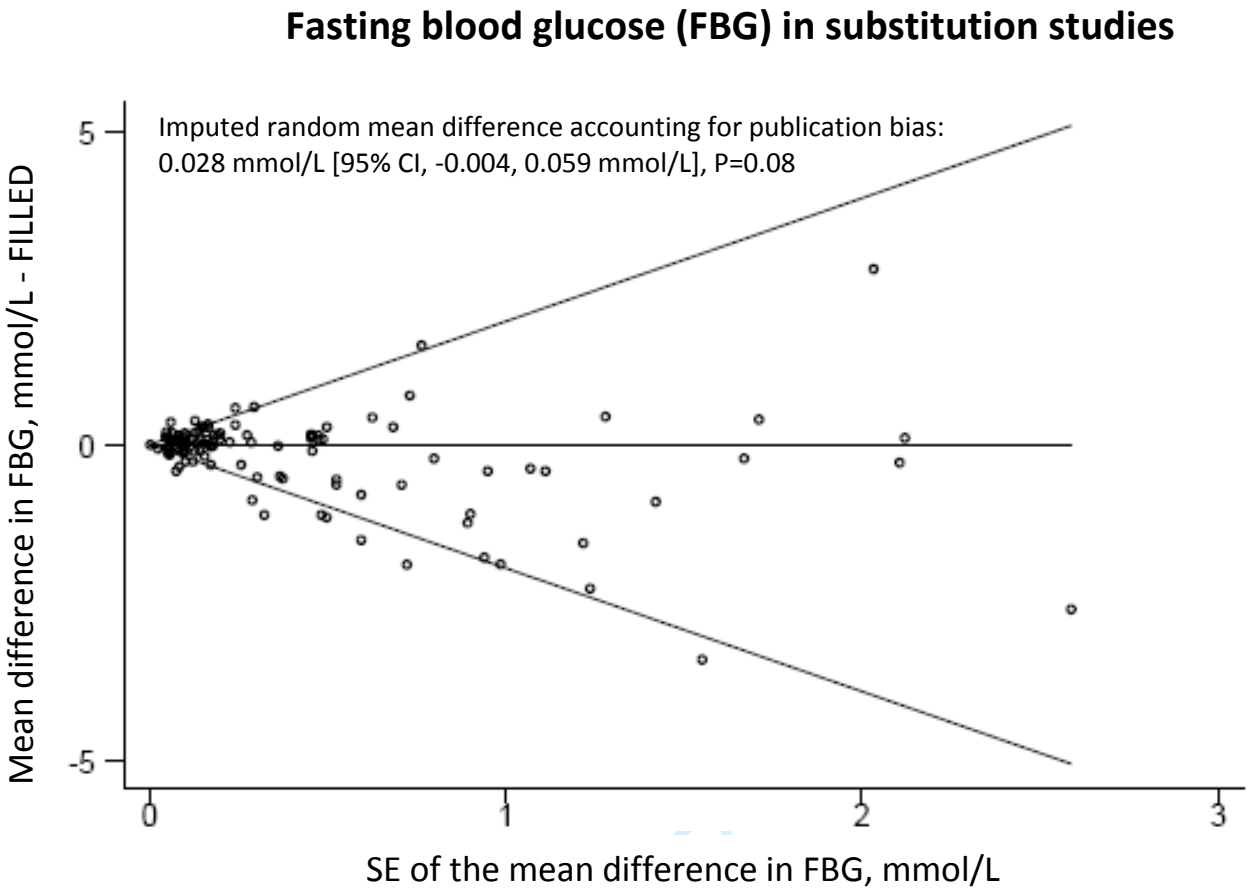
Supplementary Figure 24. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution studies investigating the effect of isocaloric exchange of food sources of fructose-containing sugars for other macronutrients on fasting blood insulin. Point estimates for each subgroup level 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 $p < 0.05$.



Supplementary Figure 27. Trim and Fill funnel plot for the effect of food sources of fructose-containing sugars on fasting blood glucose in substitution studies. The horizontal line represents the pooled effect estimate expressed as mean difference. The diagonal lines represent the pseudo-95% confidence limits, the circles represent the effect estimate for each included study, and squares represent the effect estimate for each imputed "missed" study. Imputed random mean difference is provided, p<0.05 is considered evidence of small-study effects.

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 April 25, 2018. 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 (energy from sugars added to diet); subtraction (energy from sugars subtracted from diet); or *ad libitum* (energy from sugars freely replaced). Outcomes were HbA1c, fasting glucose, and fasting insulin. Four independent reviewers extracted data and assessed risk of bias. Data were pooled using the inverse variance method. GRADE assessed the certainty of the evidence.

Study Answer and limitations: We included 155 controlled intervention studies (N=5,086). Whereas total fructose containing sugars had no adverse effect on any outcome in substitution or subtraction studies with a decrease in HbA1c (mean difference, -0.18% [95% confidence interval, -0.29, -0.06%]) in substitution studies, there was an increasing-effect on fasting insulin in addition (4.68pmol/L [1.40, 7.96]) and *ad libitum* (7.24pmol/L [0.47, 14.00]) studies. There was an interaction by food source with specific food sources showing decreasing-effects (fruit and fruit juice) or increasing-effects (sweetened-milk and mixed sources) in substitution studies and increasing-effects (SSBs and fruit juice) in addition studies across outcomes. 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.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7-8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10-12

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14 and Supplementary Figure 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-19 and Figures 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Figure 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-19
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-27
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	27-28
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28-29
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	30

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.