Food sources of fructose-containing sugars and glycemic control: A systematic review and meta-analysis of controlled trials

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Food sources of fructose-containing sugars and glycemic control: A systematic review and meta-analysis of controlled trials

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ABSTRACT

Objective: As dietary guidelines move to more dietary pattern-based recommendations, public health advice to reduce free sugars does not distinguish between food sources of sugars. We conducted a synthesis of controlled trials, to assess whether the effects on glycemic control are uniform across different food sources of fructose-containing sugars.

Design: Systematic review and meta-analysis

Data Sources: MEDLINE, EMBASE, and The Cochrane library were searched through Nov 3, 2015.

Eligibility criteria for selecting studies: We included trials ≥ 7-days assessing the effect of fructose-containing sugars from different food sources on glycemic control in people with and without diabetes. Outcomes were fasting blood glucose, insulin and HbA1c.

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

Results: Eligibility criteria were met by 160 trials (N=5139) including 4 levels of energy control: substitution trials (sugars in energy matched comparisons with other macronutrients); addition trials (excess energy from sugars supplementing diets); subtraction trials (excess energy from sugars displaced from diets); and ad libitum trials (sugars freely replaced by other macronutrients without strict energy control). In substitution trials, total food sources of fructose-containing sugars decreased HbA1c (-0.14% [-0.25 to -0.04%], moderate quality evidence, p=0.007) without affecting fasting glucose (high quality evidence) or insulin (moderate quality evidence), and the effect was stronger for fruit as a food source. In addition trials, total food sources of fructose-containing sugars increased fasting glucose (0.07 mmol/L [0.002 to 0.13], moderate quality evidence, p=0.04) and insulin (5.33 pmol/L [2.26 to 8.41], moderate quality evidence, p=0.0007) without affecting HbA1c (high quality evidence), and the effect was stronger for sugars-sweetened beverages as a food source. There was no effect of total food

sources of fructose-containing sugars in subtraction (low to high quality evidence) or ad libitum trials (very low to high quality evidence).

Conclusions: Pooled analyses showed that fructose-containing sugars from various food sources, especially fruit, are no worse in their effects on glycemic control in energy-matched comparisons with other macronutrient-containing foods. However, total food sources of fructose-containing sugars, especially sugars-sweetened beverages, supplementing diets with excess energy appear to have adverse effects. Longer, larger, high quality trials are required.

Systematic review registration: ClinicalTrials.gov identifier, NCT02716870.

INTRODUCTION

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

Despite early considerations for the use of fructose as an alternative sweetener in people with diabetes due to its observed potential to lower postprandial glycemic excursions when compared to isocaloric amounts of starch (5), a mounting body of evidence has suggested that fructose may be particularly detrimental to metabolic health, even more so than other sugars (6). This view has received support from ecological evidence(4) as well as animal (7-9) and select human trials(10-12). However, higher levels of evidence from prospective cohort studies have not shown a clear association between fructose-containing sugars and diabetes risk (13, 14), with the one exception being sugars-sweetened beverages (SSBs)(15, 16). A synthesis of data investigating the role of fructose on glycemic control in people with diabetes also failed to demonstrate adverse glycemic effects unique to fructose, and have even suggested potential benefit on glycated blood proteins when fructose was isocalorically exchanged for other carbohydrates in the diet(17).

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 (18). 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 (19). 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 an 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 fruits and vegetables also co-exist with glucose in catalytic amounts (≤10-g/meal). These fructose-containing sugars are found in the diet in a variety of food sources, ranging from "nutrient poor" sources of added sugars such as sugars-sweetened beverages (SSBs), to "nutrient dense" sources of bound sugars such as fruits. However, despite the high sugar composition of each, evidence from prospective cohorts on diabetes risk have shown differential associations depending on the food source of the sugars (positive associations with SSBs(20, 21) and inverse association with fruits)(22, 23). Whether various food sources of fructose-containing sugars differ in their effects on surrogate markers of type 2 diabetes in controlled trials have not yet been determined. This question has become increasingly important, as dietary guidelines have shifted from nutrient-based recommendations to more food and dietary pattern-based recommendations(24). To help address this gap, we conducted a systematic review and meta-analysis of controlled trials to determine the effect of fructose-containing food sources on measures of 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(25), with all results reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) guidelines (26). The study protocol was registered at ClinicalTrials.gov, (identification number, NCT02716870).

Data Sources

Medline, EMBASE and the Cochrane Central Register of Controlled Trials were searched through November 3, 2015 using the following search terms: fructose OR dietary sucrose, OR HFCS OR sugar OR sugar* sweetened beverage* OR honey AND glyc?em* OR insulin OR HbA1c OR fructosamine OR blood glucose OR gly* albumin (**Supplementary Table 1**). Validated filters from McMaster University Health

Information Research Unit were applied to limit the database search to controlled trials only (27), and electronic searches were supplemented with manual searches of references from included studies.

Study Selection

Inclusion criteria for our analysis included controlled trials in humans lasting ≥7 days investigating the role of fructose-containing sugars (fructose, sucrose, HFCS, honey, fruit sugars) from various food sources on measures of glycemic control (fasting glucose, fasting insulin, and HbA1c). Four trial designs were identified: 1) 'substitution' trials, in which fructose-containing sugars added to foods and beverages were compared with other macronutrient sources under energy matched conditions; (2) 'addition' trials, in which fructose-containing sugars supplemented a diet with excess energy compared to the same diet supplemented with the equivalent amounts of non-caloric food and beverages or the same diet alone without the excess energy from fructose-containing sugars; (3) 'subtraction' trials, in which energy from fructose-containing sugars was reduced through displacement with water and/or no-calorie or low-calorie sweeteners or by eliminating it altogether from the background diet; and (4) 'ad libitum' trials, in which energy from fructose-containing sugars were freely replaced with other food and beverages without any strict control of either the study foods or the background diet.

Patient involvement

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

Data Extraction

Data from included reports were individually extracted twice by four separate reviewers with all discrepancies resolved through consensus. Relevant information included number of participants, health status of participants, study design, level of feeding control, randomization, comparator form, fructose-containing sugar form and food source, macronutrient profile of the diets, follow-up duration, energy balance, risk of bias and funding sources. Outcome measures included HbA1c, fasting glucose, and fasting 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 more clinically relevant and did not require the use of standardized mean differences needed to calculate pooled effects for 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 contact authors, values were extracted from figures using Plot Digitizer where available(28). Included studies were assessed for risk of bias using the Cochrane Collaboration Risk of bias Tool(29).

Data Synthesis and Analysis

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 fructose-containing sugar arm and the comparator arm. For each study, we extracted the estimates of the MD and corresponding 95% confidence intervals for each outcome. When at least two studies provided data, we performed a DerSimonian and Laird random effects meta-analysis, which yields conservative confidence intervals around effect estimates in the presence of heterogeneity. When four or fewer studies were combined, we also considered fixed effect estimates.

Heterogeneity was determined with Cochran's Q test (significant at $P<0.10$), quantified with the I^2 statistic (range from 0%-100%)(30), and used to assess inconsistency as part of the GRADE assessment of evidence quality. *A priori* subgroup analyses were conducted to explore sources of heterogeneity. Categorical subgroup analyses were conducted for energy balance, comparator form, fructose form, fructose-containing sugar dose, baseline values for fasting glucose, insulin and HbA1c, age, study design, follow-up duration, randomization, underlying health status, overall risk of bias, and individual domains of risk of bias. *Post-hoc* dose response analyses were performed using meta-regression and piecewise linear meta-regression for the continuous subgroup of fructose dose (as percentage of total energy intake) on glycemic control. If ≥10 studies were available (31, 32) and heterogeneity was substantial

(I^2>50% or P_Q<0.10)(30) we used meta-regression to explore heterogeneity by sources of fructose-containing food sources (fruits, fruit juices, sugars-sweetened beverages, liquid meal replacements, dairy products, sweets/desserts/baked goods, and mixed sources).

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

As a sensitivity analysis, we removed each single study from the meta-analyses and recalculated the summary effect (the "leave one out" approach)(33). If ≥10 studies were available(34), we explored the possibility of publication bias by inspecting funnel plots and conducting Egger's and Begg's tests (each significant at P<0.10). If publication bias was suspected, results are shown without imputation and with "missing" studies imputed with Duval and Tweedie's trim and fill method(35).

Grading of the evidence

The grading of recommendations assessment, development, and evaluation (GRADE) approach was used to assess the confidence in the effect estimates derived from the body of evidence (quality of evidence) by outcome and produce evidence profiles(36). Through this approach, evidence was graded as high, moderate, low or very low quality. Included controlled trials were graded as high quality evidence by default and downgraded based on pre-specified criteria. Criteria to downgrade evidence included risk of bias (assessed through the Cochrane Risk of Bias tool), inconsistency (substantial unexplained interstudy heterogeneity, I^2>50%), indirectness (presence of factors that limited the generalizability of the results), imprecision (the 95% CI for effect estimates were wide or crossed a minimally important difference for benefit or harm), and publication bias (significant evidence of small-study effects).

RESULTS

Search Results

The systematic search and selection of literature is shown in **Figure 1.** 3574 reports were identified from database and manual searches, of which 3353 were excluded based on title and abstract. 221 reports were reviewed in full, of which an additional 99 reports were excluded. 122 reports including a total of 160 trials in 5139 participants were included in the final analysis (5, 10-12, 37-154).

Trial Characteristics

A summary of trial characteristics are presented in **Table 1**, with an individual breakdown of study characteristics in **Supplementary Table 2**. In total, trial sizes were relatively small, ranging from a median of 15 participants (range=2 to 595) in substitution trials to 39 (range= 8-236) participants in ad libitum trials. The majority of trials were performed under an outpatient setting, with almost half of all substitution (44/110), addition (14/38) and subtraction (2/5) trials conducted in the USA, and all ad libitum trials conducted in European countries. Participants tended to be middle aged, with approximately equal ratios of males to females in substitution trials and ad libitum trials, but proportionately more females in addition and subtraction trials. Most trials were performed on healthy participants (34%) and those with diabetes (35%) in substitution trials, whereas most participants were healthy (37%) and overweight/obese (39%) in addition trials. Participants in subtraction trials were predominantly overweight or obese (80%), whereas participants in ad libitum trials were mostly healthy (67%). A majority of trials were randomized (69% of substitution trials, 66% of addition trials, 80% of subtraction trials and 88% of ad libitum trials) however, follow up duration was relatively short, ranging from a median of 4 weeks (range=1 to 52 weeks) in substitution trials to 12 weeks (range= 8.6-39.1 weeks) in subtraction trials. Fructose-containing sugar doses ranged from a median of 15% of total energy intake in substitution and subtraction trials to 23% of total energy intake in ad libitum trials, and were mostly in the form of mixed food sources in substitution (57/110) and ad libitum (6/7) trials while most addition (16/38) and subtraction (4/5) trials used sugars-sweetened beverages. Most trials 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. Lastly, very few trials were assessed as high risk of bias across the 5 domains of bias, as assessed by the Cochrane Risk of Bias Tool (**Supplementary Figure 1**).

HbA1c

The effect of fructose-containing food sources on HbA1c are shown in **Figure 2** and **Supplementary Figures 2-5**. In 32 substitution trials involving 946 participants where fructose-containing sugars were exchanged for other macronutrients of equal energy, a significant reduction in HbA1c was observed (MD=-0.14% [95% CI=-0.25, -0.04], p=0.007, I^2=81%, heterogeneity p <0.00001; moderate quality evidence) . No other significant effects were found for total food sources of fructose containing-sugars in addition (6 trials, 231 participants, high quality evidence), subtraction (1 trial, 240 participants, low quality evidence) or ad libitum trials (1 trial, 10 participants, very low quality evidence). Fructose-containing sugars from fruits significantly decreased HbA1c (MD=-0.12% [95% CI=-0.23, -0.003], p=0.04) in substitution trials. No food sources were significant in addition, subtraction or ad libitum trials. Sensitivity analyses through removal of individual trials did not change the overall significance or direction of the effect in any analyses.

A priori subgroup analyses are presented in **supplementary figures 6 and 7**. In substitution trials (**Supplementary Figure 6**), participants with higher baseline levels showed greater improvements in glycemic control on fructose-containing arms relative to controls. Post-hoc dose-response analyses are presented in **Supplementary Figure 8 and Supplementary table 3**. In substitution trials, we found no significant effect modification by dose (**Supplementary Figure 8A)** or by dose-thresholds **(Supplementary table 3A**) of fructose intake. No subgroup or dose-response analyses were conducted for addition, subtraction or ad libitum comparisons as less than 10 trials were available in each analysis.

Fasting Blood Glucose

The effects of fructose-containing food sources on fasting blood glucose are shown in **Figure 3** and **Supplementary Figures 9-12**. In 35 trials involving 985 participants under addition conditions, fructose-containing sugars from all food sources increased fasting blood glucose (MD=0.07 [95% CI=0.002, 0.13], p=0.04, I^2=72%, p heterogeneity<0.0001], moderate quality evidence), but had no effect on fasting blood glucose under substitution (101 trials, 2948 participants, moderate quality evidence), subtraction (4 trials, 585 participants, high quality evidence) or ad libitum conditions (6 trials, 459 participants, high quality evidence). Fructose-containing sugars in the form of liquid meal replacements led to a significant increase in fasting blood glucose (0.83 mmol/L [0.28, 1.39], p=0.003) when adding excess energy to the diet under addition conditions, although this was only based on one trial. Individual removal of 13 trials (49, 79, 91, 92, 98, 100, 107, 121, 132, 133, 138) from the addition comparisons changed the overall significance of the effect while keeping direction the same (**Supplementary Table 4**). Under subtraction conditions, removal of a trial by Campos et al. (G2) reversed the direction of the effect and explained all of the heterogeneity, but did not modify overall significance (**Supplementary Table 4**).

A priori subgroup analyses are presented in **supplementary figures 13-16**. *A priori* subgroup analyses revealed an effect modification by baseline fasting blood glucose under substitution conditions (**Supplementary Figure 13**), such that baseline fasting blood glucose levels of ≥6.1 mmol/L led to a greater decrease in levels of fasting blood glucose. Additionally, although fructose dose was not significant at ≤10 or >10% of energy, a significant continuous dose response was observed (P=0.01) (**Supplementary Figure 8-B**), but this effect lost significance upon removal of an outlier study using extreme doses of sucrose at 75% of energy(10). Post-hoc dose-threshold analyses also showed significant effect modification by dose at doses >50 % of energy (P<0.05), such that doses >50 % of energy resulted in higher levels of fasting blood glucose (**Supplementary Table 3B**). With the removal of the same outlier study (Hendler et al. 1990(155)), this effect was seen starting at lower doses (>20 % energy [P=0.04]). Significant subgroup effects were also observed in addition trials (**Supplementary**

Figure 14) by fructose-containing sugar form, age and underlying disease status. Particularly, fructose-containing sugars in the form of honey (3 trials) led to greater decreases in fasting blood glucose, whereas fructose in its pure monomeric form (9 trials) lead to increasing effects on fasting blood glucose when adding excess energy to the diet. Second, a greater reduction in levels of fasting blood glucose was observed for children who supplemented the diet with excess calories from fructose-containing sugars compared to adults, although only one trial in children was available for analysis. Lastly, participants with diabetes displayed greater improvements in fasting blood glucose on the fructose-containing sugars interventions compared to patients without diabetes. No a priori subgroup analyses were conducted in subtraction or ad libitum trials as too few trials were available. Post-hoc dose-threshold analyses did not show any significant effect modification by dose (**Supplementary Table 3C**).

Fasting Blood Insulin

The effect of fructose-containing food sources on fasting blood insulin are shown in **Figure 4** and **Supplementary Figures 17-20**. In 27 addition trials involving 730 participants where fructose-containing sugars supplemented the diet with excess energy compared to the diet alone or non-caloric food sources, an increasing effect on fasting blood insulin was observed from total food-sources (MD=5.33 pmol/L [95% CI=2.26, 8.41], p <0.001, moderate quality evidence). Significant food sources of fructose-containing sugars leading to an increase in fasting blood insulin included SSBs (MD=6.17 pmol/L [95% CI=1.55, 10.78], p <0.01, 13 trials), dairy products (MD=15.64 pmol/L [95% CI=5.18, 26.10], p=0.003, 1 trial) and mixed sources (MD=13.00 pmol/L [95% CI=0.81, 25.19], p =0.04, 1 trial). Total food sources of fructose-containing sugars did not demonstrate any significant effects in substitution (75 trials, 2194 participants, moderate quality evidence), subtraction (3 trials, 33 participants, moderate quality evidence) or ad libitum trials (4 trials, 302 participants, high quality evidence). However, in substitution trials, an increase in fasting blood insulin was observed when fructose-containing sugars were in the form of mixed sources (MD=4.71 pmol/L [95% CI=0.25, 9.18], p =0.04, 34 trials) as well as dairy products

(MD=26.59 [95% CI=9.51, 43.68], p<0.01, 1 trial). Sensitivity analysis through removal of a trial by Campos et al. from the subtraction analysis changed the significance of the effect and explained 78% of the heterogeneity, while overall direction of the effect remained the same (39.54 pmol/L [2.06, 75.02], p =0.02) (**Supplementary Table 4**). Similarly, removal of a trial by Markey et al. from the ad libitum analysis changed the significance of the effect and explained all of the heterogeneity while keeping direction the same (9.51 pmol/L [1.59, 17.42], p-value=0.02) (**Supplementary Table 4**). Significant heterogeneity was present in all analyses except for ad libitum trials. A priori subgroup analyses revealed a significant effect modification by fructose-containing sugar dose in addition trials (**Supplementary Figure 21**), where doses greater than 10% of total energy intake lead to larger increases in fasting blood insulin. However, a continuous dose response was not observed (P=0.12) (**Supplementary Figure 12-C**). Although fructose dose was not significant in substitution trials at ≤10 or >10% of energy (**Supplementary Figure 22**), a significant continuous dose response was observed (P=0.04) (**Supplementary Figure 12-B**). However, this effect became non-significant upon removal of two outlier studies using extreme doses of sucrose (75-95% of energy)(10, 11). No subgroup analyses were conducted for subtraction or ad libitum conditions as there were not enough trials available for each analysis. Post-hoc dose-threshold analyses did not show any significant effect modification by dose (**supplementary table 3D**) in substitution trials or addition trials (**supplementary table 3**E).

Publication Bias

There was no evidence for publication bias through visual inspection of funnel plots or Egger's and Begg's tests for the effect of fructose containing sugars on fasting blood glucose, fasting blood insulin or HbA1c for all analyses where ≥10 trials were available (**Supplementary Figure 23**).

GRADE Assessment

A summary of the quality of evidence assessment for the effect of fructose-containing food sources on measures of glycemic control can be found in **Table 2.** In general, the confidence we have in our effect

estimates for the analyses on fasting blood glucose and insulin ranged from moderate to high, whereas HbA1c analyses ranged from very low to high. Evidence for fasting blood glucose and insulin in substitution and addition trials as well as HbA1c in substitution trials were downgraded for serious inconsistency due to significant interstudy heterogeneity. Similarly, evidence for fasting blood insulin in subtraction trials was downgraded for serious imprecision as the 95% CIs for the effect estimate [-22.83, 26.83] included both clinically important benefit (<10 pmol/L) and harm (>10 pmol/L). On the other hand, evidence for HbA1c in subtraction and ad libitum trials were downgraded due to indirectness and imprecision as only 1 trial was available for each of these analyses (240 participants in the subtraction trial and 10 participants in the ad libitum trial), and the 95% CI for the effect estimate [-0.38, 0.42] included both clinically important benefit (≤-0.3%) and harm (≥0.3%) for the ad libitum trial.

DISCUSSION

The results from our systematic review and meta-analysis of 160 trials involving 5,181 participants with and without diabetes showed variable effects of food sources of fructose-containing sugars on glycemic control at median doses ranging from 12-23% energy over median follow-up durations of 4-12 weeks. In substitution trials, in which food sources of fructose-containing sugars were compared with other macronutrient sources matched for energy, a decrease in HbA1c for total food sources of fructose-containing sugars, especially from fruit, was observed with no effects on fasting glucose or fasting insulin. In addition trials, in which food sources of fructose-containing sugars supplemented diets with excess energy compared to the same diet alone without the excess energy (with or without the use of non-caloric sweeteners), an adverse effect was observed for total food sources of fructose-containing sugars, especially from SSBs, on fasting blood insulin and glucose but not HbA1c. No effect of food sources of fructose-containing sugars were observed on glycemic control in subtraction or ad libitum trials.

Results in the context of other studies

These findings agree with two previously conducted systematic reviews and meta-analyses which demonstrated a beneficial effect of isocalorically exchanging fructose for other carbohydrates on glycated blood proteins in participants with diabetes (SMD =-0.25 [95% CI -0.46 to -0.04], p-value= 0.02; equivalent to ~0.53% reduction in HbA1c)(17), and without diabetes (fructose intake <90 g/d significantly improved HbA1c dependent on dose, study duration and severity of dysglcemia) (156). Although the modest decrease in HbA1c from our analysis (MD=-0.14% [-0.25 to -0.04]) did not exceed the clinically meaningful threshold of 0.3% proposed by the U.S Food and Drug administration for the development of new drugs for diabetes as observed in the previous meta-analysis (157), our findings suggest that fructose-containing sugars may have modest benefits for glycemic control when they replace other macronutrients on a calorie-for-calorie basis. On the other hand, our results suggest that fructose-containing sugars providing excess energy to the diet may raise fasting blood glucose and insulin agreeing with observed findings from the previous meta-analysis on fructose and glycemic control (17).

The adverse effects of SSB consumption are concordant with findings from several large observational studies, showing an increased risk of developing type 2 diabetes with higher SSB consumption(20, 21) and a decreased risk of type 2 diabetes with higher fruit intake(22, 23).

Potential mechanisms

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

An alternative mechanism accounting for the observed beneficial effects of fructose-containing sugars on HbA1c in substitution trials suggests that small catalytic fructose doses of ≤10-g/meal (typically found in low GI fruits) 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 (161) and increased glycogen synthesis(162). This may explain the decrease in HbA1c observed in substitution trials particularly when fruits were compared to other fructose-containing food sources. Although the benefit of fruits did not extend to fasting blood glucose and insulin, the summary effects for both endpoints tended to be in the direction of benefit, with the possibility of additional trials allowing sufficient power to confirm any beneficial effects.

In contrast, the observed adverse effects of fructose-containing sugars on glycemic control under addition conditions appear to be largely driven by the energy contribution of the sugars. Excess calories in the form of fructose-containing sugars supplementing the background diet may promote ectopic weight gain, contributing to downstream insulin resistance and impaired glycemic control. This mechanism is not unique to sugars per se and would be expected for the overconsumption of any dietary macronutrient. Similar effects have been observed under fructose overfeeding for body weight (163), blood pressure(164), uric acid(165), NAFLD(166) and postprandial triglycerides (167).

A priori and posthoc subgroup analyses

In subgroup analyses, greater improvements in fasting blood glucose were observed in those trials which enrolled participants with higher baseline fasting glucose (substitution and addition trials) and greater improvements HbA1c were observed in those trials enrolling participants with higher baseline HbA1c (substitution trials), suggesting a regression-to-the-mean phenomenon. These effects were concordant with the observed subgroup modification by underlying health status demonstrating greatest benefits on fasting blood glucose for patients with diabetes in addition trials, suggesting a potential benefit in using sugars with higher fructose content, particularly in the form of fruit, as an

alternative sweetener to replace higher GI carbohydrates in the diet of patients with diabetes. Additionally, a significant subgroup effect by fructose-containing sugar form was observed under addition conditions, whereby the addition of honey to the diet led to greater decreases in fasting blood glucose when compared to other fructose-containing sugars. Although the underlying mechanism and potential use of honey as an effective antidiabetic agent currently remains inconclusive, a few preliminary studies in animals and humans have suggested that honey, through its small but measurable concentration of non-digestible short chain oligosaccharides as well as polyphenols, mineral and other antioxidant components, may exert beneficial metabolic effects including altering glucose metabolism(168), lowering insulin resistance (169)and reducing hepatic oxidative stress(170, 171). On the other hand, while subgroup analyses by fructose form in addition trials suggested a modest increase in fasting blood glucose when fructose was compared to other fructose-containing sugars, the supraphysiological doses of fructose used in these addition trials (average intake=172.8 ± 57.8 g/d) have been shown to greatly exceed estimated levels of national dietary intake (average intake=49 ± 1.0 g/d, NHANES 1977-2004)(172). As with the overconsumption of any macronutrient, observed adverse effects may be irrelevant under normal levels of dietary consumption and are likely due to excess calories rather than unique metabolic attributes of fructose per se.

Dietary guidelines informing the consumption of sugars have proposed upper limits of <5-10% based on food modeling patterns as well as the development of dental caries and obesity (155, 173). Our categorical subgroup analyses revealed a significant effect modification by fructose dose at levels of ≤10% or >10% energy on levels of fasting blood insulin in addition trials. However, significant effect modification was not seen for the continuous subgroup analyses, and post-hoc analyses also did not identify a threshold for dose (data not shown). On the other hand, while a categorical dose effect was not observed for the remaining subgroup analyses, continuous subgroup analyses suggested significant dose gradients for the effect of fructose-containing sugars on fasting blood glucose and fasting blood

insulin under substitution conditions. However, removal of a trial by Hendler et al.(10) providing a liquid meal replacement containing 75% of energy as sucrose compared to a liquid meal replacement containing 75% of energy as fat eliminated this dose response in fasting glucose trials. Similarly, removal of two trials by Hendler et al. (10, 11) providing liquid meal replacements containing 75% or 95% of energy as sucrose compared to 75% or 95% of energy as fat or protein respectively also eliminated the observed dose response gradient in fasting insulin trials. Although both trials by Hendler et al. may suggest a potential for harm when substituting sucrose for fat or protein as a primary source of calories in the diet, the dose of sucrose used in these trials were 150-190 grams per day, exceeding estimated levels of average intake from added sugars (approximately 10% energy or ~50 grams/day(174)) by three- to four-fold. Thus, removal of these outlier studies providing extreme doses of sucrose suggested the lack of a true dose response when fructose-containing sugars were isocalorically substituted for other macronutrients in the diet.

Project Implications

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

blood insulin in substitution trials, this effect was bordering significance (p=0.04), and individual removal of 18 of the 34 trials (12, 55-57, 68, 70, 81, 95, 102, 103, 140, 148, 153), led to non-significant results. Additionally, while fructose-containing sugars in the form of fruits showed a modest decrease in levels of HbA1c in substitution trials, individual removal of 5 of the 8 trials (43, 50, 61, 77, 108) eliminated the significance of the effect although direction remained the same. On the other hand, pooled analyses from 13 trials of fructose-containing sugars in the form of SSBs lead to significant increases in fasting insulin when providing excess energy to the diet (6.17 pmol/L [1.55, 10.78], p=0.009), and these results were not sensitive to removal of any individual trial.

Taken together, as dietary guidelines have shifted towards a food-based approach, our findings may have implications for guiding recommendations on important food sources of fructose-containing sugars towards the prevention and management of diabetes. Particularly, as fructose-containing sugars in the form of fruits tended to demonstrate improvements on HbA1c, encouraging fruit consumption to replace other dietary sweeteners may be an effective strategy for improving glycemic control, especially in people with diabetes. Additionally, as SSBs tended to impair fasting glucose and insulin when adding excess energy to the diet, public health strategies to reduce consumption of this fructose-containing food source may be useful, especially as SSBs have recently come under scrutiny for providing empty calories in absence of any nutritional “value”.

Strengths and Limitations

Our systematic review and meta-analysis presented several strengths, including: 1) a rigorous search and selection process of available literature examining the effect of fructose-containing food sources on glycemic control, 2) inclusion of controlled trials which give the greatest protection against bias (noting that results did not differ between randomized and non randomized trials), 3) the collation and synthesis of data from 160 controlled trials involving 5181 human participants, and 4) an assessment of overall quality of evidence using the GRADE assessment tool.

Several of our analyses also presented limitations. In particular, significant unexplained heterogeneity was present for all substitution analyses, as well as addition analyses for fasting blood glucose and fasting blood insulin. Second, serious indirectness was suggested for several 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. Third, as the effect estimates in subtraction trials on fasting insulin as well as subtraction and ad libitum trials on HbA1c crossed the minimally important difference for benefit or harm, imprecision in these results reduced confidence in the overall effect. Lastly, a majority of the trials were small and short in duration, with a median follow up of less than 8 weeks for substitution and addition trials and a median trial size ranging from 14 participants in substitution trials to 39 participants in ad libitum trials. Additionally, as Hba1c reflects average blood glucose levels over 8-12 weeks, our ability to determine longer term effects on glycemic control may be limited.

Based on the strengths and limitations, our GRADE assessment graded the evidence as very low to high quality for HbA1c and moderate to high quality for fasting blood glucose and insulin.

CONCLUSION

In conclusion, the effects of fructose-containing sugars on glycemic control are both energy and source dependent. Fructose-containing sugars, especially from fruit, exchanged for equal amounts of calories from other macronutrient sources led to improvements in HbA1c without adversely affecting fasting blood glucose or insulin. However, when fructose-containing sugars added excess energy to the diet, particularly in the form of SSBs, a significant increase in fasting blood insulin and fasting blood glucose was observed. No significant effects were observed under subtraction or ad libitum conditions. The lack of harm and even advantages were most pronounced in those with higher baseline levels or who had diabetes. While our findings may suggest that important food sources of fructose-containing sugars do not have adverse effects on glycemic control in energy matched replacement or even free replacement

of other less sugary foods, our GRADE assessment suggest that more research is likely to have an important influence on many of our estimates. Longer, larger, high quality trials using a variety of fructose-containing food sources are required to assess the durability of these effects under real world conditions.

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CONTRIBUTORS

VLC 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. Study supervision: JLS and DJAJ.

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COMPETING INTERESTS

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EXCLUSIVE LICENCE

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TRANSPARENCY DECLARATION

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

ETHICS APPROVAL

Not required.

DATA SHARING STATEMENT

No additional data are available.

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Figures and Tables

Figure 1. Flow of literature for the effect of Fructose-containing sugars on glycemic control.

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

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

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

Table 1. Summary of Trial Characteristics

Trial Characteristics	Substitution Trials	Addition Trials	Subtraction Trials	Ad Libitum Trials
Trial Number (N)	110	38	5	7
Trial Size (participants)[2]	15 (2-595)	21 (6-92)	15 (12-318)	39 (8-236)
Male: Female[3]	44: 56	39: 61	12: 88	41: 59
Age (years)[1]	40.1 (23.2-53.9)	35.8 (25.0-50.1)	33.5 (29.1-42.2)	37.4 (34-39)
Setting (Inpatient: Outpatient)[3]	25: 75	10: 90	0: 100	0: 100
Baseline Fasting Glucose (mmol/L)[1]	5.4 (4.9-8.0)	5.1 (4.9-5.4)	5.1 (5.1-5.2)	4.9 (4.9-5.4)
Baseline Fasting Insulin (pmol/L)[1]	89.6 (57.9-131.6)	53.5 (40.6-81.5)	109.8 (97.8-121.7)	32.5 (31.8-45.9)
Baseline HbA1c (%)[1]	7.3 (6.7-8.4)	7.2 (7.1-7.2)	N/A[4]	N/A[4]
Study Design (Crossover: Parallel)[3]	62: 38	50: 50	20: 80	57: 43
Feeding Control (Met: Supp: DA)[3]	49: 39: 14	15: 83: 2	0: 67: 33	14: 57: 29
Randomization (Yes: No)[3]	69: 31	66: 34	80: 20	88: 12
Fructose Containing Sugar Dosage (%E)[1]	15.0 (9.6-23.6)	11.6 (5.0-25.0)	15.0 (13.8-15.0)	23.0 (13.0-26.0)
Follow-Up Duration (Weeks)[2]	4 (1-52)	7 (1-26)	12 (8.6-39.1)	8 (2-78)
Funding Sources (A: I: AI: NR)[3]	31: 27: 19: 23	48: 15: 30: 7	60: 40: 0: 0	0: 17: 50: 33
Fructose-Containing Sugar Form (N)	Fructose=52; Fruit=13; HFCS=1; Sucrose=50	Fructose=10; Fruit=17; HFCS=2; Honey=3; Sucrose=9	Sucrose= 5; HFCS=4	Fructose=1; Sucrose=7
Comparator Form (N)	D-maltose=3; Fat=9; Galactose=2 Glucose=25; Isomaltulose=2; Lactose=4; Maltodextrin=1; Mixed Comparator=13; Protein=1; Starch=55	Diet alone=28; Sweetener=4; Water=8	Water=2; Sweetener=3; No sucrose=1	Fat=2; Mixed comparator=2; Starch=4; Sweetener=3
Food Source of Fructose-Containing Sugar	Baked Goods, Sweets and Desserts=11; Dairy=1; Fruit=13; LMRs=7; Mixed Sources= 57; SSBs=21	Baked Goods, Sweets and Desserts=1; Dairy=1; Fruits=12; Fruit Juice=3; LMRs=1 SSBs=16; Mixed Sources=4	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; LMRs=liquid meal replacements; Met=metabolic; N=number of trials; NR=not reported; SSBs=sugars-sweetened beverages; Supp=supplemented

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

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

Table 2. GRADE Quality of Evidence Assessment

Quality assessment							Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Fasting Blood Glucose in Substitution Trials							
101	randomized and non-randomized trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
Fasting Blood Glucose in Addition Trials							
35	randomized and non-randomized trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
Fasting Blood Glucose in Subtraction Trials							
4	randomized and non-randomized trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	no serious imprecision[4]	none[5]	⊕⊕⊕⊕ HIGH
Fasting Blood Glucose in Ad Libitum Trials							
6	randomized and non-randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[5]	⊕⊕⊕⊕ HIGH
Fasting Blood Insulin in Substitution Trials							
75	randomized and non-randomized trials	no serious risk of bias	serious[6]	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
Fasting Blood Insulin in Addition Trials							
27	randomized and non-randomized trials	no serious risk of bias	serious[7]	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
Fasting Blood Insulin in Subtraction Trials							
3	randomized and non-randomized trials	no serious risk of bias	no serious inconsistency[8]	no serious indirectness	serious[9]	none[5]	⊕⊕⊕O MODERATE
Fasting Blood Insulin in Ad Libitum Trials							
4	randomized and non-randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[5]	⊕⊕⊕⊕ HIGH
HbA1c in Substitution Trials							
32	randomized and non-randomized trials	no serious risk of bias	serious[10]	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
HbA1c in Addition Trials							
6	randomized and non-randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	⊕⊕⊕⊕ HIGH
HbA1c in Subtraction Trials							
1	randomized and non-randomized trials	no serious risk of bias	no serious inconsistency	serious[11]	no serious imprecision	none[5]	⊕⊕⊕O MODERATE
HbA1c in Ad Libitum Trials							
1	randomized and non-randomized trials	no serious risk of bias	no serious inconsistency	serious[11]	very serious[12]	none[5]	⊕OOO VERY LOW

[1] Serious inconsistency for the effect of fructose-containing sugars on fasting blood glucose, as there was evidence of significant interstudy heterogeneity (I^2=67%, p<0.0001).

[2] Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin, as there was evidence of significant intersudy heterogeneity (I^2=72%, p<0.0001).

[3] No serious inconsistency for the effect of fructose-containing sugars on fasting plasma glucose. Even though there was evidence of significant interstudy heterogeneity (I^2=59%, p=0.06), removal of a trial by Campos et al. (G2) explained all of the heterogeneity. While removal of this trial changed the direction of the effect, overall results remained non-significant.

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

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

[6] Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin, as there was evidence of significant interstudy heterogeneity (I^2=57%, p<0.0001).

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

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

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

[10] Serious inconsistency for the effect of fructose-containing sugars on HbA1c, as there was evidence of significant interstudy heterogeneity (I^2=81%, p<0.00001).

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

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

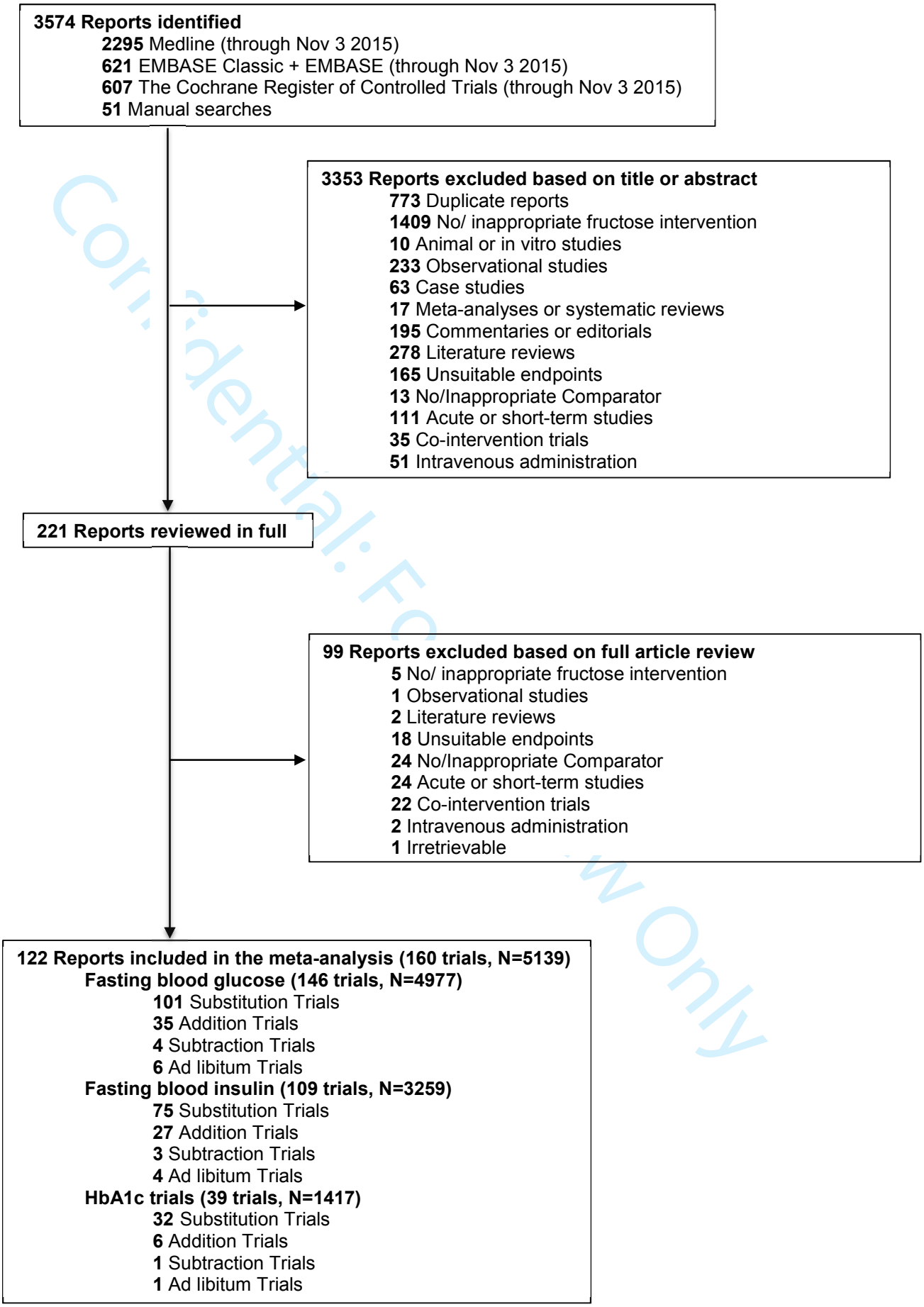


Figure 2. Summary super-plot for the effect of fructose-containing sugars on HbA1c.

Comparison	Trials	N	Weight	MD [95% CI]	I^2	P-value
SUBSTITUTION TRIALS						
Fruits	8	453	38.1%	-0.12 [-0.23, 0.00]	71%	0.04
Sugars-Sweetened Beverages	2	35	4.6%	-0.57 [-1.21, 0.07]	40%	0.08
Liquid Meal Replacements	3	92	7.1%	0.10 [-0.14, 0.34]	0%	0.43
Baked Goods, Sweets and Desserts	1	10	2.0%	-0.50 [-1.12, 0.12]	-	0.11
Mixed Sources	18	356	48.1%	-0.14 [-0.33, 0.06]	86%	0.17
Total Food Sources	**32**	**946**	**100.0%**	**-0.14 [-0.25, -0.04]**	**81%**	**<0.01**
ADDITION TRIALS						
Fruits	2	130	77.7%	-0.01 [-0.13, 0.14]	51%	0.95
Baked Goods, Sweets and Desserts	1	24	4.0%	0.40 [-0.28, 1.08]	-	0.25
Mixed Sources	3	77	18.2%	0.08 [-0.40, 0.57]	54%	0.74
Total Food Sources	**6**	**231**	**100.0%**	**0.03 [-0.12, 0.17]**	**33%**	**0.71**
SUBTRACTION TRIALS						
Sugars-Sweetened Beverages	1	240	100.0%	-0.05 [-0.14, 0.04]	-	0.30
Total Food Sources	**1**	**240**	**100.0%**	**-0.05 [-0.14, 0.04]**	**-**	**0.30**
AD LIBITUM TRIALS						
Baked Goods, Sweets and Desserts	1	10	100.0%	0.02 [-0.38, 0.42]	-	0.92
Total Food Sources	**1**	**10**	**100.0%**	**0.02 [-0.38, 0.42]**	**-**	**0.92**

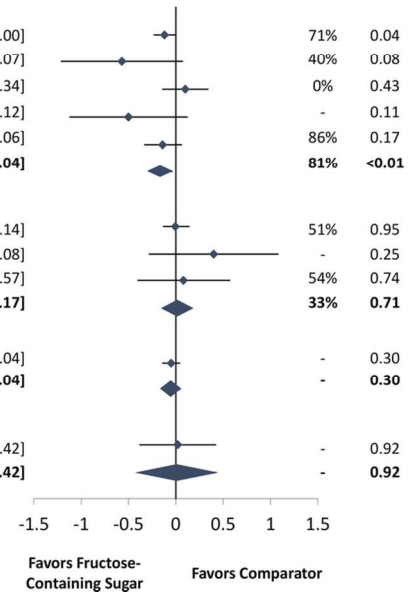


Figure 2. Summary super-plot for the effect of fructose-containing sugars on HbA1c.

109x70mm (300 x 300 DPI)

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

Comparison	Trials	N	Weight	MD [95% CI]	I^2	P-value
SUBSTITUTION TRIALS						
Fruits	12	697	11.2%	-0.10 [-0.26, 0.06]	71%	0.22
Sugars-Sweetened Beverages	20	455	31.7%	0.05 [-0.02, 0.11]	76%	0.18
Liquid Meal Replacements	7	118	7.5%	0.15 [-0.15, 0.45]	85%	0.33
Dairy Products	1	95	1.8%	-0.10 [-0.28, 0.08]	-	0.28
Baked Goods, Sweets and Desserts	10	156	6.1%	0.01 [-0.12, 0.13]	0%	0.93
Mixed Sources	51	1427	41.7%	0.04 [-0.03, 0.11]	57%	0.31
Total Food Sources	**101**	**2948**	**100.0%**	**0.03 [-0.01, 0.07]**	**67%**	**0.13**
ADDITION TRIALS						
Fruits	11	327	30.8%	0.03 [-0.04, 0.10]	29%	0.42
Sugars-Sweetened Beverages	16	346	53.1%	0.08 [-0.01, 0.18]	79%	0.10
Fruit Juice	2	106	6.3%	0.13 [0.00, 0.26]	0%	0.06
Liquid Meal Replacements	1	14	1.1%	0.83 [0.28, 1.39]	-	<0.01
Dairy Products	1	92	4.4%	0.09 [-0.03, 0.20]	-	0.11
Mixed Sources	4	100	4.4%	-0.55 [-1.41, 0.31]	83%	0.21
Total Food Sources	**35**	**985**	**100.0%**	**0.07 [0.00, 0.13]**	**72%**	**0.04**
SUBTRACTION TRIALS						
Sugars-Sweetened Beverages	4	585	100.0%	-0.01 [-0.10, 0.07]	59%	0.79
Total Food Sources	**4**	**585**	**100.0%**	**-0.01 [-0.10, 0.07]**	**59%**	**0.79**
AD LIBITUM TRIALS						
Mixed Sources	6	459	100.0%	-0.02 [-0.07, 0.04]	0%	0.56
Total Food Sources	**6**	**459**	**100.0%**	**-0.02 [-0.07, 0.04]**	**0%**	**0.56**

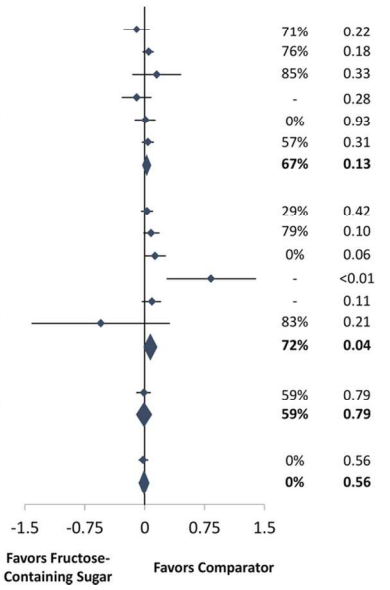


Figure 3. Summary super-plot for the effect of fructose-containing sugars on fasting blood glucose.

109x71mm (300 x 300 DPI)

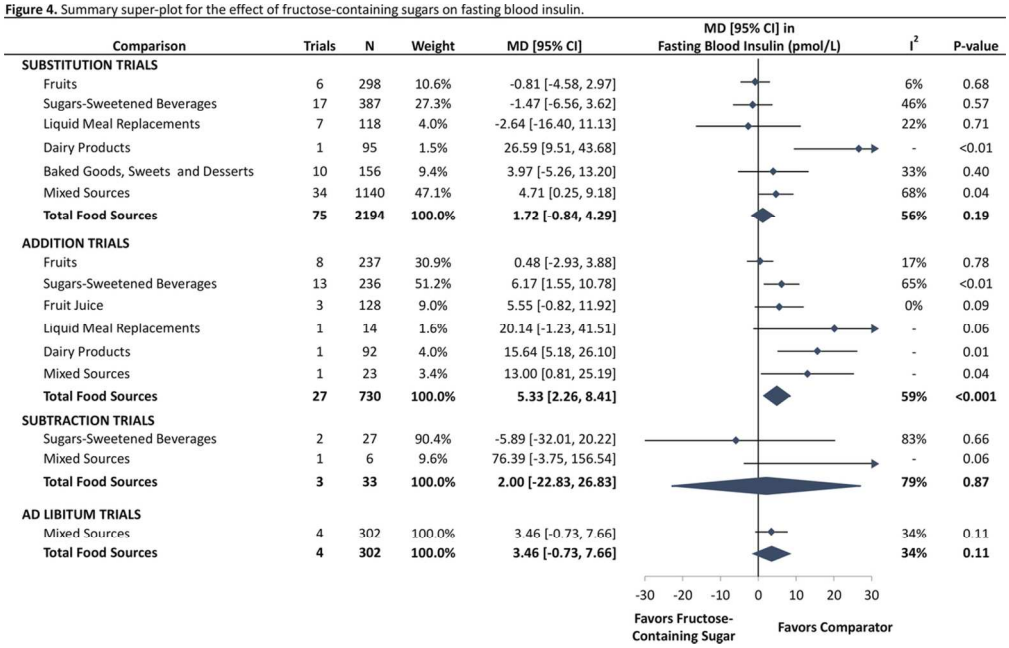


Figure 4. Summary super-plot for the effect of fructose-containing sugars on fasting blood insulin.

108x69mm (300 x 300 DPI)

Supplementary Tables and Figures

SUPPLEMENTARY TABLES

SUPPLEMENTARY FIGURES

Supplementary Figure 9. Forest plot for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood glucose.

Supplementary Figure 10. Forest plot for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on fasting blood glucose.

Supplementary Figure 11. Forest plot for subtraction trials investigating the effect of removing calories from the diet in the form of fructose-containing food sources on fasting blood glucose.

Supplementary Figure 12. Forest plot for ad libitum trials investigating the effect of freely replacing calories from fructose-containing food sources with other dietary sources on fasting blood glucose.

Supplementary Figure 13. Subgroup analyses for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood glucose.

Supplementary Figure 14. Subgroup analyses for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on fasting blood glucose.

Supplementary Figure 15. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood glucose.

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

Supplementary Figure 17. Forest plot for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood insulin.

Supplementary Figure 18. Forest plot for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on fasting blood insulin.

Supplementary Figure 19. Forest plot for subtraction trials investigating the effect of removing calories from the diet in the form of fructose-containing food sources on fasting blood insulin.

Supplementary Figure 20. Forest plot for ad libitum trials investigating the effect of freely replacing calories from fructose-containing food sources with other dietary sources on fasting blood insulin.

Supplementary Figure 21. Subgroup analyses for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on fasting blood insulin.

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

Supplementary Figure 23. Publication bias funnel plots for the effect of fructose-containing sugars on glycemic control in substitution and addition trials.

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

Database	Search Period		Search Terms
MEDLINE	Through November 3 2015	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**
EMBASE	Through November 3 2015	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	exp fructosamine blood level/ or fructosamine.mp.
		11	exp glucose blood level/
		12	exp glycosylated 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**
The Cochrane Library of Controlled Trials	Through November 3 2015	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	Hemoglobin A, Glycosylated/ or HbA1c.mp.
		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**

Supplementary Table 2. Trial characteristics

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
Substitution Trials (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 (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 (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				
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				
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)[g]	Fruit	Incorporate ≥ 2 fruit/d into diet				
Control	31 DM2 (13 M, 18 W)	57 (12)	91.2 kg (17)	32(6)		6.53 (1.1)							Mixed Comparator	Incorporate ≤ 2 fruit/d into diet				
Conceição et al. 2003		44.0 (4.5)		-	OP, Brazil	5.2 (0.9)	74.7 (57.3)	-	P	Supp	Yes				55:30:15	Negative	12 wk	I
Intervention	26 OW/OB, HCL (0 M, 26 W)	43.7 (4.8)	77.7 kg (10.8)			5.3 (1.0)	85.4 (62.5)					Apple, 22.8 (~5.6) ; pear, 19.2 (~3.8)	Fruit	300 g/d apple, 300g/d pear				
Control	9 OW/OB, HCL (0 M, 9 W)	45.0 (3.8)	78.9 kg (9.7)			5.1 (0.6)	43.8 (17.4)						Mixed Comparator	Oat Cookie				
Hegde et al. 2013		58.0 (9.2)	-	24.9 (3.9)	OP, India	8.3 (2.5)	-	8.0 (1.4)	P	DA	No				NR	Positive	3 mo	A
Intervention	60 DM2	58.5 (9.6)		24.4 (3.9)		7.9 (1.5)		8.0 (1.3)				~16.5 (~3.3)[g]	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				
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				
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)[f]	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)[f]	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				

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
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)[g]	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			
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. 2014 (JPAH)	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)				
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				

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
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				
Liquid Meal Replacements																		
Hendler et al. 1990	16 OB (0 M, 16 W)	42.7 (9.2)	107.9 kg (28.9)	40.5 (12.2)	IP, USA	5.2 (0.4)	85.5 (68.5)	-	P	Met	No					Negative	14 d	A
Intervention	9 OB (0 M, 9 W)	40.4 (9)	100.1 kg (18.3)	37.7 (9.9)		5.3 (0.5)	88.0 (87.9)					~150 (75)	Sucrose	Sucrose- and protein-containing liquid meal replacement	75:05:20			
Control	7 OB (0 M, 7 W)	45.6 (9.3)	118 kg (37.8)	44.2 (14.6)		5.1 (0.3)	82.2 (37.6)					~10 (5)	Fat	Fat- and protein-containing liquid meal replacement	05:75:20			
Johnson et al. 2015	51 OB, PCOS (0 M, 51 OB)	29.0 (5.9)	122.9 kg (17.1)	43.5 (5.7)	OP, Norway	5.3 (1.0)	135 (72)	5.6 (0.5)	P	Supp	Yes					Negative	8 wk	A
Intervention	24 OB, PCOS (0 M, 24 W)	29.0 (6.3)	121.5 kg (16.5)	43.0 (5.6)		5.3 (1.0)	142 (70)	5.6 (0.6)				85 (~32)	Fructose	Fructose-containing liquid meal replacement	44:18:38			
Control	27 OB, PCOS (0 m, 27 W)	29.0 (5.6)	124.1 kg (17.8)	44.0 (5.8)		5.3 (1.0)	129 (76)	5.6 (0.4)				17 (~6)	Starch	Whole grain crispbread	45:20:34			
Rizkalla et al. 1986 (EXP 1)	23 OB (7 M, 16 W)	22 (14.6) [h]	70.1 kg (11.6)	-	OP, France	4.5 (0.4)	82.3 (35.6)	6.5 (1.4)	P	Met	Yes				~25:25:50	Negative	2 wk	I
Intervention	8 OB		69.8 kg (15)			4.6 (0.5)	88.2 (39.3)	6.1 (1.4)				36 (~25)	Fructose	Liquid meal replacement with 36 g fructose				
Control	15 OB		70.2 kg (10.0)			4.5 (0.4)	79.1 (34.4)	6.8 (1.4)					Glucose, galactose	Liquid meal replacement with 36 g glucose or galactose				
Rizkalla et al. 1986 (EXP 2)	18 OB	22 (14.6) [h]	70.6 kg (10.6)	-	OP, France	4.2 (0.4)	88.0 (48.9)	6.8 (0.7)	P	Met	Yes				~25:25:50	Negative	2 wk	I
Intervention	6 OB		70.4 kg (12.9)			4.2 (0.4)	88.2 (17.0)	6.9 (0.7)				36 (~25)	Fructose	Liquid meal replacement with 36 g fructose				
Control	12 OB		70.7 kg (9.8)			4.2 (0.4)	87.9 (59.7)	6.7 (0.6)					Glucose, galactose	Liquid meal replacement with 36 g glucose or galactose				

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
Turner et al. 1979 (HC)	4 MetS (4 M, 0 W)	46.8 (8.0)	82.6 kg (9.9)	-	IP, USA	5.0 (0.4)	-	-	C	Met	No	~122 (17)			85:00:15	Neutral	~2 wk	A, I
Intervention													Fructose	Liquid meal replacement (20% CHO from fructose)				
Control													D-Maltose	Liquid meal replacement (all CHO from D-maltose)				
Turner et al, 1979 (LC DM)	2 DM (2 M, 0 W)	41 (1.4)	84 kg (19.8)	-	IP, USA	5.9 (0.2)	-	-	C	Met	No	~39.5 (9)			45:40:15	Neutral	~2 wk	A, I
													Fructose	Liquid meal replacement (20% CHO from fructose)				
													D-Maltose	Liquid meal replacement (all CHO from D-maltose)				
Turner et al, 1979 (LC Non-DM)	4 MetS (4 M, 0 W)	48 (8.8)	78.8 kg (5.6)	-	IP, USA	4.8 (0.2)	-	-	C	Met	No	~39.5 (9)			45:40:15	Neutral	~2 wk	A, I
Intervention													Fructose	Liquid meal replacement (20% CHO from fructose)				
Control													D-Maltose	Liquid meal replacement (all CHO from D-maltose)				
Dairy products																		
Lowndes et al. 2015	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 Glucose, lactose	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 (0.4)	54.9 (44.6)							Glucose sweetened milk, unsweetened milk	~52:30:19			
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			
da 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)[i]	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)[i]	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[j]	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				

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
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				
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 MD2 (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				
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				
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				
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				
Brunner et al. 2012	101 DM2 (65 M, 35 W)	60.6 (8.1)	-		OP, Germany	8.0 (1.5)	-	7.3 (0.6)	P	Supp	Yes	50 (~10)				Neutral	12 wk	I
Intervention	49 DM2 (32 M, 17 W)	60.5 (8.7)		32.3 (4.5)		8.0 (1.5)		7.4 (0.7)					Sucrose	Biscuits, toffees, milk drinks, soft drinks	~45:37:18			
Control	52 DM2 (34 M, 18 W)	60.6 (7.5)		29.9 (4.2)		7.9 (1.6)		7.2 (0.6)					Isomaltulose	Biscuits, toffees, milk drinks, soft drinks	~43:38:18			
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				

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
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				
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			
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	
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				
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			
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)[i]	Sucrose	Hot beverages, cereals, gelatin desserts, jelly spreads, beverages	50:35:15, 65:21:14[k]			
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				
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. 1983	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				
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			
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			

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
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				
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)[l]	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				
Pinheiro 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)[m]	21.7 (20.2-25.0)[m]								110 (~22)	Sucrose	High sucrose diet	59:28:13			
Control	5 H (0 M, 5 W)		55.8 (48.0-65.6)[m]	21.3 (19.4-24.8)[m]								10 (~2)	Fat	High fat diet	42:45:13			
Pinheiro 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			
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)		7.5 (1.7)		5.6 (0.8)					Starch	Traditional diabetic diet	55:28:18			

Supplementary Table 2. Trial characteristics (Continued)

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

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
Volp et al. 2008 (G1)	6 H (0 M, 6 W)	21 (19-24) [m]	-	21.4 (20.2-22.8) [m]	OP, Brazil	5.5 (5.2-5.8)	89.6 (59.7-100.0)	-	C	DA	Yes					Neutral	14 d	A, I
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			
Vrolix et al. 2010	15 MetS (9 M, 6 W)	53 (11.1)	90.7 kg (6.4)	30.8 (2.8)	OP, Netherlands	5.9 (0.6)	62.1 (28.4)	-	C	Supp	Yes					Neutral	11 wk	A, I
Intervention												~47.3 (~9)	Sucrose	High sucrose bread, cake, cookie and fruit drink	51:30:16			
Control													Starch, isomaltulose	High flour bread, cake, cookie, and isomaltulose containing fruit drink	52:30:15			
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 Trials (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) [g]	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) [g]	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) [g]	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) [g]	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	
[x] **Ellis et al. 2010**	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) [g]	Fruit	Freeze dried strawberry beverage equivalent to ~100 g/d fresh strawberries			6 wk	
Control													Diet alone	No beverage			7 d	
Lehtonen et al. 2011	80 OW/OB (0 M, 80 W)	44.2 (6.2)	81.6 kg (8.5)	29.6 (2.1)	OP, Finland	5.3 (0.4)	53.5 (24.3)	-	C	Supp	No				NR	Neutral	~34 d	A, I
Intervention												~3.6 (~0.7) [f]	Fruit	100 g/d of bilberries or sea buckthorn berries				
Control													Diet alone	Berry extract, berry oil				
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) [g]	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					Neutral	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) [g]	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	Neutral	4 wk	A
Intervention												~51 (~10) [n]	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				

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
Silver et al. 2011		38.1 (8.1)	99.7 kg (13.5)	36.0 (3.3)	OP, USA	-	-	-	P	Supp	Yes				50:30:20	Negative	12 wk	A
Intervention	29 OB (11 M, 18 W)	37.6 (7.4)	99.8 kg (13.8)	36.3 (3.1)								~20.3 (~3.2) [g]	Fruit	1/2 Grapefruit before breakfast, lunch and dinner				
Control	28 OB (7 M, 21 W)	38.7 (8.8)	99.5 kg (13.5)	35.7 (3.5)									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				
Ellis et al. 2010	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			
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	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	25 OW/ OB (8 M, 17 W)	39 (8)	97.1 kg (18.1)	32.5 (4.2)		5.4 (0.6)	79.8 (45.8)						Sweetener, Water	Diet beverage, water				
Majid et al. 2013		20.1 (0.8)	-	-	IP, Pakistan	5.0 (0.3)	-	-	P	Met	Yes				NR	Positive	4 wk	A
Intervention	32 H (32 M, 0 W)	20.1 (0.1)				5.0 (0.1)						70 (~11)	Honey	Honey dissolved in tap water				
Control	31 H (31 M, 0 W)	20.0 (0.2)				4.9 (0.1)							Diet Alone	No beverage				
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				
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) [i]	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			
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	Neutral	2 wk	A
Intervention													Fructose	Fructose SSB				
Control													Diet alone	No Beverage				

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
Stanhope et al. (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	Neutral	2 wk	A
Intervention													HFCS	HFCS SSB				
Control													Diet alone	No Beverage				
Fruit Juice																		
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			
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	Neutral	4 wk	A
Intervention												~61 (~12.2) [n]	fruit	Polyphenolic and pectin restricted diet with clear or cloudy apple juice (~500 mL/d)				
Control													Diet alone	Polyphenolic and pectin restricted diet				
Silver et al. 2011		39.3 (8.5)	97.7 kg (12.5)	35.4 (3.3)	OP, USA	-	-	-	P	Supp	Yes				50:30:20	Negative	12 wk	A
Intervention	28 OB (3 M, 25 W)	39.8 (8.4)	95.9 kg (11.5)	35.2 (3.1)								~17.5 (~2.5) [g]	fruit	Grapefruit Juice				
Control	28 OB (7 M, 21 W)	38.7 (8.8)	99.5 kg (13.5)	35.7 (3.5)									Water	Water				
Liquid Meal Replacements																		
Rizkalla et al. 1986 (EXP 2) (XX)	14 OB	22 (14.6)		-	OP, France	4.0 (0.6)	91.3 (50.8)	6.7 (0.4)	P	Met	Yes			Fructose		Negative	14 d	I
Intervention	7 OB		73.3 kg (7.7)			3.8 (0.4)	68.1 (33.1)	6.6 (0.3)				100 (~49)	Fructose	Fructose-containig liquid meal replacement	49:18:33			
Control	7 OB		75.8 kg (13.7)			4.2 (0.7)	114.6 (57.0)	6.7 (0.5)					Diet alone	Fructose-free liquid meal replacement	0:35:65			
Dairy products																		
Lowndes et al. 2015	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 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)	
Mixed sources																		
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				
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				
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			

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
Subtraction Trials (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			
Campos et al. 2015 (G2)	15 OW/OB (11 M, 4 W)	29.1 (6.9)	-	-	OP, Switzerland	5.5 (0.6)	133.7 (54.5)	-	P	Supp	Yes					Negative	12 wk	A
Intervention	7 OW/OB					5.2 (0.5)	127.1 (60.6)						Sweetener	Replace SSB with ASB	~46:38:16			
Control	8 OW/OB					5.7 (0.5)	140.3 (51.4)					86.8 (~15)	Sucrose, HFCS	Habitual SSB consumption (≥ 2 SSB/d)	~51:34:15			
Hernandez-Cordero et al. 2014	240 OW/OB (0 M, 240 W)				OP, Mexico	5.0 (0.2)	-	5.8 (0.1)	P	Supp	Yes				NR	Negative	9 mo	I
Intervention	120 OW/OB (0 M, 120 W)	33.5 (6.7)	76.9 kg (3.3)	31.0 (1.1)		5.0 (0.2)		5.8 (0.1)					Water	Substitute water for SSBs, general recommendations for healthy eating				
Control	120 OW/OB (0 M, 120 W)	33.4 (6.7)	76.0 kg (3.3)	31.0 (1.1)		5.0 (0.2)		5.8 (0.1)				~73 (19.3)	Sucrose, HFCS	Habitual SSB consumption (≥250 kcal/d), general recommendations for healthy eating				
Tate et al. 2012					OP, USA	5.1 (0.9)			P	Supp, DA	Yes				NR	Negative	6 mo	I
Intervention	213 OW/ OB (35 M, 178 W)	42.2 (10.9)	99.6 kg (18.5)	35.9 (5.7)		5.1 (1.0)	-	-				~33.7 (~8.7)	Sweetener, water	Diet beverage, Water				
Control	105 OW/OB (15 M, 90 W)	41.6 (10.4)	102.6 kg (18.3)	36.8 (6.2)		4.9 (0.6)	-	-				~55.7 (~13.8)	Sucrose, HFCS	Habitual SSB consumption (≥280 kcal/d)				
Mixed sources																		
Friedman et al. 1970	6 HTG (6 M, 0 W)	45 (4.2)	103.2 kg (16.7)	-	OP, USA	-	-	-	C	DA	No					Negative		A
Intervention												~24 (~6)[n]	No sucrose	Avoid sucrose containing foods from habitual diet	25:45:30		60 d	
Control												~58 (~10)[n]	Sucrose	Habitual diet	29:39:32		7 d	
Ad Libitum Trials (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[o]				-	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				

Supplementary Table 2. Trial characteristics (Continued)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m^2 (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control[a]	Randomization	Fructose-Containing Sugar Dosage, g/d (% E)[b]	Intervention or comparator form	Food source	Diet[c]	Energy Balance[d]	Follow-Up	Funding Sources[e]
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) [p]	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) [q]	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			
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) [q]	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) [q]	Starch, Mixed comparator	Ad libitum low-fat high CCHO diet, Ad libitum control diet	Starch, ~52:28:18; Mixed, ~46:37:18			

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; 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 sugar dose estimated based on data from Finland National Food Composition Database

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

[h] Represents average of entire study cohort, including other study arms not from comparison of interest

[i] Fructose-containing sugar was given at 2 different doses.

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

[k] Dietary breakdown of the high and intermediate sucrose diets respectively

[l] Represents estimated sugar intake excluding underreporters

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

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

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

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

[q] Fructose-containing sugar dose estimated from simple carbohydrate intake

Supplementary Table 3. Post-hoc piecewise linear meta-regression analyses for the effect of fructose dose (%E) on glycemic control in substitution and addition trials.

A. HbA1c (%) in substitution trials

Dose threshold, Sugars (% Energy)	Dose ranges, Sugars (% Energy)	β (95% CIs)	Residual I^2 (%)	P-value
10	≤10	-0.05 (-0.17, 0.06)	81.85	0.32
	>10	0.02 (-0.03, 0.08)		
20	≤20	-0.01 (-0.07, 0.05)	81.87	0.69
	>20	0.04 (-0.14, 0.21)		
30	≤30	0.00 (-0.04, 0.04)	82.04	0.92
	>30	0.09 (-1.65, 1.82)		

B. Fasting blood glucose (mmol/L) in substitution trials

Dose threshold, Sugars (% Energy)	Dose ranges, Sugars (% Energy)	β (95% CIs)	Residual I^2 (%)	P-value
10	≤10	0.01 (-0.02, 0.04)	63.75	0.58
	>10	0.01 (0.00, 0.01)		
20	≤20	0.01 (-0.00, 0.02)	64.00	0.79
	>20	0.01 (-0.00. 0.01)		
30	≤30	0.01 (-0.00, 0.01)	63.99	0.76
	>30	0.01 (-0.00, 0.02)		
40	≤40	0.00 (-0.00, 0.01)	63.91	0.20
	>40	0.01 (0.00, 0.03)		
50	≤50	0.00 (-0.00, 0.01)	62.23	0.01
	>50	0.03 (0.01, 0.05)		
60	≤60	0.00 (0.00, 0.01)	60.93	<0.01
	>60	0.05 (0.02, 0.09)		
70	≤70	0.00 (0.00, 0.01)	60.93	<0.01
	>70	0.16 (0.06, 0.26)		

C. Fasting blood glucose (mmol/L) in addition trials

Dose threshold, Sugars (% Energy)	Dose ranges, Sugars (% Energy)	β (95% CIs)	Residual I^2 (%)	P-value
10	≤10	0.00 (-0.03, 0.03)	71.46	0.93
	>10	0.00 (-0.01, 0.01)		
20	≤20	0.01 (-0.01, 0.02)	71.00	0.64
	>20	0.00 (-0.01, 0.01)		
30	≤30	0.00 (-0.01, 0.01)	71.18	0.92
	>30	0.00 (-0.02, 0.03)		
40	≤40	0.00 (-0.01, 0.01)	71.09	0.90
	>40	0.01 (-0.05, 0.06)		

Supplementary Table 3. Post-hoc piecewise linear meta-regression analyses for the effect of fructose dose (%E) on glycemic control in substitution and addition trials (Continued).

D. Fasting blood insulin (mmol/L) in substitution trials

Dose threshold, Sugars (% Energy)	Dose ranges, Sugars (% Energy)	β (95% CIs)	Residual I^2 (%)	P-value
10	≤10	-0.04 (-1.98, 1.90)	54.87	0.75
	>10	0.29 (0.01, 0.56)		
20	≤20	-0.09 (-0.78, 0.60)	53.16	0.27
	>20	0.39 (0.06, 0.72)		
30	≤30	0.12 (-0.35, 0.60)	53.45	0.47
	>30	0.39 (-0.04, 0.83)		
40	≤40	0.27 (-0.12, 0.66)	54.62	0.99
	>40	0.27 (-0.28, 0.82)		
50	≤50	0.36 (0.00, 0.72)	55.16	0.49
	>50	0.03 (-0.69, 0.76)		
60	≤60	0.38 (0.04, 0.72)	55.26	0.34
	>60	-0.20 (-1.20, 0.81)		
70	≤70	0.38 (0.06, 0.70)	55.29	0.29
	>70	-0.54 (-2.05, 0.98)		
80	≤80	0.37 (0.06, 0.67)	55.27	0.27
	>80	-1.15 (-3.68, 1.39)		
90	≤90	0.37 (0.06, 0.67)	55.27	0.27
	>90	-4.18 (-12.09, 3.73)		

E. Fasting blood insulin (mmol/L) in addition trials

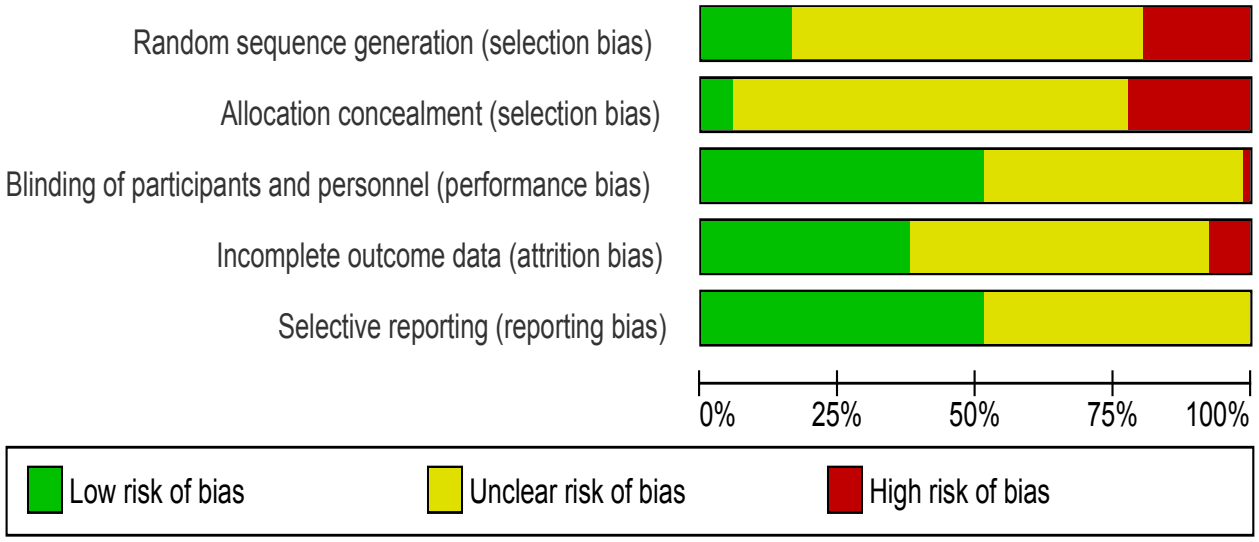
Dose threshold, Sugars (% Energy)	Dose ranges, Sugars (% Energy)	β (95% CIs)	Residual I^2 (%)	P-value
10	≤10	0.31 (-1.00, 1.62)	52.99	0.90
	>10	0.20 (-0.24, 0.64)		
20	≤20	0.32 (-0.23, 0.87)	53.47	0.67
	>20	0.09 (-0.59, 0.78)		
30	≤30	0.17 (-0.19, 0.54)	52.45	0.62
	>30	0.54 (-0.80, 1.88)		
40	≤40	0.19 (-0.12, 0.50)	52.05	0.53
	>40	1.18 (-1.93, 4.28)		

β is the slope derived from the piecewise linear meta-regression analyses and represents the treatment effect on glycemic control for doses above and below each dose-threshold representing sugars (% Energy); The residual I^2 value indicates heterogeneity unexplained by each dose-threshold.

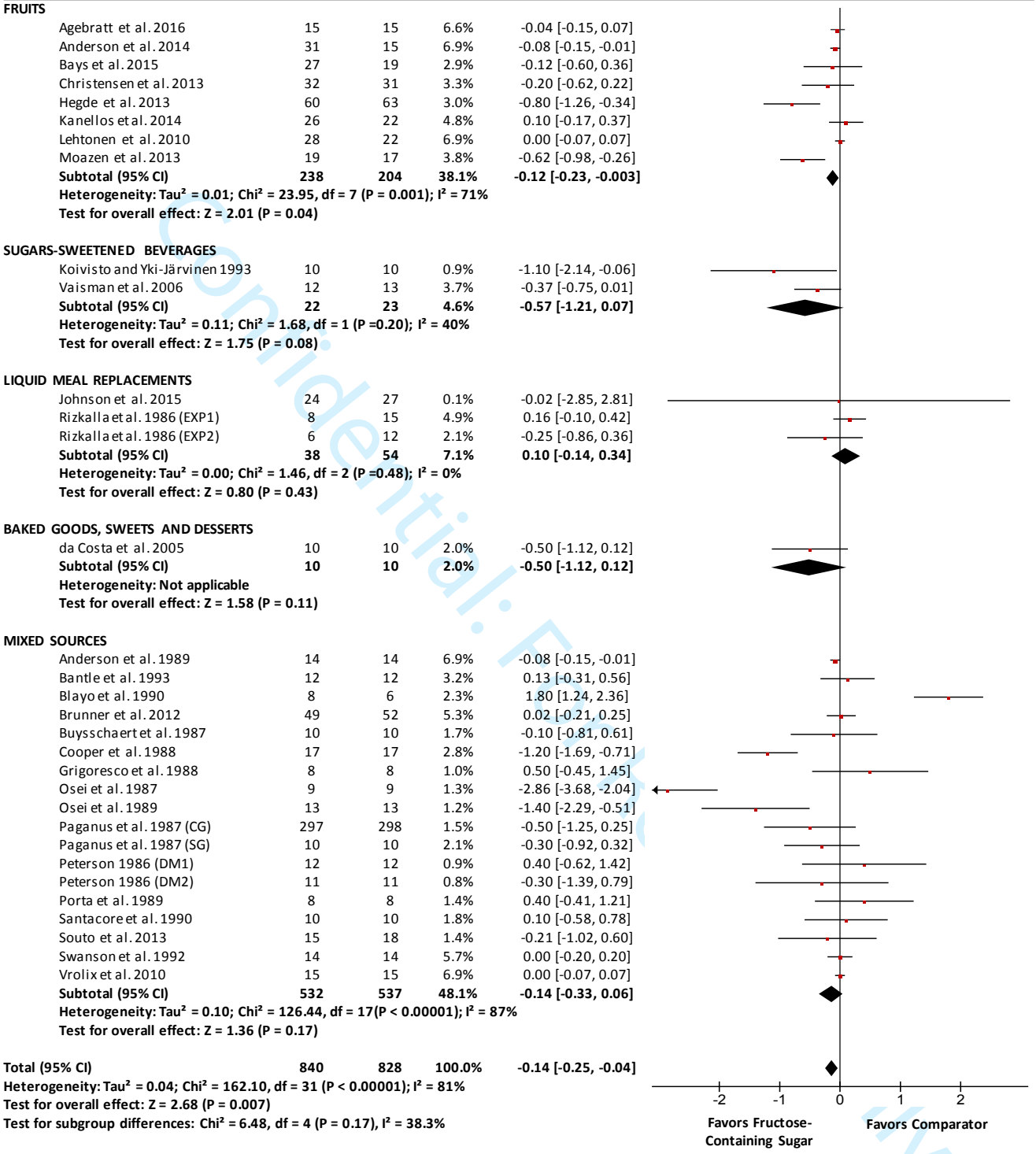
Supplementary Table 4. Sensitivity analyses for the effect of fructose-containing sugars on glycemic control.

Removal of	MD	95% CI	P-value	I^2
Fasting Blood Glucose				
Addition Trials				
Basu et al. 2010 (SB)	0.06	[0.00, 0.13]	0.06	73%
Hollis et al. 2009 (SSB)	0.06	[0.00, 0.13]	0.05	73%
Le et al. 2006	0.06	[0.00, 0.13]	0.06	72%
Le et al. 2009 (ODM2)	0.06	[-0.01, 0.12]	0.07	71%
Maersk et al. 2012	0.06	[0.00, 0.13]	0.06	73%
Mitsou et al. 2011	0.06	[-0.01, 0.12]	0.07	71%
Silbernagel et al. 2011	0.06	[0.00, 0.13]	0.06	72%
Stanhope et al. 2011 (AJCN)	0.06	[0.00, 0.12]	0.06	67%
Hollis et al. 2009 (Fruit Juice)	0.06	[0.00, 0.13]	0.06	73%
Silver et al. 2011 (Fruit Juice)	0.07	[0.00, 0.13]	0.05	73%
Rizkalla et al. 1986 (EXP 2)	0.06	[0.00, 0.12]	0.06	71%
Lowndes et al. 2015	0.07	[0.00, 0.13]	0.05	73%
Raben et al. 2011	0.07	[0.00, 0.13]	0.05	73%
Subtraction Trials				
Campos et al. 2015 (G2)	0.02	[-0.07, 0.11]	0.63	0%
Fasting Blood Insulin				
Subtraction Trials				
Campos et al. 2015 (G2)	39.54	[4.06, 75.02]	0.03	1%
Ad Libitum Trials				
Markey et al. 2015	9.51	[1.59. 17.42]	0.02	0 %

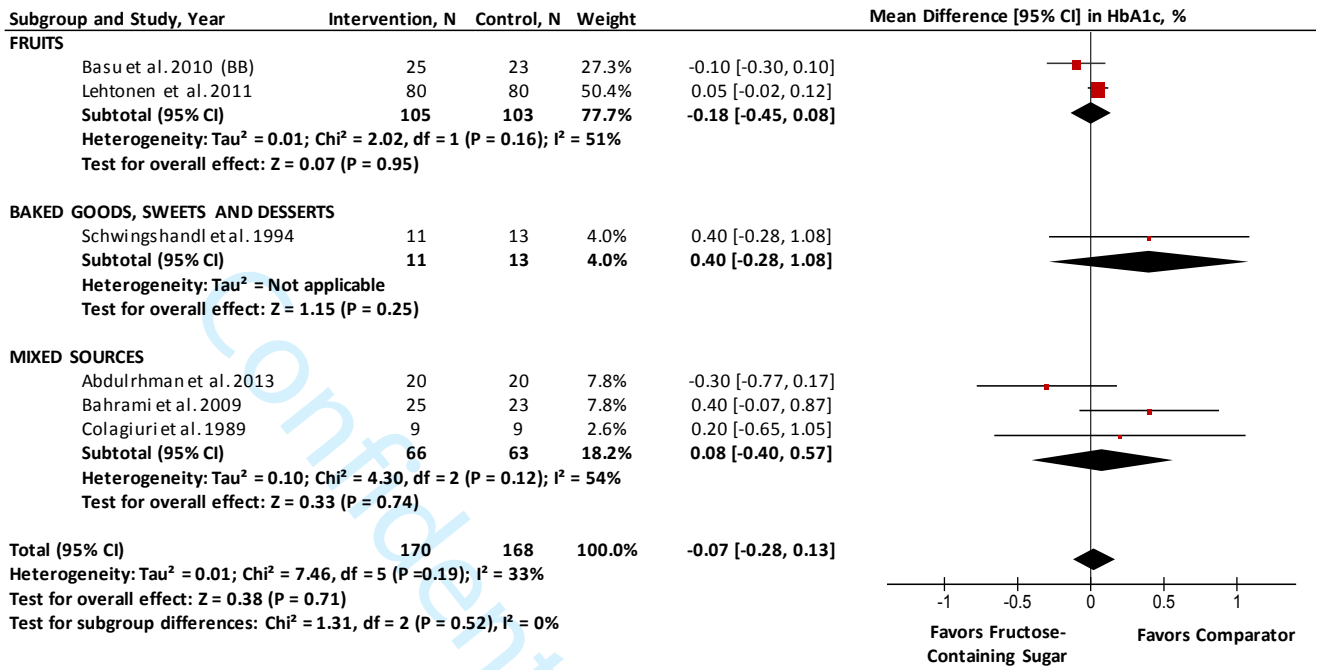
SB= strawberry; SSB= sugars-sweetened beverage; ODM2= offspring of type 2 diabetes patients; AJCN= American Journal of Clinical Nutrition; EXP 2= experiment 2. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested 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 moderate heterogeneity, ≥ 50 % represent substantial heterogeneity and ≥ 75%, considerable heterogeneity. The residual I^2 value indicates the interstudy heterogeneity unexplained by the removal of each trial.



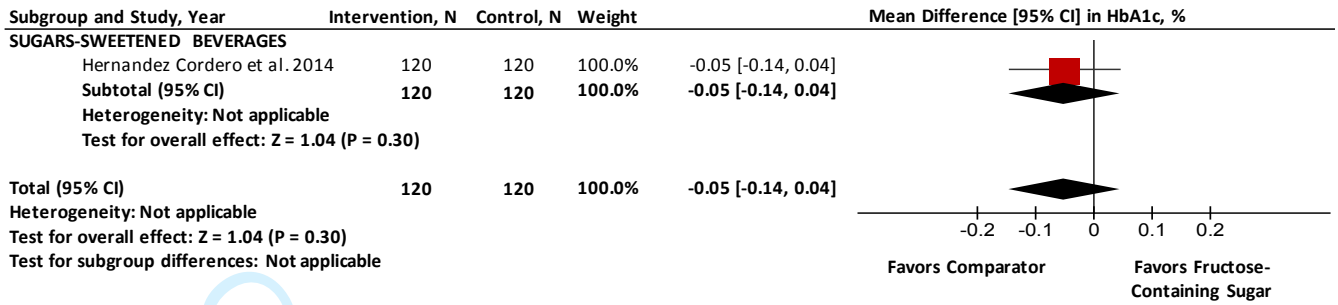
Supplementary Figure 1. Risk of bias summary for the effect of fructose-containing food sources on glycemic control. Colored bars represent the proportion of studies assessed as low (green), unclear (yellow) or high (red) risk of bias for the 5 domains of bias above according to criteria set by the Cochrane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



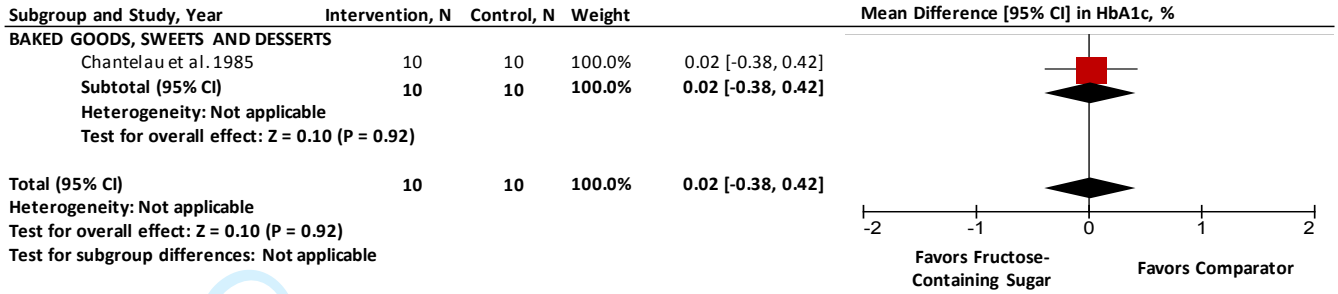
Supplementary Figure 2. Forest plot for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on HbA1c. CG= control group; SG= study group; df= degrees of freedom; DM1= type 1 diabetes mellitus; DM2= type 2 diabetes mellitus; 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 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



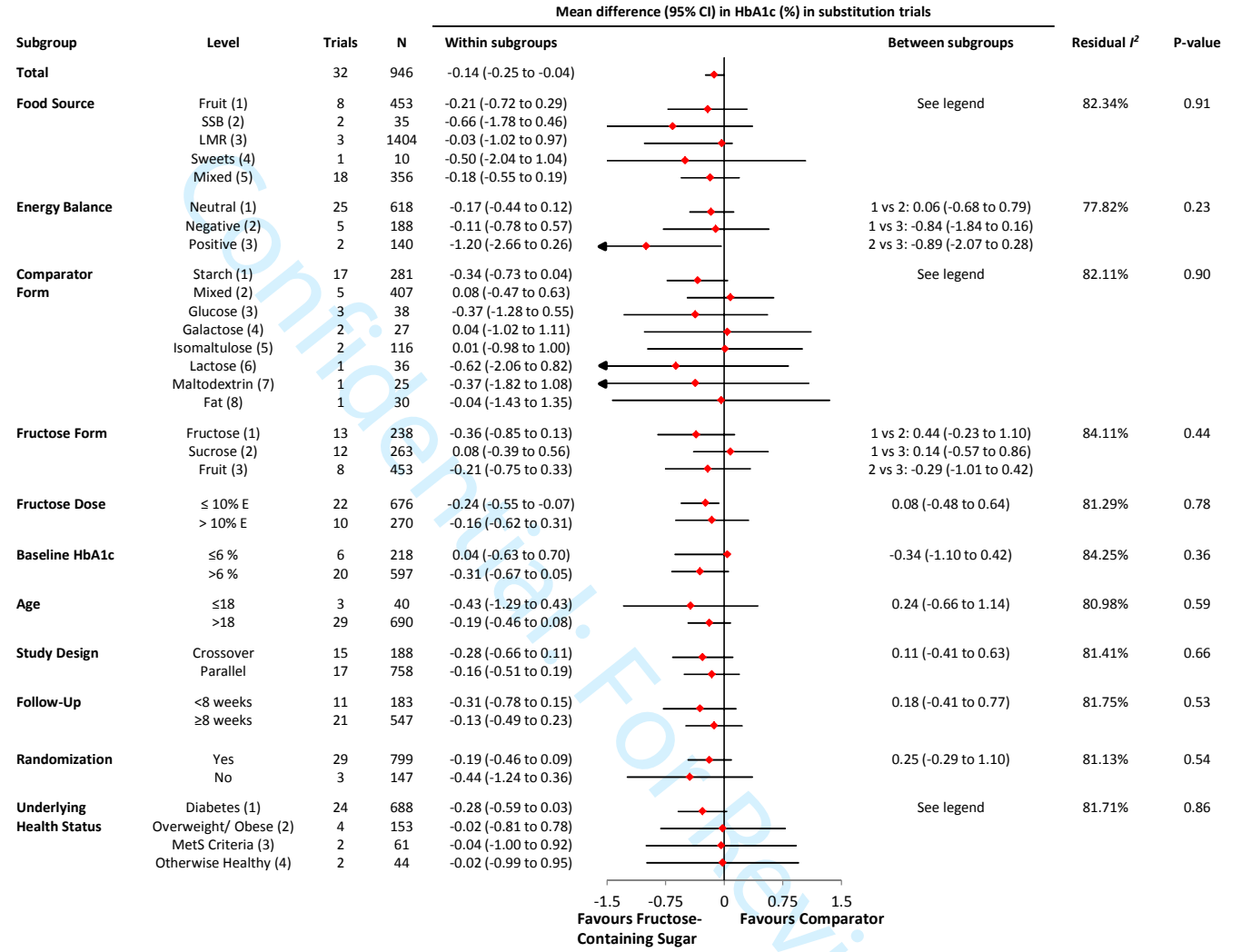
Supplementary Figure 3. Forest plot for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on HbA1c. BB= blueberries; HbA1c= hemoglobin A1c; N= number of participants. Pooled effect estimates for each subgroup and overall effect 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 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



Supplementary Figure 4. Forest plot for subtraction trials investigating the effect of removing calories from the diet in the form of fructose-containing food sources on HbA1c. 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 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.

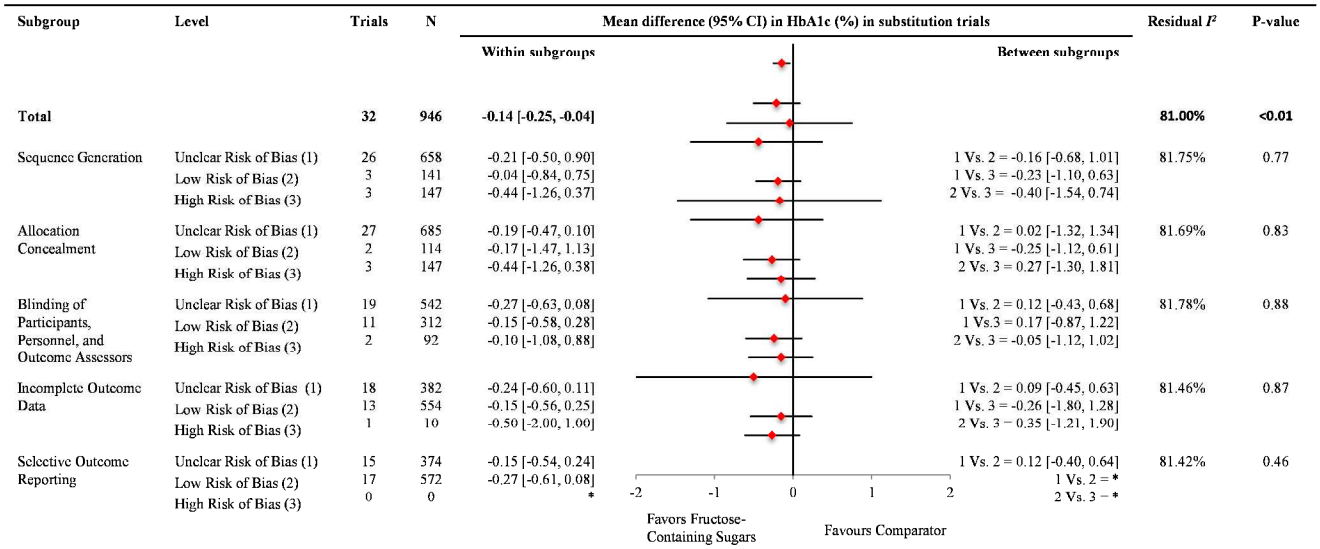


Supplementary Figure 5. Forest plot for ad libitum trials investigating the effect of freely replacing calories from fructose-containing food sources with other dietary sources on HbA1c. HbA1c= hemoglobin A1c; N= number of participants. Pooled effect estimates for each subgroup and overall effect are 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 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



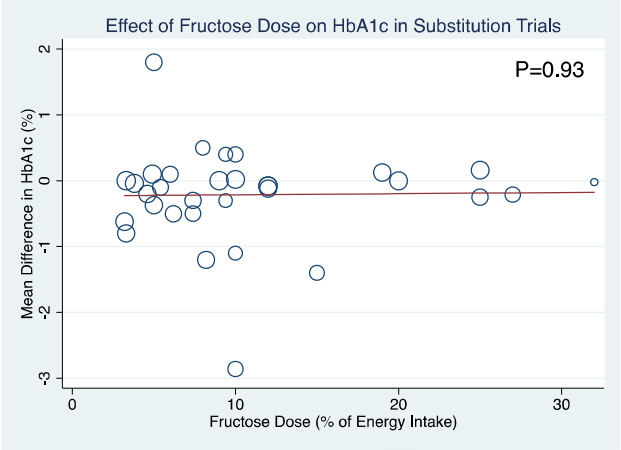
Subgroup	Level	Trials	N	Within subgroups	Between subgroups	Residual I^2	P-value
Total		32	946	-0.14 (-0.25 to -0.04)			
Food Source	Fruit (1)	8	453	-0.21 (-0.72 to 0.29)	See legend	82.34%	0.91
	SSB (2)	2	35	-0.66 (-1.78 to 0.46)			
	LMR (3)	3	1404	-0.03 (-1.02 to 0.97)			
	Sweets (4)	1	10	-0.50 (-2.04 to 1.04)			
	Mixed (5)	18	356	-0.18 (-0.55 to 0.19)			
Energy Balance	Neutral (1)	25	618	-0.17 (-0.44 to 0.12)	1 vs 2: 0.06 (-0.68 to 0.79)	77.82%	0.23
	Negative (2)	5	188	-0.11 (-0.78 to 0.57)	1 vs 3: -0.84 (-1.84 to 0.16)		
	Positive (3)	2	140	-1.20 (-2.66 to 0.26)	2 vs 3: -0.89 (-2.07 to 0.28)		
Comparator Form	Starch (1)	17	281	-0.34 (-0.73 to 0.04)	See legend	82.11%	0.90
	Mixed (2)	5	407	0.08 (-0.47 to 0.63)			
	Glucose (3)	3	38	-0.37 (-1.28 to 0.55)			
	Galactose (4)	2	27	0.04 (-1.02 to 1.11)			
	Isomaltulose (5)	2	116	0.01 (-0.98 to 1.00)			
	Lactose (6)	1	36	-0.62 (-2.06 to 0.82)			
	Maltodextrin (7)	1	25	-0.37 (-1.82 to 1.08)			
	Fat (8)	1	30	-0.04 (-1.43 to 1.35)			
Fructose Form	Fructose (1)	13	238	-0.36 (-0.85 to 0.13)	1 vs 2: 0.44 (-0.23 to 1.10)	84.11%	0.44
	Sucrose (2)	12	263	0.08 (-0.39 to 0.56)	1 vs 3: 0.14 (-0.57 to 0.86)		
	Fruit (3)	8	453	-0.21 (-0.75 to 0.33)	2 vs 3: -0.29 (-1.01 to 0.42)		
Fructose Dose	≤ 10% E	22	676	-0.24 (-0.55 to -0.07)	0.08 (-0.48 to 0.64)	81.29%	0.78
	> 10% E	10	270	-0.16 (-0.62 to 0.31)			
Baseline HbA1c	≤6 %	6	218	0.04 (-0.63 to 0.70)	-0.34 (-1.10 to 0.42)	84.25%	0.36
	>6 %	20	597	-0.31 (-0.67 to 0.05)			
Age	≤18	3	40	-0.43 (-1.29 to 0.43)	0.24 (-0.66 to 1.14)	80.98%	0.59
	>18	29	690	-0.19 (-0.46 to 0.08)			
Study Design	Crossover	15	188	-0.28 (-0.66 to 0.11)	0.11 (-0.41 to 0.63)	81.41%	0.66
	Parallel	17	758	-0.16 (-0.51 to 0.19)			
Follow-Up	<8 weeks	11	183	-0.31 (-0.78 to 0.15)	0.18 (-0.41 to 0.77)	81.75%	0.53
	≥8 weeks	21	547	-0.13 (-0.49 to 0.23)			
Randomization	Yes	29	799	-0.19 (-0.46 to 0.09)	0.25 (-0.29 to 1.10)	81.13%	0.54
	No	3	147	-0.44 (-1.24 to 0.36)			
Underlying Health Status	Diabetes (1)	24	688	-0.28 (-0.59 to 0.03)	See legend	81.71%	0.86
	Overweight/ Obese (2)	4	153	-0.02 (-0.81 to 0.78)			
	MetS Criteria (3)	2	61	-0.04 (-1.00 to 0.92)			
	Otherwise Healthy (4)	2	44	-0.02 (-0.99 to 0.95)			

Supplementary Figure 6. Subgroup analyses for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources 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 form are as follows: 1 vs 2: 0.42 (-0.25to 1.09); 1 vs 3: -0.02 (-1.02 to 0.97); 1 vs 4: 0.39 (-0.75 to 1.52); 1 vs 5: 0.35 (-0.71 to 1.41); 1 vs 6: -0.28 (-1.77 to 1.22); 1 vs 7: -0.03 (-1.52 to 1.47) 1 vs 8: 0.30 (-1.15 to 1.75); 2 vs 3: 0.45 (-0.62 to 1.51); 2 vs 4: 0.04 (-1.16 to 1.23); 2 vs 5: 0.07 (-1.06 to 1.20); 2 vs 6: 0.70 (-0.84 to 2.25); 2 vs 7: 0.45 (-1.10 to 2.00); 2 vs 8: 0.12 (-1.38 to 1.62); 3 vs 4: -0.41 (-1.81 to 0.99); 3 vs 5: -0.38 (-1.73 to 0.97); 3 vs 6: -0.25 (-1.96 to 1.46); 3 vs 7: 0.004 (-1.71 to 1.72); 3 vs 8: 0.41 (-1.38 to 2.21); 4 vs 5: 0.03 (-1.42 to 1.49); 4 vs 6: -0.66 (-2.46 to 1.13); 4 vs 7: 0.41 (-1.38 to 2.21); 4 vs 8: 0.08 (-1.67 to 1.84); 5 vs 6: -0.63 (-2.38 to 1.12); 5 vs 7: 0.38 (-1.38 to 2.14); 5 vs 8: 0.05 (-1.66 to 1.76); 6 vs 7: -0.25 (-2.30 to 1.80); 6 vs 8: -0.58 (-2.59 to 1.43); 7 vs 8: -0.33 (-2.34 to 1.68) Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: 0.27 (-0.59 to 1.12); 1 vs 3: 0.24 (-0.77 to 1.26); 1 vs 4: 0.26 (-0.76 to 1.28); 2 vs 3: -0.02 (-1.27 to 1.22); 2 vs 4: 0.002 (-1.26 to 1.25); 3 vs 4: -0.02 (-1.39 to 1.35).

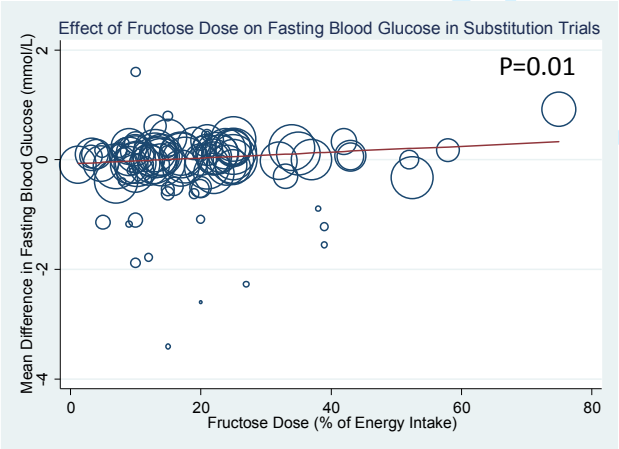


Supplementary Figure 7. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on HbA1c. Point estimates for each subgroup level are the pooled effect estimates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

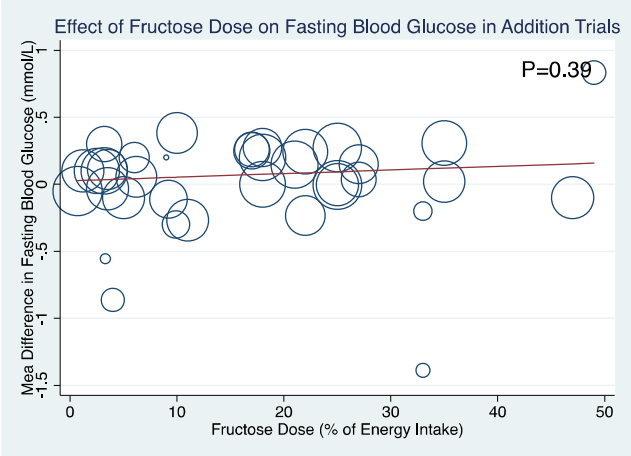
A. HbA1c in substitution trials



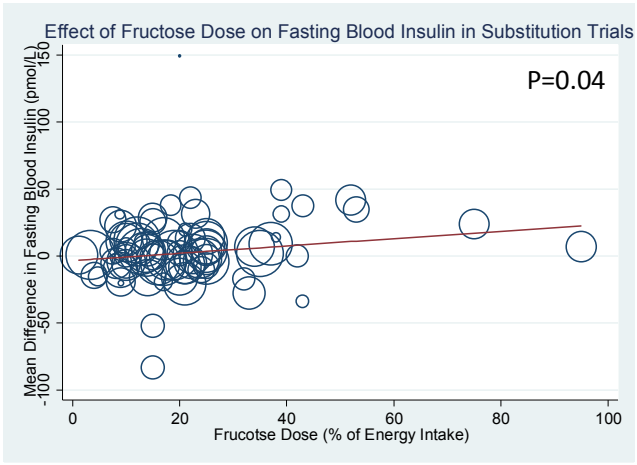
B. Fasting blood glucose in substitution trials



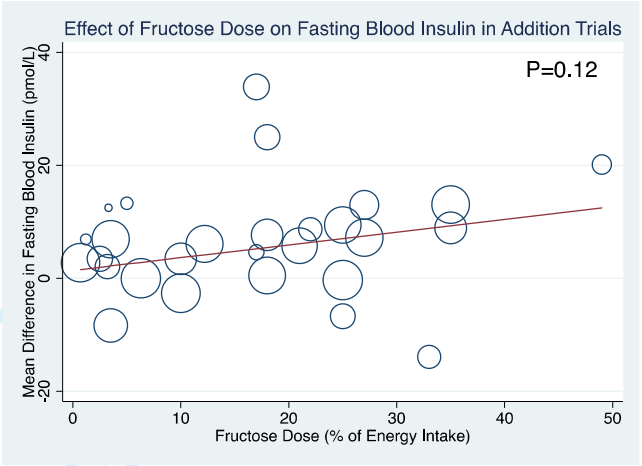
C. Fasting blood glucose in addition trials



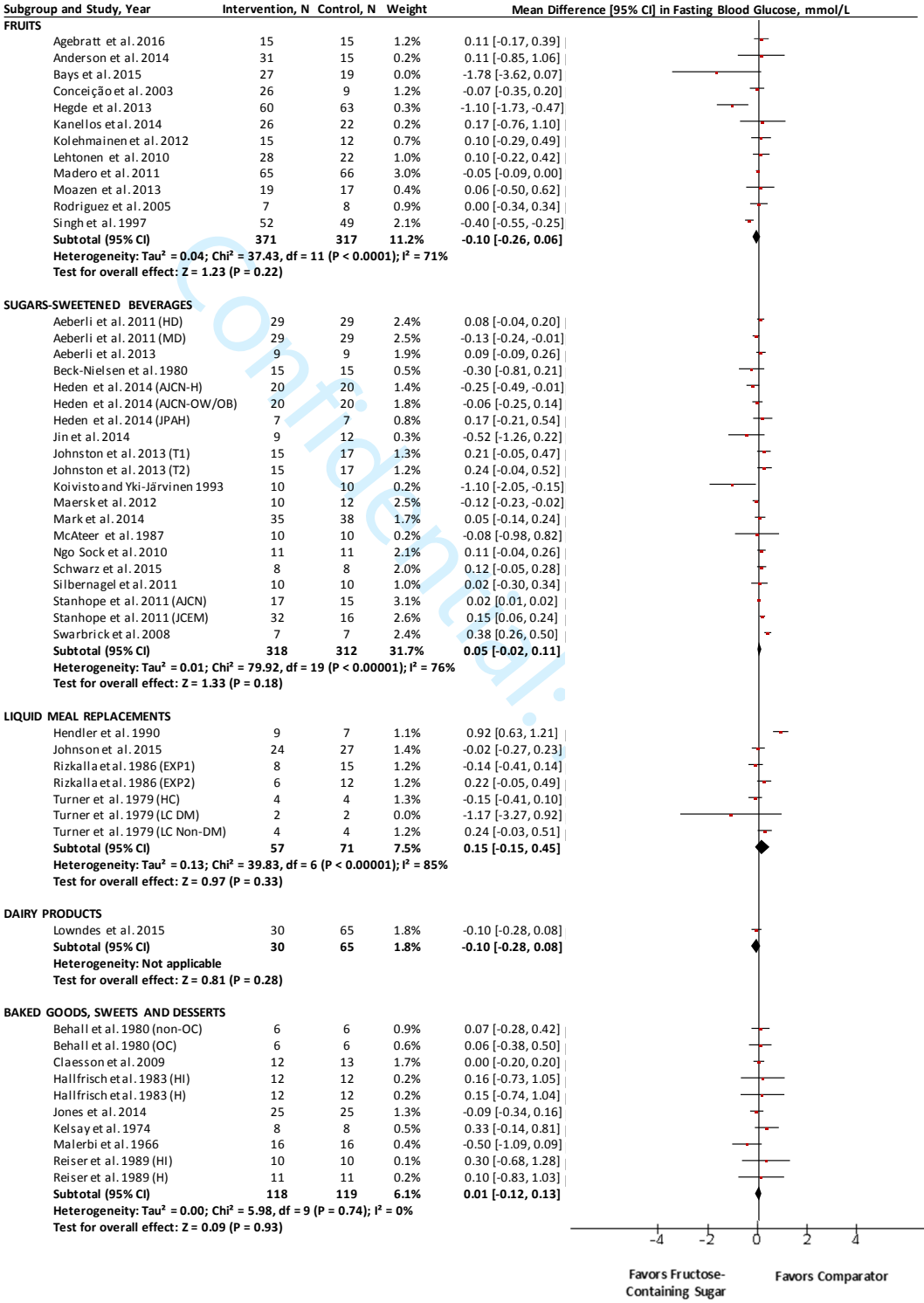
D. Fasting blood insulin in substitution trials



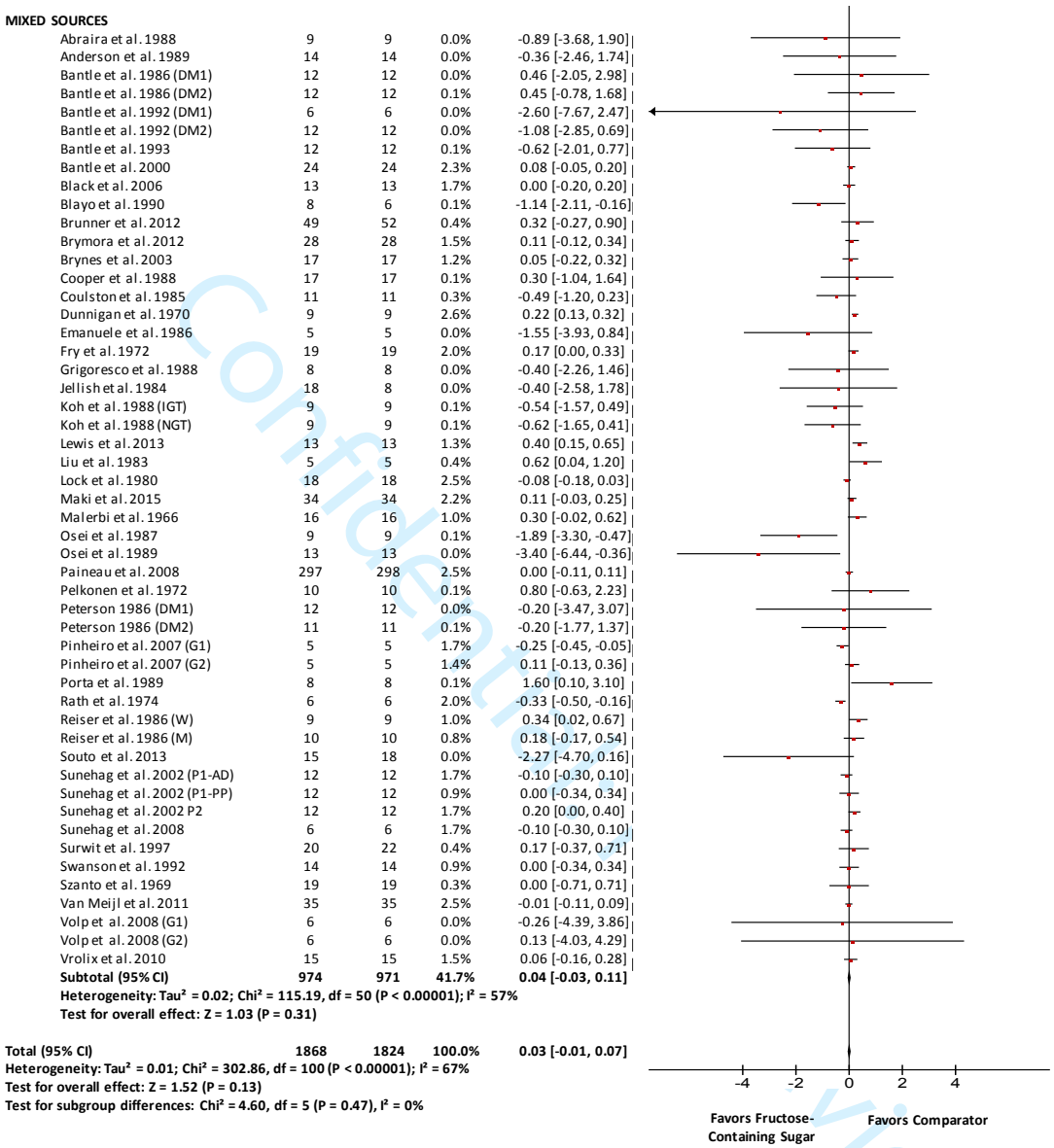
E. Fasting blood insulin in addition trials



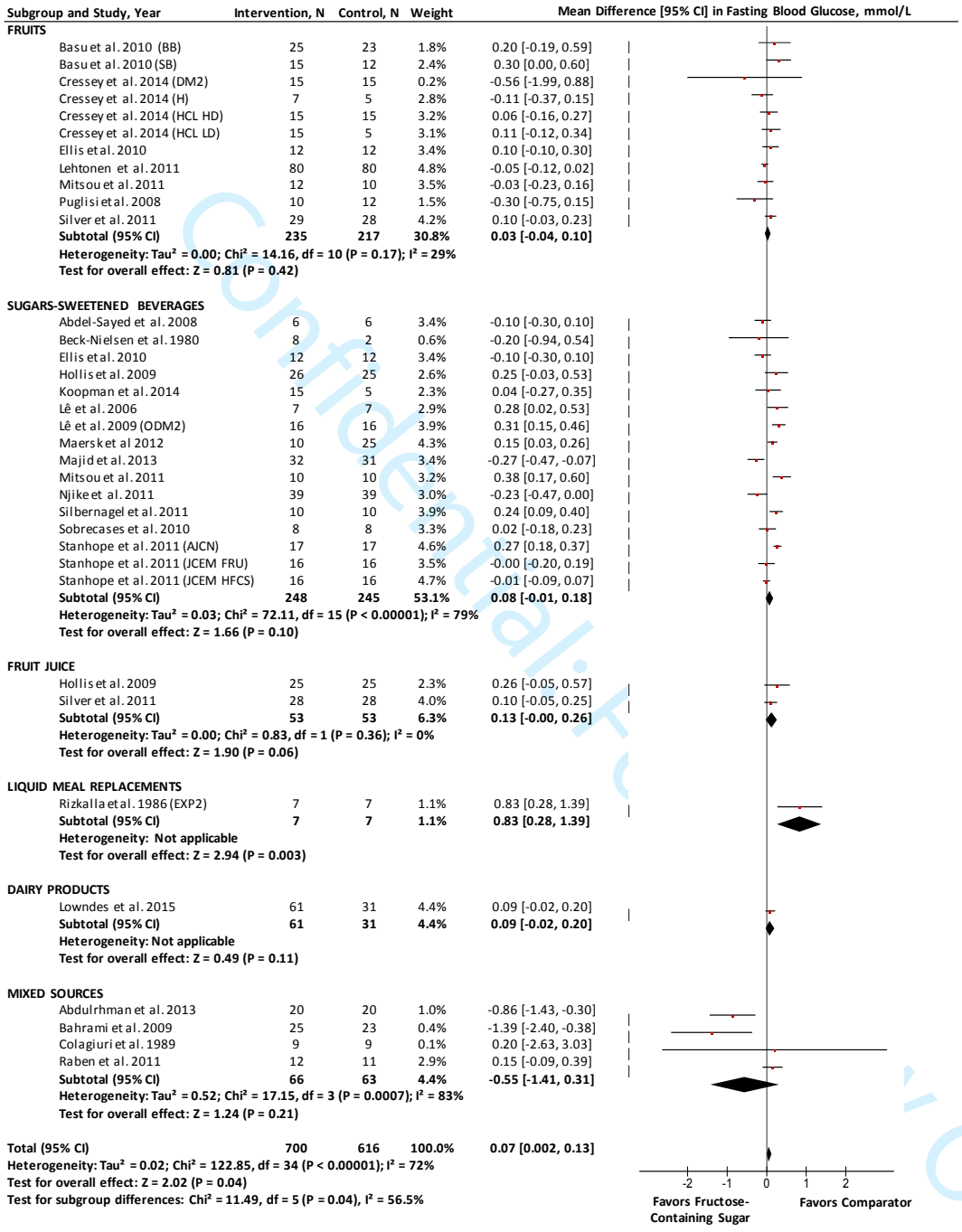
Supplementary Figure 8. Post-hoc meta-regression analyses for the effect of fructose dose (%E) on glycemic control in substitution and addition trials. Individual studies are represented by the circles, with their weight in the overall analysis represented by the size of the circles. The straight line represents the estimate dose response for amount of fructose-containing sugars consumed (% of total energy intake) on fasting blood glucose (mmol/L).



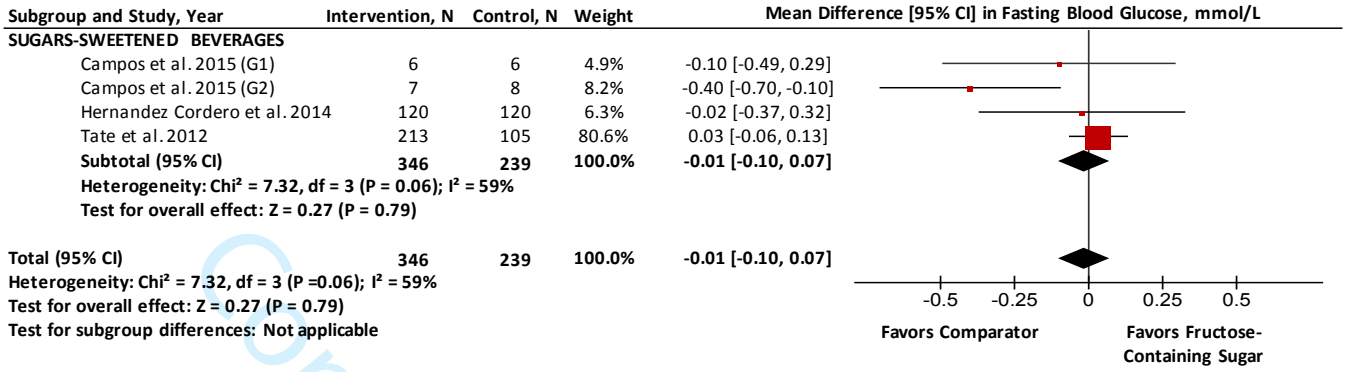
Supplementary Figure 9. Forest plot for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood glucose (continues next page).



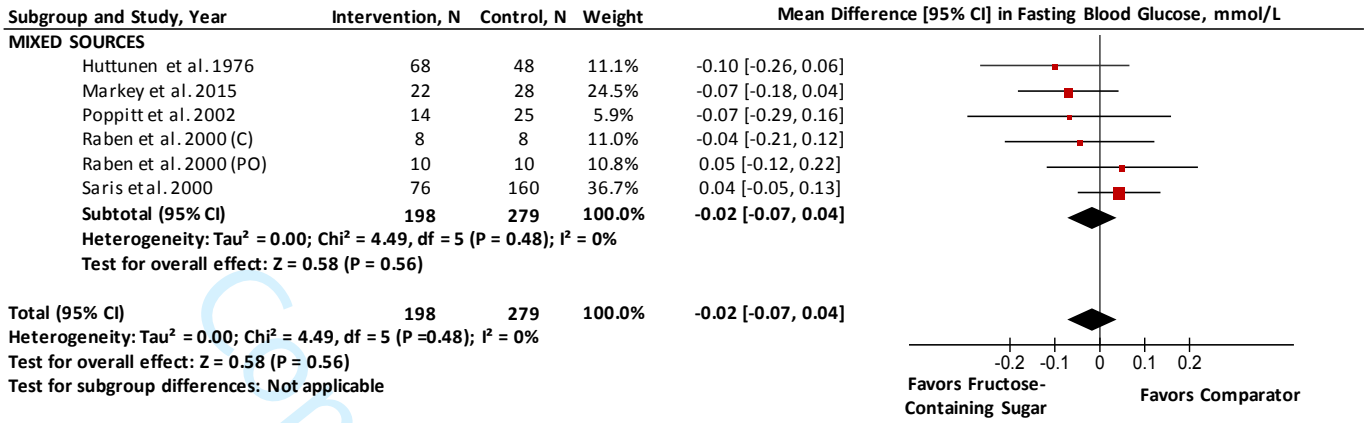
Supplementary Figure 9. Forest plot for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood glucose (continued). AJCN = American Journal of Clinical Nutrition; DM= diabetes mellitus; EXP1= experiment 1; EXP2= 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 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



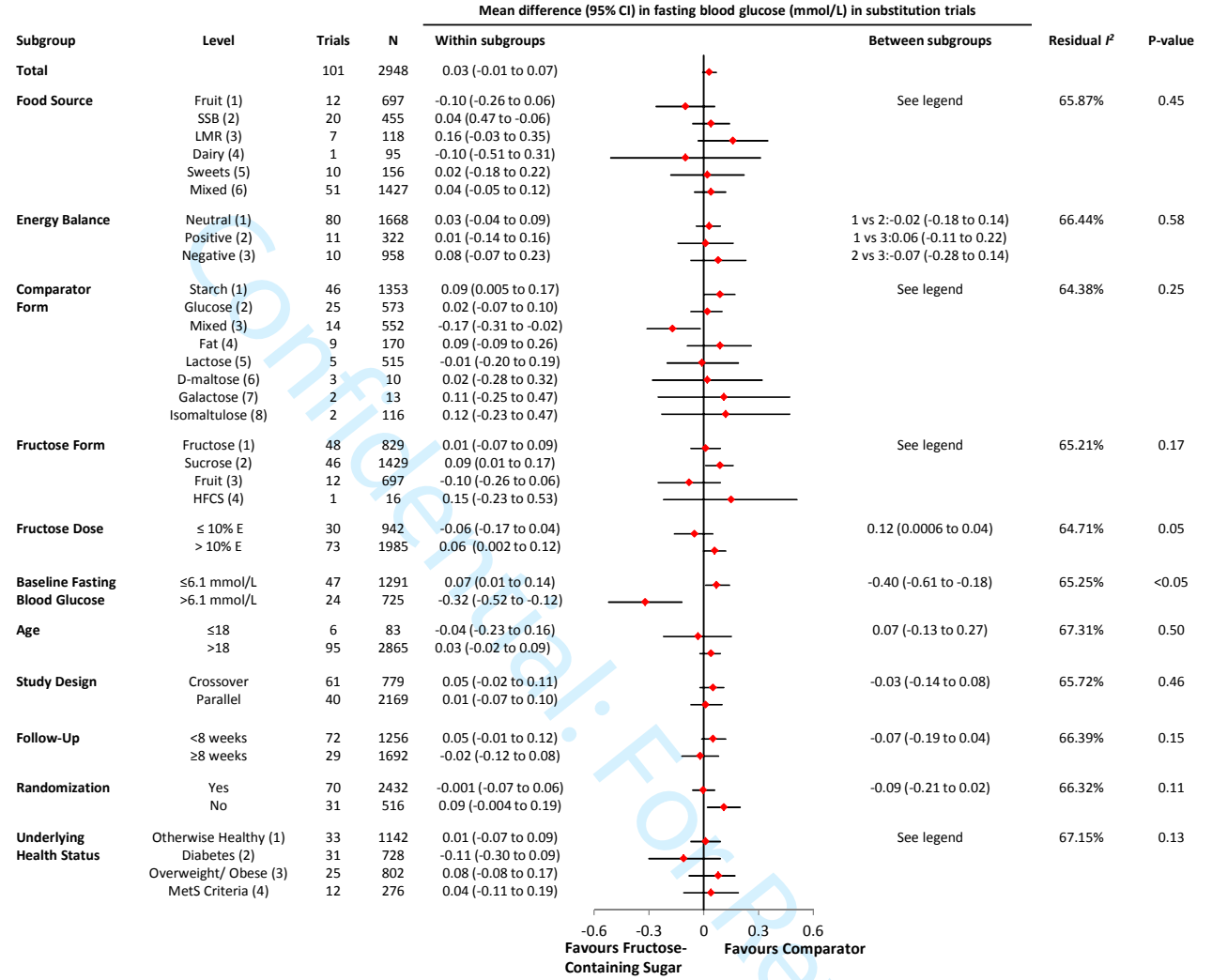
Supplementary Figure 10. Forest plot for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on fasting blood glucose. AJCN = American Journal of Clinical Nutrition; BB= blueberries; DM2= type 2 diabetes mellitus; EXP2= experiment 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 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



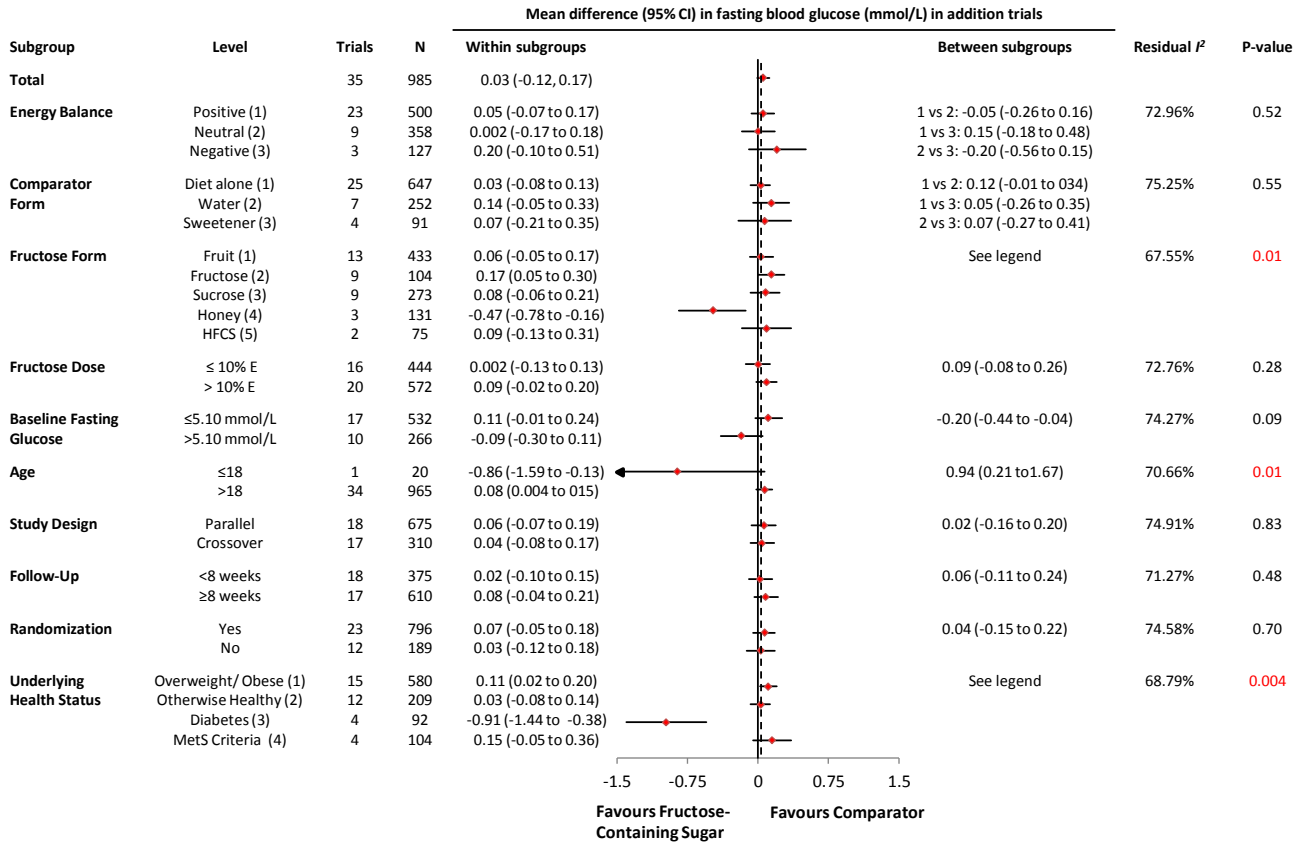
Supplementary Figure 11. Forest plot for subtraction trials investigating the effect of removing calories from the diet in the form of fructose-containing food sources on fasting blood glucose. G1= group 1; G2= group 2; N= number of participants. Pooled effect estimates for each subgroup and overall 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 random effects models. Paired analyses were applied to all crossover trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



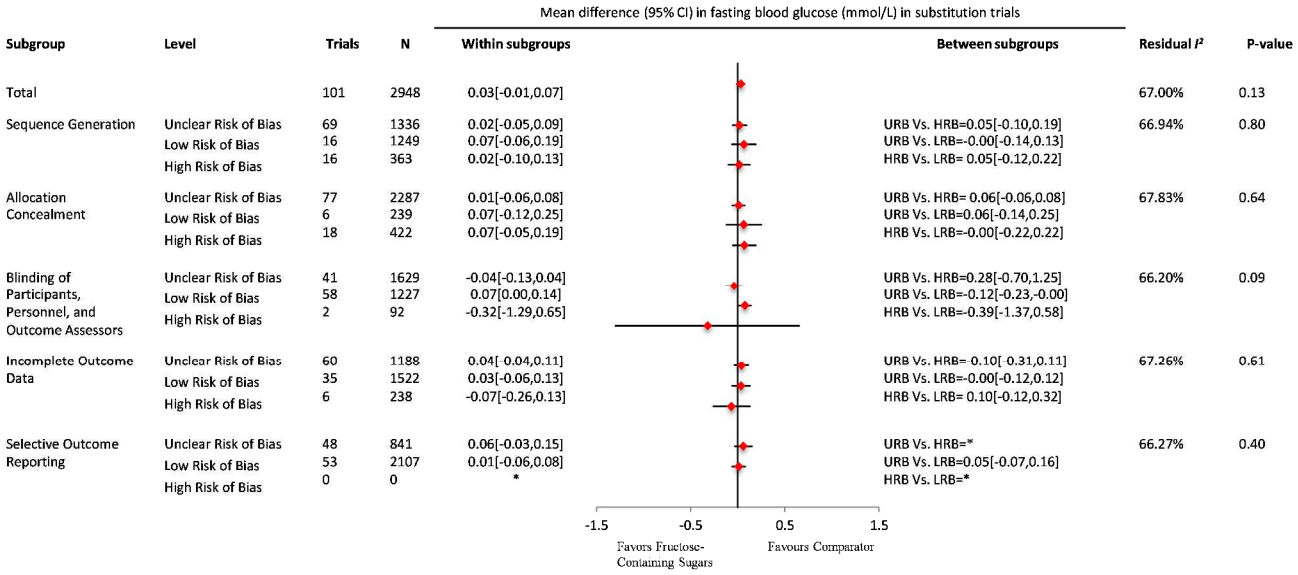
Supplementary Figure 12. Forest plot for ad libitum trials investigating the effect of freely replacing calories from fructose-containing food sources with other dietary sources on fasting blood glucose. C= controls; N= number of participants; PO= post-obese. Pooled effect estimates for each subgroup 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 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



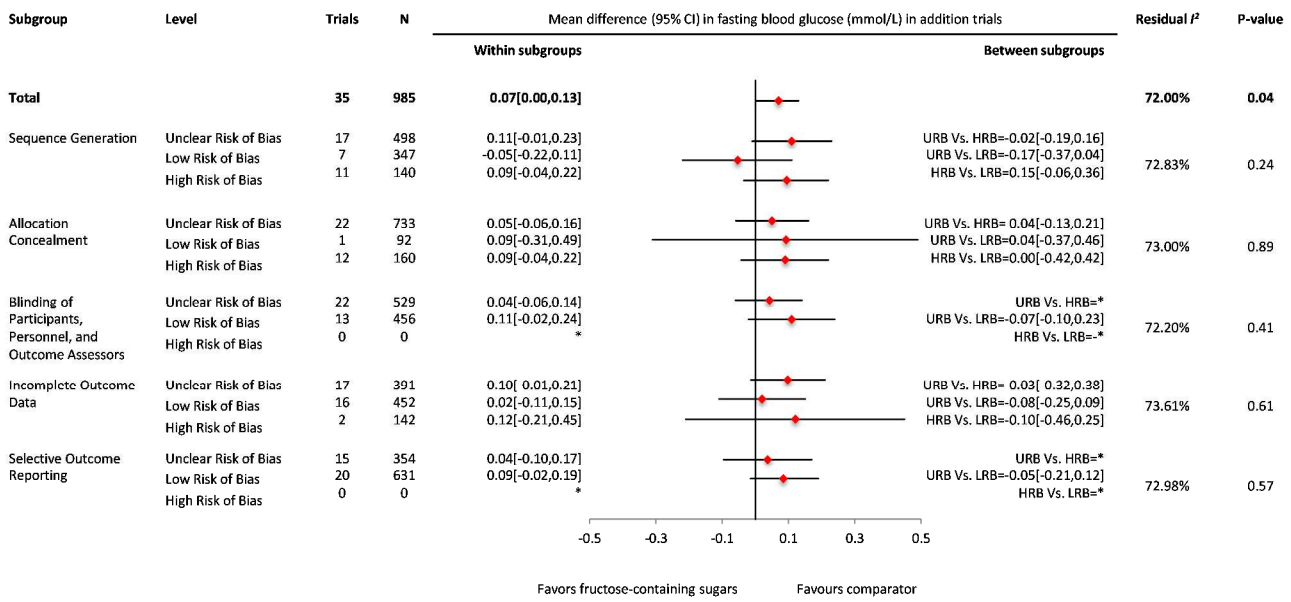
Supplementary Figure 13. Subgroup analyses for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood glucose. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. Pooled 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 fructose form are as follows: 1 vs 2:0.08 (-0.03 to 0.19); 1 vs 3: -0.09 (-0.28 to 0.10); 1 vs 4: 0.14 (-0.24 to 0.51); 2 vs 3: -0.17 (-0.35 to 0.02); 2 vs 4: -0.06 (-0.44 to 0.31); 3 vs 4: -0.23 (-0.63 to 0.18). Pairwise between-subgroup mean differences (95% CI) for comparator form are as follows: 1 vs 2: -0.07 (-0.19 to 0.05); 1 vs 3: -0.26 (-0.43 to 0.08); 1 vs 4: -0.003 (-0.19 to 0.19); 1 vs 5: -0.10 (-0.31 to 0.11); 1 vs 6: -0.07 (-0.38 to 0.24); 1 vs 7: 0.02 (-0.35 to 0.39); 1 vs 8: 0.03 (-0.33 to 0.39); 2 vs 3: -0.18 (-0.35 to 0.01); 2 vs 4: -0.07 (-0.26 to 0.12); 2 vs 5: -0.02 (-0.23 to 0.19); 2 vs 6: -0.002 (-0.32 to 0.31); 2 vs 7: -0.09 (-0.46 to 0.28); 2 vs 8: -0.10 (-0.46 to 0.26); 3 vs 4: -0.25 (-0.48 to -0.03); 3 vs 5: -0.16 (-0.40 to 0.08); 3 vs 6: -0.18 (-0.52 to 0.15); 3 vs 7: -0.28 (-0.67 to 0.11); 3 vs 8: -0.29 (-0.67 to 0.09); 4 vs 5: -0.09 (-0.35 to 0.16); 4 vs 6: -0.07 (-0.41 to 0.28); 4 vs 7: 0.02 (-0.38 to 0.42); 4 vs 8: 0.03 (-0.36 to 0.42); 5 vs 6: -0.03 (-0.38 to 0.33); 5 vs 7: -0.12 (-0.53 to 0.29); 5 vs 8: -0.13 (-0.53 to 0.27); 6 vs 7: 0.09 (-0.38 to 0.56); 6 vs 8: -0.10 (-0.56 to 0.36); 7 vs 8: -0.01 (-0.51 to 0.49). Pairwise between-subgroup mean differences (95% CI) for underlying health status are as follows: 1 vs 2: -0.12 (-0.33 to 0.09); 1 vs 3: 0.07 (-0.05 to 0.19); 1 vs 4: 0.03 (-0.14 to 0.20); 2 vs 3: -0.19 (-0.40 to 0.02); 2 vs 4: 0.15 (-0.10 to 0.39); 3 vs 4: -0.04 (-0.22 to 0.13).



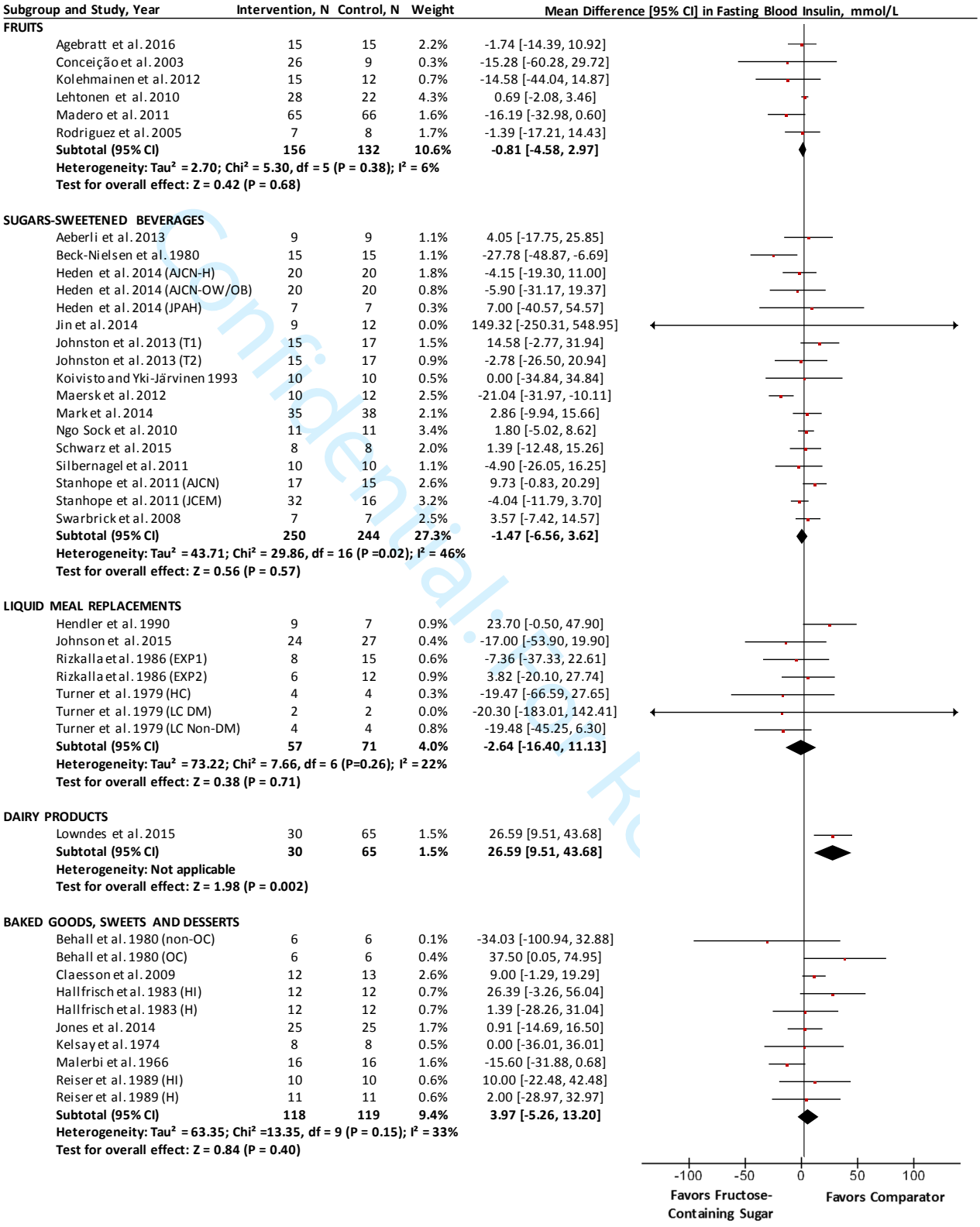
Supplementary Figure 14. Subgroup analyses for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on fasting blood glucose. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. Pooled 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 form are as follows: 1 vs 2: 0.11 (-0.08 to 0.30); 1 vs 3: 0.04 (-0.15 to 0.24); 1 vs 4: -0.52 (-0.89 to -0.14); 1 vs 5: 0.58 (0.14 to 1.02); 2 vs 3: 0.06 (-0.14 to 0.27); 2 vs 4: 0.63 (0.25 to 1.01); 2 vs 5: 0.05 (-0.25 to 0.35); 3 vs 4: 0.56 (0.18 to 0.95); 3 vs 5: -0.02 (-0.32 to 0.29); 4 vs 5: 0.58 (0.14 to 1.02). Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: -0.08 (-0.22 to 0.06); 1 vs 3: -1.08 (-1.52 to 0.65); 1 vs 4: 0.04 (-0.18 to 0.27); 2 vs 3: 1.00 (0.57 to 1.44); 2 vs 4: 0.12 (-0.10 to 0.35); 3 vs 4: 1.13 (0.66 to 1.60).



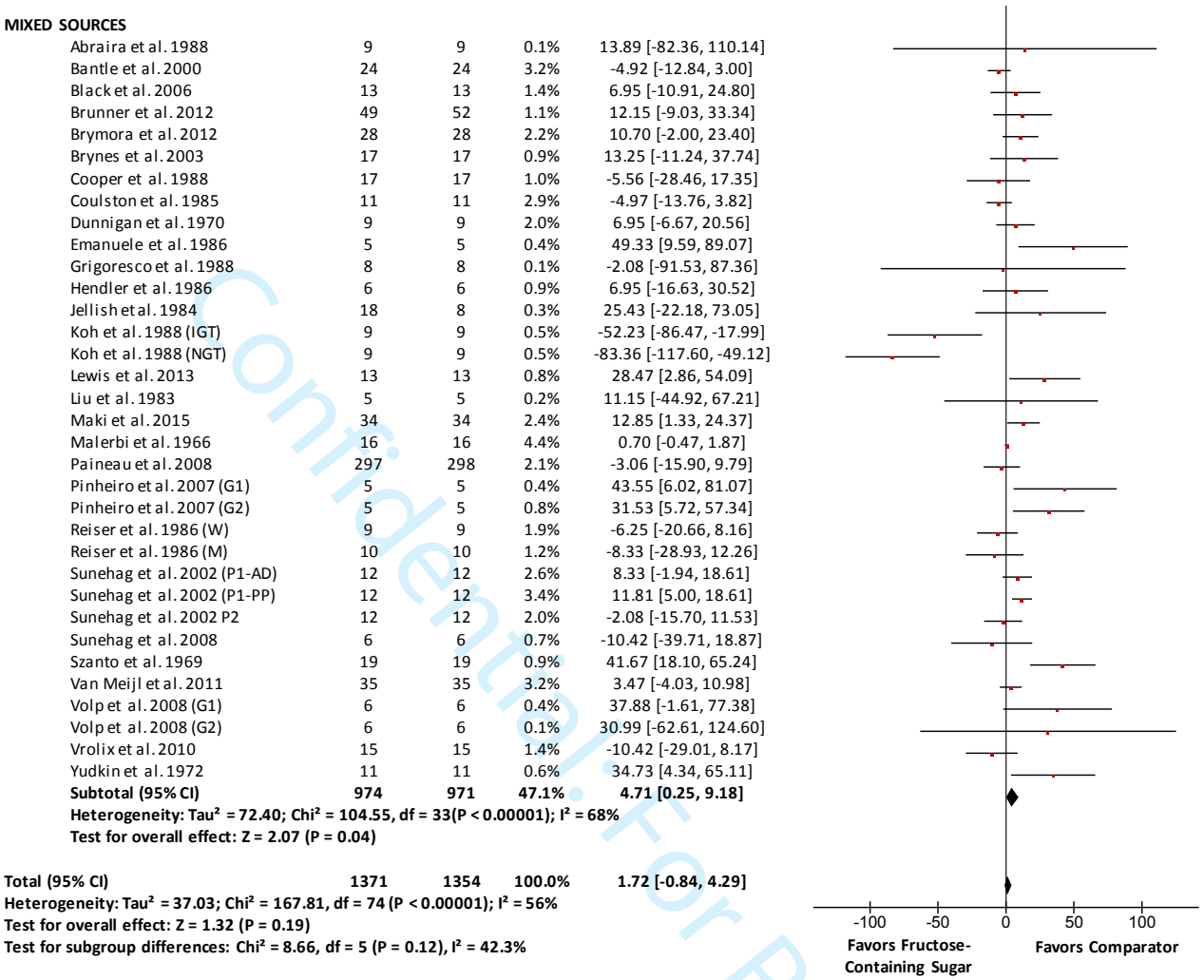
Supplementary Figure 15. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood glucose. Point estimates for each subgroup level are the 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).



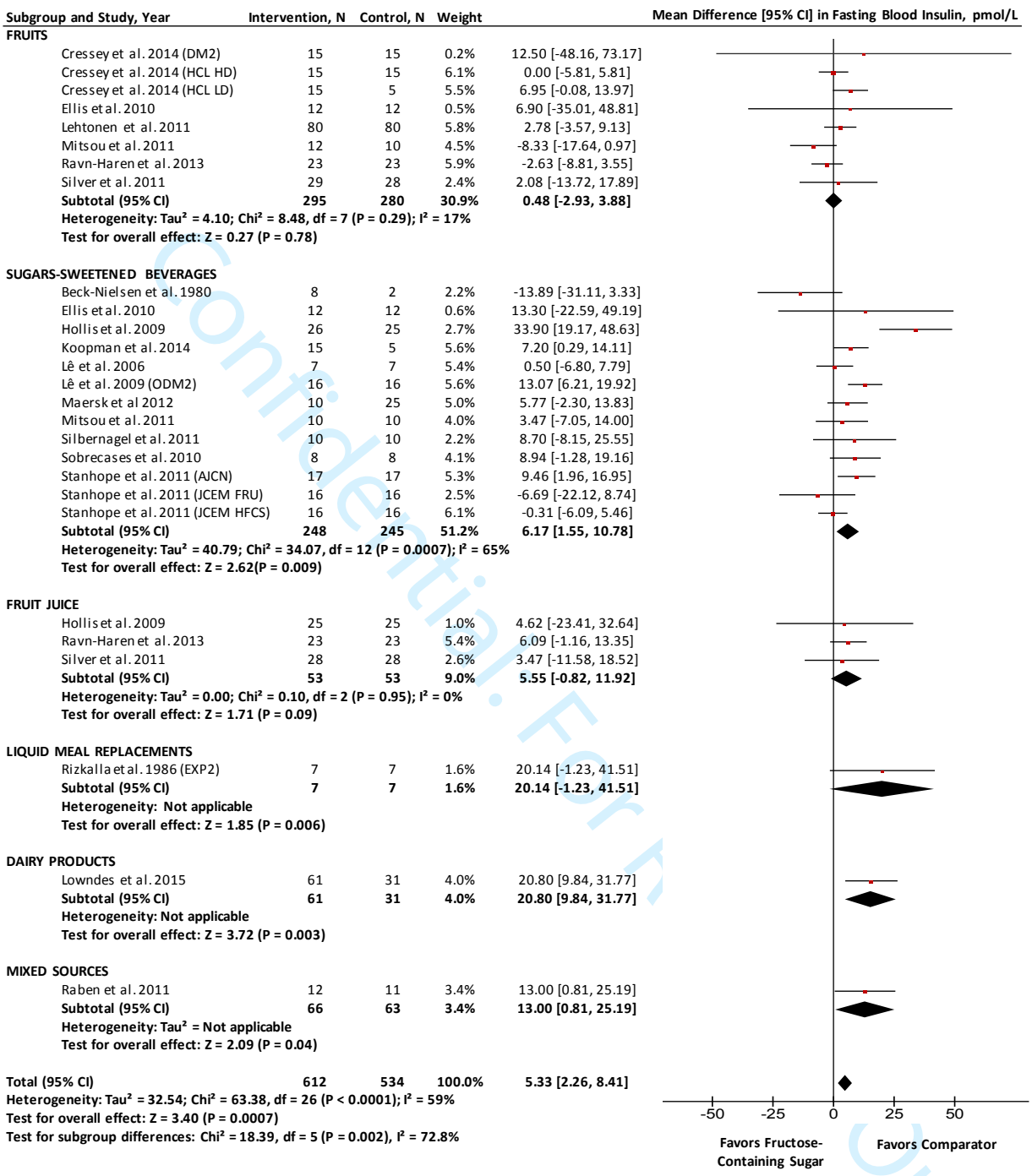
Supplementary Figure 16. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for addition trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood glucose. Point estimates for each subgroup level are the pooled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



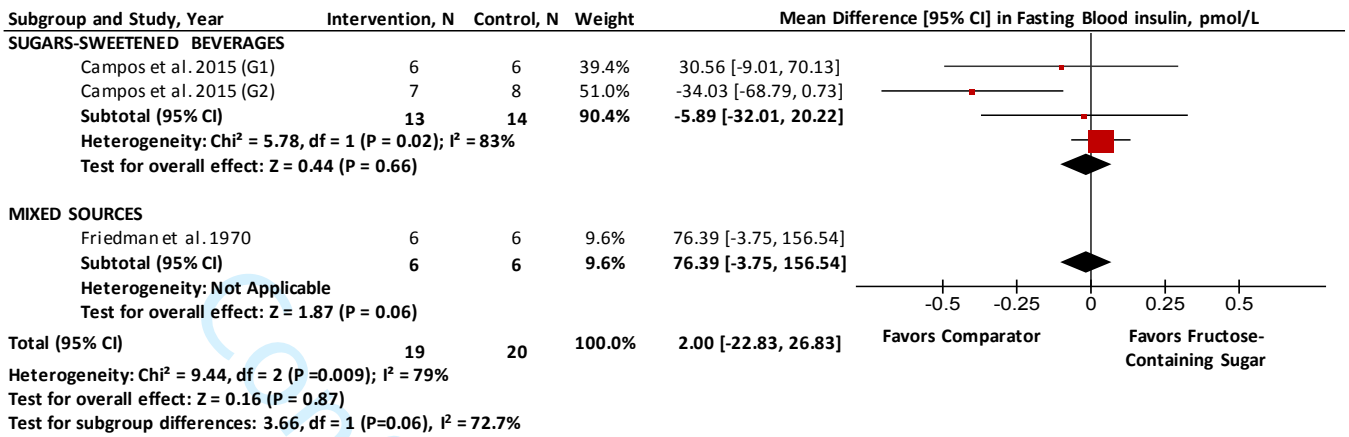
Supplementary Figure 17. Forest plot for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood insulin (Continues next page).



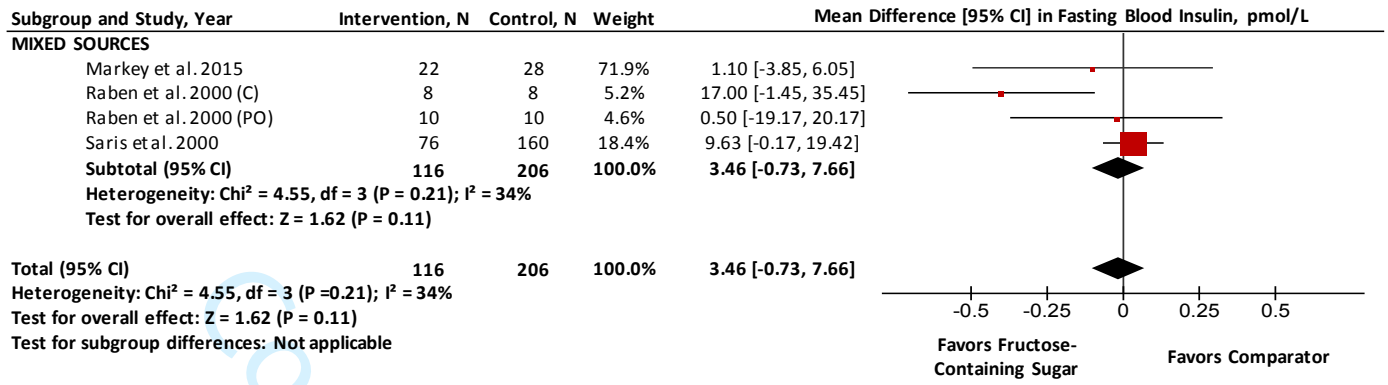
Supplementary Figure 17. Forest plot for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood insulin (continued). AD= adolescent; AJCN = American Journal of Clinical Nutrition; DM= diabetes mellitus; EXP1= experiment 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 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



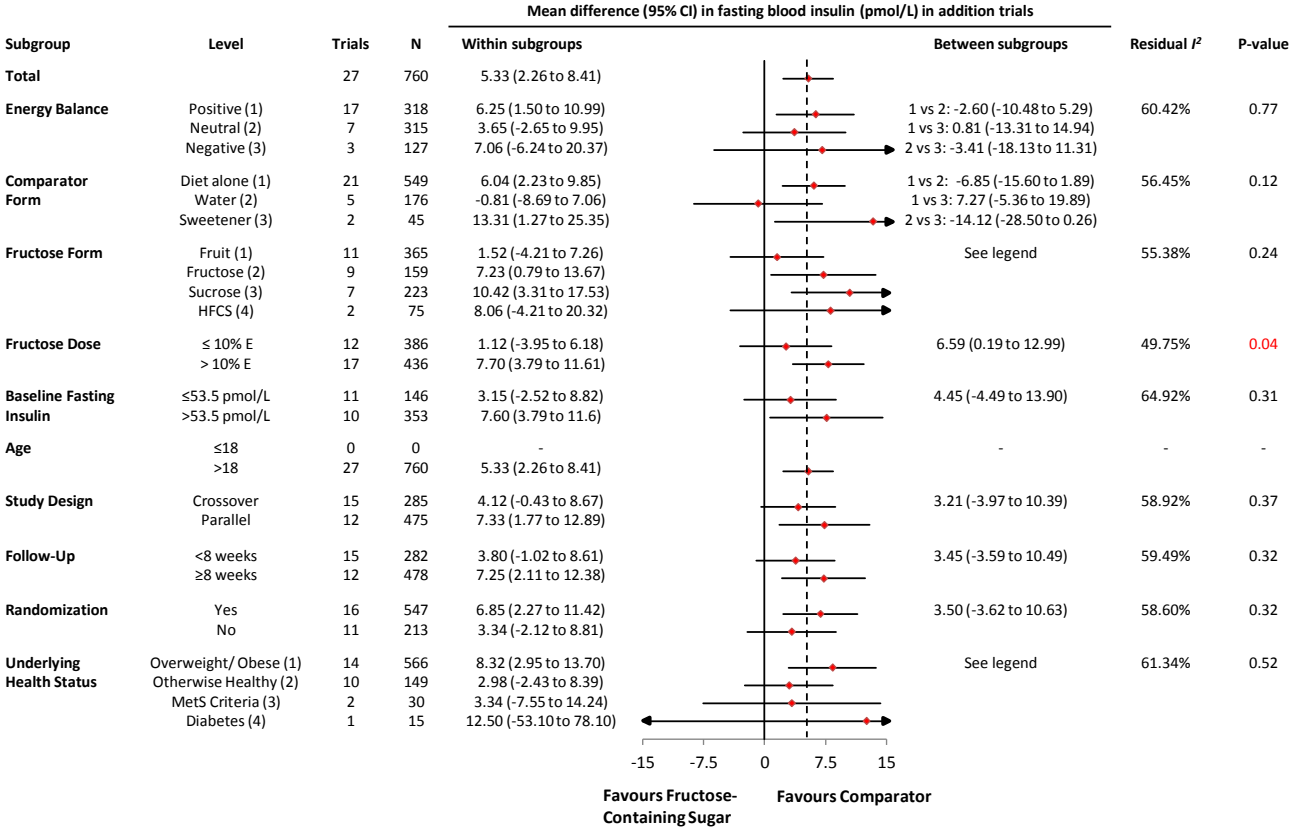
Supplementary Figure 18. Forest plot for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on fasting blood insulin. AJCN = American Journal of Clinical Nutrition; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructose; 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 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



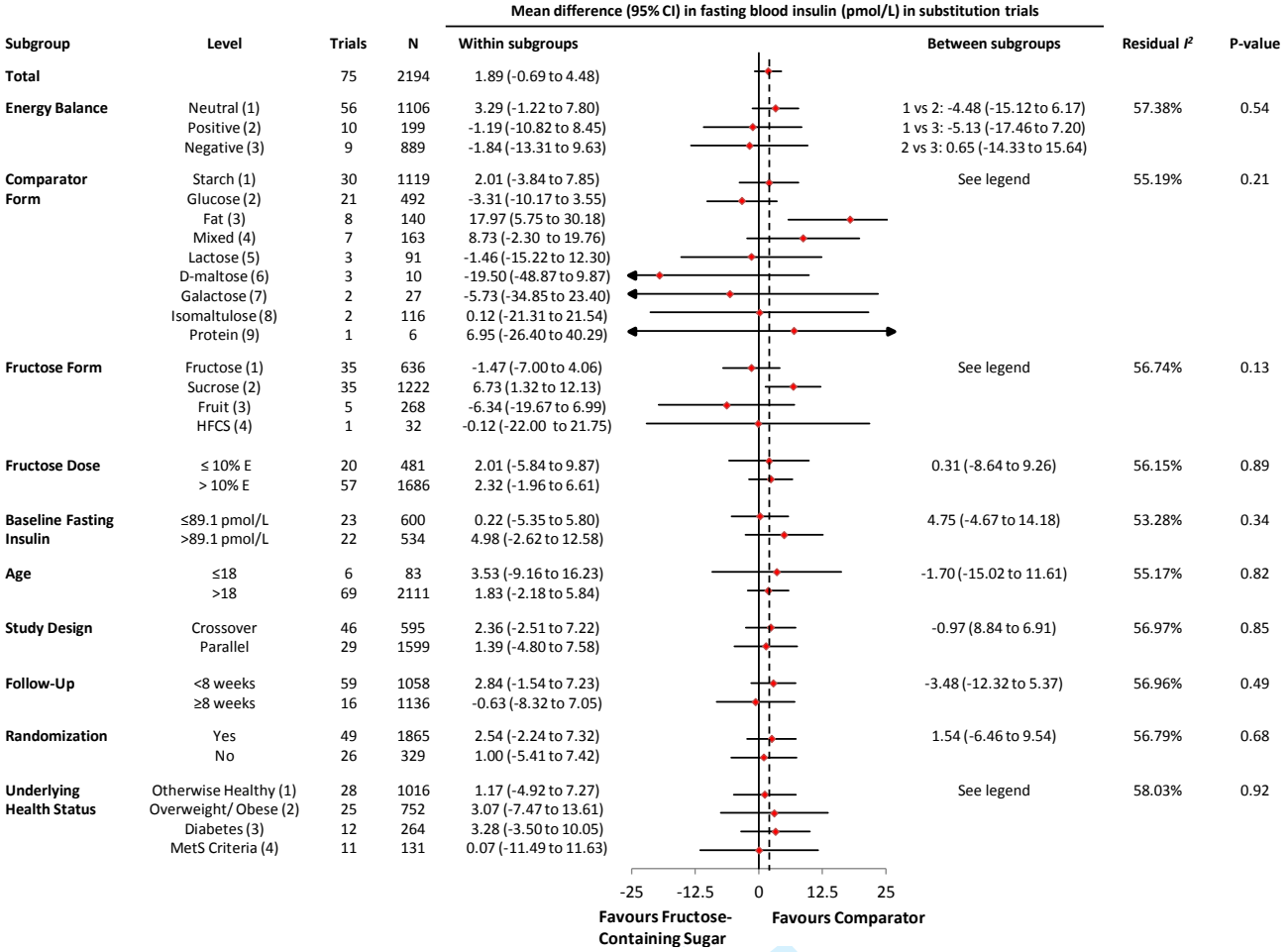
Supplementary Figure 19. Forest plot for subtraction trials investigating the effect of removing calories from the diet in the form of fructose-containing food sources on fasting blood insulin. G1= group 1; G2= group 2; N= number of participants. Pooled effect estimates for each subgroup and overall 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 random effects models. Paired analyses were applied to all crossover trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.



Supplementary Figure 20. Forest plot for ad libitum trials investigating the effect of freely replacing calories from fructose-containing food sources with other dietary sources on fasting blood insulin. 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 random effects models. Paired analyses were applied to all crossover trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of $p < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity.

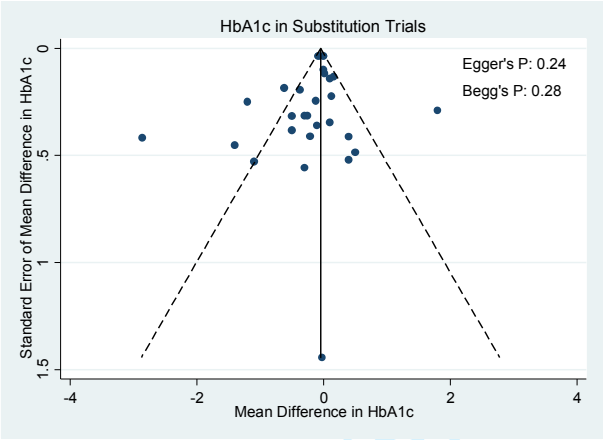


Supplementary Figure 21. Subgroup analyses for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on fasting blood insulin. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants. Pooled 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 form are as follows: 1 vs 2: 5.70 (-2.92 to 14.32); 1 vs 3: 8.90 (-0.23 to 18.03); 1 vs 4: 6.53 (-7.01 to 20.07); 2 vs 3: -3.19 (-12.78 to 6.40); 2 vs 4: -0.83 (-14.68 to 13.03); 3 vs 4: 2.36 (-11.81 to 16.54). Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: -5.35 (-12.98 to 2.28); 1 vs 3:-4.98 (-17.13 to 7.17); 1 vs 4: 4.18 (-61.64 to 69.99); 2 vs 3: 0.37 (-11.80 to 12.53); 2 vs 4:-9.52 (-75.34 to 56.30); 3 vs 4: -9.16 (-75.65 to 57.34).

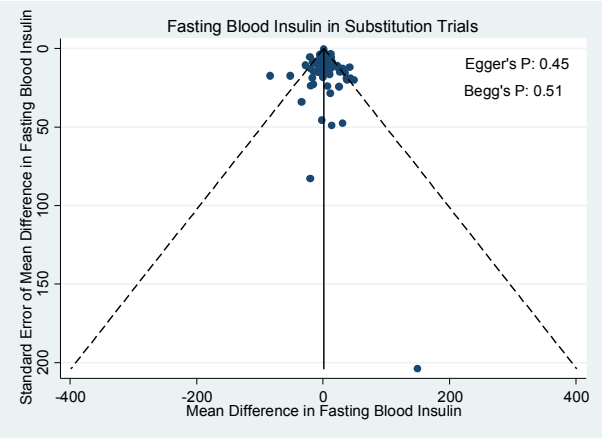


Supplementary Figure 22. Subgroup analyses for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood insulin. E= energy; HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants.Pooled 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 form are as follows: 1 vs 2: -5.32 (-14.33 to 3.70); 1 vs 3: 15.96 (2.42 to 29.50); 1 vs 4: 6.72 (-5.76 to 19.21); 1 vs 5: -3.46 (-18.41 to 11.49); 1 vs 6: -21.50 (-51.45 to 8.44); 1 vs 7: -7.73 (-37.44 to 21.97); 1 vs 8: -1.89 (-24.10 to 20.32); 1 vs 9: 4.94 (-28.91 to 38.79); 2 vs 3: -21.27 (-35.28 to -7.26); 2 vs 4: 12.04 (-0.95 to 25.03); 2 vs 5: 1.85 (-13.52 to 17.23); 2 vs 6: 16.19 (-13.97 to 46.35); 2 vs 7: 2.42 (-27.50 to 32.34); 2 vs 8: -3.42 (-25.92 to 19.07); 2 vs 9:-10.25 (-44.30 to 23.79); 3 vs 4: -9.24 (-25.69 to 7.22); 3 vs 5: -19.42 (-37.82 to -1.02); 3 vs 6: -37.46 (-69.27 to 5.66); 3 vs 7: -23.69 (-55.27 to 7.89); 3 vs 8: -17.85 (-42.51 to 6.81); 3 vs 9: 11.02 (-24.49 to 46.53); 4 vs 5: 10.19 (-7.45 to 27.82) ; 4 vs 6: 28.23 (-3.14 to 59.60); 4 vs 7: 14.46 (-16.68 to 45.60); 4 vs 8: 8.61 (-15.49 to 32.71); 4 vs 9: 1.79 (-33.34 to 36.91); 5 vs 6: 18.04 (-14.39 to 50.47); 5 vs 7: 4.27 (-27.94 to 36.48); 5 vs 8: -1.57 (-27.04 to 23.89); 5 vs 9: -8.40 (-44.47 to 27.67); 6 vs 7: 13.77 (-27.59 to 55.13); 6 vs 8: -19.61 (-55.97 to 16.74); 6 vs 9: -26.44 (-70.88 to 17.99) ; 7 vs 8: -5.84 (-42.00 to 30.31); 7 vs 9: -12.67 (-56.94 to 31.60); 8 vs 9: -6.83 (-46.46 to 32.80). Pairwise between-subgroup mean differences (95% CI) for fructose form are as follows: 1 vs 2: 8.20 (0.47 to 15.93); 1 vs 3: -4.87 (-19.30 to 9.57); 1 vs 4: 1.35 (-21.22 to 23.91); 2 vs 3: -13.07 (-27.45 to 1.32); 2 vs 4: 6.85 (-15.68 to 29.39); 3 vs 4: -6.21 (-31.83 to 19.40). Pairwise between-subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: 2.10 (-7.01 to 11.22); 1 vs 3: 1.90 (-10.15 to 13.94); 1 vs 4: -1.11 (-14.03 to 11.82); 2 vs 3: -0.21 (-12.74 to 12.32); 2 vs 4: -3.21 (-16.61 to 10.19); 3 vs 4: -3.00 (-19.01 to 13.00).

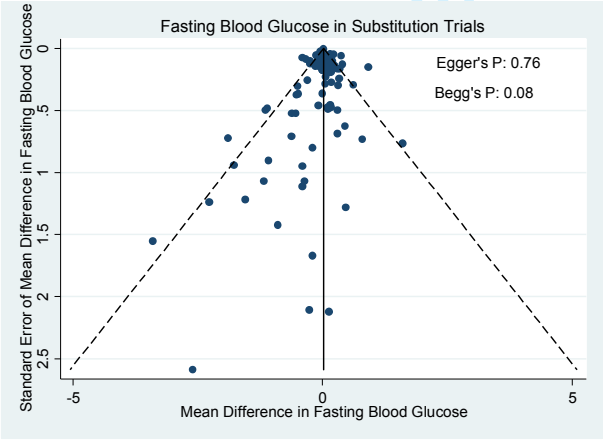
A. HbA1c in Substitution Trials



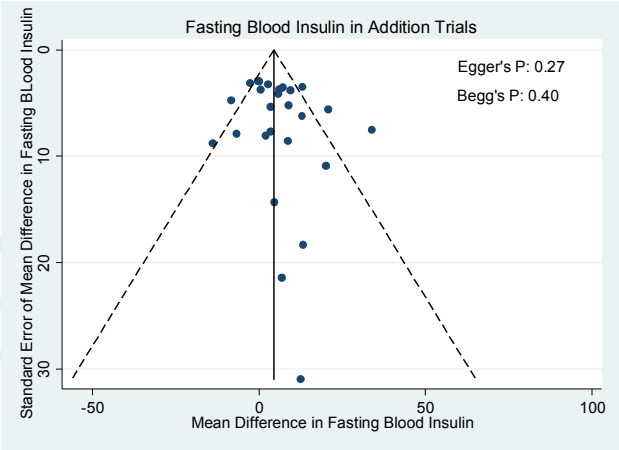
D. Fasting Blood Insulin in Substitution Trials



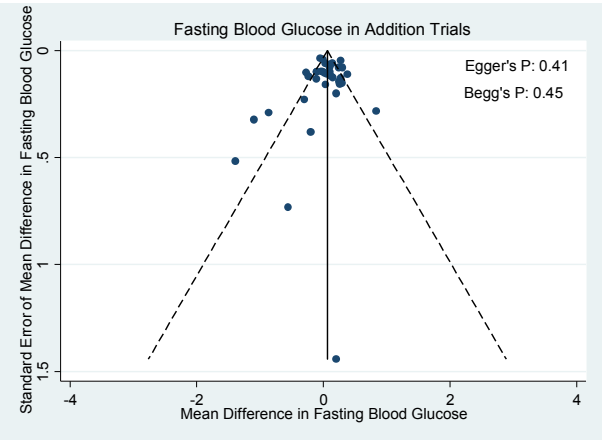
B. Fasting Blood Glucose in Substitution Trials



E. Fasting Blood Insulin in Addition Trials



C. Fasting Blood Glucose in Addition Trials



Supplementary Figure 23. Publication bias funnel plots for the effect of fructose-containing sugars on glycemic control in substitution and addition trials. 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 $p < 0.05$.