

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

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19	Keywords: fructose, HFCS, sucrose, glycemic control, diabetes, meta-analysis
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1	Food sources of fructose-containing sugars and glycemic control: A systematic review and meta-
2	analysis of controlled trials
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2 3	29	ABSTRACT
4 5 6	30	Objective: As dietary guidelines move to more dietary pattern-based recommendations, public health
7 8	31	advice to reduce free sugars does not distinguish between food sources of sugars. We conducted a
9 10 11	32	synthesis of controlled trials, to assess whether the effects on glycemic control are uniform across
12 13	33	different food sources of fructose-containing sugars.
14 15	34	Design: Systematic review and meta-analysis
16 17	35	Data Sources: MEDLINE, EMBASE, and The Cochrane library were searched through Nov 3, 2015.
18 19 20	36	Eligibility criteria for selecting studies: We included trials ≥ 7-days assessing the effect of fructose-
20 21 22	37	containing sugars from different food sources on glycemic control in people with and without diabetes.
23 24	38	Outcomes were fasting blood glucose, insulin and HbA1c.
25 26	39	Data extraction and synthesis: Four independent reviewers extracted relevant data and assessed risk of
27 28 29	40	bias. Data were pooled using the inverse variance method and expressed as mean differences with 95%
30 31	41	confidence intervals. The overall quality of the evidence was assessed by the GRADE approach.
32 33	42	<b>Results:</b> Eligibility criteria were met by 160 trials (N=5139) including 4 levels of energy control:
34 35	43	substitution trials (sugars in energy matched comparisons with other macronutrients); addition trials
36 37	44	(excess energy from sugars supplementing diets); subtraction trials (excess energy from sugars displaced
38 39 40	45	from diets); and ad libitum trials (sugars freely replaced by other macronutrients without strict energy
41 42	46	control). In substitution trials, total food sources of fructose-containing sugars decreased HbA1c (-0.14%
43 44	47	[-0.25 to -0.04%], moderate quality evidence, p=0.007) without affecting fasting glucose (high quality
45 46	48	evidence) or insulin (moderate quality evidence), and the effect was stronger for fruit as a food source.
47 48 49	49	In addition trials, total food sources of fructose-containing sugars increased fasting glucose (0.07
50 51	50	mmol/L [0.002 to 0.13], moderate quality evidence, p=0.04) and insulin (5.33 pmol/L [2.26 to 8.41],
52 53	51	moderate quality evidence, p=0.0007) without affecting HbA1c (high quality evidence), and the effect
54 55	52	was stronger for sugars-sweetened beverages as a food source. There was no effect of total food
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3 4	53	sources of fructose-containing sugars in subtraction (low to high quality evidence) or ad libitum trials
5 6	54	(very low to high quality evidence).
7 8	55	Conclusions: Pooled analyses showed that fructose-containing sugars from various food sources,
9 10 11	56	especially fruit, are no worse in their effects on glycemic control in energy-matched comparisons with
12 13	57	other macronutrient-containing foods. However, total food sources of fructose-containing sugars,
14 15	58	especially sugars-sweetened beverages, supplementing diets with excess energy appear to have adverse
16 17	59	effects. Longer, larger, high quality trials are required.
18 19 20	60	Systematic review registration: ClinicalTrials.gov identifier, NCT02716870.
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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 

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3 4	85	form. Similarly, less refined sources of fructose-containing sugars, including honey, agave and maple
5 6	86	syrup, are composed of varying proportions of fructose and glucose, while natural sources of fructose
7 8	87	present in various fruits and vegetables also co-exist with glucose in catalytic amounts (≤10-g/meal).
9 10 11	88	These fructose-containing sugars are found in the diet in a variety of food sources, ranging from
12 13	89	"nutrient poor" sources of added sugars such as sugars-sweetened beverages (SSBs), to "nutrient
14 15	90	dense" sources of bound sugars such as fruits. However, despite the high sugar composition of each,
16 17	91	evidence from prospective cohorts on diabetes risk have shown differential associations depending on
18 19	92	the food source of the sugars (positive associations with SSBs(20, 21) and inverse association with
20 21 22	93	fruits)(22, 23). Whether various food sources of fructose-containing sugars differ in their effects on
23 24	94	surrogate markers of type 2 diabetes in controlled trials have not yet been determined. This question
25 26	95	has become increasingly important, as dietary guidelines have shifted from nutrient-based
27 28	96	recommendations to more food and dietary pattern-based recommendations(24). To help address this
29 30 31	97	gap, we conducted a systematic review and meta-analysis of controlled trials to determine the effect of
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32	98	fructose-containing food sources on measures of glycemic control in people with and without diabetes.
	98 99	fructose-containing food sources on measures of glycemic control in people with and without diabetes. METHODS
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32 33 34 35 36 37 38 39	99	METHODS
32 33 34 35 36 37 38 39 40 41	99 100	<b>METHODS</b> This systematic review and meta-analysis was conducted according to the Cochrane Handbook for
32 33 34 35 36 37 38 39 40	99 100 101	<b>METHODS</b> 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
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	99 100 101 102	<b>METHODS</b> 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
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$\begin{array}{c} 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\end{array}$	99 100 101 102 103 104 105 106 107	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
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	99 100 101 102 103 104 105 106 107	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

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109 Information Research Unit were applied to limit the database search to controlled trials only (27), and 110 electronic searches were supplemented with manual searches of references from included studies. 111 **Study Selection** 

112 Inclusion criteria for our analysis included controlled trials in humans lasting  $\geq 7$  days investigating the 113 role of fructose-containing sugars (fructose, sucrose, HFCS, honey, fruit sugars) from various food 114 sources on measures of glycemic control (fasting glucose, fasting insulin, and HbA1c). Four trial designs 115 were identified: 1) 'substitution' trials, in which fructose-containing sugars added to foods and 116 beverages were compared with other macronutrient sources under energy matched conditions; (2) 117 'addition' trials, in which fructose-containing sugars supplemented a diet with excess energy compared 118 to the same diet supplemented with the equivalent amounts of non-caloric food and beverages or the 119 same diet alone without the excess energy from fructose-containing sugars; (3) 'subtraction' trials, in 120 which energy from fructose-containing sugars was reduced through displacement with water and/or no-121 calorie or low-calorie sweeteners or by eliminating it altogether from the background diet; and (4) 'ad 122 libitum' trials, in which energy from fructose-containing sugars were freely replaced with other food and 123 beverages without any strict control of either the study foods or the background diet. 124 Patient involvement No patients/service users/carers/lay people were involved in the design of this study. 125 **Data Extraction** 126 127 Data from included reports were individually extracted twice by four separate reviewers with all 128 discrepancies resolved through consensus. Relevant information included number of participants, health 129 status of participants, study design, level of feeding control, randomization, comparator form, fructose-130 containing sugar form and food source, macronutrient profile of the diets, follow-up duration, energy 131 balance, risk of bias and funding sources. Outcome measures included HbA1c, fasting glucose, and 132 fasting insulin. HbA1c was reported instead of total glycated blood proteins as originally indicated in our

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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 $l^2$
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,

statistic (range from 0%-100%)(30), and use 

of evidence quality. A priori subgroup analys 

Categorical subgroup analyses were conduct

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  $\geq 10$  studies were available (31, 32) and heterogeneity was substantial

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 $(l^2>50\% \text{ or } P_0<0.10)(30)$  we used meta-regression to explore heterogeneity by sources of fructosecontaining 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  $\geq 10$  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

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180 The systematic search and selection of literature is shown in **Figure 1.** 3574 reports were identified from 181 database and manual searches, of which 3353 were excluded based on title and abstract. 221 reports 182 were reviewed in full, of which an additional 99 reports were excluded. 122 reports including a total of 183 160 trials in 5139 participants were included in the final analysis (5, 10-12, 37-154).

184 **Trial Characteristics** 185 A summary of trial characteristics are presented in **Table 1**, with an individual breakdown of study 186 characteristics in **Supplementary Table 2**. In total, trial sizes were relatively small, ranging from a 187 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 188 189 substitution (44/110), addition (14/38) and subtraction (2/5) trials conducted in the USA, and all ad 190 libitum trials conducted in European countries. Participants tended to be middle aged, with 191 approximately equal ratios of males to females in substitution trials and ad libitum trials, but 192 proportionately more females in addition and subtraction trials. Most trials were performed on healthy 193 participants (34%) and those with diabetes (35%) in substitution trials, whereas most participants were 194 healthy (37%) and overweight/obese (39%) in addition trials. Participants in subtraction trials were 195 predominantly overweight or obese (80%), whereas participants in ad libitum trials were mostly healthy 196 (67%). A majority of trials were randomized (69% of substitution trials, 66% of addition trials, 80% of 197 subtraction trials and 88% of ad libitum trials) however, follow up duration was relatively short, ranging 198 from a median of 4 weeks (range=1 to 52 weeks) in substitution trials to 12 weeks (range= 8.6-39.1 199 weeks) in subtraction trials. Fructose-containing sugar doses ranged from a median of 15% of total 200 energy intake in substitution and subtraction trials to 23% of total energy intake in ad libitum trials, and 201 were mostly in the form of mixed food sources in substitution (57/110) and ad libitum (6/7) trials while 202 most addition (16/38) and subtraction (4/5) trials used sugars-sweetened beverages. Most trials were 203 funded by agency sources (government, not-for-profit health agency or university sources), except for

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2 3	204	ad libitum trails which were primarily funded by agency-industry funding. Lastly, very few trials were
4	204	ad libitum trails which were primarily funded by agency-industry funding. Lastly, very few thats were
5 6 7	205	assessed as high risk of bias across the 5 domains of bias, as assessed by the Cochrane Risk of Bias Tool
7 8 9	206	(Supplementary Figure 1).
9 10 11	207	HbA1c
12 13	208	The effect of fructose-containing food sources on HbA1c are shown in Figure 2 and Supplementary
14 15	209	Figures 2-5. In 32 substitution trials involving 946 participants where fructose-containing sugars were
16 17	210	exchanged for other macronutrients of equal energy, a significant reduction in HbA1c was observed
18 19 20	211	(MD=-0.14% [95% CI=-0.25, -0.04], p=0.007, I <sup>2</sup> =81%, heterogeneity p <0.00001; moderate quality
20 21 22	212	evidence) . No other significant effects were found for total food sources of fructose containing-sugars
23 24	213	in addition (6 trials, 231 participants, high quality evidence), subtraction (1 trial, 240 participants, low
25 26	214	quality evidence) or ad libitum trials (1 trial, 10 participants, very low quality evidence). Fructose-
27 28	215	containing sugars from fruits significantly decreased HbA1c (MD=-0.12% [95% CI=-0.23, -0.003], p=0.04)
29 30 31	216	in substitution trials. No food sources were significant in addition, subtraction or ad libitum trials.
32 33	217	Sensitivity analyses through removal of individual trials did not change the overall significance or
34 35	218	direction of the effect in any analyses.
36 37	219	A priori subgroup analyses are presented in supplementary figures 6 and 7. In substitution trials
38 39 40	220	(Supplementary Figure 6), participants with higher baseline levels showed greater improvements in
41 42	221	glycemic control on fructose-containing arms relative to controls. Post-hoc dose-response analyses are
43 44	222	presented in Supplementary Figure 8 and Supplementary table 3. In substitution trials, we found no
45 46	223	significant effect modification by dose (Supplementary Figure 8A) or by dose-thresholds
47 48 49	224	(Supplementary table 3A) of fructose intake. No subgroup or dose-response analyses were conducted
50 51	225	for addition, subtraction or ad libitum comparisons as less than 10 trials were available in each analysis.
52 53	226	Fasting Blood Glucose
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2 3 4	227	The effects of fructose-containing food sources on fasting blood glucose are shown in Figure 3 and
5 6 7 8 9 10 11	228	Supplementary Figures 9-12. In 35 trials involving 985 participants under addition conditions, fructose-
	229	containing sugars from all food sources increased fasting blood glucose (MD=0.07 [95% CI=0.002, 0.13],
	230	p=0.04, I <sup>2</sup> =72%, p heterogeneity<0.0001], moderate quality evidence), but had no effect on fasting
12 13	231	blood glucose under substitution (101 trials, 2948 participants, moderate quality evidence), subtraction
14 15	232	(4 trials, 585 participants, high quality evidence) or ad libitum conditions (6 trials, 459 participants, high
16 17	233	quality evidence). Fructose-containing sugars in the form of liquid meal replacements led to a significant
18 19	234	increase in fasting blood glucose (0.83 mmol/L [0.28, 1.39], p=0.003) when adding excess energy to the
20 21 22	235	diet under addition conditions, although this was only based on one trial. Individual removal of 13 trials
22 23 24 25 26 27 28 29 30 31	236	(49, 79, 91, 92, 98, 100, 107, 121, 132, 133, 138) from the addition comparisons changed the overall
	237	significance of the effect while keeping direction the same (Supplementary Table 4). Under subtraction
	238	conditions, removal of a trial by Campos et al. (G2) reversed the direction of the effect and explained all
	239	of the heterogeneity, but did not modify overall significance (Supplementary Table 4).
31 32 33	240	A priori subgroup analyses are presented in supplementary figures 13-16. A priori subgroup analyses
34 35	241	revealed an effect modification by baseline fasting blood glucose under substitution conditions
36 37	242	(Supplementary Figure 13), such that baseline fasting blood glucose levels of ≥6.1 mmol/L led to a
38 39 40 41 42	243	greater decrease in levels of fasting blood glucose. Additionally, although fructose dose was not
	244	significant at ≤10 or >10% of energy, a significant continuous dose response was observed (P=0.01)
43 44	245	(Supplementary Figure 8-B), but this effect lost significance upon removal of an outlier study using
45 46	246	extreme doses of sucrose at 75% of energy(10). Post-hoc dose-threshold analyses also showed
47 48	247	significant effect modification by dose at doses >50 % of energy (P<0.05), such that doses >50 % of
49 50 51	248	energy resulted in higher levels of fasting blood glucose (Supplementary Table 3B). With the removal of
52 53	249	the same outlier study (Hendler et al. 1990(155)), this effect was seen starting at lower doses (>20 %
54 55	250	energy [P=0.04]). Significant subgroup effects were also observed in addition trials (Supplementary
56 57 58		Dage <b>17</b> of <b>47</b>

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251	Figure 14) by fructose-containing sugar form, age and underlying disease status. Particularly, fructose-
252	containing sugars in the form of honey (3 trials) led to greater decreases in fasting blood glucose,
253	whereas fructose in its pure monomeric form (9 trials) lead to increasing effects on fasting blood glucose
254	when adding excess energy to the diet. Second, a greater reduction in levels of fasting blood glucose
255	was observed for children who supplemented the diet with excess calories from fructose-containing
256	sugars compared to adults, although only one trial in children was available for analysis. Lastly,
257	participants with diabetes displayed greater improvements in fasting blood glucose on the fructose-
258	containing sugars interventions compared to patients without diabetes. No a priori subgroup analyses
259	were conducted in subtraction or ad libitum trials as too few trials were available. Post-hoc dose-
260	threshold analyses did not show any significant effect modification by dose (Supplementary Table 3C).
261	Fasting Blood Insulin
262	The effect of fructose-containing food sources on fasting blood insulin are shown in Figure 4 and
263	Supplementary Figures 17-20. In 27 addition trials involving 730 participants where fructose-containing
264	sugars supplemented the diet with excess energy compared to the diet alone or non-caloric food
265	sources, an increasing effect on fasting blood insulin was observed from total food-sources (MD=5.33
266	pmol/L [95% CI=2.26, 8.41], p <0.001, moderate quality evidence). Significant food sources of fructose-
267	containing sugars leading to an increase in fasting blood insulin included SSBs (MD=6.17 pmol/L [95%
268	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
269	trial) and mixed sources (MD=13.00 pmol/L [95% CI=0.81, 25.19], p =0.04, 1 trial). Total food sources of
270	fructose-containing sugars did not demonstrate any significant effects in substitution (75 trials, 2194
271	participants, moderate quality evidence), subtraction (3 trials, 33 participants, moderate quality
272	evidence) or ad libitum trials (4 trials, 302 participants, high quality evidence). However, in substitution
273	trials, an increase in fasting blood insulin was observed when fructose-containing sugars were in the
274	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

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3 4	275	(MD=26.59 [95% CI=9.51, 43.68], p<0.01, 1 trial). Sensitivity analysis through removal of a trial by
5 6 7 8 9 10	276	Campos et al. from the subtraction analysis changed the significance of the effect and explained 78% of
	277	the heterogeneity, while overall direction of the effect remained the same (39.54 pmol/L [2.06, 75.02], p
	278	=0.02) ( <b>Supplementary Table 4</b> ). Similarly, removal of a trial by Markey et al. from the ad libitum
11 12 13	279	analysis changed the significance of the effect and explained all of the heterogeneity while keeping
14 15	280	direction the same (9.51 pmol/L [1.59, 17.42], p-value=0.02) (Supplementary Table 4).
16 17	281	Significant heterogeneity was present in all analyses except for ad libitum trials. A priori subgroup
18 19	282	analyses revealed a significant effect modification by fructose-containing sugar dose in addition trials
20 21 22	283	(Supplementary Figure 21), where doses greater than 10% of total energy intake lead to larger increases
22 23 24	284	in fasting blood insulin. However, a continuous dose response was not observed (P=0.12)
25 26	285	(Supplementary Figure 12-C). Although fructose dose was not significant in substitution trials at ≤10 or
27 28 29 30 31 32 33	286	>10% of energy (Supplementary Figure 22), a significant continuous dose response was observed
	287	(P=0.04) (Supplementary Figure 12-B). However, this effect became non-significant upon removal of
	288	two outlier studies using extreme doses of sucrose (75-95% of energy)(10, 11). No subgroup analyses
34 35	289	were conducted for subtraction or ad libitum conditions as there were not enough trials available for
36 37	290	each analysis. Post-hoc dose-threshold analyses did not show any significant effect modification by dose
38 39	291	(supplementary table 3D) in substitution trials or addition trials (supplementary table 3E).
40 41	292	Publication Bias
42 43 44	293	There was no evidence for publication bias through visual inspection of funnel plots or Egger's and
45 46	294	Begg's tests for the effect of fructose containing sugars on fasting blood glucose, fasting blood insulin or
47 48	295	HbA1c for all analyses where ≥10 trials were available ( <b>Supplementary Figure 23</b> ).
49 50	296	GRADE Assessment
51 52	297	A summary of the quality of evidence assessment for the effect of fructose-containing food sources on
53 54 55	298	measures of glycemic control can be found in <b>Table 2.</b> In general, the confidence we have in our effect
56 57		
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299	estimates for the analyses on fasting blood glucose and insulin ranged from moderate to high, whereas
300	HbA1c analyses ranged from very low to high. Evidence for fasting blood glucose and insulin in
301	substitution and addition trials as well as HbA1c in substitution trials were downgraded for serious
302	inconsistency due to significant interstudy heterogeneity. Similarly, evidence for fasting blood insulin in
303	subtraction trials was downgraded for serious imprecision as the 95% CIs for the effect estimate [-22.83,
304	26.83] included both clinically important benefit (<10 pmol/L) and harm (>10 pmol/L). On the other
305	hand, evidence for HbA1c in subtraction and ad libitum trials were downgraded due to indirectness and
306	imprecision as only 1 trial was available for each of these analyses (240 participants in the subtraction
307	trial and 10 participants in the ad libitum trial), and the 95% CI for the effect estimate [-0.38, 0.42]
308	included both clinically important benefit (≤-0.3%) and harm (≥0.3%) for the ad libitum trial.
309	DISCUSSION
310	The results from our systematic review and meta-analysis of 160 trials involving 5,181 participants with
311	and without diabetes showed variable effects of food sources of fructose-containing sugars on glycemic
312	control at median doses ranging from 12-23% energy over median follow-up durations of 4-12 weeks. In
313	substitution trials, in which food sources of fructose-containing sugars were compared with other
314	macronutrient sources matched for energy, a decrease in HbA1c for total food sources of fructose-
315	containing sugars, especially from fruit, was observed with no effects on fasting glucose or fasting
316	insulin. In addition trials, in which food sources of fructose-containing sugars supplemented diets with
317	excess energy compared to the same diet alone without the excess energy (with or without the use of
318	non-caloric sweeteners), an adverse effect was observed for total food sources of fructose-containing
319	sugars, especially from SSBs, on fasting blood insulin and glucose but not HbA1c. No effect of food
320	sources of fructose-containing sugars were observed on glycemic control in subtraction or ad libitum
321	trials.
322	Results in the context of other studies

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3 4	323	These findings agree with two previously conducted systematic reviews and meta-analyses which
5 6	324	demonstrated a beneficial effect of isocalorically exchanging fructose for other carbohydrates on
7 8	325	glycated blood proteins in participants with diabetes (SMD =-0.25 [95% CI -0.46 to -0.04], p-value= 0.02;
9 10	326	equivalent to ~0.53% reduction in HbA1c)(17), and without diabetes (fructose intake <90 g/d
11 12 13	327	significantly improved HbA1c dependent on dose, study duration and severity of dysglcemia) (156).
14 15	328	Although the modest decrease in HbA1c from our analysis (MD=-0.14% [-0.25 to -0.04]) did not exceed
16 17	329	the clinically meaningful threshold of 0.3% proposed by the U.S Food and Drug administration for the
18 19	330	development of new drugs for diabetes as observed in the previous meta-analysis (157), our findings
20 21	331	suggest that fructose-containing sugars may have modest benefits for glycemic control when they
22 23 24	332	replace other macronutrients on a calorie-for-calorie basis. On the other hand, our results suggest that
24 25 26	333	fructose-containing sugars providing excess energy to the diet may raise fasting blood glucose and
27 28	334	insulin agreeing with observed findings from the previous meta-analysis on fructose and glycemic
29 30	335	control (17).
31 32	336	The adverse effects of SSB consumption are concordant with findings from several large observational
33 34 35	337	studies, showing an increased risk of developing type 2 diabetes with higher SSB consumption(20, 21)
36 37	338	and a decreased risk of type 2 diabetes with higher fruit intake(22, 23).
38 39	339	Potential mechanisms
40 41	340	Several proposed mechanisms may explain the observed beneficial effect of fructose-containing sugars
42 43		
44 45	341	on HbA1c when substituted for other calories in the diet. Fructose has a relatively low glycemic index of
45 46 47	342	16 compared to reference carbohydrates such as starch with a GI of 100 (158). As a majority of the
48 49	343	comparators used in substitution trials were in the form of starch, replacement of these high-GI
50 51	344	carbohydrates with fructose may have reduced the overall GI of the diet, leading to long term glycemic
52 53	345	improvement through alleviation of pancreatic stress (159, 160).
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3 4	346	An alternative mechanism accounting for the observed beneficial effects of fructose-containing sugars
5	347	on HbA1c in substitution trials suggests that small catalytic fructose doses of ≤10-g/meal (typically found
7 3	348	in low GI fruits) may improve glycaemia by the ability of fructose-1-P to up regulate glucokinase activity
9 10	349	through the glucokinase regulatory protein, resulting in decreased hepatic glucose production (161) and
1  2  3	350	increased glycogen synthesis(162). This may explain the decrease in HbA1c observed in substitution
14 15	351	trials particularly when fruits were compared to other fructose-containing food sources. Although the
16 17	352	benefit of fruits did not extend to fasting blood glucose and insulin, the summary effects for both
18 19	353	endpoints tended to be in the direction of benefit, with the possibility of additional trials allowing
20 21 22	354	sufficient power to confirm any beneficial effects.
22 23 24	355	In contrast, the observed adverse effects of fructose-containing sugars on glycemic control under
25 26	356	addition conditions appear to be largely driven by the energy contribution of the sugars. Excess calories
27 28	357	in the form of fructose-containing sugars supplementing the background diet may promote ectopic
29 30 31	358	weight gain, contributing to downstream insulin resistance and impaired glycemic control. This
32 33	359	mechanism is not unique to sugars per se and would be expected for the overconsumption of any
34 35	360	dietary macronutrient. Similar effects have been observed under fructose overfeeding for body weight
36 37	361	(163), blood pressure(164), uric acid(165), NAFLD(166) and postprandial triglycerides (167).
38 39 40	362	A priori and posthoc subgroup analyses
41 42	363	In subgroup analyses, greater improvements in fasting blood glucose were observed in those trials
13 14	364	which enrolled participants with higher baseline fasting glucose (substitution and addition trials) and
45 46	365	greater improvements HbA1c were observed in those trials enrolling participants with higher baseline
17 18 19	366	HbA1c (substitution trials), suggesting a regression-to-the-mean phenomenon. These effects were
50 51	367	concordant with the observed subgroup modification by underlying health status demonstrating
52 53	368	greatest benefits on fasting blood glucose for patients with diabetes in addition trials, suggesting a
54 55	369	potential benefit in using sugars with higher fructose content, particularly in the form of fruit, as an
56 57		Dage <b>17</b> of <b>42</b>

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2 3 4	370	alternative sweetener to replace higher GI carbohydrates in the diet of patients with diabetes.
5 6 7 8 9 10 11 12 13	371	Additionally, a significant subgroup effect by fructose-containing sugar form was observed under
	372	addition conditions, whereby the addition of honey to the diet led to greater decreases in fasting blood
	373	glucose when compared to other fructose-containing sugars. Although the underlying mechanism and
	374	potential use of honey as an effective antidiabetic agent currently remains inconclusive, a few
14 15	375	preliminary studies in animals and humans have suggested that honey, through its small but measurable
16 17 18 19 20	376	concentration of non-digestible short chain oligosaccharides as well as polyphenols, mineral and other
	377	antioxidant components, may exert beneficial metabolic effects including altering glucose
21	378	metabolism(168), lowering insulin resistance (169)and reducing hepatic oxidative stress(170, 171). On
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40	379	the other hand, while subgroup analyses by fructose form in addition trials suggested a modest increase
	380	in fasting blood glucose when fructose was compared to other fructose-containing sugars, the
	381	supraphysiological doses of fructose used in these addition trials (average intake=172.8 $\pm$ 57.8 g/d) have
	382	been shown to greatly exceed estimated levels of national dietary intake (average intake=49 $\pm$ 1.0 g/d,
	383	NHANES 1977-2004)(172). As with the overconsumption of any macronutrient, observed adverse
	384	effects may be irrelevant under normal levels of dietary consumption and are likely due to excess
	385	calories rather than unique metabolic attributes of fructose per se.
	386	Dietary guidelines informing the consumption of sugars have proposed upper limits of <5-10% based on
40 41 42	387	food modeling patterns as well as the development of dental caries and obesity (155, 173). Our
43 44	388	categorical subgroup analyses revealed a significant effect modification by fructose dose at levels of
45 46	389	≤10% or >10% energy on levels of fasting blood insulin in addition trials. However, significant effect
47 48	390	modification was not seen for the continuous subgroup analyses, and post-hoc analyses also did not
49 50 51	391	identify a threshold for dose (data not shown). On the other hand, while a categorical dose effect was
52 53	392	not observed for the remaining subgroup analyses, continuous subgroup analyses suggested significant
54 55	393	dose gradients for the effect of fructose-containing sugars on fasting blood glucose and fasting blood
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394	insulin under substitution conditions. However, removal of a trial by Hendler et al.(10) providing a liquid
395	meal replacement containing 75% of energy as sucrose compared to a liquid meal replacement
396	containing 75% of energy as fat eliminated this dose response in fasting glucose trials. Similarly, removal
397	of two trials by Hendler et al. (10, 11) providing liquid meal replacements containing 75% or 95% of
398	energy as sucrose compared to 75% or 95% of energy as fat or protein respectively also eliminated the
399	observed dose response gradient in fasting insulin trials. Although both trials by Hendler et al. may
400	suggest a potential for harm when substituting sucrose for fat or protein as a primary source of calories
401	in the diet, the dose of sucrose used in these trials were 150-190 grams per day, exceeding estimated
402	levels of average intake from added sugars (approximately 10% energy or ~50 grams/day(174)) by three-
403	to four-fold. Thus, removal of these outlier studies providing extreme doses of sucrose suggested the
404	lack of a true dose response when fructose-containing sugars were isocalorically substituted for other
405	macronutrients in the diet.
406	Project Implications
407	To our knowledge, this has been the first systematic review and meta-analysis to assess the effect of
408	different food sources of fructose-containing sugars on glycemic control. Various food sources of
409	fructose-containing sugars led to significant differences in glycemic control measurements, however
410	several analyses only had limited number of trials using a particular food source, or lacked robustness in
411	their observed effects. For example, under addition conditions, fructose-containing sugars in the form
412	of liquid meal replacements significantly increased levels of fasting blood glucose, fructose-containing
413	sugars in the form of dairy products and mixed sources increased levels of fasting insulin, and under
414	substitution trials, fructose-containing sugars in the form of dairy products increased fasting blood
415	insulin. However, as only one trial was available for each of these analyses, additional trials are
416	warranted to determine any meaningful effects. Furthermore, although fructose-containing sugars in
417	the form of mixed dietary sources (food and beverages) led to a modest increase in levels of fasting
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2 3 4	418	blood insulin in substitution trials, this effect was bordering significance (p=0.04), and individual removal
5 6	419	of 18 of the 34 trials (12, 55-57, 68, 70, 81, 95, 102, 103, 140, 148, 153), led to non-significant results.
7 8	420	Additionally, while fructose-containing sugars in the form of fruits showed a modest decrease in levels
9 10 11	421	of HbA1c in substitution trials, individual removal of 5 of the 8 trials (43, 50, 61, 77, 108) eliminated the
12 13	422	significance of the effect although direction remained the same. On the other hand, pooled analyses
14 15	423	from 13 trials of fructose-containing sugars in the form of SSBs lead to significant increases in fasting
16 17	424	insulin when providing excess energy to the diet (6.17 pmol/L [1.55, 10.78], p=0.009), and these results
18 19 20	425	were not sensitive to removal of any individual trial.
20 21 22	426	Taken together, as dietary guidelines have shifted towards a food-based approach, our findings may
23 24	427	have implications for guiding recommendations on important food sources of fructose-containing sugars
25 26	428	towards the prevention and management of diabetes. Particularly, as fructose-containing sugars in the
27 28 29	429	form of fruits tended to demonstrate improvements on HbA1c, encouraging fruit consumption to
30 31	430	replace other dietary sweeteners may be an effective strategy for improving glycemic control, especially
32 33	431	in people with diabetes. Additionally, as SSBs tended to impair fasting glucose and insulin when adding
34 35	432	excess energy to the diet, public health strategies to reduce consumption of this fructose-containing
36 37 38	433	food source may be useful, especially as SSBs have recently come under scrutiny for providing empty
39 40	434	calories in absence of any nutritional "value".
41 42	435	Strengths and Limitations
43 44	436	Our systematic review and meta-analysis presented several strengths, including: 1) a rigorous search
45 46 47	437	and selection process of available literature examining the effect of fructose-containing food sources on
47 48 49	438	glycemic control, 2) inclusion of controlled trials which give the greatest protection against bias (noting
50 51	439	that results did not differ between randomized and non randomized trials), 3) the collation and
52 53	440	synthesis of data from 160 controlled trials involving 5181 human participants, and 4) an assessment of
54 55	441	overall quality of evidence using the GRADE assessment tool.
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3 4	442	Several of our analyses also presented limitations. In particular, significant unexplained heterogeneity
5 6	443	was present for all substitution analyses, as well as addition analyses for fasting blood glucose and
7 8	444	fasting blood insulin. Second, serious indirectness was suggested for several analyses as only one trial
9 10	445	in 240 overweight and obese women was available in the HbA1c subtraction analysis, and similarly, on
11 12 13	446	trial in 10 patients with diabetes was available in the HbA1c ad libitum analysis. Third, as the effect
14 15	447	estimates in subtraction trials on fasting insulin as well as subtraction and ad libitum trials on HbA1c
16 17	448	crossed the minimally important difference for benefit or harm, imprecision in these results reduced
18 19	449	confidence in the overall effect. Lastly, a majority of the trials were small and short in duration, with a
20 21 22	450	median follow up of less than 8 weeks for substitution and addition trials and a median trial size rangin
22 23 24	451	from 14 participants in substitution trials to 39 participants in ad libitum trials. Additionally, as Hba1c
25 26	452	reflects average blood glucose levels over 8-12 weeks, our ability to determine longer term effects on
27 28	453	glycemic control may be limited.
29 30	454	Based on the strengths and limitations, our GRADE assessment graded the evidence as very low to high
31 32 33	455	quality for HbA1c and moderate to high quality for fasting blood glucose and insulin.
34 35	456	CONCLUSION
36 37	457	In conclusion, the effects of fructose-containing sugars on glycemic control are both energy and source
38 39	458	dependent. Fructose-containing sugars, especially from fruit, exchanged for equal amounts of calories
40 41 42	459	from other macronutrient sources led to improvements in HbA1c without adversely affecting fasting
43 44	460	blood glucose or insulin. However, when fructose-containing sugars added excess energy to the diet,
45 46	461	particularly in the form of SSBs, a significant increase in fasting blood insulin and fasting blood glucose
47 48	462	was observed. No significant effects were observed under subtraction or ad libitum conditions. The la
49 50 51	463	of harm and even advantages were most pronounced in those with higher baseline levels or who had
52 53	464	diabetes. While our findings may suggest that important food sources of fructose-containing sugars do
54 55	465	not have adverse effects on glycemic control in energy matched replacement or even free replacemen
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3 4	466	of other less sugary foods, our GRADE assessment suggest that more research is likely to have an
5 6	467	important influence on many of our estimates. Longer, larger, high quality trials using a variety of
7 8 9	468	fructose-containing food sources are required to assess the durability of these effects under real world
9 10 11	469	conditions.
12 13	470	ACKNOWLEDGEMENTS
14 15	471	The authors thank Teruko Kishibe, Information Specialist, Scotiabank Health Sciences Library at St.
16 17 18	472	Michael's Hospital, for her help in the development of search terms used, and to Zujaja-Tul-Noor for her
19 20	473	help in the creation of some figures. Aspects of this work were presented at the 34 <sup>th</sup> International
21 22	474	Symposium on Diabetes and Nutrition (ISDN), Diabetes and Nutrition Study Group (DNSG) of the
23 24	475	European Association of the Study of Diabetes (EASD), Prague, Czech Republic, June 29-July 1, 2016.
25 26 27	476	CONTRIBUTORS
27 28 29	477	VLC and JLS had full access to all of the data in the study and take responsibility for the integrity of the
30 31	478	data and the accuracy of the data analysis. Study concept and design: VLC, JLS and DJAJ. Acquisition,
32 33	479	analysis and interpretation of data: VLC, EV, SBM, AIC, VH, LAL, TMSW, TAK, DJAJ and JLS. Drafting of the
34 35 36	480	manuscript: VLC. Critical revision of the manuscript for important intellectual content: All authors.
37 38	481	Statistical analysis: VLC. Study supervision: JLS and DJAJ.
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41 42	483	This work was funded by the Canadian Diabetes Association (grant # CS-5-15-4771-JS). The Diet,
43 44 45	484	Digestive tract, and Disease (3-D) Centre, funded through the Canada Foundation for Innovation (CFI)
45 46 47	485	and the Ministry of Research and Innovation's Ontario Research Fund (ORF), provided the infrastructure
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New Investigator Award. None of the sponsors had a role in any aspect of the present study, including

design and conduct of the study; collection, management, analysis, and interpretation of the data; and

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf and

declare: no support from any organisation for the submitted work; Thomas M S Wolever is a part owner

and the President of Glycemic Index Laboratories, Inc, Toronto, Canada, and has authored several

popular diet books on the glycemic index for which he has received royalties from Phillipa Sandall

research support from or served on the scientific advisory board for CIHR, CDA, Dairy Farmers of

Canada, McCain Foods, Temasek Polytechnic, Northwestern University, Royal Society of London,

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the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Loblaw

Growers, Barilla, Bayer, the Canola Council of Canada, the Coca-Cola Company, Danone, General Mills,

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Control Council, CIHR, the Canola Council of Canada, the Coca-Cola Company (investigator initiated,

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preparation, review, approval of the manuscript or decision to publish.

**COMPETING INTERESTS** 

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1 2		
- 3 4	514	Companies Ltd., the Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms,
5 6	515	the Peanut Institute, PepsiCo, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Solae,
7 8	516	Sun-Maid, Tate and Lyle, and Unilever. He is on the Dietary Guidelines Committee for the Diabetes
9 10 11	517	Nutrition Study Group of the European Association for the Study of Diabetes and has served on the
12 13	518	scientific advisory board for the Almond Board of California, the International Tree Nut Council, Oldways
14 15	519	Preservation Trust, Paramount Farms and Pulse Canada. Russell J de Souza was previously funded by a
16 17	520	CIHR Postdoctoral Fellowship Award and has received research support from the CIHR, the Calorie
18 19 20	521	Control Council, the Canadian Foundation for Dietetic Research and the Coca-Cola Company
20 21 22	522	(investigator initiated, unrestricted grant) and travel support from the World Health Organization (WHO)
23 24	523	to attend group meetings. He has served as an external resource person to WHO's Nutrition Guidelines
25 26	524	Advisory Group and is the lead author of 2 systematic reviews and meta-analyses commissioned by
27 28	525	WHO of the relation of saturated fatty acids and trans fatty acids with health outcomes. David J.A.
29 30 31	526	Jenkins has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts
32 33	527	Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network,
34 35	528	Loblaw Companies Ltd., Unilever, Barilla, the Almond Board of California, the Coca-Cola Company
36 37	529	(investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafti, the
38 39 40	530	International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the
40 41 42	531	Canola and Flax Councils of Canada, the Calorie Control Council, the CIHR, the Canada Foundation for
43 44	532	Innovation and the Ontario Research Fund. He has received an honorarium from the United States
45 46	533	Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013
47 48 49	534	Award for Excellence in Research from the International Nut and Dried Fruit Council. He received
50 51	535	funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini
52 53	536	cases for the Canadian Diabetes Association. He has been on the speaker's panel, served on the
54 55	537	scientific advisory board, and/or received travel support and/or honoraria from the Almond Board of
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538	California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd, the Griffin Hospital (for the
539	development of the NuVal scoring system), the Coca- Cola Company, Saskatchewan Pulse Growers,
540	Sanitarium Company, Orafti, the Almond Board of California, the American Peanut Council, the
541	International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute,
542	Herbalife International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla,
543	Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats,
544	Procter and Gamble, the Coca-Cola Company, the Griffin Hospital, Abbott Laboratories, the Canola
545	Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the
546	Alpro Foundation, Pioneer Hi- Bred International, DuPont Nutrition and Health, Spherix Consulting and
547	WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada,
548	the Nutritional Fundamentals for Health, AgriCulture and Agri-Food Canada, the Canadian Agri-Food
549	Policy Institute, Pulse Canada, the Saskatchewan Pulse Growers, the Soy Foods Association of North
550	America, the Nutrition Foundation of Italy (NFI), Nutra-Source Diagnostics, the McDougall Program, the
551	Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic
552	Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of
553	Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition,
554	Metabolism and Diabetes. John L Sievenpiper has received research support from the Canadian
555	Institutes of health Research (CIHR), Canadian Diabetes Association (CDA), PSI Foundation, Calorie
556	Control Council, Banting and Best Diabetes Centre (BBDC), American Society for Nutrition (ASN), Dr.
557	Pepper Snapple Group (investigator initiated, unrestricted donation), INC International Nut and Dried
558	Fruit Council, and The Tate and Lyle Nutritional Research Fund at the University of Toronto. He has
559	received speaker fees and/or honoraria from the Canadian Diabetes Association (CDA), Canadian
560	Nutrition Society (CNS), University of Alabama at Birmingham, Abbott Laboratories, Canadian Sugar
561	Institute, Dr. Pepper Snapple Group, The Coca-Cola Company, Dairy Farmers of Canada, Nutrition

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2 3 4	562	Foundation of Italy (NFI), C3 Collaborating for Health, WhiteWave Foods, Rippe Lifestyle, mdBriefcase,
5 6	563	Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, and Pulse Canada. He has ad hoc
7 8	564	consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle. He is a member
9 10 11	565	of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines
12 13	566	Expert Committees of the Canadian Diabetes Association (CDA), European Association for the study of
14 15	567	Diabetes (EASD), and Canadian Cardiovascular Society (CCS), as well as an expert writing panel of the
16 17	568	American Society for Nutrition (ASN). He serves as an unpaid scientific advisor for the Food, Nutrition,
18 19	569	and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life
20 21 22	570	Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality
23 24	571	Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the
25 26	572	EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an
27 28	573	employee of Unilever Canada. No competing interests were declared by Vivian L Choo, Effie Viguiliouk,
29 30 31	574	Sonia Blanco Mejia, Adrian I Cozma, Tauseef A Khan, Vanessa Ha, and Lawrence A Leiter. There are no
31 32 33	575	patents, products in development or marketed products to declare.
34 35	576	EXCLUSIVE LICENCE
36 37	577	The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all
38 39	578	authors, a worldwide license
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7 8	588	party to do any or all of the above.
9 10	589	TRANSPARENCY DECLARATION
11 12 13	590	The lead author affirms that this manuscript is an honest, accurate, and transparent account of the
14 15	591	study being reported; that no important aspects of the study have been omitted; and that any
16 17	592	discrepancies from the study as planned (and, if relevant, registered) have been explained.
18 19	593	ETHICS APPROVAL
20 21 22	594	Not required.
23 24	595	DATA SHARING STATEMENT
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	596 597	DATA SHARING STATEMENT No additional data are available.
57 58		Page <b>27</b> of <b>42</b>
59 60		https://mc.manuscriptcentral.com/bmj

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3	598	References
4	599	
5	600	1. Bray GA, Popkin BM. Dietary sugar and body weight: have we reached a crisis in the epidemic of
6		
7	601	obesity and diabetes?: health be damned! Pour on the sugar. Diabetes care. 2014;37(4):950-6.
8 9	602	2. Kahn R, Sievenpiper JL. Dietary sugar and body weight: have we reached a crisis in the epidemic
9 10	603	of obesity and diabetes?: we have, but the pox on sugar is overwrought and overworked. Diabetes care.
11	604	2014;37(4):957-62.
12	605	3. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play
13	606	a role in the epidemic of obesity. The American journal of clinical nutrition. 2004;79(4):537-43.
14	607	4. Goran MI, Ulijaszek SJ, Ventura EE. High fructose corn syrup and diabetes prevalence: a global
15	608	perspective. Global public health. 2013;8(1):55-64.
16	609	5. Bantle JP, Laine DC, Thomas JW. Metabolic effects of dietary fructose and sucrose in types I and
17	610	II diabetic subjects. Jama. 1986;256(23):3241-6.
18	611	6. Lustig RH. Fructose: it's "alcohol without the buzz". Advances in nutrition. 2013;4(2):226-35.
19	612	7. Huang BW, Chiang MT, Yao HT, Chiang W. The effect of high-fat and high-fructose diets on
20	613	glucose tolerance and plasma lipid and leptin levels in rats. Diabetes, obesity & metabolism.
21 22	614	2004;6(2):120-6.
22	615	8. de Moura RF, Ribeiro C, de Oliveira JA, Stevanato E, de Mello MA. Metabolic syndrome signs in
24	616	Wistar rats submitted to different high-fructose ingestion protocols. The British journal of nutrition.
25	617	2009;101(8):1178-84.
26	618	9. Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension
27	619	in rats. Hypertension. 1987;10(5):512-6.
28	620	10. Hendler R, Bonde AA. Effects of sucrose on resting metabolic rate, nitrogen balance, leucine
29	621	turnover and oxidation during weight loss with low calorie diets. International journal of obesity.
30	622	1990;14(11):927-38.
31	623	11. Hendler RG, Walesky M, Sherwin RS. Sucrose substitution in prevention and reversal of the fall
32 33	624	in metabolic rate accompanying hypocaloric diets. The American journal of medicine. 1986;81(2):280-4.
33 34	625	12. Yudkin J, Szanto S. Increased levels of plasma insulin and eleven hydroxycorticosteroid induced
35	626	by sucrose, and their reduction by phenformin. Hormone and metabolic research = Hormon- und
36	627	Stoffwechselforschung = Hormones et metabolisme. 1972;4(6):417-20.
37	628	13. Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Diet and risk of clinical
38	629	diabetes in women. The American journal of clinical nutrition. 1992;55(5):1018-23.
39	630	14. Janket SJ, Manson JE, Sesso H, Buring JE, Liu S. A prospective study of sugar intake and risk of
40	631	type 2 diabetes in women. Diabetes care. 2003;26(4):1008-15.
41	632	15. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened
42	633	beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. Jama.
43	634	2004;292(8):927-34.
44 45	635	16. Montonen J, Jarvinen R, Knekt P, Heliovaara M, Reunanen A. Consumption of sweetened
45 46		
47	636 637	beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. The Journal of
48		nutrition. 2007;137(6):1447-54.
49	638	17. Cozma AI, Sievenpiper JL, de Souza RJ, Chiavaroli L, Ha V, Wang DD, et al. Effect of fructose on
50	639	glycemic control in diabetes: a systematic review and meta-analysis of controlled feeding trials. Diabetes
51	640	care. 2012;35(7):1611-20.
52	641	18. White JS. Challenging the fructose hypothesis: new perspectives on fructose consumption and
53	642	metabolism. Advances in nutrition. 2013;4(2):246-56.
54 57	643	19. Theytaz F, de Giorgi S, Hodson L, Stefanoni N, Rey V, Schneiter P, et al. Metabolic fate of
55 56	644	fructose ingested with and without glucose in a mixed meal. Nutrients. 2014;6(7):2632-49.
56 57		
57 58		Page <b>28</b> of <b>42</b>
59		
60		https://mc.manuscriptcentral.com/bmj

Page 30 of 91

20. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. BMJ. 2015;351:h3576. Greenwood DC, Threapleton DE, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, et al. 21. Association between sugar-sweetened and artificially sweetened soft drinks and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. The British journal of nutrition. 2014;112(5):725-34. Li S, Miao S, Huang Y, Liu Z, Tian H, Yin X, et al. Fruit intake decreases risk of incident type 2 22. diabetes: an updated meta-analysis. Endocrine. 2015;48(2):454-60. 23. Muraki I, Imamura F, Manson JE, Hu FB, Willett WC, van Dam RM, et al. Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. BMJ. 2013;347:f5001. 24. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at http://health.gov/dietaryguidelines/2015/guidelines/. 25. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane collaboration Available from www.cochrane-handbookorg. 2011. 26. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery. 2010;8(5):336-41. 27. Wilczynski NL, Morgan D, Haynes RB, Hedges T. An overview of the design and methods for retrieving high-quality studies for clinical care. BMC medical informatics and decision making. 2005;5:20. 28. Huwaldt, J.A., 2015. Plot digitizer. Free software distributed from http://plotdigitizer.sourceforge.net/ Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane 29. Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. 30. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. Borenstein M, Hedges LV, Higgins JP, H.R. R. Introduction to meta-analysis. Wiley J, editor2008. 31. 32. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-73. Greenhouse JB, Iyengar S. Sensitivity analysis and diagnostics. In: Cooper HM, Hedges LV, 33. Valentine JC, eds. The handbook of research synthesis and meta-analysis. 2nd ed. Russell Sage Foundation 2009. 34. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000;53(11):1119-29. 35. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455-63. 36. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94. Abdel-Sayed A, Binnert C, Le KA, Bortolotti M, Schneiter P, Tappy L. A high-fructose diet impairs 37. basal and stress-mediated lipid metabolism in healthy male subjects. The British journal of nutrition. 2008;100(2):393-9. 38. Abdulrhman MM, El-Hefnawy MH, Aly RH, Shatla RH, Mamdouh RM, Mahmoud DM, et al. Metabolic effects of honey in type 1 diabetes mellitus: a randomized crossover pilot study. Journal of medicinal food. 2013;16(1):66-72. Abraira C, Derler J. Large variations of sucrose in constant carbohydrate diets in type II diabetes. 39. The American journal of medicine. 1988;84(2):193-200. Page 29 of 42 

Page 31 of 91

1

60

BMJ

2		
3	692	40. Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I, et al. Low to moderate
4	693	sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes
5	694	inflammation in healthy young men: a randomized controlled trial. The American journal of clinical
6	695	nutrition. 2011;94(2):479-85.
7	696	41. Aeberli I, Hochuli M, Berneis K. Response to Comment on: Aeberli et al. Moderate amounts of
8	690 697	fructose consumption impair insulin sensitivity in healthy young men: a randomized controlled trial.
9		
10 11	698 600	Diabetes Care 2013;36:150-156. Diabetes care. 2013;36(7):e105.
12	699	42. Anderson JW, Story LJ, Zettwoch NC, Gustafson NJ, Jefferson BS. Metabolic effects of fructose
13	700	supplementation in diabetic individuals. Diabetes care. 1989;12(5):337-44.
14	701	43. Anderson JW, Weiter KM, Christian AL, Ritchey MB, Bays HE. Raisins compared with other snack
15	702	effects on glycemia and blood pressure: a randomized, controlled trial. Postgraduate medicine.
16	703	2014;126(1):37-43.
17	704	44. Bahrami M, Ataie-Jafari A, Hosseini S, Foruzanfar MH, Rahmani M, Pajouhi M. Effects of natural
18	705	honey consumption in diabetic patients: an 8-week randomized clinical trial. International journal of
19	706	food sciences and nutrition. 2009;60(7):618-26.
20	707	45. Bantle JP, Raatz SK, Thomas W, Georgopoulos A. Effects of dietary fructose on plasma lipids in
21	708	healthy subjects. The American journal of clinical nutrition. 2000;72(5):1128-34.
22	709	46. Bantle JP, Swanson JE, Thomas W, Laine DC. Metabolic effects of dietary fructose in diabetic
23 24	710	subjects. Diabetes care. 1992;15(11):1468-76.
24 25	711	47. Bantle JP, Swanson JE, Thomas W, Laine DC. Metabolic effects of dietary sucrose in type II
26	712	diabetic subjects. Diabetes Care. 1993;16(9):1301-5.
27	713	48. Basu A, Du M, Leyva MJ, Sanchez K, Betts NM, Wu M, et al. Blueberries decrease cardiovascular
28	714	risk factors in obese men and women with metabolic syndrome. The Journal of nutrition.
29	715	2010;140(9):1582-7.
30	716	49. Basu A, Fu DX, Wilkinson M, Simmons B, Wu M, Betts NM, et al. Strawberries decrease
31	717	atherosclerotic markers in subjects with metabolic syndrome. Nutrition research. 2010;30(7):462-9.
32	718	50. Bays H, Weiter K, Anderson J. A randomized study of raisins versus alternative snacks on
33	719	glycemic control and other cardiovascular risk factors in patients with type 2 diabetes mellitus. The
34 25	720	Physician and sportsmedicine. 2015;43(1):37-43.
35 36	721	51. Beck-Nielsen H, Pedersen O, Lindskov HO. Impaired cellular insulin binding and insulin sensitivity
37	722	induced by high-fructose feeding in normal subjects. The American journal of clinical nutrition.
38	723	1980;33(2):273-8.
39	724	52. Behall KM, Moser PB, Kelsay JL, Prather ES. The effect of kind of carbohydrate in the diet and
40	725	use of oral contraceptives on metabolism of young women. III. Serum glucose, insulin, and glucagon. The
41	726	American journal of clinical nutrition. 1980;33(5):1041-8.
42	727	53. Black RN, Spence M, McMahon RO, Cuskelly GJ, Ennis CN, McCance DR, et al. Effect of eucaloric
43	728	high- and low-sucrose diets with identical macronutrient profile on insulin resistance and vascular risk: a
44	729	randomized controlled trial. Diabetes. 2006;55(12):3566-72.
45	730	54. Blayo A, Fontevieille S, Rizkalla S, Bruzzo F, Slama G. Effets métaboliques de la consommation
46		
47 49	731	quotidienne pendant un an de saccharose ou de fructose par des diabétiques. Médecine et Nutrition.
48 49	732	1990;26(1):11-4.
49 50	733	55. Brunner S, Holub I, Theis S, Gostner A, Melcher R, Wolf P, et al. Metabolic effects of replacing
51	734	sucrose by isomaltulose in subjects with type 2 diabetes: a randomized double-blind trial. Diabetes care.
52	735	2012;35(6):1249-51.
53	736	56. Brymora A, Flisinski M, Johnson RJ, Goszka G, Stefanska A, Manitius J. Low-fructose diet lowers
54	737	blood pressure and inflammation in patients with chronic kidney disease. Nephrology, dialysis,
55	738	transplantation : official publication of the European Dialysis and Transplant Association - European
56	739	Renal Association. 2012;27(2):608-12.
57		
58 59		Page <b>30</b> of <b>42</b>
77		

Page 32 of 91

BMJ

1 2

60

3	740	57. Brynes AE, Mark Edwards C, Ghatei MA, Dornhorst A, Morgan LM, Bloom SR, et al. A randomised
4	741	four-intervention crossover study investigating the effect of carbohydrates on daytime profiles of
5	742	insulin, glucose, non-esterified fatty acids and triacylglycerols in middle-aged men. The British journal of
6	743	nutrition. 2003;89(2):207-18.
7 8	744	58. Buysschaert M, Sory R, Mpoy M, Lambert AE. Effect of the addition of simple sugars to mixed
o 9	745	meals on the glycemic control of insulin treated diabetic patients. Diabete & metabolisme.
9 10	746	1987;13(6):625-9.
11	747	59. Campos V, Despland C, Brandejsky V, Kreis R, Schneiter P, Chiolero A, et al. Sugar- and artificially
12	748	sweetened beverages and intrahepatic fat: A randomized controlled trial. Obesity. 2015;23(12):2335-9.
13	749	60. Chantelau EA, Gosseringer G, Sonnenberg GE, Berger M. Moderate intake of sucrose does not
14	750	impair metabolic control in pump-treated diabetic out-patients. Diabetologia. 1985;28(4):204-7.
15	751	61. Christensen AS, Viggers L, Hasselstrom K, Gregersen S. Effect of fruit restriction on glycemic
16	752	control in patients with type 2 diabetesa randomized trial. Nutrition journal. 2013;12:29.
17	753	
18		
19 20	754	candy, but not peanuts, increases insulin levels and body weight. Scandinavian journal of clinical and
20 21	755	laboratory investigation. 2009;69(5):598-605.
22	756	63. Colagiuri S, Miller JJ, Edwards RA. Metabolic effects of adding sucrose and aspartame to the diet
23	757	of subjects with noninsulin-dependent diabetes mellitus. The American journal of clinical nutrition.
24	758	1989;50(3):474-8.
25	759	64. Conceicao de Oliveira M, Sichieri R, Sanchez Moura A. Weight loss associated with a daily intake
26	760	of three apples or three pears among overweight women. Nutrition. 2003;19(3):253-6.
27	761	65. Cooper PL, Wahlqvist ML, Simpson RW. Sucrose versus saccharin as an added sweetener in non-
28	762	insulin-dependent diabetes: short- and medium-term metabolic effects. Diabetic medicine : a journal of
29	763	the British Diabetic Association. 1988;5(7):676-80.
30	764	66. Costa PC, Franco LJ. [Introduction of sucrose in the diet plan of persons with type 1 diabetes: its
31 32	765	influence in the glycemic control]. Arquivos brasileiros de endocrinologia e metabologia.
33	766	2005;49(3):403-9.
34	767	67. Cressey R, Kumsaiyai W, Mangklabruks A. Daily consumption of banana marginally improves
35	768	blood glucose and lipid profile in hypercholesterolemic subjects and increases serum adiponectin in type
36	769	2 diabetic patients. Indian journal of experimental biology. 2014;52(12):1173-81.
37	770	68. Dunnigan MG, Fyfe T, McKiddie MT, Crosbie SM. The effects of isocaloric exchange of dietary
38	771	starch and sucrose on glucose tolerance, plasma insulin and serum lipids in man. Clinical science.
39	772	1970;38(1):1-9.
40	773	69. Ellis CL, Edirisinghe I, Kappagoda T, Burton-Freeman B. Attenuation of meal-induced
41 42	774	inflammatory and thrombotic responses in overweight men and women after 6-week daily strawberry
42 43	775	(Fragaria) intake. A randomized placebo-controlled trial. Journal of atherosclerosis and thrombosis.
44	776	2011;18(4):318-27.
45	777	70. Emanuele MA, Abraira C, Jellish WS, DeBartolo M. A crossover trial of high and low sucrose-
46	778	carbohydrate diets in type II diabetics with hypertriglyceridemia. Journal of the American College of
47	779	Nutrition. 1986;5(5):429-37.
48	780	71. Friedman M, Rosenman RH, Byers SO, Elevitch FR. Effect of low sugar intake upon blood lipids
49	781	and insulin levels of hyperlipemic subjects. Proceedings of the Society for Experimental Biology and
50	782	Medicine Society for Experimental Biology and Medicine. 1970;135(3):785-91.
51	783	72. Fry AJ. The effect of a 'sucrose-free' diet on oral glucose tolerance in man. Nutrition and
52 53	784	metabolism. 1972;14(5):313-23.
53 54	785	73. Grigoresco C, Rizkalla SW, Halfon P, Bornet F, Fontvieille AM, Bros M, et al. Lack of detectable
55	786	deleterious effects on metabolic control of daily fructose ingestion for 2 mo in NIDDM patients. Diabetes
56	787	care. 1988;11(7):546-50.
57		
58		Page <b>31</b> of <b>42</b>
59		-

BMJ

2		
3	788	74. Hallfrisch J, Ellwood KC, Michaelis OEt, Reiser S, O'Dorisio TM, Prather ES. Effects of dietary
4	789	fructose on plasma glucose and hormone responses in normal and hyperinsulinemic men. The Journal of
5	790	nutrition. 1983;113(9):1819-26.
6	791	75. Heden TD, Liu Y, Park YM, Nyhoff LM, Winn NC, Kanaley JA. Moderate amounts of fructose- or
7		
8	792	glucose-sweetened beverages do not differentially alter metabolic health in male and female
9	793	adolescents. The American journal of clinical nutrition. 2014;100(3):796-805.
10	794	76. Heden TD, Liu Y, Park YM, Winn NC, Kanaley JA. Walking Reduces Postprandial Insulin Secretion
11	795	in Obese Adolescents Consuming a High-Fructose or High-Glucose Diet. Journal of physical activity &
12 13	796	health. 2015;12(8):1153-61.
14	797	77. Hegde SV, Adhikari P, M N, D'Souza V. Effect of daily supplementation of fruits on oxidative
15	798	stress indices and glycaemic status in type 2 diabetes mellitus. Complementary therapies in clinical
16	799	practice. 2013;19(2):97-100.
17	800	78. Hernandez-Cordero S, Barquera S, Rodriguez-Ramirez S, Villanueva-Borbolla MA, Gonzalez de
18	801	Cossio T, Dommarco JR, et al. Substituting water for sugar-sweetened beverages reduces circulating
19	802	triglycerides and the prevalence of metabolic syndrome in obese but not in overweight Mexican women
20	803	in a randomized controlled trial. The Journal of nutrition. 2014;144(11):1742-52.
21	804	79. Hollis JH, Houchins JA, Blumberg JB, Mattes RD. Effects of concord grape juice on appetite, diet,
22	805	body weight, lipid profile, and antioxidant status of adults. Journal of the American College of Nutrition.
23	806	2009;28(5):574-82.
24	807	80. Huttunen JK, Makinen KK, Scheinin A. Turku sugar studies XI. Effects of sucrose, fructose and
25 26	808	xylitol diets on glucose, lipid and urate metabolism. Acta odontologica Scandinavica. 1976;34(6):345-51.
20 27	809	81. Jellish WS, Emanuele MA, Abraira C. Graded sucrose/carbohydrate diets in overtly
28	810	hypertriglyceridemic diabetic patients. The American journal of medicine. 1984;77(6):1015-22.
29	811	82. Jin R, Welsh JA, Le NA, Holzberg J, Sharma P, Martin DR, et al. Dietary fructose reduction
30	812	improves markers of cardiovascular disease risk in Hispanic-American adolescents with NAFLD.
31	813	Nutrients. 2014;6(8):3187-201.
32	814	83. Johnson LK, Holven KB, Nordstrand N, Mellembakken JR, Tanbo T, Hjelmesaeth J. Fructose
33	815	content of low calorie diets: effect on cardiometabolic risk factors in obese women with polycystic
34	816	ovarian syndrome: a randomized controlled trial. Endocrine connections. 2015;4(3):144-54.
35	817	84. Johnston RD, Stephenson MC, Crossland H, Cordon SM, Palcidi E, Cox EF, et al. No difference
36		
37	818	between high-fructose and high-glucose diets on liver triacylglycerol or biochemistry in healthy
38	819	overweight men. Gastroenterology. 2013;145(5):1016-25 e2.
39 40	820	85. Kanellos PT, Kaliora AC, Tentolouris NK, Argiana V, Perrea D, Kalogeropoulos N, et al. A pilot,
40	821	randomized controlled trial to examine the health outcomes of raisin consumption in patients with
42	822	diabetes. Nutrition. 2014;30(3):358-64.
43	823	86. Kelsay JL, Behall KM, Holden JM, Prather ES. Diets high in glucose or sucrose and young women.
44	824	The American journal of clinical nutrition. 1974;27(9):926-36.
45	825	87. Koh ET, Ard NF, Mendoza F. Effects of fructose feeding on blood parameters and blood pressure
46	826	in impaired glucose-tolerant subjects. Journal of the American Dietetic Association. 1988;88(8):932-8.
47	827	88. Koivisto VA, Yki-Jarvinen H. Fructose and insulin sensitivity in patients with type 2 diabetes.
48	828	Journal of internal medicine. 1993;233(2):145-53.
49	829	89. Kolehmainen M, Mykkanen O, Kirjavainen PV, Leppanen T, Moilanen E, Adriaens M, et al.
50	830	Bilberries reduce low-grade inflammation in individuals with features of metabolic syndrome. Molecular
51 52	831	nutrition & food research. 2012;56(10):1501-10.
52 53	832	90. Koopman KE, Caan MW, Nederveen AJ, Pels A, Ackermans MT, Fliers E, et al. Hypercaloric diets
53 54	833	with increased meal frequency, but not meal size, increase intrahepatic triglycerides: a randomized
55	834	controlled trial. Hepatology. 2014;60(2):545-53.
56		
57		
58		Page <b>32</b> of <b>42</b>
59		

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BMJ

91. Le KA, Faeh D, Stettler R, Ith M, Kreis R, Vermathen P, et al. A 4-wk high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans. The American journal of clinical nutrition. 2006;84(6):1374-9. 92. Le KA, Ith M, Kreis R, Faeh D, Bortolotti M, Tran C, et al. Fructose overconsumption causes dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes. The American journal of clinical nutrition. 2009;89(6):1760-5. 93. Lehtonen HM, Suomela JP, Tahvonen R, Vaarno J, Venojarvi M, Viikari J, et al. Berry meals and risk factors associated with metabolic syndrome. European journal of clinical nutrition. 2010;64(6):614-21. 94. Lehtonen HM, Suomela JP, Tahvonen R, Yang B, Venojarvi M, Viikari J, et al. Different berries and berry fractions have various but slightly positive effects on the associated variables of metabolic diseases on overweight and obese women. European journal of clinical nutrition. 2011;65(3):394-401. 95. Lewis AS, McCourt HJ, Ennis CN, Bell PM, Courtney CH, McKinley MC, et al. Comparison of 5% versus 15% sucrose intakes as part of a eucaloric diet in overweight and obese subjects: effects on insulin sensitivity, glucose metabolism, vascular compliance, body composition and lipid profile. A randomised controlled trial. Metabolism: clinical and experimental. 2013;62(5):694-702. Liu G, Coulston A, Hollenbeck C, Reaven G. The effect of sucrose content in high and low 96. carbohydrate diets on plasma glucose, insulin, and lipid responses in hypertriglyceridemic humans. The Journal of clinical endocrinology and metabolism. 1984;59(4):636-42. 97. Lock S, Ford MA, Bagley R, Green LF. The effect on plasma lipids of the isoenergetic replacement of table sucrose by dried glucose syrup (maize-syrup solids) in the normal diet of adult men over a period of 1 year. The British journal of nutrition. 1980;43(2):251-6. 98. Lowndes J, Sinnett SS, Rippe JM. No Effect of Added Sugar Consumed at Median American Intake Level on Glucose Tolerance or Insulin Resistance. Nutrients. 2015;7(10):8830-45. 99. Madero M, Arriaga JC, Jalal D, Rivard C, McFann K, Perez-Mendez O, et al. The effect of two energy-restricted diets, a low-fructose diet versus a moderate natural fructose diet, on weight loss and metabolic syndrome parameters: a randomized controlled trial. Metabolism: clinical and experimental. 2011;60(11):1551-9. 100. Maersk M, Belza A, Stodkilde-Jorgensen H, Ringgaard S, Chabanova E, Thomsen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. The American journal of clinical nutrition. 2012;95(2):283-9. Majid M, Younis MA, Naveed AK, Shah MU, Azeem Z, Tirmizi SH. Effects of natural honey on 101. blood glucose and lipid profile in young healthy Pakistani males. Journal of Ayub Medical College, Abbottabad : JAMC. 2013;25(3-4):44-7. 102. Maki KC, Nieman KM, Schild AL, Kaden VN, Lawless AL, Kelley KM, et al. Sugar-sweetened product consumption alters glucose homeostasis compared with dairy product consumption in men and women at risk of type 2 diabetes mellitus. The Journal of nutrition. 2015;145(3):459-66. 103. Malerbi DA, Paiva ES, Duarte AL, Wajchenberg BL. Metabolic effects of dietary sucrose and fructose in type II diabetic subjects. Diabetes care. 1996;19(11):1249-56. 104. Mark AB, Poulsen MW, Andersen S, Andersen JM, Bak MJ, Ritz C, et al. Consumption of a diet low in advanced glycation end products for 4 weeks improves insulin sensitivity in overweight women. Diabetes care. 2014;37(1):88-95. 105. Markey O, Le Jeune J, Lovegrove JA. Energy compensation following consumption of sugar-reduced products: a randomized controlled trial. European journal of nutrition. 2015. 106. McAteer EJ, O'Reilly G, Hadden DR. The effects of one month high fructose intake on plasma glucose and lipid levels in non-insulin-dependent diabetes. Diabetic medicine : a journal of the British Diabetic Association. 1987;4(1):62-4. 

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BMJ

107. Mitsou EK, Kougia E, Nomikos T, Yannakoulia M, Mountzouris KC, Kyriacou A. Effect of banana consumption on faecal microbiota: a randomised, controlled trial. Anaerobe. 2011;17(6):384-7. 108. Moazen S, Amani R, Homayouni Rad A, Shahbazian H, Ahmadi K, Taha Jalali M. Effects of freeze-dried strawberry supplementation on metabolic biomarkers of atherosclerosis in subjects with type 2 diabetes: a randomized double-blind controlled trial. Annals of nutrition & metabolism. 2013;63(3):256-64. 109. Ngo Sock ET, Le KA, Ith M, Kreis R, Boesch C, Tappy L. Effects of a short-term overfeeding with fructose or glucose in healthy young males. The British journal of nutrition. 2010;103(7):939-43. 110. Njike VY, Faridi Z, Shuval K, Dutta S, Kay CD, West SG, et al. Effects of sugar-sweetened and sugar-free cocoa on endothelial function in overweight adults. International journal of cardiology. 2011;149(1):83-8. Osei K, Bossetti B. Dietary fructose as a natural sweetener in poorly controlled type 2 diabetes: a 111. 12-month crossover study of effects on glucose, lipoprotein and apolipoprotein metabolism. Diabetic medicine : a journal of the British Diabetic Association. 1989;6(6):506-11. Osei K, Falko J, Bossetti BM, Holland GC. Metabolic effects of fructose as a natural sweetener in 112. the physiologic meals of ambulatory obese patients with type II diabetes. The American journal of medicine. 1987;83(2):249-55. 113. Paganus A, Maenpaa J, Akerblom HK, Stenman UH, Knip M, Simell O. Beneficial effects of palatable guar and guar plus fructose diets in diabetic children. Acta paediatrica Scandinavica. 1987;76(1):76-81. 114. Paineau DL, Beaufils F, Boulier A, Cassuto DA, Chwalow J, Combris P, et al. Family dietary coaching to improve nutritional intakes and body weight control: a randomized controlled trial. Archives of pediatrics & adolescent medicine. 2008;162(1):34-43. Pelkonen R, Aro A, Nikkila EA. Metabolic effects of dietary fructose in insulin dependent 115. diabetes of adults. Acta medica Scandinavica Supplementum. 1972;542:187-93. 116. Peterson DB, Lambert J, Gerring S, Darling P, Carter RD, Jelfs R, et al. Sucrose in the diet of diabetic patients--just another carbohydrate? Diabetologia. 1986;29(4):216-20. Poppitt SD, Keogh GF, Prentice AM, Williams DE, Sonnemans HM, Valk EE, et al. Long-term 117. effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. The American journal of clinical nutrition. 2002;75(1):11-20. 118. Porta M, Pigino M, Minonne A, Morisio Guidetti L. Moderate Amounts of Sucrose with Mixed Meals do not Impair Metabolic Control in Patients with Type II (Non-Insulin Dependent) Diabetes. Diabetes, Nutrition & Metabolism. 1989;2(2):133-7. 119. Puglisi MJ, Vaishnav U, Shrestha S, Torres-Gonzalez M, Wood RJ, Volek JS, et al. Raisins and additional walking have distinct effects on plasma lipids and inflammatory cytokines. Lipids in health and disease. 2008;7:14. 120. Raben A, Astrup A. Leptin is influenced both by predisposition to obesity and diet composition. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2000;24(4):450-9. 121. Raben A, Moller BK, Flint A, Vasilaris TH, Christina Moller A, Juul Holst J, et al. Increased postprandial glycaemia, insulinemia, and lipidemia after 10 weeks' sucrose-rich diet compared to an artificially sweetened diet: a randomised controlled trial. Food & nutrition research. 2011;55. 122. Rath R, Masek J, Kujalova V, Slabochova Z. Effect of a high sugar intake on some metabolic and regulatory indicators in young men. Die Nahrung. 1974;18(4):343-53. 123. Ravn-Haren G, Dragsted LO, Buch-Andersen T, Jensen EN, Jensen RI, Nemeth-Balogh M, et al. Intake of whole apples or clear apple juice has contrasting effects on plasma lipids in healthy volunteers. European journal of nutrition. 2013;52(8):1875-89. Page 34 of 42 

https://mc.manuscriptcentral.com/bmj

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BMJ

124. Reiser S, Hallfrisch J, Fields M, Powell A, Mertz W, Prather ES, et al. Effects of sugars on indices of glucose tolerance in humans. The American journal of clinical nutrition. 1986;43(1):151-9. 125. Reiser S, Powell AS, Scholfield DJ, Panda P, Fields M, Canary JJ. Day-long glucose, insulin, and fructose responses of hyperinsulinemic and nonhyperinsulinemic men adapted to diets containing either fructose or high-amylose cornstarch. The American journal of clinical nutrition. 1989;50(5):1008-14. 126. Rizkalla SW, Baigts F, Fumeron F, Rabillon B, Bayn P, Ktorza A, et al. Comparative effects of several simple carbohydrates on erythrocyte insulin receptors in obese subjects. Pharmacology, biochemistry, and behavior. 1986;25(3):681-8. 127. Rodriguez MC, Parra MD, Marques-Lopes I, De Morentin BE, Gonzalez A, Martinez JA. Effects of two energy-restricted diets containing different fruit amounts on body weight loss and macronutrient oxidation. Plant foods for human nutrition. 2005;60(4):219-24. Santacroce G, Forlani G, Giangiulio S, Galuppi V, Pagani M, Vannini P. Long-term effects of eating 128. sucrose on metabolic control of type 1 (insulin-dependent) diabetic outpatients. Acta diabetologica latina. 1990;27(4):365-70. Saris WH, Astrup A, Prentice AM, Zunft HJ, Formiguera X, Verboeket-van de Venne WP, et al. 129. Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs complex carbohydrates on body weight and blood lipids: the CARMEN study. The Carbohydrate Ratio Management in European National diets. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2000;24(10):1310-8. 130. Schwarz JM, Noworolski SM, Wen MJ, Dyachenko A, Prior JL, Weinberg ME, et al. Effect of a High-Fructose Weight-Maintaining Diet on Lipogenesis and Liver Fat. The Journal of clinical endocrinology and metabolism. 2015;100(6):2434-42. 131. Schwingshandl J, Rippel S, Unterluggauer M, Borkenstein M. Effect of the introduction of dietary sucrose on metabolic control in children and adolescents with type I diabetes. Acta diabetologica. 1994;31(4):205-9. 132. Silbernagel G, Machann J, Unmuth S, Schick F, Stefan N, Haring HU, et al. Effects of 4-week very-high-fructose/glucose diets on insulin sensitivity, visceral fat and intrahepatic lipids: an exploratory trial. Br J Nutr. 2011;106(1):79-86. 133. Silver HJ, Dietrich MS, Niswender KD. Effects of grapefruit, grapefruit juice and water preloads on energy balance, weight loss, body composition, and cardiometabolic risk in free-living obese adults. Nutrition & metabolism. 2011;8(1):8. Singh RB, Rastogi SS, Singh R, Niaz MA, Singh NK, Madhu SV. Effects on Plasma Ascorbic Acid and 134. Coronary Risk Factors of Adding Guava Fruit to the Usual Diet in Hypertensives with Mild to Moderate Hypercholesterolaemia. Journal of Nutritional & Environmental Medicine. 1997;7:5-14. 135. Sobrecases H, Le KA, Bortolotti M, Schneiter P, Ith M, Kreis R, et al. Effects of short-term overfeeding with fructose, fat and fructose plus fat on plasma and hepatic lipids in healthy men. Diabetes & metabolism. 2010;36(3):244-6. 136. Souto DL, Zajdenverg L, Rodacki M, Rosado EL. Does sucrose intake affect antropometric variables, glycemia, lipemia and C-reactive protein in subjects with type 1 diabetes?: a controlled-trial. Diabetology & metabolic syndrome. 2013;5(1):67. 137. Stanhope KL, Bremer AA, Medici V, Nakajima K, Ito Y, Nakano T, et al. Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women. The Journal of clinical endocrinology and metabolism. 2011;96(10):E1596-605. 138. Stanhope KL, Griffen SC, Bremer AA, Vink RG, Schaefer EJ, Nakajima K, et al. Metabolic responses to prolonged consumption of glucose- and fructose-sweetened beverages are not associated with postprandial or 24-h glucose and insulin excursions. The American journal of clinical nutrition. 2011;94(1):112-9. Page 35 of 42 

1		36
2		
3	977	139. Sunehag AL, Toffolo G, Campioni M, Bier DM, Haymond MW. Short-term high dietary fructose
4	978	intake had no effects on insulin sensitivity and secretion or glucose and lipid metabolism in healthy,
5 6	979	obese adolescents. Journal of pediatric endocrinology & metabolism : JPEM. 2008;21(3):225-35.
	980	140. Sunehag AL, Toffolo G, Treuth MS, Butte NF, Cobelli C, Bier DM, et al. Effects of dietary
7 8	981	macronutrient content on glucose metabolism in children. The Journal of clinical endocrinology and
o 9	982	metabolism. 2002;87(11):5168-78.
10	983	141. Surwit RS, Feinglos MN, McCaskill CC, Clay SL, Babyak MA, Brownlow BS, et al. Metabolic and
11	984	behavioral effects of a high-sucrose diet during weight loss. The American journal of clinical nutrition.
12	985	1997;65(4):908-15.
13	986	142. Swanson JE, Laine DC, Thomas W, Bantle JP. Metabolic effects of dietary fructose in healthy
14	987	subjects. The American journal of clinical nutrition. 1992;55(4):851-6.
15 16	988	143. Swarbrick MM, Stanhope KL, Elliott SS, Graham JL, Krauss RM, Christiansen MP, et al.
17	989	Consumption of fructose-sweetened beverages for 10 weeks increases postprandial triacylglycerol and
18	990	apolipoprotein-B concentrations in overweight and obese women. The British journal of nutrition.
19	991	2008;100(5):947-52.
20	992	144. Szanto S, Yudkin J. The effect of dietary sucrose on blood lipids, serum insulin, platelet
21	993	adhesiveness and body weight in human volunteers. Postgraduate medical journal. 1969;45(527):602-7.
22	994	145. Tate DF, Turner-McGrievy G, Lyons E, Stevens J, Erickson K, Polzien K, et al. Replacing caloric
23 24	995	beverages with water or diet beverages for weight loss in adults: main results of the Choose Healthy
24 25	996	Options Consciously Everyday (CHOICE) randomized clinical trial. Am J Clin Nutr. 2012;95(3):555-63.
26	997	146. Turner JL, Bierman EL, Brunzell JD, Chait A. Effect of dietary fructose on triglyceride transport
27	998	and glucoregulatory hormones in hypertriglyceridemic men. The American journal of clinical nutrition.
28	999	1979;32(5):1043-50.
29	1000	147. Vaisman N, Niv E, Izkhakov Y. Catalytic amounts of fructose may improve glucose tolerance in
30	1001	subjects with uncontrolled non-insulin-dependent diabetes. Clinical nutrition. 2006;25(4):617-21.
31 32	1002	148. van Meijl LE, Mensink RP. Low-fat dairy consumption reduces systolic blood pressure, but does
33	1003	not improve other metabolic risk parameters in overweight and obese subjects. Nutrition, metabolism,
34	1004	and cardiovascular diseases : NMCD. 2011;21(5):355-61.
35	1005	149. Volp AC, Hermsdorff HH, Bressan J. Glycemia and insulinemia evaluation after high-sucrose and
36	1006	high-fat diets in lean and overweight/obese women. Journal of physiology and biochemistry.
37	1007	2008;64(2):103-13.
38	1008	150. Vrolix R, Mensink RP. Effects of glycemic load on metabolic risk markers in subjects at increased
39 40	1009	risk of developing metabolic syndrome. The American journal of clinical nutrition. 2010;92(2):366-74.
41	1010	151. Jones JB, Provost M, Keaver L, Breen C, Ludy MJ, Mattes RD. A randomized trial on the effects of
42	1011	flavorings on the health benefits of daily peanut consumption. The American journal of clinical nutrition.
43	1012	2014;99(3):490-6. 152. Coulston AM, Hollenbeck CB, Donner CC, Williams R, Chiou YA, Reaven GM. Metabolic effects of
44	1013 1014	152. Coulston AM, Hollenbeck CB, Donner CC, Williams R, Chiou YA, Reaven GM. Metabolic effects of added dietary sucrose in individuals with noninsulin-dependent diabetes mellitus (NIDDM). Metabolism:
45	1014	clinical and experimental. 1985;34(10):962-6.
46 47	1015	153. Volp AC, Hermsdorff HM, Bressan J. [Effect of high sucrose- and high-fat diets ingested under
47 48	1010	free-living conditions in insulin resistance in normal weight and overweight women]. Nutricion
49	1017	hospitalaria. 2007;22(1):46-60.
50	1010	154. Agebratt C, Strom E, Romu T, Dahlqvist-Leinhard O, Borga M, Leandersson P, et al. A
51	1010	Randomized Study of the Effects of Additional Fruit and Nuts Consumption on Hepatic Fat Content,
52	1021	Cardiovascular Risk Factors and Basal Metabolic Rate. PLoS One. 2016;11(1):e0147149.
53 54	1022	155. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 –
54 55	1023	2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at
56	1024	http://health.gov/dietaryguidelines/2015/guidelines/
57		
58		Page <b>36</b> of <b>42</b>
59		https://mc.manuscriptcentral.com/bmj
60		https://incinanuscripteentral.com/binj

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3 4	1025 1026	156. Livesey G, Taylor R. Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies. The
5	1027	American journal of clinical nutrition. 2008;88(5):1419-37.
6 7	1028	157. U.S. Department of Health and Human Services. Guidance for Industry Diabetes Mellitus:
8	1029	Developing Drugs and Therapeutic Biologics for Treatment and Prevention. [Draft Guidance]. Food and
9	1030	Drug Administration Center for Drug Evaluation and Research (CDER) 2008:1-30.
10	1031	158. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and
11	1032	glycemic load values: 2008. Diabetes care. 2008;31(12):2281-3.
12	1033	159. Brand-Miller JC, Petocz P, Colagiuri S. Meta-analysis of low-glycemic index diets in the
13	1034	management of diabetes: response to Franz. Diabetes care. 2003;26(12):3363-4; author reply 4-5.
14 15	1035	160. Jenkins DJ, Wolever TM, Collier GR, Ocana A, Rao AV, Buckley G, et al. Metabolic effects of a
15 16	1036	low-glycemic-index diet. The American journal of clinical nutrition. 1987;46(6):968-75.
17	1037	161. Hawkins M, Gabriely I, Wozniak R, Vilcu C, Shamoon H, Rossetti L. Fructose improves the ability
18	1038	of hyperglycemia per se to regulate glucose production in type 2 diabetes. Diabetes. 2002;51(3):606-14.
19	1039	162. Petersen KF, Laurent D, Yu C, Cline GW, Shulman GI. Stimulating effects of low-dose fructose on
20	1040	insulin-stimulated hepatic glycogen synthesis in humans. Diabetes. 2001;50(6):1263-8.
21	1041	163. Sievenpiper JL, de Souza RJ, Mirrahimi A, Yu ME, Carleton AJ, Beyene J, et al. Effect of fructose
22	1042	on body weight in controlled feeding trials: a systematic review and meta-analysis. Ann Intern Med.
23	1043	2012;156(4):291-304.
24 25	1044	164. Ha V, Sievenpiper JL, de Souza RJ, Chiavaroli L, Wang DD, Cozma AI, et al. Effect of fructose on
26	1045	blood pressure: a systematic review and meta-analysis of controlled feeding trials. Hypertension.
27	1046	2012;59(4):787-95.
28	1047	165. Wang DD, Sievenpiper JL, de Souza RJ, Chiavaroli L, Ha V, Cozma AI, et al. The effects of fructose
29	1048	intake on serum uric acid vary among controlled dietary trials. The Journal of nutrition. 2012;142(5):916-
30	1049	23.
31 22	1050	166. Chiu S, Sievenpiper JL, de Souza RJ, Cozma AI, Mirrahimi A, Carleton AJ, et al. Effect of fructose
32 33	1051	on markers of non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of
34	1052	controlled feeding trials. European journal of clinical nutrition. 2014;68(4):416-23.
35	1053	167. David Wang D, Sievenpiper JL, de Souza RJ, Cozma AI, Chiavaroli L, Ha V, et al. Effect of fructose
36	1054	on postprandial triglycerides: a systematic review and meta-analysis of controlled feeding trials.
37	1055	Atherosclerosis. 2014;232(1):125-33.
38	1056	168. Munstedt K, Sheybani B, Hauenschild A, Bruggmann D, Bretzel RG, Winter D. Effects of
39 40	1057	basswood honey, honey-comparable glucose-fructose solution, and oral glucose tolerance test solution
40 41	1058	on serum insulin, glucose, and C-peptide concentrations in healthy subjects. Journal of medicinal food.
42	1059	2008;11(3):424-8.
43	1060	169. Fasanmade A, Alabi O. Differential Effect of Honey on Selected Variables in Alloxan-Induced and
44	1061	Fructose-Induced Diabetic Rats African Journal of Biomedical Research. 2008;11:191-6.
45	1062	170. Schramm DD, Karim M, Schrader HR, Holt RR, Cardetti M, Keen CL. Honey with high levels of
46	1063	antioxidants can provide protection to healthy human subjects. Journal of agricultural and food
47	1064	chemistry. 2003;51(6):1732-5.
48 49	1065	171. Safi SZ, Batumalaie K, Qvist R, Mohd Yusof K, Ismail IS. Gelam Honey Attenuates the Oxidative
49 50	1066	Stress-Induced Inflammatory Pathways in Pancreatic Hamster Cells. Evidence-based complementary and
51	1067	alternative medicine : eCAM. 2016;2016:5843615.
52	1068	172. Choo VL, Sievenpiper JL. The ecologic validity of fructose feeding trials: supraphysiological
53	1069	feeding of fructose in human trials requires careful consideration when drawing conclusions on
54	1070 1071	cardiometabolic risk. Front Nutr. 2015;2:12.
55	1071 1072	173. Guideline: Sugars Intake for Adults and Children. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2015.
56 57	1072	
57 58		Page <b>37</b> of <b>42</b>
59		

1073	174.	Brisbois TD, Marsden SL, Anderson GH, Sievenpiper JL. Estimated intakes and sources of total
1074	and ac	Ided sugars in the Canadian diet. Nutrients. 2014;6(5):1899-912.

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1		39
2 3 4	1076	Figures and Tables
5 6 7	1077	Figure 1. Flow of literature for the effect of Fructose-containing sugars on glycemic control.
8 9	1078	Figure 2. Summary super-plot for the effect of fructose-containing sugars on HbA1c. N= Number of
10 11 12	1079	participants. Data are expressed as weighted mean differences (MD) with 95% CIs for summary effects
12 13 14	1080	of individual food sources and total food sources of fructose-containing sugars on HbA1c. Analyses were
15 16	1081	conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects
17 18	1082	models (<5 trials available). Interstudy heterogeneity was tested using the Cochran's Q statistic (chi-
19 20 21	1083	square) at a significance level of P<0.10.
21 22 23	1084	Figure 3. Summary super-plot for the effect of fructose-containing sugars on fasting blood glucose. N=
24 25	1085	Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for
26 27	1086	summary effects of individual food sources and total food sources of fructose-containing sugars on
28 29	1087	fasting blood glucose. Analyses were conducted using generic inverse variance random-effects models
30 31 32	1088	(≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested
33 34	1089	using the Cochran's Q statistic (chi-square) at a significance level of P<0.10.
35 36	1090	Figure 4. Summary super-plot for the effect of fructose-containing sugars on fasting blood insulin. N=
37 38	1091	Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for
39 40 41	1092	summary effects of individual food sources and total food sources of fructose-containing sugars on
42 43	1093	fasting blood insulin. Analyses were conducted using generic inverse variance random-effects models (≥
44 45	1094	5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using
46 47 48	1095	the Cochran Q statistic (chi-square) at a significance level of P<0.10.
49 50		
51 52		
53 54		
55 56 57		
57 58 59		Page <b>39</b> of <b>42</b>
60		https://mc.manuscriptcentral.com/bmj

#### Table 1. Summary of Trial Characteristics

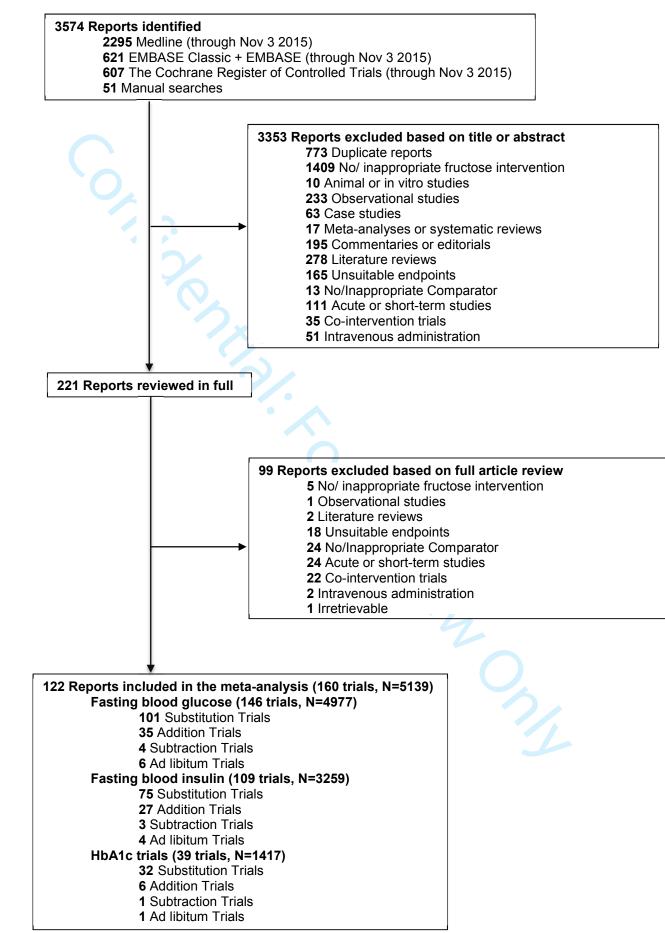
Trial Size (participants <sup>1</sup> )       15 (2-595)       21 (6-92)       15 (12-318)       39 (8)         Male: Female <sup>1</sup> 44: 56       39: 61       12: 88       41:         Age (years <sup>1</sup> )       40.1 (23.2-53.9)       35.8 (25.0-50.1)       33.5 (29.1-42.2)       37.4 (         Setting (inpatient: Outpatient) <sup>1</sup> 25: 75       10: 90       0: 100       0: 11         Baseline Fasting Glucose (mmol/L) <sup>1</sup> 5.4 (4.9-8.0)       5.1 (4.9-5.4)       5.1 (1.5-1.2)       4.9 (4         Baseline Fasting Glucose (mmol/L) <sup>1</sup> 89.6 (57.9-131.6)       53.5 (40.6-81.5)       109.8 (97.8-12.7)       32.5 (31         Baseline Fasting Succe (mmol/L) <sup>1</sup> 89.6 (57.9-131.6)       53.5 (40.6-81.5)       109.8 (97.8-12.7)       32.5 (31         Baseline Control (Met: Sup <sup>2</sup> DA)       62: 38       50: 50       20: 80       57:         Feeding Control (Met: Sup <sup>2</sup> DA)       69: 31       66: 34       80: 20       88         Fructose Containing Sugar Dosage (%E) <sup>1</sup> 15.0 (9.6-23.6)       11.6 (5.0-25.0)       15.0 (13.8-15.0)       23.0 (12         Foutose-Containing Sugar Form (N)       Fructose-S: Fruit=13; HFCS=1; Succes=50       Fructose=10; Fruit=17; HitCS=2; Honey=3; Succes=9       Sucrose=5       Fructose=10; Font=17; Matoextrin=1; Mixed       Succes=1; Succes=10; Succes=4;       Succes=4; Succes=3; Succes=9	Trial Characteristics	Substitution Trials	Addition Trials	Subtraction Trials	Ad Libitum Trials
Male: Female <sup>3</sup> 44:56       39:61       12.88       44:56         Age (years) <sup>3</sup> 40.1(23.2-53.9)       35.8(25.0-50.1)       33.5(29.1-42.2)       37.4(20.100.100.100.100.100.100.100.100.100.1	Trial Number (N)	110	38	5	7
Age (years) <sup>1</sup> 40.1 (23.2-53.9)       35.8 (25.0-50.1)       33.5 (29.1-42.2)       37.4 (         Setting (Inpatient: Outpatient) <sup>1</sup> 5.4 (4.9-8.0)       5.1 (4.9-5.4)       5.1 (5.1-5.2)       4.9 (4)         Baseline Fasting Insulin (pmol/L) <sup>1</sup> 89.6 (57.9-131.6)       53.5 (40.6-81.5)       109.8 (97.8-121.7)       32.5 (31.0-30.0-30.0-30.0-30.0-30.0-30.0-30.0-	Trial Size (participants) <sup>2</sup>	15 (2-595)	21 (6-92)	15 (12-318)	39 (8-236)
Setting (Inpatient: Outpatient) <sup>3</sup> 25:75       10:90       0:100       0:13         Baseline Fasting Glucose (mmol/L) <sup>1</sup> 5.4 (4.9-8.0)       5.1 (4.9-5.4)       5.1 (5.1-5.2)       4.9 (4.9         Baseline Hable (%) <sup>1</sup> 7.3 (67-8.4)       7.2 (7.1-7.2)       N/A <sup>4</sup> N/         Study Design (Crossover: Parallel) <sup>3</sup> 62:38       50:50       20:80       57.7         Receling Control (Met: Supp: DA)       49:39:14       15:83:2       0:67:33       14:5         Randomization (Yes: No) <sup>3</sup> 69:31       66:34       80:20       88         Fructose Containing Sugar Dosage (%E) <sup>4</sup> 15:0 (9.6-23.6)       11:6 (5.0-25.0)       15:0 (13:8-15.0)       23.0 (12:60)         Fourdos-Up Duration (Weeks) <sup>2</sup> 4 (152)       7 (1-26)       12 (8:6-39.1)       88 (20:0)       88         Furctose-Containing Sugar Porm (N)       Furctose-10: Fruit=17;       Sucrose-5: Fruit=13; HFC5-1;       Fructose-10: Fruit=17;       Sucrose-5: Fruit=13; HFC5-1;       Furctose-10: Fruit=17;       Sucrose-5: Fruit=13; Baled Goods, Sweets and Desserts-11; Dainy=1; Fruit=13;       Dist alone-28; Sweetener=4; Water=2; Sweetener=3; No: Fat=2; Mixed Sources-1; SBS-4       Baked Goods, Sweets and Desserts-1; Dainy=1; Fruit=13; Fruit=13;       Baked Goods, Sweets and Desserts-1; Dainy=1; Fruit=13; HFC5=-1; SBS=-4	Male: Female <sup>3</sup>	44: 56	39: 61	12:88	41: 59
Baseline Fasting Glucose (mmol/L)       5.4 (4.9-8.0)       5.1 (4.9-5.4)       5.1 (5.1-5.2)       4.9 (4.         Baseline Fasting Insulin (pmol/L)       89.6 (57.9-131.6)       53.5 (40.6-81.5)       109.8 (97.8-121.7)       32.5 (31.         Baseline HbA1c (%1       7.3 (6.7-8.4)       7.2 (7.1-7.2)       N/A <sup>4</sup> N/A         Study Design (Crossover: Parallel) <sup>3</sup> 62:38       50:50       20:80       57.2         Feeding Control (Met: Sup: Do)       49:39:14       15:83:2       0:67:33       14:5         Fructose Containing Sugar Dosage (%E) <sup>1</sup> 15.0 (9.6-23.6)       11.6 (5.0-25.0)       15.0 (13.8-15.0)       23.0 (13.2)         Functose Containing Sugar Dosage (%E) <sup>1</sup> 15.0 (9.6-23.6)       11.6 (5.0-25.0)       15.0 (13.8-15.0)       23.0 (13.2)         Functose-Containing Sugar Form (N)       Functose=32, Funit=13; HFCS=1; Sucrose=50       Functose=10, Funit=17; HFCS=2; Hontey=3; Sucrose=9       Diet alone=28; Sweetener=4; Water=2; Sweetener=3; No. Fat=2; Mixed of Comparator=13; Protein=1; Starch=55       Sucrose=51; Size=4       Baked Goods, Sweets and Desserts=1; Dairy=1; Funit=13; HECS=1; Size=4       Baked Goods, Sweets and Desserts=1; Dairy=1; Funit=13; Bas=16; Mixed Sources=1; Size=4       Baked Goods, Sweets and Desserts=1; Dairy=1; Funit=13; Size=4       Baked Goods, Sweets and Desserts=1; Dairy=1; Funit=13; Bas=16; Mixed Sources=4       Sources=4       Sources=4       Sources=4       Sources=4       Sourc	Age (years) <sup>1</sup>	40.1 (23.2-53.9)	35.8 (25.0-50.1)	33.5 (29.1-42.2)	37.4 (34-39)
Baseline Fasting Insulin (pmol/L) <sup>1</sup> 89.6 (57.9-131.6)       53.5 (40.6-81.5)       109.8 (97.8-121.7)       32.5 (31         Baseline HbA1c (% <sup>1</sup> )       7.3 (6.7-8.4)       7.2 (7.1-7.2)       N/A <sup>4</sup> N/V         Study Design (Crossover: Paralle) <sup>3</sup> 62:38       50:50       20:80       57:         Feeding Control (Met: Supp: DA) <sup>3</sup> 49:39:14       15:83.2       0:67:33       14:55         Randomization (Yes: No) <sup>3</sup> 69:31       66:34       80:20       88:         Fuctose Containing Sugar Dosage (%E) <sup>1</sup> 15.0 (9.6-23.6)       11.6 (5.0-25.0)       15.0 (13.8-15.0)       23.0 (13.20)         Follow-Up Duration (Weeks <sup>3</sup> 4 (15:2)       7 (1-26)       12 (8.6-39.1)       82         Fuctose-Containing Sugar Form (N)       Fructose-10; Fruit-13; HFCS-1; Sucrose-20; HFCS-2; Honey-3; Sucrose-9       Fructose-10; Fruit-17; HFCS-2; Honey-3; Sucrose-9       Sucrose-10; Fruit-13; HFCS-1; Sucrose-10; Fruit-13; HFCS-1; Sucrose-13; Protein-11;       Fructose-10; Fruit-13; HFCS-4; Sucrose-4; Water-8       Baked Goods, Sweets and Sucrose-13; Sucrose-13; Sucrose-14;       Baked Goods, Sweets and Sucrose-14; Stat-4; St       Baked Goods, Sweets and Sucrose-14; Stat-4; St       Sucrose-10; Fruit-12; Fruit-12; Fruit Liuc=3; LMRs-7; Stat-65       Mixed Sources-1; SSBs-4       Baked Goods, Sweets and Sucrose-4       Baked Goods, Sweets and Sucrose-4       Sucrose-14       Dessert-15       Sucrose-14       De	Setting (Inpatient: Outpatient) <sup>3</sup>	25: 75	10: 90	0: 100	0: 100
Baseline HbA1c (%)7.3 (6.7-8.4)7.2 (7.1-7.2)N/AN/AStudy Design (Crossover: Parallel)62:3850:5020:8057:Feeding Control (Met: Sup: DA)49:39:1415:83:20:67:3314:55Randomization (Ye:: No)69:3166:3480:2088:Fructose Containing Sugar Dosage (%E) <sup>1</sup> 15:0 (9.6-23.6)11.6 (5.0-25.0)15:0 (13.8-15.0)23.0 (13.7)Follow-Up Duration (Weeks) <sup>3</sup> 4 (1-52)7 (1-26)12 (8-39.1)8 (2.3)Fuctose Containing Sugar Form (N)Fructose-52; Fruit=13; HFC5=1; Sucrose=50Fructose=10; Fruit=17; HFC5=2; Honey=3; Sucrose=9Sucrose=50Fructose=10; Fruit=17; HFC5=2; Honey=3; Sucrose=9Sucrose=50Fat=2; Mixed of Sucrose=9Comparator Form (N)Fructose=2.6 (ucose=22; Galactose=2, Sucrose=9; Mattodextrin=1; Mixed Comparator=13; Protein=1; Starch=55Baked Goods, Sweets and Desserts=1; Dairy=1; Fruitui-12; Fructose=10; Fruitui-13; HFC5=2; Honey=3; Sucrose=1Mixed Sources=1; SSB=4Baked Goods Desserts=1; Dairy=1; Fruitui-13; HFC5=2; Sucrose=1Sucrose=10; Sucrose=1; SSB=4Baked Goods Desserts=1; SSB=4Baked Goods Desserts=1; Dairy=1; Fruitui-13; HFC5=1; Eruitui-13; Hrc12; Fruitui-13; HFC5=1; SSB=4Baked Goods, Sweets and Desserts=1; Dairy=1; Fruitui-13; HFC5=1; SSB=4Baked Goods, Sweets and Desserts=1; SSB=4Baked Goods Sources=1Food Source of Fructose-Containing SugarSSB=21UMRs-7; Mixed Sources=5; SSB=21SSB=4Baked Goods, Sweets and Desserts=1; SSB=4Baked Goods Sources=4A=agency; Al=agency-industry; DA=dietary	Baseline Fasting Glucose (mmol/L) <sup>1</sup>	5.4 (4.9-8.0)	5.1 (4.9-5.4)	5.1 (5.1-5.2)	4.9 (4.9-5.4)
Study Design (Crossover: Parallel) <sup>3</sup> 62: 38       50: 50       20: 80       57:         Feeding Control (Met: Supp: DA)       49: 39: 14       15: 83: 2       0: 67: 33       14: 55         Randomization (Yes: No) <sup>3</sup> 69: 31       66: 34       80: 20       88:         Fructose Containing Sugar Dosage (%E) <sup>4</sup> 15.0 (9.6-23.6)       11.6 (5.0-25.0)       15.0 (13.8-15.0)       23.0 (12         Foldow-Up Duration (Weeks) <sup>2</sup> 4 (1-52)       7 (1-26)       12 (8.6-39.1)       8 (2         Functose Containing Sugar Dosage (%E) <sup>4</sup> 15.0 (9.6-23.6)       11.6 (5.0-25.0)       15.0 (13.8-15.0)       23.0 (12         Functose Containing Sugar Dosage (%E) <sup>4</sup> 15.0 (9.6-23.6)       11.6 (5.0-25.0)       15.0 (13.8-15.0)       23.0 (12         Functose-Containing Sugar Form (N)       Furctose=1       Furctose=10; Fruit=3; FIFCS=4       Furctose=10; Fruit=3; Firctos=9       Furctose=10; Fruit=3; Firctos=9       Diet alone=28; Sweetsen=10; Furut=17; Sucrose=9       Sucrose=1; Sismatulose=2; Lactose=4; Maltodextrin=1; Mixed       Sucrose=1; Sismatulose=2; Comparator Form (N)       Furctose=1; Fruit=3; Firctos=1; Dairy=1; Fruit=3; Firctos=1; Sismatulose=2; Lactose=4; Sismatulose=3; Fartes; Sismatulose=3; Fartes; Sismatulose=3; Furut=3; Fruit=3; Firctos=1; Dairy=1; Fruit=3; Esse=16; Mixed Sucrees=4       A=agency; Al=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; LMRs=liquid meal replacement Met-metabolic; N=number of tr	Baseline Fasting Insulin (pmol/L) <sup>1</sup>	89.6 (57.9-131.6)	53.5 (40.6-81.5)	109.8 (97.8-121.7)	32.5 (31.8-45.9)
Feeding Control (Met: Supp: DA)       49: 39: 14       15: 83: 2       0: 67: 33       14: 5         Randomization (Yes: No) <sup>3</sup> 69: 31       66: 34       80: 20       88:         Fructose Containing Sugar Dosage (%E) <sup>3</sup> 15.0 (9.6-23.6)       11.6 (5.0-25.0)       15.0 (13.8-15.0)       23.0 (13.2-15.0)         Follow-Up Duration (Weeks) <sup>3</sup> 4 (1-52)       7 (1-26)       12 (8.6-39.1)       8 (2.2-15.0)         Funding Sources (A: I: AI: NR) <sup>3</sup> 31: 27: 19: 23       48: 15: 30: 7       60: 40: 0.0       0: 17:         Fructose-Containing Sugar Form (N)       Fructose=50       Fructose=50       Fructose=10; Fruit=12; Honey=3; Surcose=9       Diet alone=28; Sweetner=4; Water=2; Sweetner=3; No       Fat=2; Mixed of Starch=4; Surcose=1         Comparator Form (N)       Domaltose=2; Lactose=4; Maltodextrin=1; Mixed Comparator=3; Protein=1; Starch=5       Baked Goods, Sweets and Desserts=1; Dairy=1; Fruit=13; Fruit=13; Fruit=13; Fruit=13; Fruit=13; SBs=16; Mixed Sources=1; SSB=4       Baked Goods Sources=4         A=agency; Al=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; LMRs=liquid meal replacement Met-metabolic; N=number of trials; NR=not reported; SSB=sugars-sweetened beverages; Sups=supplemented 1: A'-3 Values are reported as Medians and Interquartile Ranges (IQR) <sup>1</sup> , ranges <sup>2</sup> or percent ratios <sup>3</sup> .       *aseline data were only reported for one trial.	Baseline HbA1c (%) <sup>1</sup>	7.3 (6.7-8.4)	7.2 (7.1-7.2)	N/A <sup>4</sup>	N/A <sup>4</sup>
Randomization (Yes: No) <sup>3</sup> 69: 3166: 3480: 2088: 81: 40: 01Fructose Containing Sugar Dosage (%E) <sup>1</sup> 15.0 (9.6-23.6)11.6 (5.0-25.0)15.0 (13.8-15.0)23.0 (13.6)Follow-Up Duration (Weeks) <sup>2</sup> 4 (1-52)7 (1-26)12 (8.6-39.1)8 (2Funding Sources (A: 1: Al: NR) <sup>3</sup> 31: 27: 19: 2348: 15: 30: 760: 40: 0: 00: 17:Fructose-Containing Sugar Form (N)Fructose=52; Fruit=13; HFCS=1; Sucrose=50Fructose=10; Fruit=17; HCS=2; Honey=3; Sucrose=9Sucrose=5; HFCS=4Fructose-1Comparator Form (N)D-maltose=3; Fa1=9; Galactose=2 Glucose=25; Isomaltulose=2; Lactose=4; Maltodetrin=1; Mixed Comparator=13; Protein=1; Starch=55Baked Goods, Sweets and Desserts=11; Dairy=1; Fruit=13; Desserts=11; Dairy=1; Fruits=2; Fruit Juice=3; Sources=4Mixed Sources=1; SSBs=4Baked Goods, Sources Desserts=12; Sucrose=3Mixed Sources=1; SSBs=4Baked Goods, Sources Desserts=12; Sucrose=4A=agency; Al=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose con syrup; I=industry; LMRs=liquid meal replacement A: <sup>2,3</sup> Values are reported as Medians and Interquartile Ranges (IQR) <sup>1</sup> , ranges <sup>2</sup> or percent ratios <sup>3</sup> .Mixed Sources-1; A'aseline data were only reported for one trial.Frait	Study Design (Crossover: Parallel) <sup>3</sup>	62: 38	50: 50	20: 80	57: 43
Fructose Containing Sugar Dosage (%E)115.0 (9.6-23.6)11.6 (5.0-25.0)15.0 (13.8-15.0)23.0 (13.8-15.0)Follow-Up Duration (Weeks)24 (1-52)7 (1-26)12 (8.6-39.1)8 (2Funding Sources (A: I: AI: NR)331: 27: 19: 2348: 15: 30: 760: 40: 0: 00: 17:Fructose-Containing Sugar Form (N)Fructose=52; Fruit=13; HFCS=1; Sucrose=50Fructose=10; Fruit=17; HFCS=2; Honey=3; Sucrose=9Sucrose=50Fructose=10; Fruit=17; HFCS=2; Honey=3; Sucrose=9Comparator Form (N)Galactose=2 Glucose=25; Isomaltulose=2; Lactose=4; Maltodextrin=1; Mixed Comparator=13; Protein=1; Starch=55Baked Goods, Sweets and Desserts=1; Dairy=1; Fruits=12; Fruit Luice=3; LMRs=7; Mixed Sources=57; SBs=21Mixed Sources=1; SSBs=4Baked Goods, Desserts=1; Dairy=1; Fruits=12; Fruit Luice=3; LMRs=7; Mixed Sources=4Mixed Sources=1; SSBs=4Baked Goods, Desserts=1; Dairy=1; Fruits=12; Fruit Luice=3; LMRs=7; Mixed Sources=7: Sources=4Mixed Sources=1; SSBs=4Baked Goods, Desserts=1; Dairy=1; Fruits=12; Fruit Luice=3; LMRs=7; Sucrose=4Mixed Sources=1; SSBs=4Baked Goods, Desserts=1; Dairy=1; Fruits=12; Fruit Luice=3; LMRs=7; Sucrose=4Mixed Sources=1; SSBs=4Baked Goods, Source Sources=4A=agency: Al=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; LMRs=liquid meal replacement 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 <sup>2</sup> or percent ratios <sup>3</sup> . * * * * * * * * * * * * * * * * * * * <br< td=""><td>Feeding Control (Met: Supp: DA)<sup>3</sup></td><td>49: 39: 14</td><td>15: 83: 2</td><td>0: 67: 33</td><td>14: 57: 29</td></br<>	Feeding Control (Met: Supp: DA) <sup>3</sup>	49: 39: 14	15: 83: 2	0: 67: 33	14: 57: 29
Follow-Up Duration (Weeks <sup>2</sup> )       4 (1-52)       7 (1-26)       12 (8.6-39.1)       8 (2         Funding Sources (A: I: AI: NR) <sup>3</sup> 31: 27: 19: 23       48: 15: 30: 7       60: 40: 0: 0       0: 17:         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, Fructose=10; Fruit=17; HFCS=2; Honey=3; Sucrose=9         Comparator Form (N)       D-maitose=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       Fat=2; Mixed or Starch=4; Starch=56         Food Source of Fructose-Containing Sugar       Baked Goods, Sweets and Desserts=11; Dairy=1; Fruit=13; IMRs=7; Niked Sources=57; SSBs=21       Baked Goods, Sweets and Desserts=1; Dairy=1; Fruits=12; Fruits=12; Fruits=12; Fruits=12; Fruits=12; Fruits=12; Fruits=12; Fruits=12; Fruits=12; Fruits=12; Fruits=13; IMRs=7; SBBs=16; Mixed Sources=4         A=agency; Al=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; LMRs=liquid meal replacement 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) <sup>1</sup> , ranges <sup>2</sup> or percent ratios <sup>3</sup> . <sup>4</sup> Baseline data were only reported for one trial.	Randomization (Yes: No) <sup>3</sup>	69: 31	66: 34	80: 20	88: 12
Funding Sources (A: I: AI: NR)31: 27: 19: 2348: 15: 30: 760: 40: 0: 00: 17:Fructose-Containing Sugar Form (N)Fructose=52; Fruit=13; HFCS=1; Sucrose=50Fructose=10; Fruit=17; HFCS=2; Honey=3; Sucrose=9Sucrose=5, HFCS=4Fructose=1, Fructose=1, Fructose=1, HFCS=2; Sweetener=3; No Sucrose=13; No Starch=4; SuComparator Form (N)Baked Goods, Sweets and Desserts=11; Dairy=1; Fruit=13; SBS=21Baked Goods, Sweets and Desserts=1; Dairy=1; Fruits=12; Fruit Juice=3; LMRs=7; Mixed Sources=4Mixed Sources=1; SSBs=4Baked Goods, Desserts=1; SourceFood Source of Fructose-Containing SugarBaked Goods, Sweets and Desserts=11; Dairy=1; Fruit=12; SSB=21Baked Goods, Sweets and Desserts=1; Dairy=1; Fruits=12; Fruit Juice=3; LMRs=7; Mixed Sources=4Mixed Sources=1; SSBs=4Baked Goods Desserts=3; Source Sources=4A=agency; Al=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; l=industry; LMRs=liquid meal replacement 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) <sup>1</sup> , ranges <sup>2</sup> or percent ratios <sup>3</sup> . * Baseline data were only reported for one trial.Fruits=12: Fruit ratios <sup>3</sup> .	Fructose Containing Sugar Dosage (%E) <sup>1</sup>	15.0 (9.6-23.6)	11.6 (5.0-25.0)	15.0 (13.8-15.0)	23.0 (13.0-26.0)
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, Fructose=1, Fructose=1, Fructose=1, Fructose=1, Fructose=1, Fructose=1, Fructose=1, Fructose=1, Fructose=2; Lactose=2; Lactose=3; Fructose=1, Fructose=1	Follow-Up Duration (Weeks) <sup>2</sup>	4 (1-52)	7 (1-26)	12 (8.6-39.1)	8 (2-78)
Fructose-Containing Sugar Form (N)       Sucrose=50       HFCS=2; Honey=3; Sucrose=9         D-maltose=3; Fat=9; Galactose=2 Glucose=25; Maltodextrin=1; Mixed Comparator Form (N)       D-maltose=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 of Starch=4; Starch=4; Starch=55         Food Source of Fructose-Containing Sugar       Baked Goods, Sweets and Desserts=11; Dairy=1; Fruit=13; LMRs=7; Mixed Sources=7; SSBs=21       Baked Goods, Sweets and Desserts=1; Dairy=1; LMRs=1 SSBs=16; Mixed Sources=4       Mixed Sources=1; SSBs=4 Sources=4       Baked Goods, Sweets and Desserts=1; Dairy=1; LMRs=1 SSBs=16; Mixed Sources=4       Mixed Sources=1; SSBs=4 Sources=4       Baked Goods, Sweets and Desserts=1; SSBs=16; Mixed Sources=4       Mixed Sources=1; SSBs=4 Sources=4       Pate: Protectores=1; SSBs=10; Mixed Sources=4       Pate: Protectores=1; SSBs=10; Mixed Sources=4         A=agency; Al=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; LMRs=liquid meal replacement 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) <sup>1</sup> , ranges <sup>2</sup> or percent ratios <sup>3</sup> . <sup>4</sup> Baseline data were only reported for one trial.       Pate: Pate	Funding Sources (A: I: AI: NR) <sup>3</sup>	31: 27: 19: 23	48: 15: 30: 7	60: 40: 0: 0	0: 17: 50: 33
Galactose=2 Glucose=25;       Water=8       sucrose=1       Starch=4; Sucrose=1         Comparator Form (N)       Isomaltulose=2; Lactose=4; Maltodextrin=1; Mixed Comparator=13; Protein=1; Starch=55       Baked Goods, Sweets and Desserts=1; Dairy=1; Fructose-Containing Sugar       Baked Goods, Sweets and Desserts=1; Dairy=1; Fruits=12; Fruit Juice=3; SBs=21       Mixed Sources=1; SSBs=4 Desserts=1; Dairy=1; Fruits=12; Fruit Juice=3; Sources=4       Baked Goods, Sweets and Desserts=1; Dairy=1; Fruits=12; Fruit Juice=3; Sources=4       Baked Goods, Sweets and Sources=4       Baked Goods, Sweets and Sources=4         A=agency; Al=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; LMRs=liquid meal replacement 1,2,3 Values are reported as Medians and Interquartile Ranges (IQR) <sup>1</sup> , ranges <sup>2</sup> or percent ratios <sup>3</sup> .       *       *         * Baseline data were only reported for one trial.       Painterquartile Ranges i URR) <sup>1</sup> , ranges <sup>2</sup> or percent ratios <sup>3</sup> .       *	Fructose-Containing Sugar Form (N)			Sucrose= 5; HFCS=4	Fructose=1; Sucrose=7
Food Source of Fructose-Containing Sugar       Desserts=11; Dairy=1; Fruit=13; LMRs=7; Mixed Sources=57; SSBs=21       Desserts=1; Dairy=1; Fruits=12; Fruit Juice=3; LMRs=1 SSBs=16; Mixed Sources=4       Desserts= Sources=4         A=agency; Al=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; LMRs=liquid meal replacement 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) <sup>1</sup> , ranges <sup>2</sup> or percent ratios <sup>3</sup> . <sup>4</sup> Baseline data were only reported for one trial.       Paj	Comparator Form (N)	Galactose=2 Glucose=25; Isomaltulose=2; Lactose=4; Maltodextrin=1; Mixed Comparator=13; Protein=1;		, , ,	Fat=2; Mixed comparator=2 Starch=4; Sweetener=3
A=agency; AI=agency-industry; DA=dietary advice; E=energy; HFCS=high fructose corn syrup; I=industry; LMRs=liquid meal replacement Met=metabolic; N=number of trials; NR=not reported; SSBs=sugars-sweetened beverages; Supp=supplemented <sup>1,2,3</sup> Values are reported as Medians and Interquartile Ranges (IQR) <sup>1</sup> , ranges <sup>2</sup> or percent ratios <sup>3</sup> . <sup>4</sup> Baseline data were only reported for one trial. Page		Desserts=11; Dairy=1; Fruit=13; LMRs=7; Mixed Sources= 57;	Desserts=1; Dairy=1; Fruits=12; Fruit Juice=3; LMRs=1 SSBs=16; Mixed	Mixed Sources=1; SSBs=4	Baked Goods, Sweets and Desserts=1; Mixed Sources=6
	Met=metabolic; N=number of trials; N <sup>1,2,3</sup> Values are reported as Medians ar	NR=not reported; SSBs=sugars-s ad Interquartile Ranges (IQR) <sup>1</sup> , ra	weetened beverages; Supp		al replacements;
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		https://mc.man	uscriptcentral.com/bmj		

### **Table 2.** GRADE Quality of Evidence Assessment

	-		Quality assess	sment			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
asting Blood Glucose i	n Substitution Trials						
01	randomized and non- randomized trials	no serious risk of bias	serious	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
asting Blood Glucose i	n Addition Trials						
5	randomized and non-	no serious risk of bias	serious <sup>2</sup>	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
asting Blood Glucose i	n Subtraction Trials						
	randomized and non- randomized trials	no serious risk of bias	no serious inconsistency <sup>3</sup>	no serious indirectness	no serious imprecision <sup>4</sup>	none <sup>5</sup>	⊕⊕⊕⊕ HIGH
asting Blood Glucose i	n Ad Libitum Trials						
i	randomized and non- randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none <sup>5</sup>	⊕⊕⊕⊕ HIGH
asting Blood Insulin in	Substitution Trials		-	•			
5	randomized and non- randomized trials	no serious risk of bias	serious <sup>6</sup>	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
asting Blood Insulin in	Addition Trials	•					
27	randomized and non- randomized trials	no serious risk of bias	serious <sup>7</sup>	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
asting Blood Insulin in	Subtraction Trials	•		•			
3	randomized and non- randomized trials	no serious risk of bias	no serious inconsistency <sup>8</sup>	no serious indirectness	serious	none <sup>5</sup>	⊕⊕⊕O MODERATE
asting Blood Insulin in	Ad Libitum Trials	- <b>!</b>					
	randomized and non- randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none <sup>5</sup>	⊕⊕⊕⊕ HIGH
IbA1c in Substitution T	rials	•	-	•			
32	randomized and non- randomized trials	no serious risk of bias	serious <sup>10</sup>	no serious indirectness	no serious imprecision	none	⊕⊕⊕O MODERATE
bA1c in Addition Trials	;			-	•		
	randomized and non- randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	⊕⊕⊕⊕ HIGH
IbA1c in Subtraction Tr	ials	•	•	•			
	randomized and non- randomized trials	no serious risk of bias	no serious inconsistency	serious <sup>11</sup>	no serious imprecision	none <sup>5</sup>	⊕⊕⊕0 MODERATE
IbA1c in Ad Libitum Tri	als	•	<u>.</u>	•			
	randomized and non- randomized trials	no serious risk of bias	no serious inconsistency	serious <sup>11</sup>	very serious <sup>12</sup>	none <sup>5</sup>	⊕000 VERY LOW

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1102	<sup>1</sup> Serious inconsistency for the effect of fructose-containing sugars on fasting blood glucose, as there was evidence of significant interstudy
1103	heterogeneity (I <sup>2</sup> =67%, p<0.0001).
1104	<sup>2</sup> Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin, as there was evidence of significant intersudy
1105	heterogeneity (I <sup>2</sup> =72%, p<0.0001).
1106	<sup>3</sup> No serious inconsistency for the effect of fructose-containing sugars on fasting plasma glucose. Even though there was evidence of significant
1107	interstudy heterogeneity (I <sup>2</sup> =59%, p=0.06), removal of a trial by Campos et al. (G2) explained all of the heterogeneity. While removal of this trial
1108	changed the direction of the effect, overall results remained non-significant.
1109	<sup>4</sup> No serious imprecision for the effect of fructose-containing sugars on fasting blood glucose as 585 participants were included in the analysis
1110	although only 4 trials were available.
1111	<sup>5</sup> 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).
1112	<sup>6</sup> Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin, as there was evidence of significant interstudy
1113	heterogeneity (I <sup>2</sup> =57%, p<0.0001).
1114	<sup>7</sup> Serious inconsistency for the effect of fructose-containing sugars on fasting blood insulin, as there was evidence of significant interstudy
1115	heterogeneity (I <sup>2</sup> =56%, p<0.0002).
1116	<sup>8</sup> No serious inconsistency for the effect of fructose-containing sugars on fasting plasma insulin. Even though was evidence of significant
1117	interstudy heterogeneity ( <sup>12</sup> =79%, p=0.009), removal of a trial by Campos et al. 2015 (G2) explained 78% of the heterogeneity. While removal of
1118	this trial changed the overall significance, the direction of effect remained the same.
1119	<sup>9</sup> Serious imprecision for the effect of fructose-containing sugars on fasting plasma insulin, as the 95% CIs [-22.83, 26.83] includes both clinically
1120	important benefit (<10 pmol/L) and harm (>10 pmol/L). Only 3 trials involving 33 participants were available for analysis.
1121	<sup>10</sup> Serious inconsistency for the effect of fructose-containing sugars on HbA1c, as there was evidence of significant interstudy heterogeneity
1122	( <sup>12</sup> =81%, p<0.00001).
1123	<sup>11</sup> Serious indirectness for the effect of fructose-containing sugars on HbA1c as only 1 trial in 240 overweight/ obese females was available for
1124	analysis.
1125	<sup>12</sup> 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
1126	important benefit (HbA1c ≤-0.3%) and harm (HbA1c≥0.3%). Only 1 trail in 10 participants was available for analysis.
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#### Figure 2. Summary super-plot for the effect of fructose-containing sugars on HbA1c.

Comparison	Trials	N	Weight	MD [95% CI]	MD [95% CI] in HbA1c (%)	l <sup>2</sup>	P-value
SUBSTITUTION TRIALS					I		
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]	_ <b>+</b>	0%	0.43
Baked Goods, Sweets and Desserts	1	10	2.0%	-0.50 [-1.12, 0.12]	<b>_</b>	-	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					Ĩ		
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
					· · · · · · · ·		
				-1	5 -1 -0.5 0 0.5 1	1.5	
					Favors Fructose- Containing Sugar Favors Compa	rator	

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

109x70mm (300 x 300 DPI)

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Figure 3. Summary super-plot for the effect of fructose-containing sugars on fasting blood glucose
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					MD [95% CI] in		
Comparison	Trials	N	Weight	MD [95% CI]	Fasting Blood Glucose (mmol/L)	l <sup>2</sup>	P-valu
SUBSTITUTION TRIALS					T		
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					ſ		
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					T.		
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]	4	0%	0.56
Total Food Sources	6	459	100.0%	-0.02 [-0.07, 0.04]	•	0%	0.56
					-1.5 -0.75 0 0.75	1.5	
					Favors Fructose- Containing Sugar Favors Compara	ator	

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

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

					MD [95% CI] in		
Comparison	Trials	N	Weight	MD [95% CI]	Fasting Blood Insulin (pmol/L)	1 <sup>2</sup>	P-value
SUBSTITUTION TRIALS							
Fruits	6	298	10.6%	-0.81 [-4.58, 2.97]		6%	0.68
Sugars-Sweetened Beverages	17	387	27.3%	-1.47 [-6.56, 3.62]		46%	0.57
Liquid Meal Replacements	7	118	4.0%	-2.64 [-16.40, 11.13]		22%	0.71
Dairy Products	1	95	1.5%	26.59 [9.51, 43.68]		-	< 0.01
Baked Goods, Sweets and Desserts	10	156	9.4%	3.97 [-5.26, 13.20]		33%	0.40
Mixed Sources	34	1140	47.1%	4.71 [0.25, 9.18]	_ <b>-</b>	68%	0.04
Total Food Sources	75	2194	100.0%	1.72 [-0.84, 4.29]	*	56%	0.19
ADDITION TRIALS							
Fruits	8	237	30.9%	0.48 [-2.93, 3.88]	+	17%	0.78
Sugars-Sweetened Beverages	13	236	51.2%	6.17 [1.55, 10.78]		65%	<0.01
Fruit Juice	3	128	9.0%	5.55 [-0.82, 11.92]		0%	0.09
Liquid Meal Replacements	1	14	1.6%	20.14 [-1.23, 41.51]		-	0.06
Dairy Products	1	92	4.0%	15.64 [5.18, 26.10]	· · · · · · · · · · · · · · · · · · ·	-	0.01
Mixed Sources	1	23	3.4%	13.00 [0.81, 25.19]			0.04
Total Food Sources	27	730	100.0%	5.33 [2.26, 8.41]	•	59%	<0.001
SUBTRACTION TRIALS							
Sugars-Sweetened Beverages	2	27	90.4%	-5.89 [-32.01, 20.22]		83%	0.66
Mixed Sources	1	6	9.6%	76.39 [-3.75, 156.54]		-	0.06
Total Food Sources	3	33	100.0%	2.00 [-22.83, 26.83]		79%	0.87
AD LIBITUM TRIALS							
Mixed Sources	4	302	100.0%	3.46 [-0.73, 7.66]		34%	0.11
Total Food Sources	4	302	100.0%	3.46 [-0.73, 7.66]	-	34%	0.11
					-30 -20 -10 0 10 20 30		
					Favors Fructose- Containing Sugar Favors Comparator		

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

108x69mm (300 x 300 DPI)

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45	HbA1c.
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48	substitution trials investigating the effect of isocaloric exchange of fructose-
49 50	containing food sources for other macronutrients on HbA1c.
51	Supplementary Figure 8. Post-hoc meta-regression analyses for the effect of fructose dose (%E) on
52 53	
54	glycemic control in substitution and addition trials
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3 4	Supplementary Figure 9. Forest plot for substitution trials investigating the effect of isocaloric exchange
5	of fructose-containing food sources for other macronutrients on fasting blood
6 7	glucose.
8	-
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10	to the diet in the form of fructose-containing food sources on fasting blood
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20	calories from fructose-containing food sources with other dietary sources on
21 22	fasting blood glucose.
23 24	Supplementary Figure 13. Subgroup analyses for substitution trials investigating the effect of isocaloric
25	exchange of fructose-containing food sources for other macronutrients on
26 27	fasting blood glucose.
28	Supplementary Figure 14. Subgroup analyses for addition trials investigating the effect of adding excess
29 30	calories to the diet in the form of fructose-containing food sources on fasting
31 32	blood glucose.
33	Supplementary Figure 15. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for
34 35	substitution trials investigating the effect of isocaloric exchange of fructose-
36	containing food sources for other macronutrients on fasting blood glucose.
37 38	
39	Supplementary Figure 16. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis for
40	addition trials investigating the effect of isocaloric exchange of fructose-
41 42	containing food sources for other macronutrients on fasting blood glucose.
43	Supplementary Figure 17. Forest plot for substitution trials investigating the effect of isocaloric
44 45	exchange of fructose-containing food sources for other macronutrients on
46	fasting blood insulin.
47 48	
49	Supplementary Figure 18. Forest plot for addition trials investigating the effect of adding excess calories
50 51	to the diet in the form of fructose-containing food sources on fasting blood
52	insulin.
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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.

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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.

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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.
		<ul><li>8 exp Insulin/</li><li>9 HbA1c.mp. or exp Hemoglobin A, Glycosylate</li></ul>
		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
		14 7 of 8 of 9 of 10 of 11 of 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.
		<ul><li>8 exp insulin/</li><li>9 HbA1c.mp. or exp hemoglobin A1c/</li></ul>
		10 exp fructosamine blood level/ or fructosamin
		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
	Through Nevershard 20015	24 19 and 23
The Cochrane Library of Controlled Trial	s Through November 3 2015	<ol> <li>Fructose/</li> <li>DietarySucrose/</li> <li>HFCS.mp.</li> <li>sugar.mp.</li> <li>sugar* sweetened beverage*.mp.</li> <li>Honey/</li> </ol>
		3 HFCS.mp.
		4 sugar.mp.
		5 sugar*sweetenedbeverage*.mp.
		6 Honey/ 7 glyc?em*.mp.
		8 Insulin/
		9 Hemoglobin A, Glycosylated/or HbA1c.mp.
		10 fructosamine.mp.
		<ul><li>11 Blood Glucose/</li><li>12 gly* albumin.mp.</li></ul>
		12 giy 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
		10 10 000 14
		15 15 414 14
		15 1500014

#### **Table 1** Search strategy for the effect of fructose-containing sugars on glycemic c. . . . . . .

### Supplementary Table 2. Trial characteristics

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>a</sup>	Randomiza tion	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet	Energy Balance d	Follow- Up	Fundir Source e
Substitution Trials (Isocalori	c comparison)																	
Fruit																		
Agebratt et al. 2016	30 H (18 M, 12 W)	23.5 (3.7)		22.3 (1.9)	OP, Sweden				Р	Supp	Yes						8 wk	А
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		aa a (a a)	OP, USA	5.3 (0.6)	-	5.9 (0.4)	Р	Supp	Yes			a. (1 1)	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)	Р	Supp	Yes				NR	Neutral	12 wk	I
ntervention	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)	22 (5 5)	OP,	6.6 (1.1)			р	DA	Vac				NR	Negative	12 wk	NR
				32 (5.5)	Denmark			-	F	DA	Yes			Incorporate ≥ 2 fruit/d into	ININ	Negative	12 WK	NIX
Intervention	32 DM2 (18 M, 14 W)	59 (12)	92.4 kg (17)	32 (5)		6.74 (1.2)						~23.1 (~4.6) <sup>s</sup>	Fruit	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)	-	Р	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				
legde et al. 2013		58.0 (9.2)	-	24.9 (3.9)	OP, India	8.3 (2.5)	-	8.0 (1.4)	Р	DA	No				NR	Positive	3 mo	Α
ntervention	60 DM2	58.5 (9.6)		24.4 (3.9)		7.9 (1.5)		8.0 (1.3)				~16.5 (~3.3) <sup>g</sup>	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)	Р	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)	-	Р	Supp	Yes					Neutral	8 wk	А
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) <sup>f</sup>	Fruit	200 g/d bilberry puree and 40 g/d dried bilberries equivalent to 400 g/d fresh	~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	bilberries Other Carbohydrates	~50:34:16			
Lehtonen et al. 2010	12 meto (5 m, 5 m)	42.9 (35-52)	-	52.5 (5.4)	OP,	5.0 (0.4)	57.3 (27.9)	5.3 (0.2)	Р	Supp	Yes		Startin	other carbonyarates	50.54.10	Neutral	20 wk	A, I
Intervention	28 OW (0 M, 28 W)	- ( /		29.3 (2.2)	Finland	5.1 (0.4)	55.6 (27.1)	5.3 (0.2)				~14.7 (~3.3) <sup>f</sup>	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,	5.0 (1.2)	125.1 (70.8)	-	Р	DA	Yes		comparator		50:30:15	Negative	6 wk	А
Intervention	65 OW/OB (15 M, 50 W)	40.2 (8.1)	79.1 kg (13.4)	32.8 (4.5)	Mexico	4.9 (1.2)	125.5 (71.1)		·	571	105	~60 (~14)	Fruit	Fruits	50.50.15	negutite	0	
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				
Moazen et al. 2013	36 DM2 (13 M, 23 W)	51.6 (11.1)			OP, Iran	10.0 (4.1)	-	7.3 (1.7)	Р	Supp	Yes			products		Neutral	6 wk	A, I
ntervention	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				

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### 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 <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>®</sup>	Randomi zation	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet <sup>c</sup>	Energy Balance	Follow- Up	Fundi Sourc e
Madero et al. 2011 Intervention	131 OW/OB (29 M, 102 W) 65 OW/OB (15 M, 50 W)	38.3 (8.8) 40.2 (8.1)	80.9 kg (13.4) 79.1 kg (13.4)	32.4 (4.5) 32.8 (4.5)	OP, Mexico	5.0 (1.2) 4.9 (1.2)	125.1 (70.8) 125.5 (71.1)	-	Ρ	DA	Yes	~60 (~14)	Fruit	Fruits Low fructose diet	50:30:15	Negative	6 wk	A
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	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)	Р	Supp	Yes			For any dated strengtheres.		Neutral	6 wk	А,
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 Intervention	7 OB (0 M, 7 W)	32.6 (5.8)	91.6 kg (6.0)	34.2 (2.6)	OP, Spain	5.1 (0.5) 5.2 (0.5)	46.1 (44.3) 52.8 (59.0)	-	Р	DA	Yes	~45.0 (13.8)	Fruit	High fruit diet	55:30:15	Negative	8 wk	A
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				
Singh et al. 1997		50.5 (8.5)		-	OP, India	6.1 (0.6)	-	-	Р	Supp	Yes			carbohydrates		Neutral	24 wk	NF
Intervention Control	52 HTN, HCL (43 M, 9 W) 49 HTN, HCL (45 M, 4 W)	49.1 (7.5) 52.0 (9.2)	67.8 kg (9.6) 69.2 kg (11.4)			6.1 (0.6) 6.2 (0.7)						~36.8 (~7) <sup>8</sup>	Fruit Mixed comparator	412 g/d guava Refined CHO, saturated fat and cholesterol	63:23:14 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)	-	-	С	Supp	Yes	80 (~13)				Neutral	3 wk	А,
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)	-	-	с	Supp	Yes	40 (~7)				Neutral	3 wk	A
Intervention Control													Fructose Glucose, starch	Fructose SSB Glucose SSB, low fructose diet	~51:35:14 ~49:35:15			
Aeberli et al. 2013	9 H (9 M, 0 W)	22.8 (1.7)	-	22.6 (1.4)	OP, Switzerland	-	-	-	с	Supp	Yes	80 (~14)				Neutral	3 wk	Å
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)	-	Р	Supp	Yes				44:38:18	Positive	7 d	А
Intervention Control			61.5 kg (9.9) 60.9 kg (7.4)			5.2 (0.6) 5.8 (0.5)	27.8 (19.6) 48.6 (36.7)					250 (~33)	Fructose Glucose	Fructose dissolved in water 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	-	-	-	С	Supp	Yes	50 (~10)			NR	Positive	2 wk	ļ
Intervention Control													Fructose Glucose	Fructose SSB 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	-	-	-	с	Supp	Yes	50 (~10)			NR	Positive	2 wk	A
Intervention Control													Fructose Glucose	Fructose SSB 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	-	-	-	с	Supp	Yes	50 (~10)	Glucose	Glucose 556	NR	Positive	2 wk	A
Intervention													Fructose	Fructose SSB with walking (≥12000 steps per day) Glucose SSB with walking				
Control													Glucose	(≥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)	-	Р	Supp	Yes				NR	Neutral	4 wk	,
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 Johnston et al. 2013 (T1)	12 OW (8 M, 4 W) 32 OW (32 M, 0 W)	13.0 (2.5) 34 (9.9)	82.0 kg (4.27)		OP, UK	5.0 (1.3) 4.6 (0.3)	252.1 (233.5) 112.1 (38.5)		D	Met	Yes		Glucose	Glucose SSB	55:30:15	Neutral	2 wk	
Intervention	15 OW (15 M, 0 W)	35 (11)	96.8 kg (7.4)	30.0 (1.4)	01,01	4.5 (0.2)	124.3 (35.4)	-	F	WICL	103	~221 (25)	Fructose	Fructose dissolved in water	55.30.15	neutrai	2 WK	,
Control Johnston et al. 2013 (T2)	17 OW (17 M, 0 W) 32 OW (32 M, 0 W)	33 (9) 34 (9.9)	93.9 kg (8.7)	28.9 (1.7)	OP, UK	4.7 (0.4) 4.6 (0.3)	101.4 (38.9)	-	Р	Supp	Yes		Glucose	Glucose dissolved in water	NR	Positive	2 wk	
Intervention Control	15 OW (15 M, 0 W) 17 OW (17 M, 0 W)	35 (11) 33 (9)	96.8 kg (7.4)	30.0 (1.4) 28.9 (1.7)	. ,	4.5 (0.2) 4.7 (0.4)	124.3 (35.4) 101.4 (38.9)			- · FF		~221 (25)	Fructose Glucose	Fructose dissolved in water Glucose dissolved in water				
Koivisto and Yki-Järvinen	17 OW (17 M, 0 W) 10 DM2 (4 M, 6 W)	33 (9) 61 (10)	93.9 kg (8.7) 81.9 kg (15.4)	28.9 (1.7)	IP, Finland	4.7 (U.4)	101.4 (38.9)		с	Met	Yes		GIUCOSE	GIULOSE DISSOIVED IN WATER	50:30:20	Neutral	4 wk	А
1993 Intervention	10 DIVIZ (4 IVI, 0 W)	01 (10)	81.9 kg (15.4) 82.0 kg (15.8)	27.3 (4.1)	iP, Fillidilü	9.7 (3.2)	83 (44.3)	9.0 (1.6)	C	wiet	res	~55 (~10)	Fructose	Fructose dissolved in water	50:50:20	neural	4 WK	A
Control			81.8 kg (15.8)			10.0 (2.5)	89 (60.1)	9.5 (1.9)				33 ( 10)	Glucose	Glucose dissolved in water				

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Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>ª</sup>	Randomi zation	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet <sup>c</sup>	Energy Balance d	Follow- Up	Fundin Source
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)	-	Ρ	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)	Dennark	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)	-	Р	Supp	Yes				~20:45:34	Neutral	4 wk	А
Intervention Control	35 OW (0 M, 35 W) 38 OW (0 M, 38 W)					5.4 (0.4) 5.5 (0.4)	58.2 (43.6) 62.6 (36.3)					60 (~13.6)	Fructose Glucose	Fructose dissolved in water Glucose dissolved in water				
McAteer et al. 1987	10 DM2	64.4 (54-71)	59.3 kg (5.4)	-	OP, Ireland	-	-	-	С	Supp	No		Glacose		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)	-	с	Met	Yes				55:30:15	Positive	7 d	А
Intervention												~214 (35)	Fructose	20% fructose solution				
Control 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)	-	с	Met	No		Glucose	20% glucose solution	50:35:15	Neutral	9 d	A
Intervention						. ,	. ,					~112.5	Fructose	Fructose SSB				
Control												(~22.5)	Starch	Isocaloric exchange of				
control					OP,								Startin	fructose for CCHO				
Silbernagel et al. 2011	20 H (12 M, 8 W)	30.5 (8.9)		25.9 (2.3)	Germany	4.85 (0.3)	47.9 (29.2)	-	Р	Supp	Yes				50:35:15	Positive	4 wk	А
Intervention Control	10 H (7 M, 3 W) 10 H (5 M, 5 W)	32.8 (9.3) 28.2 (8.4)	80.3 kg (9.1) 80.7 kg (7.5)	25.5 (2.2) 26.2 (2.4)		4.8 (0.3) 4.9 (0.2)	45.4 (36.7) 50.6 (20.9)					150 (~22)	Fructose Glucose	Fructose dissolved in water Glucose dissolved in water				
Stanhope et al. 2011	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)	-	Р	Met/	No					Positive	8 wk	А
(AJCN) Intervention	17 OW/ OB(9 M, 8 W)	52.5 (9.3)	85.8 kg (10.7)	29.3 (2.6)	, 61, 65,1	4.9 (0.2)	99.2 (45.0)		•	Supp		158 (25)	Fructose	Fructose SSB	~55:30:15	1 Ostive	0	
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)	-	Р	Met/ Supp	No				55:30:15	Neutral	2 wk	А
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)	-	с	Met	No			Fructose SSB (12 % solution	55:30:15	Neutral	10 wk	А
Intervention												~125 (25)	Fructose	flavored with unsweetened				
														drink mix) Complex CHO sources				
Control													Starch	(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)	Р	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)	-	Ρ	Met	No					Negative	14 d	А
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	Feplacement 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)	Р	Supp	Yes					Negative	8 wk	А
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) <sup>h</sup>	70.1 kg (11.6)	-	OP, France	4.5 (0.4)	82.3 (35.6)	6.5 (1.4)	Р	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 Liquid meal replacement				
Control	15 OB		70.2 kg (10.0)			4.5 (0.4)	79.1 (34.4)	6.8 (1.4)					Glucose, galactose	with 36 g glucose or galactose				
Rizkalla et al. 1986 (EXP 2)	18 OB	22 (14.6) <sup>h</sup>	70.6 kg (10.6)	-	OP, France	4.2 (0.4)	88.0 (48.9)	6.8 (0.7)	Р	Met	Yes				~25:25:50	Negative	2 wk	I
z) 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				
	12 OB		70.7 kg (9.8)			4.2 (0.4)	87.9 (59.7)	6.7 (0.6)				50 ( 25)	Glucose,	with 36 g fructose Liquid meal replacement with 36 g glucose or				

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Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>a</sup>	Randomi zation	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet	Energy Balance	Follow- Up	Fu So
Turner et al. 1979 (HC) Intervention Control	4 MetS (4 M, 0 W)	46.8 (8.0)	82.6 kg (9.9)	-	IP, USA	5.0 (0.4)	-	-	С	Met	No	~122 (17)	Fructose D-Maltose	Liquid meal replacement (20% CHO from fructose) Liquid meal replacement (all	85:00:15	Neutral	~2 wk	
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)	-	-	С	Met	No	~39.5 (9)	Fructose D-Maltose	CHO from D-maltose) Liquid meal replacement (20% CHO from fructose) Liquid meal replacement (all	45:40:15	Neutral	~2 wk	
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)	-	-	С	Met	No	~39.5 (9)		CHO from D-maltose) Liquid meal replacement	45:40:15	Neutral	~2 wk	
Intervention Control													Fructose D-Maltose	(20% CHO from fructose) Liquid meal replacement (all CHO from D-maltose)				
Dairy products																		
Lowndes et al. 2015 Intervention Control	95 OW/ OB (43 M, 52 W) 30 OW/OB (16 M, 14 W) 65 OW/OB (27 M, 38 W)	36.0 (11.5) 35.6 (10.4) 36.2 (12.0)	74.3 kg (12.5) 74.3 kg (13.1) 74.3 kg (12.3)	26.0 (3.5) 26.0 (3.8) 26.1 (3.4)	OP, USA	5.0 (0.4) 4.9 (0.4) 5.0 (0.4)	55.1 (40.8) 55.6 (31.9) 54.9 (44.6)	-	Ρ	Supp	Yes	~49.5 (9)	Fructose Glucose, lactose	Fructose sweetened milk Glucose sweetened milk, unsweetened milk	~52:29:20 ~52:30:19	Neutral	10 wk	
Baked goods, desserts and sw	reets																	
Behall et al. 1980 (non-OC) Intervention Control	6 (0 M, 6 W)	(19-25)	63 kg	-	OP, USA	4.4 (0.4) 4.4 (0.3)	141.7 (35.7) 147.2 (66.3)	-	С	Met	No	~214 (~43)	Sucrose Starch	Sucrose Pattie Starch Pattie	51:36:13	Neutral	4 wk	
Behall et al. 1980 (OC) Intervention	6 (0 M, 6 W)	(19-25)	64 kg	-	OP, USA	4.4 (0.4)	132.6 (42.5)	-	С	Met	No	~214 (~43)	Sucrose	Sucrose Pattie	51:36:13	Neutral	4 wk	
Control					OP,	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)	Sweden	4.7 (0.4)	26 (13)	-	Ρ	Supp	Yes					Positive	2 wk	
Intervention Control	12 H (5 M, 7 W) 13 H (6 M, 7 W)	23.2 (3.5) 23.6 (1.8)	67.3 kg (7.6) 68.7 kg (6.1)	22.2 (1.4) 22.2 (2.0)		4.7 (0.5) 4.7 (0.3)	27 (11) 24 (15)					278 (~37) 92 (~12)	Sucrose Fat	Candy Peanuts	65:21:10 32:48:18			
da Costa et al. 2005 Intervention	10 DM1 (7 M, 3 W)	(14-18)	58.5 kg (11.8)	21.7 (3.2)	OP, Brazil	-	-	8.3	С	DA	No	~37.5 (~6.2)	Sucrose	Sweets	50:30:20	Neutral	4 mo	
Control													Starch	Other CHO sources	48:32:21			
Hallfrisch et al. 1983 HI Intervention	12 HI (12 M, 0 W)	39.5 (7.3)	81.4 kg (8.0)	-	IP/OP, USA	-	164.6 (19.0)	-	С	Met	No	~50.6 (7.5), ~101.3 (15)	Fructose	Fructose wafer	43:42:15	Neutral	5 wk	
Control 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)	-	С	Met	No	~50.6 (7.5),	Starch	Starch wafer	43:42:15	Neutral	5 wk	
Intervention Control												~101.3 (15)	Fructose Starch	Fructose wafer Starch wafer				
Jones et al. 2014 Intervention Control	25 H 25 H	26.2 (7.2)	69.0 kg (16.0)	23.6 (3.7)	OP, USA	4.8 (0.3) 4.8 (0.5)	59.4 (46.3) 48.7 (30.4)		Ρ	Supp	Yes	6 (~1.2)	Sucrose <sup>1</sup> Fat	Honey roasted peanuts unsalted peanuts	NR	Neutral	12 wk	
Kelsay et al. 1974 Intervention	8 H (0 M, 8 W)	(18-23)	(43.6-65.3 kg)	-	OP, USA	-	-	-	C	Met	Yes	~212.5 (~42)	Sucrose	Sucrose Uncooked fondant pattie made with fat and sucrose Uncooked fondant pattie	50:38:12	Neutral	4 wk	
Control 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)	С	Met	No		Glucose	made with fat and glucose 85% of fructose incorporated		Neutral	4 wk	
Intervention												63.2 (20)	Fructose Starch	into a papaya frozen cream sorbet, remaining 15% from natural sources such as fruits and vegetables Storeb continuing foode	55:30:15 50:35:15			
Control	10 HI (10 M, 0 W)	47.4	85 kg	25.7	IP/OP, USA	-	-	-	С	Met	No			Starch contianing foods	51:36:13	Neutral	5 wk	
Control Reiser et al. 1989 (HI) Intervention												168 (20)	Fructose	Fructose fondant				

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>®</sup>	Randomization	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet <sup>c</sup>	Energy Balance d	Follow- Up	Fundir Source e
eiser et al. 1989 (H) Itervention ontrol	11 H (11 M, 0 W)	38.10	79 kg	24.4	IP/OP, USA	-	-	-	С	Met	No	168 (20)	Fructose Starch	Fructose fondant Starch muffin	51:36:13	Neutral	5 wk	NR
Mixed Sources																		
Abraira et al. 1988	18 DM2 (17 M, 1 W)			-	IP, USA	8.7 (3.4)	149.3 (142.6)	-	Р	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 Anderson et al. 1989	9 MD2 (8 M, 1 W) 14 DM2 (14 M, 0 W)	61.4 (7.2) 60 (15.0)	82.6 kg (18.1) 112 % DBW (15)		IP/OP, USA	9.2 (3.8) 11.2 (4.2)	166.7 (145.8)	10.6	с	Met	No	~55 (12)	Starch	Bread, potatoes, pasta	55:20:25	Neutral	24 wk	A, I
	14 DIVIZ (14 IVI, 0 VV)	00 (13.0)	112 % DBW (15)		IF/OF, 03A	11.2 (4.2)		(1.9)	C	wiet	NO	35 (12)		Cookies, lemonade-	55.20.25	Neutrai	24 WK	А,
Intervention													Fructose	flavored drink, crystalline fructose				
Control Bantle et al. 1986 (DM1)	12 DM1 (6 M, 6 W)	23 (15-32)	103 % MRW (82-	-	IP, USA			9.9	с	Met	Yes	~137 (21)	Starch	Starch containing foods	55:30:15	Neutral	8 d	А,
	12 DM1 (0 M, 0 W)	23 (13-32)	123)		IF, 03A			(1.8)	C	Wet	Tes	137 (21)	Fructose,	Baked goods, beverages,	55.50.15	Neutrai	οu	А,
Intervention Control													sucrose Starch	breakfast cereals Starch containing foods				
Bantle et al. 1986 (DM2)	12 DM2 (5 M, 7 W)	62 (36-80)	129 % MRW		IP, USA			8.5	с	Met	Yes	~137 (21)	Staren	Fructose, sucrose	55:30:15	Neutral	8 d	А,
Intervention	12 0112 (011) / 11)	02 (30 00)	(106-160)		11 ) 05/1			(2.4)	c	mee	105	137 (21)	Fructose,	Baked goods, beverages,	55.50.15	iteatiai	00	.,
Control													sucrose Starch	breakfast cereals 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)	С	Met	Yes	~120 (20)			55:30:15	Neutral	28 d	А,
Intervention						10.6 (4.0)							Fructose	Baked goods, beverages, breakfast cereals				
Control Bantle et al. 1992 (DM2)	12 DM2 (4 M, 8 W)	62 (40-72)	136 % MRW (99-		IP/OP, USA	10.3 (4.2)		7.2	с	Met	Yes	~120 (20)	Starch	Starch containing foods	55:30:15	Neutral	28 d	A,
	12 DW2 (4 W, 8 W)	02 (40-72)	170)		IF/OF, 03A	9.3 (2.3)		(2.1)	C	Wet	Tes	120 (20)	Fructose	Baked goods, beverages,	55.50.15	Neutrai	28 U	А,
Intervention						9.3 (2.3) 8.2 (1.4)							Starch	breakfast cereals Starch containing foods				
Bantle et al. 1993	12 DM2 (4 M, 8 W)	62 (40-72)		-	OP, USA		-		С	Met	Yes	~114 (19)			55:30:15	Neutral	28 d	A,
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)	-	-	С	Met	Yes	~85 (17)		Baked goods, beverages,	55:30:15	Neutral	6 wk	A
Intervention			74.1 kg (7.3)										Fructose	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)	С	Met	Yes	~199 (25)	6		55:33:12	Neutral	6 wk	Α
Intervention Control													Sucrose Starch	High sucrose diet (25% E) Low sucrose diet (10% E)				
Blayo et al. 1990	14 DM1, 6 DM2 8 DM1, 4 DM2	46.9 (13.1) 49.5 (14.1)	-	22.6 (1.9) 23.0 (2.1)	OP, France	9.8 9.4	-	8.8 7.8	Р	Supp	Yes	~25 (5)	Fructose,	20-30 g sugar/d in drinks,	55:30:15	Neutral	12 mo	А,
Intervention												25 (5)	sucrose	desserts, meals Isocaloric substitution of				
Control	6 DM1, 2 DM2	43.0 (11.0)		22.0 (1.6)	0.0	10.4		9.5					Starch	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)	Р	Supp	Yes	50 (~10)				Neutral	12 wk	1
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)	-	С	DA	No		Fructose,		55:30:15	Neutral	6 wk	A
Intervention												~56 (~10)	sucrose	Regualr diet Isocaloric low fructose diet				
Control												12 (~2)	Starch	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	-	-	-	с	Supp	Yes	132 (~22)		ž		Neutral	24 d	
Intervention	,												Sucrose	Table sugar Olive oil, instant potato,	51:33:16			
Control					0.0			0.5					Fat, starch	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)	С	Met	Yes			Current land in the	45:35:20	Neutral	3 mo	N
Intervention						https://	/mc.man	uscript	centra	al.com/	′bmj	19 (~5.4)	Sucrose	Sucrose incorporated into desserts and/ or soft drinks				
Control													Starch	Conventional diabetic diet				

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m² (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>a</sup>	Randomiza tion	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet <sup>c</sup>	Energy Balance	Follow- Up	Fun Sou
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)	с	Supp	Yes	28 (8.2)	Sucrose	28 g sucrose added to hot beverages, fruit juice, milk, cereals, stewed fruit	NR	Positive	6 wk	
Control													Starch	30 g starch and saccharin added to hot beverages, fruit juice, milk, cereals, stewed fruit				
Coulston et al. 1985 Intervention Control	11 DM2 (5 M, 6 W)	62 (6.6)		27.8 (2.3)	OP, USA	7.8 (1.7)	-	-	С	Met	No	~80 (16) ~5 (1)	Sucrose Starch	Sucrose added diet Sucrose free diet	53:29:18 51:30:19	Neutral	15 d	
Dunnigan et al. 1970	8 CND, 1 CAD (6 M, 3 W)	51.8 (8.1)	63.1 kg (10.5)	-	IP, Scotland	-	-	-	С	Met	No				45:40:15	Neutral	4 wk	
Intervention Control												169 (~34)	Sucrose Starch	70% CHO intake as sucrose 85% CHO intake as wheat,				
Emanuele et al. 1986	5 DM2, HLP (5 M, 0 W)	59 (6.7)	117 % IBW (14.5)	-	OP, USA				с	Met	Yes			potato or maize starch		Neutral	4 wk	
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	-	-	-	С	Met	No				44:43:13	Neutral		I
Intervention Control		·										97 (~13)	Sucrose	Sucrose-containing diet Sucrose-free diet with glucose syrup and calcium cyclamate			18 wk 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)	С	Supp	Yes			,	50:30:20	Neutral	8 wk	
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 Intervention	6 OB (0 M, 6 W)	(20-44)	(56-126 % IBW)	-	OP, USA	-	-	-	С	Met	No	~190 (95)	Sucrose	High sucrose diet	96:04:00	Negative	15 d	ļ
Control Jellish et al. 1984		59.5 (9.6)	92.6 kg (19.2)	-	IP, USA	11.7 (4.0)	166.7 (106.2)	-	Р	Met	Yes		Protein	High protein diet	96:04:00	Neutral	4 wk	1
Intervention	18 DM2 (18 M, 0 W)	60.7 (8.9)	92.4 kg (19.4)		,	(,						120 (~21), 220 (~39) <sup>'</sup>	Sucrose	Hot beverages, cereals, gelatin desserts, jelly spreads, beverages	50:35:15, 65:21:14 <sup>k</sup>			
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	-	-	-	С	Supp	No		comparator			Neutral	4 wk	I
Intervention												~64 (15)	Fructose	Fructose packets added to Fruit juice, milk, water or baked goods Glucose packets added to	~53:32:16			
Control													Glucose	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	-	-	-	С	Supp	No			Fructose packets added to		Neutral	4 wk	١
Intervention												~78.5 (15)	Fructose	Fruit juice, milk, water or baked goods Glucose packets added to	~53:32:16			
Control													Glucose	Fruit juice, milk, water or baked goods				
Lewis et al. 2013 Intervention Control	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)	-	-	С	Met	Yes	~101.8 (15)	Sucrose Starch	High sucrose diet (15% E) Low sucrose diet (5% E)	~55:33:12 ~55:33:12	Neutral	6 wk	
Liu et al. 1983 Intervention Control	10 HTG (4 M, 6 W) 5 HTG 5 HTG	52 (4.5) 55 (4.5)	-	29.6 (4.5) 28.9 (4.0)	IP, USA	-	-	-	Ρ	Met	Yes	~65 (13) ~45 (9)	Sucrose Starch	13 % sucrose diet 9 % sucrose diet	40:41:19	Neutral	15 d	
Lock et al. 1980	18 (18 M, 0 W)	(31-62)	-	-	OP,	-	-	-	С	Supp	No	10 (0)	startin	5 76 Such USE LIFE		Neutral	12 mo	
Intervention		,			England				-		-	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)	-	С	Supp	Yes			Non-diet soda and non-		Neutral	6 wk	,
Intervention					h	ttps://m	c.manusc	riptcent	ral.com	n/bmi		~92 (~17)	Sucrose	dairy pudding 2% milk and sugar-free low	57:29:15			
Control						1		1					Lactose	fat yogurt	47:33:19			

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>a</sup>	Randomi zation	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet <sup>c</sup>	Energy Balance	Follow- Up	Fund Sour 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)	с	Met	No					Neutral	4 wk	I
Intervention												77.8 (19)	Sucrose	Sucrose used to sweeten fruits, milk, beverages and coffee	55:30:15			
Control 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)	Р	Supp	Yes		Starch	Starch contianing foods	50:35:15 50:35:15	Neutral	12 wk	A
Intervention	9 DM2 (2 M, 7 W)	57 (8.7)	82.8 kg (15.6)		01,034	12.4 (4.0)		11.5 (1.5)	·	Jupp	103	60 (~10)	Fructose	Crystalline fructose added to cereals and non-alcoholic beverages	50.55.15	Neutral	12 WK	
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				
Osei et al. 1989	13 DM2 (5 M, 8 W)	54 (11)		29.6 (9.4)	OP, USA		-		С	Supp	Yes			carbohydrates Crystalline fructose	50:35:15	Neutral	6 mo	A
Intervention			87.7 kg (27.4)			12.6 (4.0)		11.3 (1.4)				60 (15)	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	-	-	-	с	Met	Yes				50:30:20	Neutral	3 wk	
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	-	-	-	с	Met	Yes				50:30:20	Neutral	3 wk	
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	-	-	-	Ρ	DA	Yes				-	Negative	8 mo	
Intervention	297 (55 M, 242 W)	40.4 (5.3)	66.8 kg (13.5)	24.2 (4.5)								~80.1 (~17.6) <sup> </sup>	Sucrose	Reduced fat, increased CCHO Reduced fat, reduced				
Control	298 (48 M, 250 W)	40.3 (5.4)	67.3 kg (16.0)	24.6 (5.7)									Starch	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	-	-	-	с	Met	No				40:40:20	Neutral	10 d	
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	-	-	-	с	DA	Yes			45 g CCHO replaced by	50:30:20	Neutral	6 wk	I
Intervention												45 (~9.4)	Sucrose	sucrose in food British Diabetic Association				
	44 0142 /214 4140	56 (0)		24.7 (20.1-28.0)	00.111								Staten	recommended diet	50.20.20	Manadaral	Curl	
Peterson et al. 1986 (DM2) Intervention	11 DM2 (7 M, 4 W)	56 (9)	-	24.7 (20.1-28.0)	OP, UK	-	-	-	С	DA	Yes	45 (~9.4)	Sucrose	45 g CCHO replaced by sucrose British Diabetic	50:30:20	Neutral	6 wk	
Control													Starch	Association recommended diet				
Pinheiro et al. 2007 (G1)	10 H (0 M, 10 W)	22.5 (2.1)			OP, Brazil	-	-	-	Ρ	DA	Yes					Neutral	14 d	
Intervention Control	5 H (0 M, 5 W) 5 H (0 M, 5 W)		54.9 (48.8-64.5) <sup>m</sup> 55.8 (48.0-65.6) <sup>m</sup>	21.7 (20.2-25.0) <sup>m</sup> 21.3 (19.4-24.8) <sup>m</sup>								110 (~22) 10 (~2)	Sucrose Fat	High sucrose diet High fat diet	59:28:13 42:45:13			
Pinheiro et al. 2007 (G2)	10 OW ( 0 M, 10 W)	21.8 (2.8)			OP, Brazil	-	-	-	Ρ	DA	Yes					Neutral	14 d	
Intervention Control	5 OW (0 M, 5 W) 5 OW (0 M, 5 W)		73.9 72	29.1 28.7								130 (~23) 10 (2)	Sucrose Fat	High sucrose diet High fat diet	59:28:13 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)	Р	Supp	Yes			10% of starch replaced		Neutral	6 mo	
Intervention	8 DM2 (4 M, 4 W)	60 (8.5)		27.4 (3.1)	la 44 m m /	9.3 (2.5)		6.0 (1.4)	/	:		~38.1 (10)	Sucrose	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)	nttps://	menna	nuscript	central.c	om/br	nı			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 <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>a</sup>	Randomi zation	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet <sup>c</sup>	Energy Balance	Follow- Up	Fundi Sourc e
Rath et al. 1974 Intervention	6 H (6 M, 0 W)	21.5 (2.7)	65.8 kg (10.2)	-	IP, Prague	-	-	-	С	Met	No	400 (52.5)	Sucrose	High sugar diet (400 g/d sugar)	72:16:12	Neutral	24 d	N
Control												120 (17.1)	Mixed comparator	Control diet (120 g/d sugar)	50:33:17			
Reiser et al. 1986 (W) Intervention	9 H (0 M, 9 W)	(27-48)	-	-	IP/OP, USA	4.9 (1.2)	128.5 (45.8)	-	С	Met	No	141.8 (~21)	Sucrose	High sugar diet (20 %E) Low sugar diet with	50:35:15	Neutral	6 wk	N
Control													Starch	isocaloric exchange of sugar for CCHO				
Reiser et al. 1986 (M) Intervention	10 H (10 M, 0 W)	(24-56)	107 % DBW	-	IP/OP, USA	5.2 (0.6)	123.6 (24.2)	-	С	Met	No	141.8 (~21)	Sucrose	High sugar diet (20 %E) Low sugar diet with	50:35:15	Neutral	6 wk	N
Control													Starch	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)	С	Met	Yes	00 (110)		Sucrose added to foods	52:31:17	Neutral	2 mo	N
Intervention								6.8 (1.0)				30 (~6)	Sucrose	and mixed meals High glycemic index				
Control Souto et al. 2013	33 DM1 (21 M, 12 W)	21.7 (5)	-		OP, Brazil	10.0 (3.8)	-	6.9 (1.0) 7.6 (1.6)	Р	DA	Yes		Starch	bread		Negative	3 mo	N
Intervention	15 DM1 (8 M, 7 W)	21.7 (3)		24.0 (2.6)	0F, BI 8211	10.0 (3.8)		8.0 (2.1)	F	DA	Tes	~162 (27)	Sucrose	Sucrose containing	58:26:20	Negative	3 1110	IN I
														foods Isocaloric exchange of				
Control	18 DM1 (12 M, 6 W)			22.4 (2.7)		9.4 (3.9)		7.3 (1.1)					Starch	sucrose for other carbohydrates	53:24:20			
Sunehag et al. 2002 (P1-AD) Intervention	12 H (6 M, 6 W)	14.5 (1.1)	55.5 kg (10.7)	20.2 (3.1)	IP/ OP, Italy	-	-	÷	С	Met	Yes	~74.9 (~12.1)	Fructose	High CHO low fat diet (20% CHO from fructose)	60:25:15	Neutral	7 d	A
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	-	-	-	С	Met	Yes					Neutral	7 d	A
Intervention												~50.6 (~12.1)	Fructose	High CHO low fat diet (20% CHO from fructose) Low CHO high fat diet	60:25:15			
Control												~27.7 (~6.3)	Mixed comparator	(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	-	-	-	С	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	-	-	-	С	Met	Yes	~149.1 (24)	Fructose	White bread, fruit, fruit juice, canned fruit in heavy syrup, candy, soft	60:25:15	Neutral	7 d	Α,
Control												~38 (6)	Starch	drinks Isocaloric exchange of fructose from other				
Surwit et al. 1997	42 OB (0 M, 42 W)	40.2 (7.6)			OP, England	4.9 (0.6)	-	-	Р	Met	Yes			carbohydrates		Negative	6 wk	А,
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)	С	Met	Yes			Fructose Crystalline fructose added to baked goods,	55:30:15	Neutral	28 d	А,
Intervention			68.6 kg (3.1)			4.9 (0.4)		5.1 (0.4)				100 (20)	Fructose	beverages, breakfast cereals, and natural fructose in fruits and				
Control			68.5 kg (3.0)			5.2 (0.4)		4.9 (0.4)				14 (<3)	Starch	vegetables 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-	-	с	DA	No			and commour, oats	NR	Neutral	2 wk	А
Intervention Control	· · · ·						180.6)					438 (~52)	Sucrose Starch	High sucrose diet 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)	-	-	с	Supp	Yes			Facility (COD		Neutral	8 wk	I
Intervention												70.2 (~12.8) <sup>n</sup>	Sucrose	Fruit Juice (600 mL), fruit biscuits (43 g)	53:30:16			
Control					http	s://mc.ma	nuscriptco	entral.co	om/bm	i			Lactose	Low fat milk (500 mL), low fat yogurt (150 g)	46:33:19			

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>®</sup>	Random ization	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet	Energy Balance	Follow- Up	Fund Sour
/olp et al. 2008 (G1)	6 H (0 M, 6 W)	21 (19-24) <sup>m</sup>	-	21.4 (20.2- 22.8) <sup>m</sup>	OP, Brazil	5.5 (5.2-5.8)	89.6 (59.7- 100.0)	-	с	DA	Yes					Neutral	14 d	A
Intervention Control												~81.1 (18.4) ~11.2 (2.6)	Sucrose Fat	High sucrose diet High fat diet	65:22:16 50:36:17			
Volp et al. 2008 (G2)	6 OW/OB (0 M, 6 W)	21 (19-22) <sup>m</sup>	-	28.6 (25.1- 32.1) <sup>m</sup>	OP, Brazil	5.9 (5.4-6.0)	124.3 (77.1- 157.0)	-	с	DA	Yes					Neutral	14 d	A
Intervention Control				,			,					~47.1 (8.8) ~10.5 (2.4)	Sucrose Fat	High sucrose diet High fat diet	63:26:15 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)	-	С	Supp	Yes					Neutral	11 wk	А
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	-	-	-	С	DA	No					Neutral		
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 co	mparison)	=	- <u>m</u>	-		-	-	• •		-	-	-	-	-		-	-	
Fruit					_													
Basu et al. 2010 (BB)		49.8 (15.3)	-	37.8 (11.2)	OP, USA	-	-	-	Р	Supp	Yes				NR	Neutral	8 wk	
Intervention	25 MetS (2 M, 23 W)	51.5 (15.0)		38.1 (7.5)								30 (~6) "	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)	-	-	Р	Supp	Yes					Neutral	8 wk	
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) <sup>8</sup>	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,			_	С	Supp	No					Positive		
Intervention			61.8 kg (13.3)	25.8 (4.7)	Thailand	7.3 (2.5)	97.2 (117.4)					~18.1 (~3.3) 8	Fruit	1 banana/d (250 g)	~57:25:18		4 wk	
Control			62.3 kg (13.0)	25.9 (4.6)	OP,	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)	Thailand	4.6 (0.5)	-	-	Р	Supp	Yes					Positive		
Intervention	7 H	41 (13.7)	54.5 kg (5.6)	21.5 (2.9)		4.7 (0.4)						~36.2 (~9.2) 8	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)	OP,	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)			Thailand			-	С	Supp	No					Positive		
Intervention Control			59.6 kg (11.8) 59.3 kg (12.1)	24.0 (3.94) 24.1 (4.2)		5.7 (0.4) 5.1 (0.4)	22.9 (14.6) 19.4 (11.1)					~36.2 (~6.3) 8	Fruit Diet alone	2 banana/d (500 g) No banana	~57:26:17 ~49:34:17		12 wk 8 wk	
Cressey et al. 2014 (HCL LD)	15 HCL	44.8 (10.3)			OP, Thailand			-	с	Supp	No					Positive		
Intervention			61.5 kg (10.9)	24.8 (4.0)	Inaliand	5.5 (0.4)	21.5 (11.1)					~18.1 (~3.5) 8	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	
<sup>a</sup> Ellis et al. 2010	12 OW/OB	50.9 (15.0)	86.6 kg (12.9)	29.2 (2.3)	OP, USA	-	-	-	С	Supp	No			Freeze dried strawberry	NR	Positive		,
Intervention												~5.9 (~1.2) 8	Fruit	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)	-	С	Supp	No		_	100 g/d of bilberries or sea	NR	Neutral	~34 d	,
Intervention												~3.6 (~0.7) <sup>f</sup>	Fruit	buckthorn berries				
Control	22.011/02/04.22.11	24	74.2 1- (0, 4)	27.6 (2.7)	00.0	F A (0 A)	52 0 (4 4 C)			<b>C</b>			Diet alone	Berry extract, berry oil	ND	Destation	<b>CO</b> -1	
Mitsou et al. 2011 Intervention	22 OW/OB (0 M, 22 W) 12 OW/OB (0 M, 12 W)	31	74.2 kg (9.4) 74.6 kg (11.4)	27.6 (2.7) 27.6 (2.9)	OP, Greece	5.1 (0.4) 5.1 (0.5)	53.8 (14.6) 53.5 (15.3)	-	Р	Supp	Yes	~17.4 (~3.5) 8	Fruit	240 g/d Dessert Banana	NR	Positive	60 d	
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 Intervention Control	10 H (5 M, 5 W) 12 H (6 M, 6 W)	56.3 (4.6) 57.8 (5.2) 55.0 (3.8)	78.6 kg (16.0) 78.4 kg (15.9) 78.7 kg (16.8)	27.7 (3.8) 27.5 (3.8) 27.9 (3.9)	OP, USA	5.4 (0.6) 5.22 (0.41) 5.52 (0.7)	-	-	Р	Supp	Yes	~49.7 (~9.9) <sup>s</sup>	Fruit Diet alone	Walking + 1 cup raisins/d Walking	57:29:15 43:40:16	Neutral	6 wk	
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)	-	с	Supp	Yes		Dictulone		NR	Neutral	4 wk	
Intervention												~51 (~10) "	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				

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### 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 <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>®</sup>	Randomi zation	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet <sup>c</sup>	Energy Balance	Follow- Up	Fund Sour e
Silver et al. 2011		38.1 (8.1)	99.7 kg (13.5)	36.0 (3.3)	OP, USA	-	-	-	Р	Supp	Yes			1/2 Grapefruit before	50:30:20	Negative	12 wk	,
Intervention	29 OB (11 M, 18 W)	37.6 (7.4)	99.8 kg (13.8)	36.3 (3.1)								~20.3 (~3.2) <sup>s</sup>	Fruit	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	-	-	-	с	Met	Yes	234 (~47)				Positive	7 d	
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	-	Р	Supp	Yes				44:38:18	Positive	7 d	,
Intervention Control	8 H 2 H		61.5 kg (9.9) 57 kg			5.2 (0.6) 5.4	27.8 (19.6) 34.7					250 (~33)	Fructose Diet alone	Fructose SSB No beverage				
Ellis et al. 2010	12 OW/OB	50.9 (15.0)	86.6 kg (12.9)	29.2 (2.3)	OP, USA	-	-	-	С	Supp	No				NR	Positive		
Intervention												25.9 (~5) total sugar	Sucrose	Strawberry flavored beverage			6 wk	
Control		27 (0)	70.2 1- (10.4)	27.4 (4.5)	00.1104	47(07)	70.0 (20.7)			6			Diet alone	No beverage		Positive	7 d	
Hollis et al. 2009 Intervention Control	26 OW 25 OW	27 (9) 26 (9) 28 (10)	78.3 kg (10.4) 79.0 kg (10.7) 77.6 kg (10.3)	27.1 (1.5) 27.0 (1.5) 27.3 (1.5)	OP, USA	4.7 (0.7) 4.7 (0.8) 4.7 (0.5)	78.9 (36.7) 78.6 (30.3) 79.2 (43.0)	-	P	Supp	Yes	82 (~17)	sucrose Diet alone	Grape flavored drink No beverage	~48:36:16 ~50:34:16	Positive	12 wk	
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)	-	Р	Supp	Yes					Positive	6 wk	
Intervention	15 H (15 M , 0 W)	21.9 (2.6)	79.9 kg (8.3)	22.2 (1.5)	Nethenanus	4.8 (0.2) 4.8 (0.4)	48.0 (24.1)					~237 (~27)	Sucrose	Sucrose SSB	~57:28:12			
Control Lê et al. 2006	5 H (5 M, 0 W)	23.0 (3.1)	76.6 kg (7.7)	22.6 (2.3)	OP,		45.0 (13.4)		6	6	N		Diet alone	No beverage	55.20.45	De sitti se	41	
Intervention Control	7 H (7 M, 0 W)	24.7 (3.4)	69.3 kg (6.9)	(19-25)	Switzerland	4.9 (0.3)	50.4 (9.5)	-	С	Supp	No	~104 (18) <20	Fructose Diet alone	20% fructose solution No beverage	55:30:15	Positive	4 wk	
Lê et al. 2009 (ODM2)	16 ODM2 (16 M, 0 W)	24.7 (5.2)	-	-	OP, Switzerland	-	-	-	с	Met	Yes	~220 (35)		, i i i i i i i i i i i i i i i i i i i	55:30:15	Positive	7 d	
Intervention Control													Fructose Diet alone	20% fructose solution 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)	-	Р	Supp	Yes				NR	Neutral	6 mo	
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 Sweetener,	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)						Water	Diet beverage, water				
Majid et al. 2013		20.1 (0.8)	-	-	IP, Pakistan	5.0 (0.3)	-	-	Р	Met	Yes			Honey dissolved in tap	NR	Positive	4 wk	
Intervention	32 H (32 M, 0 W)	20.1 (0.1)				5.0 (0.1)						70 (~11)	Honey	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)	-	Р	Supp	Yes	50 6 (840)	C	Denne fleren deletet	NR	Positive	60 d	
Intervention Control	10 OW/OB (0 M, 10 W) 10 OW/OB (0 M, 10 W)		68.8 kg (7.7) 73.8 kg (6.9)	25.8 (1.8) 27.5 (2.5)		5.0 (0.3) 5.0 (0.4)	43.1 (24.3) 54.2 (14.6)					50.6 (~10)	Sucrose Water	Banana flavored drink Water				
Njike et al. 2011	39 OW (6 M, 33 W)	52.2 (10.6)			OP, USA	()	-	-	С	Supp	Yes			Sucrose		Positive	6 wk	
Intervention			81.7 kg (10.7)	30.4 (3.4)		5.1 (0.5)						Sugar- sweetened cocoa, 91 (~18) ; Placebo, 110 (~26) <sup>i</sup>	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)						( 20)	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)	-	С	Supp	Yes				50:35:15	Positive		
Intervention												150 (~22)	Fructose	Fructose dissolved in water			4 wk	
Control					00								Diet alone	No beverage			2 wk	
Sobrecases et al. 2010 (XX) Intervention Control	8 H (8 M, 0 W)	24.8 (3.2)	-	(19-25)	OP, Switzerland	-	-	-	с	Supp	No	~214 (35)	Fructose Diet alone	Fructose SSB No beverage	55:30:15	Positive	7 d	
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)	-	с	Met/	No				~55:30:15	Positive		
Intervention Control	· · ·									Supp		158 (25)	Fructose Diet alone	Fructose SSB No beverage			8 wk 2 wk	
Stanhope et al. 2011 (JCEM FRU) Intervention Control	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)	-	с	Met/ Supp	No	~125 (25)	Fructose Diet alone	Fructose SSB No Beverage	55:30:15	Neutral	2 wk	

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m <sup>2</sup> (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>a</sup>	Randomi zation	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet <sup>c</sup>	Energy Balance d	Follow- Up	Fun Sou
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)	-	С	Met/ Supp	No	~125 (25)			55:30:15	Neutral	2 wk	
Intervention Control													HFCS Diet alone	HFCS SSB No Beverage				
Fruit Juice																		
Hollis et al. 2009 Intervention Control	25 OW 25 OW	25 (8.1) 22 (4) 28 (10)	78.3 kg (9.3) 79.0 kg (8.4) 77.6 kg (10.3)	27.2 (1.5) 27.0 (1.6) 27.3 (1.5)	OP, USA	4.5 (0.6) 4.4 (0.6) 4.7 (0.5)	81.5 (70.1) 83.8 (90.4) 79.2 (43.0)	-	Ρ	Supp	Yes	82 (~17)	fruit Diet alone	Concord grape juice No beverage	~50:35:15 ~50:34:16	Positive	12 wk	
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)	-	С	Supp	Yes				NR	Neutral	4 wk	
Intervention					Denmark							~61 (~12.2) <sup>n</sup>	fruit	Polyphenolic and pectin restricted diet with clear or cloudy apple juice (~500 mL/d) Polyphenolic and pectin				
Control													Diet alone	restricted diet				
Silver et al. 2011 Intervention Control	28 OB (3 M, 25 W) 28 OB (7 M, 21 W)	39.3 (8.5) 39.8 (8.4) 38.7 (8.8)	97.7 kg (12.5) 95.9 kg (11.5) 99.5 kg (13.5)	35.4 (3.3) 35.2 (3.1) 35.7 (3.5)	OP, USA	-	-	-	Ρ	Supp	Yes	~17.5 (~2.5) <sup>s</sup>	fruit Water	Grapefruit Juice Water	50:30:20	Negative	12 wk	
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)	Р	Met	Yes			Fructose		Negative	14 d	
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)	-	Р	Supp	Yes					Neutral	10 wk	
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)	Р	DA	No			Sucrose		Positive		
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 Intervention Control	20 DM1 (10 M, 10 W)	11.4 (4.2)	105 % IBW (12.1)	-	OP, Egypt	9.4 (1.1)	-	7.2 (0.8)	С	Supp	Yes	~26.6 (~4.0)	Honey Diet alone	Honey added to diet Regular diet	NR	Neutral	12 wk	
Bahrami et al. 2009 Intervention Control	48 DM2 (13 M, 35 W) 25 DM2 23 DM2	57.2 (8.4)	70.8 kg (10.6) 71.3 kg (12.7) 70.3 kg (8.1)	-	OP, Iran	8.0 (2.5) 8.5 (2.4) 7.5 (2.5)	-	7.1 (1.2) 7.1 (1.2) 7.1 (1.3)	Р	Supp	Yes	~125 (~33)	Honey Diet alone	Honey added to diet Regular diet	64:23:15 60:22:15	Positive	8 wk	
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)	с	Supp	No				NR	Positive	6 wk	
Intervention					. tosci and							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)	-	Р	Supp	Yes					Positive	10 wk	
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			

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### Supplementary Table 2. Trial characteristics (Continued)

28.3 (6.5) 29.1 (6.9) ) 33.5 (6.7) ) 33.4 (6.7) /) 42.2 (10.9) ) 41.6 (10.4) 45 (4.2)	- - 76.9 kg (3.3) 76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3) 103.2 kg (16.7)	- 31.0 (1.1) 31.0 (1.1) 35.9 (5.7) 36.8 (6.2)	OP, Switzerland OP, Switzerland OP, Mexico OP, USA	5.1 (0.5) 4.9 (0.5) 5.2 (0.5) 5.5 (0.6) 5.2 (0.5) 5.7 (0.5) 5.0 (0.2) 5.0 (0.2) 5.0 (0.2) 5.1 (1.0) 4.9 (0.6)	85.8 (40.6) 104.9 (42.5) 66.7 (30.6) 133.7 (54.5) 127.1 (60.6) 140.3 (51.4) - -	- 5.8 (0.1) 5.8 (0.1) 5.8 (0.1) - -	P P P	Supp Supp Supp DA	Yes Yes Yes Yes	86.8 (~15) 86.8 (~15) ~73 (19.3) ~33.7 (~8.7) ~55.7 (~13.8)	Sweetener Sucrose, HFCS Sweetener Sucrose, HFCS Water Sucrose, HFCS Sweetener, water Sucrose, HFCS	Replace SSB with ASB Habitual SSB consumption (≥ 2 SSB/d) Replace SSB with ASB Habitual SSB consumption (≥ 2 SSB/d) Substitute water for SSBs, general recommendations for healthy eating Habitual SSB consumption (≥250 kcal/d), general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (≥280 kcal/d)	~46:38:16 ~51:34:15 ~46:38:16 ~51:34:15 NR	Negative Negative Negative	12 wk 12 wk 9 mo
29.1 (6.9) ) 33.5 (6.7) ) 33.4 (6.7) /) 42.2 (10.9) ) 41.6 (10.4)	76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3)	31.0 (1.1) 35.9 (5.7)	Switzerland OP, Switzerland OP, Mexico OP, USA	4.9 (0.5) 5.2 (0.5) 5.5 (0.6) 5.2 (0.5) 5.7 (0.5) 5.0 (0.2) 5.0 (0.2) 5.0 (0.2) 5.1 (0.9) 5.1 (1.0)	104.9 (42.5) 66.7 (30.6) 133.7 (54.5) 127.1 (60.6) 140.3 (51.4)	5.8 (0.1) 5.8 (0.1) -	P	Supp Supp Supp,	Yes	86.8 (~15) ~73 (19.3) ~33.7 (~8.7)	Sucrose, HFCS Sweetener Sucrose, HFCS Water Sucrose, HFCS Sweetener, water Sucrose,	Habitual SSB consumption (2 2 SSB/d) Replace SSB with ASB Habitual SSB consumption (2 2 SSB/d) Substitute water for SSBs, general recommendations for healthy eating Habitual SSB consumption (2250 kcal/d), general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (2280	~51:34:15 ~46:38:16 ~51:34:15 NR	Negative	12 wk 9 mo
29.1 (6.9) ) 33.5 (6.7) ) 33.4 (6.7) /) 42.2 (10.9) ) 41.6 (10.4)	76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3)	31.0 (1.1) 35.9 (5.7)	Switzerland OP, Switzerland OP, Mexico OP, USA	4.9 (0.5) 5.2 (0.5) 5.5 (0.6) 5.2 (0.5) 5.7 (0.5) 5.0 (0.2) 5.0 (0.2) 5.0 (0.2) 5.1 (0.9) 5.1 (1.0)	104.9 (42.5) 66.7 (30.6) 133.7 (54.5) 127.1 (60.6) 140.3 (51.4)	5.8 (0.1) 5.8 (0.1) -	P	Supp Supp Supp,	Yes	86.8 (~15) ~73 (19.3) ~33.7 (~8.7)	Sucrose, HFCS Sweetener Sucrose, HFCS Water Sucrose, HFCS Sweetener, water Sucrose,	Habitual SSB consumption (2 2 SSB/d) Replace SSB with ASB Habitual SSB consumption (2 2 SSB/d) Substitute water for SSBs, general recommendations for healthy eating Habitual SSB consumption (2250 kcal/d), general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (2280	~51:34:15 ~46:38:16 ~51:34:15 NR	Negative	12 wk 9 mo
) 33.5 (6.7) 33.4 (6.7) 1) 42.2 (10.9) ) 41.6 (10.4)	76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3)	31.0 (1.1) 35.9 (5.7)	OP, Mexico OP, USA	5.2 (0.5) 5.5 (0.6) 5.2 (0.5) 5.7 (0.5) 5.0 (0.2) 5.0 (0.2) 5.0 (0.2) 5.1 (0.9) 5.1 (1.0)	66.7 (30.6) 133.7 (54.5) 127.1 (60.6) 140.3 (51.4)	5.8 (0.1) 5.8 (0.1) -	P	Supp Supp,	Yes	86.8 (~15) ~73 (19.3) ~33.7 (~8.7)	Sucrose, HFCS Sweetener Sucrose, HFCS Water Sucrose, HFCS Sweetener, water Sucrose,	Habitual SSB consumption (2 2 SSB/d) Replace SSB with ASB Habitual SSB consumption (2 2 SSB/d) Substitute water for SSBs, general recommendations for healthy eating Habitual SSB consumption (2250 kcal/d), general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (2280	~51:34:15 ~46:38:16 ~51:34:15 NR	Negative	9 mo
) 33.5 (6.7) 33.4 (6.7) 1) 42.2 (10.9) ) 41.6 (10.4)	76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3)	31.0 (1.1) 35.9 (5.7)	OP, Mexico OP, USA	5.5 (0.6) 5.2 (0.5) 5.7 (0.5) 5.0 (0.2) 5.0 (0.2) 5.0 (0.2) 5.1 (0.9) 5.1 (1.0)	133.7 (54.5) 127.1 (60.6) 140.3 (51.4)	5.8 (0.1) 5.8 (0.1) -	P	Supp Supp,	Yes	86.8 (~15) ~73 (19.3) ~33.7 (~8.7)	HFCS Sweetener Sucrose, HFCS Water Sucrose, HFCS Sweetener, water Sucrose,	SSB/d) Replace SSB with ASB Habitual SSB consumption (2 2 SSB/d) Substitute water for SSBs, general recommendations for healthy eating Habitual SSB consumption (2250 kcal/d), general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (2280	~46:38:16 ~51:34:15 NR	Negative	9 mo
) 33.5 (6.7) 33.4 (6.7) 1) 42.2 (10.9) ) 41.6 (10.4)	76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3)	31.0 (1.1) 35.9 (5.7)	OP, Mexico OP, USA	5.2 (0.5) 5.7 (0.5) 5.0 (0.2) 5.0 (0.2) 5.0 (0.2) 5.1 (0.9) 5.1 (1.0)	127.1 (60.6) 140.3 (51.4)	5.8 (0.1) 5.8 (0.1) -	P	Supp Supp,	Yes	~73 (19.3) ~33.7 (~8.7)	Sucrose, HFCS Water Sucrose, HFCS Sweetener, water Sucrose,	Habitual SSB consumption (≥ 2 SSB/d) Substitute water for SSBs, general recommendations for healthy eating Habitual SSB consumption (≥250 kcal/d) general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (≥280	~51:34:15 NR	Negative	9 mo
) 33.5 (6.7) ) 33.4 (6.7) /) 42.2 (10.9) ) 41.6 (10.4)	76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3)	31.0 (1.1) 35.9 (5.7)	OP, USA	5.7 (0.5) 5.0 (0.2) 5.0 (0.2) 5.0 (0.2) 5.1 (0.9) 5.1 (1.0)	140.3 (51.4)	5.8 (0.1) 5.8 (0.1) -		Supp,		~73 (19.3) ~33.7 (~8.7)	Sucrose, HFCS Water Sucrose, HFCS Sweetener, water Sucrose,	Habitual SSB consumption (≥ 2 SSB/d) Substitute water for SSBs, general recommendations for healthy eating Habitual SSB consumption (≥250 kcal/d) general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (≥280	~51:34:15 NR		
) 33.5 (6.7) ) 33.4 (6.7) /) 42.2 (10.9) ) 41.6 (10.4)	76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3)	31.0 (1.1) 35.9 (5.7)	OP, USA	5.0 (0.2) 5.0 (0.2) 5.0 (0.2) 5.1 (0.9) 5.1 (1.0)		5.8 (0.1) 5.8 (0.1) -		Supp,		~73 (19.3) ~33.7 (~8.7)	HFCS Water Sucrose, HFCS Sweetener, water Sucrose,	SSB/d) Substitute water for SSBs, general recommendations for healthy eating Habitual SSB consumption (2250 kcal/d), general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (2280	NR		
) 33.5 (6.7) ) 33.4 (6.7) /) 42.2 (10.9) ) 41.6 (10.4)	76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3)	31.0 (1.1) 35.9 (5.7)	OP, USA	5.0 (0.2) 5.0 (0.2) 5.1 (0.9) 5.1 (1.0)		5.8 (0.1) 5.8 (0.1) -		Supp,		~33.7 (~8.7)	Sucrose, HFCS Sweetener, water Sucrose,	SSBs, general recommendations for healthy eating Habitual SSB consumption (2250 kcal/d), general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (2280			
) 33.4 (6.7) /) 42.2 (10.9) ) 41.6 (10.4)	76.0 kg (3.3) 99.6 kg (18.5) 102.6 kg (18.3)	31.0 (1.1) 35.9 (5.7)		5.0 (0.2) 5.1 (0.9) 5.1 (1.0)	-	5.8 (0.1)	Ρ	Supp, DA	Yes	~33.7 (~8.7)	Sucrose, HFCS Sweetener, water Sucrose,	recommendations for healthy eating Habitual SSB consumption (2250 kcai/d), general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (2280	NR	Negative	6 mo
/) 42.2 (10.9) ) 41.6 (10.4)	99.6 kg (18.5) 102.6 kg (18.3)	35.9 (5.7)		5.1 (0.9) 5.1 (1.0)		-	Ρ	Supp, DA	Yes	~33.7 (~8.7)	HFCS Sweetener, water Sucrose,	Habitual SSB consumption (>250 kcal(d) general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (>280	NR	Negative	6 mo
/) 42.2 (10.9) ) 41.6 (10.4)	99.6 kg (18.5) 102.6 kg (18.3)	35.9 (5.7)		5.1 (0.9) 5.1 (1.0)		-	Ρ	Supp, DA	Yes	~33.7 (~8.7)	HFCS Sweetener, water Sucrose,	kcal/d), general recommendations for healthy eating Diet beverage, Water Habitual SSB consumption (2280	NR	Negative	6 mo
) 41.6 (10.4)	102.6 kg (18.3)			5.1 (1.0)	-	-	Ρ	Supp, DA	Yes		Sweetener, water Sucrose,	healthy eating Diet beverage, Water Habitual SSB consumption (≥280	NR	Negative	6 mo
) 41.6 (10.4)	102.6 kg (18.3)			5.1 (1.0)	-	-	Ρ	Supp, DA	Yes		water Sucrose,	Habitual SSB consumption (≥280	NR	Negative	6 mo
) 41.6 (10.4)	102.6 kg (18.3)		OP, USA		-	-					water Sucrose,	Habitual SSB consumption (≥280			
		36.8 (6.2)	OP, USA	4.9 (0.6)	-	-				~55.7 (~13.8)		consumption (≥280			
45 (4.2)	103.2 kg (16.7)	-	OP, USA		- -	_					HFCS	kcal/d)			
45 (4.2)	103.2 kg (16.7)	-	OP, USA	-	-										
45 (4.2)	103.2 kg (16.7)	-	OP, USA	-	-										
						-	С	DA	No			Avoid sucrose		Negative	
										~24 (~6) "	No sucrose	containing foods from habitual diet	25:45:30		60 d
										~58 (~10) <sup>n</sup>	Sucrose	Habitual diet	29:39:32		7 d
(25.42)	(C 7 k - (7 C)	26.4 (2.4)	OP,			7.6 (0.4)			No.				52-26-22	Desibles	4 wk
(25-43)	66.7 Kg (7.6)	26.4 (2.1)	Germany	-	-	7.6 (0.4)	Ľ		Yes			Ad libitum sucrose-	52:26:22	Positive	4 WK
								DA		24 (~5)	Sucrose	containing food consumption; sucrose-			
												containing soft drinks discouraged			
								Supp			Sweetener	Ad libitum sodium cyclamate tablets and			
												liquids			
(13-55)	-	-	OP, Finland	-	-	-	Р	Supp	Partial <sup>°</sup>			Ad libitum fructoro	-	Neutral	18 mo
										~72 (~14)	Fructose, sucrose	and sucrose			
												Ad libitum xylitol			
											Sweetener	avoidance of sweet			
												containing products			
				(13-55) OP, Finland	(13-55) OP, Finland -	(13-55) - OP, Finland	(13-55) OP, Finland	(13-55) OP, Finland P	(25-43) 66.7 kg (7.6) 26.4 (2.1) Germany 7.6 (0.4) C DA Supp	(25-43) bb.7 kg (7.b) 26.4 (2.1) Germany 7.5 (0.4) C Yes DA Supp (13-55) OP, Finland P Supp Partial <sup>o</sup>	(13-55) - OP, Finland P Supp Partial <sup>4</sup> ~72 (~14)	(13-55) OP, Finland P Supp Partial <sup>o</sup> -72 (~14) Fructose, Sweetener	(25-43) b6.7kg (r.6) 20.4 (2.1) Germany 75 (0.4) C res DA 24 (~5) Sucrose Ad libitum sucrose- containing food diloitum sucrose- containing soft drinks discursed (13-55) - OP, Finland P Supp Partial <sup>®</sup> (13-55) - OP, Finland P Supp Partial <sup>®</sup> -72 (~14) Fructose, sucrose Ad libitum fructose sucrose containing food swith and sucrose containing food swith and sucrose containing food swith and sucrose containing food swith avidiate of sweetener drinks containing food swith avidiate of sweetener drinks and sucrose containing food swith avidiate of sw	(13-55) - OP, Finland P Supp Partial <sup>a</sup> (13-55) OP, Finland	(13-55) - OP, Finland P Supp Partial <sup>®</sup> - Neutral - "72 (~14)

Study, Year	Participants	Mean Age, years (SD or Range)	Mean BW, units (SD or range)	Mean BMI, kg/m² (SD)	Setting	Glucose, mmol/L (SD or range)	Insulin, pmol/L (SD or range)	HbA1c, % (SD)	Design	Feeding Control <sup>a</sup>	Randomiz ation	Fructose- Containing Sugar Dosage, g/d (% E) <sup>b</sup>	Intervention or comparator form	Food source	Diet	Energy Balance	Follow- Up	Fund Sourc
Markey et al. 2015	50 H (16 M, 34 W) 22 H (7 M, 15 W)	31.3 (9.6) 31.6 (10.2)	69.8 kg (11.4) 70.5 kg (13.1)	24.0 (3.3) 24.2 (3.3)	OP, UK	4.9 (0.4) 5.0 (0.5)	31.0 (14.3) 34.0 (16.9)	-	С	Supp	Yes	62 (~12) <sup>p</sup>	Sucose	Exchange ≥1 food portion and ≥1 beverage per day from habitual diet with sugar containing products	54:30:14	Neutral	8 wk	1
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)	-	-	Р	Partial Met	Yes					Neutral	6 mo	А
Intervention	14 MetS (6 M, 8 W)	45.9 (5.0)	89.3 kg (15.7)	30.9 (3.0)		5.6 (0.5)				Wiet		~165.4 (29) <sup>q</sup>	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			-	с	Met	Yes					Neutral	2 wk	,
Intervention					Berninark	4.6 (0.2)	33 (18)					~156.7 (23)	Sucrose	Ad libitum sucrose diet	59:28:13 Starch,			
Control						4.8 (0.3)	32 (21)						Starch, fat	Ad libitum starch diet, ad libitum fat diet	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			-	с	Met	Yes					Neutral	2 wk	
Intervention					Definitian	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)	-	Р	Partial Met	Yes					Neutral	6 mo	
Intervention	76 OW/OB (36 M, 40 W)	41 (9)	90.7 kg (12.7)	30.9 (2.8)	Nethenanus					IVICL		~183 (~29.5) °	Sucrose	Ad libitum Low-fat high SCHO diet	~56:26:16 Starch,			
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) <sup>q</sup>	Starch, Mixed comparator	Ad libitum low-fat high CCHO diet, Ad libitum control diet	Starch, ~52:28:18; Mixed, ~46:37:18			

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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=group 2; 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 contraceotive users; ODM2

= offspring of parent with Type 2 Diabetes; OW= overweight; P1= 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 

<sup>a</sup> 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.

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.

<sup>c</sup> Total energy intake in the form of carbohydrate:fat:protein

<sup>d</sup> 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. 

<sup>e</sup> Agency funding included government, not-for profit health agencies or University sources.

<sup>f</sup> Fructose-containing sugar dose estimated based on data from Finland National Food Composition Database

<sup>g</sup> Fructose-containing sugar dose estimated based on data from United States Department of Agriculture (USDA) nutrient database 

<sup>h</sup> Represents average of entire study cohort, including other study arms not from comparison of interest

<sup>1</sup>Fructose-containing sugar was given at 2 different doses.

<sup>1</sup>Although honey roasted peanuts were provided as the intervention, sucrose was the main sugar used to sweeten the study products. 

<sup>k</sup>Dietary breakdown of the high and intermediate sucrose diets respectively 

<sup>1</sup>Represents estimated sugar intake excluding underreporters

<sup>m</sup>Values reported as medians and inter-quartile ranges (IQR)

<sup>n</sup> Fructose-containing sugar dose estimated from total sugars used in study products 

<sup>o</sup> Half of the participants were assigned to groups according to personal preference, while the other half of the participants were randomly allocated

<sup>P</sup>Fructose-containing sugar dose estimated from non-milk extrinsic sugar intake

<sup>9</sup> 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% Cls)	Residual I <sup>2</sup> (%)	P-value
10	≤10	-0.05 (-0.17, 0.06)	81.85	0.32
10	>10	0.02 (-0.03, 0.08)	61.85	0.32
20	≤20	-0.01 (-0.07, 0.05)	01.07	0.60
20	>20	0.04 (-0.14, 0.21)	81.87	0.69
20	≤30	0.00 (-0.04, 0.04)	82.04	0.02
30	>30	0.09 (-1.65, 1.82)	82.04	0.92
	ĨQ.			

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

Dose threshold, Sugars (% Energy)	Dose ranges, Sugars (% Energy)	β (95% Cls)	Residual I <sup>2</sup> (%)	P-value
10	≤10	0.01 (-0.02, 0.04)	63.75	0.59
10	>10	0.01 (0.00, 0.01)	03.75	0.58
20	≤20	0.01 (-0.00, 0.02)	64.00	0.70
20	>20	0.01 (-0.00. 0.01)	64.00	0.79
20	≤30	0.01 (-0.00, 0.01)	62.00	0.76
30	>30	0.01 (-0.00, 0.02)	63.99	0.76
40	≤40	0.00 (-0.00, 0.01)	(2.01	0.20
40	>40	0.01 (0.00, 0.03)	63.91	0.20
50	≤50	0.00 (-0.00, 0.01)	62.23	0.01
50	>50	0.03 (0.01, 0.05)	02.23	0.01
60	≤60	0.00 (0.00, 0.01)	60.02	<0.01
60	>60	0.05 (0.02, 0.09)	60.93	<0.01
70	≤70	0.00 (0.00, 0.01)	C0.02	-0.01
70	>70	0.16 (0.06, 0.26)	60.93	<0.01
2. Fasting blood gluc	ose (mmol/L) in addit	ion trials	Q	

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

Dose threshold, Sugars (% Energy)	Dose ranges, Sugars (% Energy)	β (95% Cls)	Residual I <sup>2</sup> (%)	P-value
10	≤10	0.00 (-0.03, 0.03)	71.46	0.02
10	>10	0.00 (-0.01, 0.01)	71.40	0.93
20	≤20	0.01 (-0.01, 0.02)	71.00	0.64
20	>20	0.00 (-0.01, 0.01)	71.00	0.64
20	≤30	0.00 (-0.01, 0.01)	71.10	0.02
30	>30	0.00 (-0.02, 0.03)	71.18	0.92
40	≤40	0.00 (-0.01, 0.01)	71.00	0.00
40	>40	0.01 (-0.05, 0.06)	71.09	0.90

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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 ranges, Sugars (% Energy)	β (95% Cls)	Residual I <sup>2</sup> (%)	P-value
≤10	-0.04 (-1.98, 1.90)	F 4 97	0.75
>10	0.29 (0.01, 0.56)	54.87	
≤20	-0.09 (-0.78, 0.60)	F2 16	
>20	0.39 (0.06, 0.72)	53.10	0.27
≤30	0.12 (-0.35, 0.60)	52.45	0.47
>30	0.39 (-0.04, 0.83)	53.45	
≤40	0.27 (-0.12, 0.66)	54.62	0.99
>40	0.27 (-0.28, 0.82)	54.62	
≤50	0.36 (0.00, 0.72)	55.46	0.49
>50	0.03 (-0.69, 0.76)	55.16	
≤60	0.38 (0.04, 0.72)	55.20	0.34
>60	-0.20 (-1.20, 0.81)	55.26	
≤70	0.38 (0.06, 0.70)	55.20	0.29
>70	-0.54 (-2.05, 0.98)	55.29	
≤80	0.37 (0.06, 0.67)	55.27	0.27
>80	-1.15 (-3.68, 1.39)	55.27	
≤90	0.37 (0.06, 0.67)	55.27	0.27
>90	-4.18 (-12.09, 3.73)	55.27	
	$\leq 10$ >10 $\leq 20$ >20 $\leq 30$ $\geq 30$ $\leq 40$ $\geq 40$ $\leq 40$ $\geq 50$ $\leq 50$ $\leq 50$ $\leq 50$ $\leq 60$ $\geq 60$ $\leq 70$ $\geq 70$ $\geq 70$ $\leq 80$ $\geq 80$ $\geq 80$ $\leq 90$	Sugars (% Energy) $\beta$ (95% Cls)<10	Sugars (% Energy) $\beta$ (95% Cls)Residual 1² (%) $\leq 10$ $-0.04$ (-1.98, 1.90) $-54.87$ >10 $0.29$ (0.01, 0.56) $-54.87$ $\leq 20$ $-0.09$ (-0.78, 0.60) $-33.16$ >20 $0.39$ (0.06, 0.72) $-33.16$ $\leq 30$ $0.12$ (-0.35, 0.60) $-33.45$ $\leq 30$ $0.12$ (-0.35, 0.60) $-33.45$ $\leq 30$ $0.39$ (-0.04, 0.83) $-33.45$ $\leq 40$ $0.27$ (-0.12, 0.66) $-34.62$ $\leq 40$ $0.27$ (-0.28, 0.82) $-54.62$ $\leq 50$ $0.36$ (0.00, 0.72) $-55.16$ $\leq 50$ $0.36$ (0.04, 0.72) $-55.16$ $\leq 60$ $0.38$ (0.04, 0.72) $-55.26$ $\leq 60$ $0.38$ (0.06, 0.70) $-55.29$ $\leq 70$ $0.38$ (0.06, 0.70) $-55.29$ $\leq 70$ $0.37$ (0.06, 0.67) $-55.27$ $\leq 80$ $0.37$ (0.06, 0.67) $-55.27$ $\leq 90$ $0.37$ (0.06, 0.67) $-55.27$

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

Dose threshold, Sugars (% Energy)	Dose ranges, Sugars (% Energy)	β (95% Cls)	Residual I <sup>2</sup> (%)	P-value
10	≤10	0.31 (-1.00, 1.62)	52.99	0.00
10	>10	0.20 (-0.24, 0.64)	52.99	0.90
20	≤20	0.32 (-0.23, 0.87)	F2 47	0.67
20	>20	0.09 (-0.59, 0.78)	53.47	0.67
20	≤30	0.17 (-0.19, 0.54)	F2.4F	0.62
30	>30	0.54 (-0.80, 1.88)	52.45	0.62
40	≤40	0.19 (-0.12, 0.50)	F2.0F	0.52
40	>40	1.18 (-1.93, 4.28)	52.05	0.53

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<sup>2</sup> value indicates heterogeneity unexplained by each dose-threshold.

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Fasting Blood Glucose Addition Trials Basu et al. 2010 (SB) Hollis et al. 2009 (SSB) Le et al. 2006 Le et al. 2009 (ODM2)	0.06 0.06 0.06	[0.00, 0.13] [0.00, 0.13]	0.06	
Basu et al. 2010 (SB) Hollis et al. 2009 (SSB) Le et al. 2006	0.06			
Hollis et al. 2009 (SSB) Le  et al. 2006	0.06			
Le et al. 2006		[0.00, 0.13]		73
	0.06		0.05	73
Le et al. 2009 (ODM2)		[0.00, 0.13]	0.06	72
	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	19
Ad Libitum Trials				
Markey et al. 2015	9.51	[1.59. 17.42]	0.02	0
SB= strawberry; SSB= sugars-sweetened beve American Journal of Clinical Nutrition; EXP 2= with 95% CI, using generic inverse-variance ra using the Cochrane's Q statistic ( $I^2$ ) at a signifi represent moderate heterogeneity, $\ge 50$ % re heterogeneity. The residual $I^2$ value indicates each trial.	experiment andom-effect icance level present sub	t 2. Data are express ts models. Interstud of P < 0.10 and quar stantial heterogenei	ed as mean differ y heterogeneity v tified by I <sup>2</sup> , levels ty and ≥ 75%, cor	ences (I vas test ≤ 50% nsiderab remova

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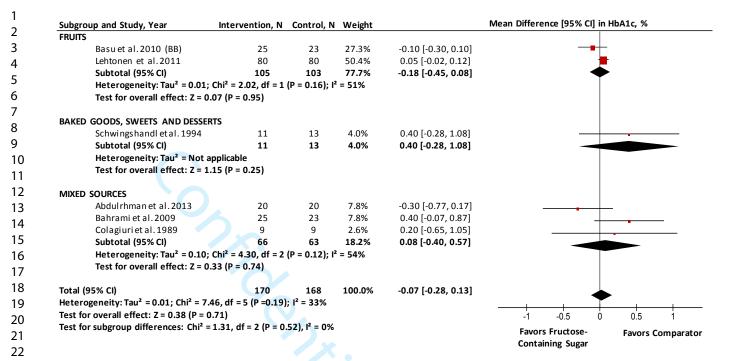
Low risk of bias	Unclear risk of bia	S	Hig	h risk of bia	S	
		0%	25%	50%	75%	100%
Selective r	reporting (reporting bias)					
Incomplete outc	ome data (attrition bias)					
Blinding of participants and person	nel (performance bias)					
Allocation conce	ealment (selection bias)					
Random sequence gen	eration (selection bias)					

Supplementary Figure 1. Risk of bias summary for the effect of fructose-containing food sources on k c. rs represent u.c., the 5 domains of bias above. 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.

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	Intervention, N	Control, N	Weight	Mean I	Difference [95% CI] in HbA1c, %
FRUITS			· ·		
Agebratt et al. 2016	15	15	6.6%	-0.04 [-0.15, 0.07]	+
Anderson et al.2014 Bays et al.2015	31 27	15 19	6.9% 2.9%	-0.08 [-0.15, -0.01] -0.12 [-0.60, 0.36]	-
Christensen et al. 2013	32	31	3.3%	-0.20 [-0.62, 0.22]	
Hegde et al. 2013	60	63	3.0%	-0.80 [-1.26, -0.34]	
Kanellos et al. 2014	26	22	4.8%	0.10 [-0.17, 0.37]	
Lehtonen et al.2010	28	22	6.9%	0.00 [-0.07, 0.07]	+
Moazen et al. 2013	19	17	3.8%	-0.62 [-0.98, -0.26]	
Subtotal (95% CI)	238	204	38.1%	-0.12 [-0.23, -0.003]	◆
Heterogeneity: Tau <sup>2</sup> = 0.01; Ch		(P = 0.001	); I² = 71%		
Test for overall effect: Z = 2.01	L (P = 0.04)				
SUGARS-SWEETENED BEVERAGES					
Koivisto and Yki-Järvinen 1993	10	10	0.9%	-1.10 [-2.14, -0.06]	
Vaisman et al. 2006	12	13	3.7%	-0.37 [-0.75, 0.01]	
Subtotal (95% CI)	22	23	4.6%	-0.57 [-1.21, 0.07]	
Heterogeneity: Tau <sup>2</sup> = 0.11; Cł	ni² = 1.68, df = 1 (l	P =0.20); I <sup>2</sup>	² = 40%	• / •	
Test for overall effect: Z = 1.75	5 (P = 0.08)				
LIQUID MEAL REPLACEMENTS			0.44		
Johnson et al. 2015	24 8	27	0.1%	-0.02 [-2.85, 2.81] -	
Rizkalla et al. 1986 (EXP1) Rizkalla et al. 1986 (EXP2)	6	15 12	4.9% 2.1%	0.16 [-0.10, 0.42]	
Rizkalla et al. 1986 (EXP2) Subtotal (95% CI)	38	54	7.1%	-0.25 [-0.86, 0.36] <b>0.10 [-0.14, 0.34]</b>	
Heterogeneity: Tau <sup>2</sup> = 0.00; Cl				0.10 [-0.14, 0.54]	
Test for overall effect: Z = 0.80					
BAKED GOODS, SWEETS AND DESSERTS	5				
da Costa et al. 2005	10	10	2.0%	-0.50 [-1.12, 0.12]	
Subtotal (95% CI)	10	10	2.0%	-0.50 [-1.12, 0.12]	
Heterogeneity: Not applicable Test for overall effect: Z = 1.58					
Test for overall effect. 2 – 1.56	5 (F - 0.11)				
MIXED SOURCES					
Anderson et al. 1989	14	14	6.9%	-0.08 [-0.15, -0.01]	-
Bantle et al. 1993	12	12	3.2%	0.13 [-0.31, 0.56]	
Blayo et al. 1990	8	6	2.3%	1.80 [1.24, 2.36]	
Brunner et al. 2012	49	52	5.3%	0.02 [-0.21, 0.25]	+
Buysschaert et al. 1987	10	10	1.7%	-0.10 [-0.81, 0.61]	
Cooper et al. 1988	17	17	2.8%	-1.20 [-1.69, -0.71]	
Grigoresco et al. 1988 Osei et al. 1987	8 9	8 9	1.0% 1.3%	0.50 [-0.45, 1.45] -2.86 [-3.68, -2.04]	
Osei et al. 1989	13	13	1.2%	-1.40 [-2.29, -0.51]	
Paganus et al. 1987 (CG)	297	298	1.5%	-0.50 [-1.25, 0.25]	
Paganus et al. 1987 (SG)	10	10	2.1%	-0.30 [-0.92, 0.32]	
Peterson 1986 (DM1)	12	12	0.9%	0.40 [-0.62, 1.42]	
Peterson 1986 (DM2)	11	11	0.8%	-0.30 [-1.39, 0.79]	
Porta et al. 1989	8	8	1.4%	0.40 [-0.41, 1.21]	
Santacore et al. 1990	10	10	1.8%	0.10 [-0.58, 0.78]	
Souto et al. 2013	15	18	1.4%	-0.21 [-1.02, 0.60]	
Swanson et al. 1992 Vrolix et al. 2010	14 15	14 15	5.7% 6.9%	0.00 [-0.20, 0.20]	+
Vrolix et al. 2010 Subtotal (95% CI)	<b>532</b>	537	6.9% 48.1%	0.00 [-0.07, 0.07] - <b>0.14 [-0.33, 0.06]</b>	
Heterogeneity: Tau <sup>2</sup> = 0.10; Cl					
Test for overall effect: Z = 1.36					
Total (95% CI)	840	828	100.0%	-0.14 [-0.25, -0.04]	$\blacklozenge$
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 162		.00001); I²	= 81%		
Test for overall effect: Z = 2.68 (P = 0.0	•				-2 -1 0 1 2
Test for subgroup differences: Chi <sup>2</sup> = 6.	48, df = 4 (P = 0.1	.7), I <sup>2</sup> = 38.	.3%		Favors Fructose- Favors Comparato
					Containing Sugar

49 Supplementary Figure 2. Forest plot for substitution trials investigating the effect of isocaloric exchange of 50 fructose-containing food sources for other macronutrients on HbA1c. CG= control group; SG= study group; 51 df= degrees of freedom; DM1= type 1 diabetes mellitus; DM2= type 2 diabetes mellitus; EXP=experiment; 52 HbA1c= hemoglobin A1c; N= number of participants. Pooled effect estimates for each subgroup and overall 53 effect are represented by the diamonds. Data are expressed as weighted mean differences with 95% 54 confidence intervals (CIs), using the generic inverse-variance method with random effects models. Paired 55 analyses were applied to all crossover trials. Inter-study heterogeneity was tested by the Cochran Q-statistic 56 at a significance level of p < 0.10 and quantified by  $l^2$ , levels  $\leq$  50% represent moderate heterogeneity,  $\geq$  50 % 57 58 representing substantial heterogeneity and  $\geq$  75%, considerable heterogeneity. 59

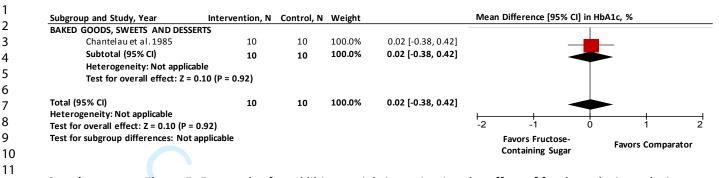


Supplementary Figure 3. Forest plot for addition trials investigating the effect of adding excess calories to the diet in the form of fructose-containing food sources on HbA1c. BB= blueberries; HbA1c= hemoglobin A1c; N= number of participants. Pooled effect estimates for each subgroup and overall effect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

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	ention, N	Control, N	Weight		Mean Difference [95% CI] i	n HbA1c, %
SUGARS-SWEETENED BEVERAGES Hernandez Cordero et al. 2014	120	120	100.0%	-0.05 [-0.14, 0.04]	_	
Subtotal (95% CI)	120 120	120 120	100.0%	-0.05 [-0.14, 0.04] -0.05 [-0.14, 0.04]		
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0	0.30)					
Total (95% CI)	120	120	100.0%	0.05[0.14_0.04]		
Heterogeneity: Not applicable	120	120	100.0%	-0.05 [-0.14, 0.04]		
Test for overall effect: Z = 1.04 (P = 0.30)					-0.2 -0.1 (	0.1 0.2
Test for subgroup differences: Not applicable	•				Favors Comparator	Favors Fructose-
						<b>Containing Sugar</b>
Supplementary Figure 4. Forest	t plot fo	or subtra	action tria	als investigating	the effect of removi	ng calories from
the diet in the form of fructose-		ning foo	d source	s on HbA1c. HbA	1c= hemoglobin A1c	: N= number of
participants. Pooled effect estin		-			_	
					•	•
Data are expressed as weighted						-
inverse-variance method with ra					•••	
Inter-study heterogeneity was t						
quantified by $l^2$ , levels $\leq 50\%$ re	present	tmoder	ate hetei	°ogeneitv. ≥ 50 %	6 representing substa	antial
heterogeneity and $\geq$ 75%, consid	-			5, = = = 5 ,	1	
			ochercy.			



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 diffe. ffects m. the Cochran rate heterogene. erogeneity. 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  $\leq$  50% represent moderate heterogeneity,  $\geq$  50% representing substantial heterogeneity and  $\geq$  75%, considerable heterogeneity. 

				Ме	an difference (95% Cl) in HbA1c	: (%) in substitution trials		
Subgroup	Level	Trials	N	Within subgroups		Between subgroups	- Residual I <sup>2</sup>	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) Mixed (5)	1 18	10 356	-0.50 (-2.04 to 1.04) -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
Energy balance	Negative (2)	5	188	-0.17 (-0.44 to 0.12) -0.11 (-0.78 to 0.57)		1 vs 2: 0.06 (-0.68 to 0.79) 1 vs 3: -0.84 (-1.84 to 0.16)	11.82%	0.25
	Positive (3)	2	140	-1.20 (-2.66 to 0.26)		2 vs 3: -0.89 (-2.07 to 0.28)		
Comparator	Starch (1)	17	281	-0.34 (-0.73 to 0.04)		See legend	82.11%	0.90
Form	Mixed (2)	5	407	0.08 (-0.47 to 0.63)	,	See legend	02.11/0	0.50
	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) Fat (8)	1 1	25 30	-0.37 (-1.82 to 1.08) -0.04 (-1.43 to 1.35)				
Fructose Form	Fructose (1) Sucrose (2)	13 12	238 263	-0.36 (-0.85 to 0.13) 0.08 (-0.39 to 0.56)		1 vs 2: 0.44 (-0.23 to 1.10) 1 vs 3: 0.14 (-0.57 to 0.86)	84.11%	0.44
	Fruit (3)	8	453	-0.21 (-0.75 to 0.33)		2 vs 3: -0.29 (-1.01 to 0.42)		
							o	
Fructose Dose	≤ 10% E > 10% E	22 10	676 270	-0.24 (-0.55 to -0.07) -0.16 (-0.62 to 0.31)		0.08 (-0.48 to 0.64)	81.29%	0.78
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)		0120 ( 0120 (0 1120)	0111070	0.51
Underlying	Diabetes (1)	24	688	-0.28 (-0.59 to 0.03)		See legend	81.71%	0.86
	verweight/ Obese (2)	4	153	-0.02 (-0.81 to 0.78)		_		
	MetS Criteria (3)	2	61	-0.04 (-1.00 to 0.92)				
C	Otherwise Healthy (4)	2	44	-0.02 (-0.99 to 0.95)		<u> </u>		
					-1.5 -0.75 0 0	0.75 1.5		
						urs Comparator		
					Containing Sugar			

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<sup>2</sup> 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). 

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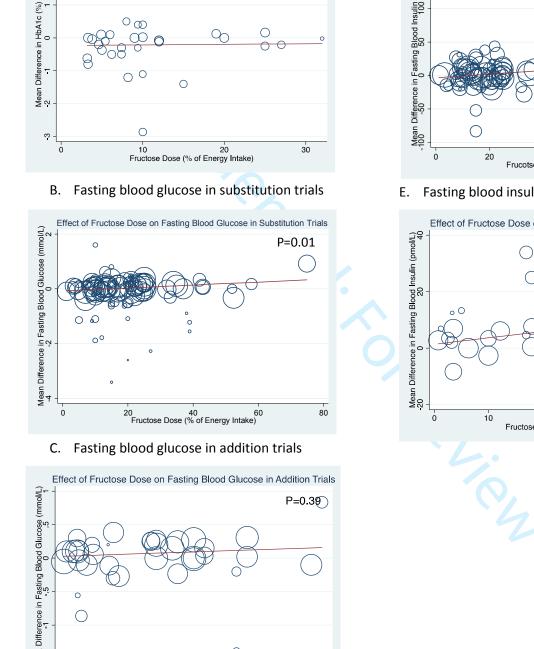
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Subgroup	Level	Trials	Ν	Ν	lean differen	ice (95% CI) i	n HbA1c (	%) in subs	titution trials		Residual I <sup>2</sup>	P-value
				Within subgroups			•		H	letween subgroups		
Total		32	946	-0.14 [-0.25, -0.04]		_	-	_			81.00%	<0.01
Sequence Generation	Unclear Risk of Bias (1) Low Risk of Bias (2) High Risk of Bias (3)	26 3 3	658 141 147	-0.21 [-0.50, 0.90] -0.04 [-0.84, 0.75] -0.44 [-1.26, 0.37]	_	-	-		1 Vs. 3 =	= -0.16 [-0.68, 1.01] = -0.23 [-1.10, 0.63] -0.40 [-1.54, 0.74]	81.75%	0.77
Allocation Concealment	Unclcar Risk of Bias (1) Low Risk of Bias (2) High Risk of Bias (3)	27 2 3	685 114 147	-0.19 [-0.47, 0.10] -0.17 [-1.47, 1.13] -0.44 [-1.26, 0.38]		_	-		1 Vs. 3 =	= 0.02 [-1.32, 1.34] = -0.25 [-1.12, 0.61] = 0.27 [-1.30, 1.81]	81.69%	0.83
Blinding of Participants, Personnel, and Outcome Assessors	Unclear Risk of Bias (1) Low Risk of Bias (2) High Risk of Bias (3)	19 11 2	542 312 92	-0.27 [-0.63, 0.08] -0.15 [-0.58, 0.28] -0.10 [-1.08, 0.88]		_	-		1 Vs.3	= 0.12 [-0.43, 0.68] = 0.17 [-0.87, 1.22] = -0.05 [-1.12, 1.02]	81,78%	0,88
Incomplete Outcome Data	Unclear Risk of Bias (1) Low Risk of Bias (2) High Risk of Bias (3)	18 13 1	382 554 10	-0.24 [-0.60, 0.11] -0.15 [-0.56, 0.25] -0.50 [-2.00, 1.00]			•		1 Vs. 3 =	= 0.09 [-0.45, 0.63] = -0.26 [-1.80, 1.28] = 0.35 [-1.21, 1.90]	81.46%	0.87
Selective Outcome Reporting	Unclear Risk of Bias (1) Low Risk of Bias (2) High Risk of Bias (3)	15 17 0	374 572 0	-0.15 [-0.54, 0.24] -0.27 [-0.61, 0.08] *		-1 Fructose- ning Sugars	0 Fa	l vours Com	2	= 0.12 [-0.40, 0.64] 1 Vs. 2 = * 2 Vs. 3 - *	81.42%	0.46

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 1<sup>2</sup> 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).

N



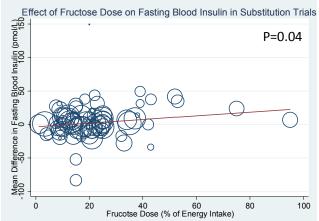
P=0.93

HbA1c in substitution trials A.

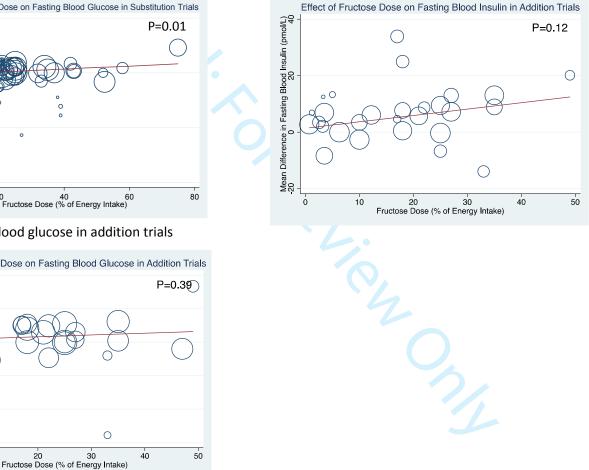
Effect of Fructose Dose on HbA1c in Substitution Trials

D. Fasting blood insulin in substitution trials

BMJ



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).

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IITS	tervention, N	Control, N	Weight	Mean Differen	ce [95% CI] in Fasting Blood Glucose, mmol/L
Agebratt et al. 2016	15	15	1.2%	0.11 [-0.17, 0.39]	1
Anderson et al. 2014	31	15	0.2%	0.11 [-0.85, 1.06]	
Bays et al. 2015	27	19	0.2%	-1.78 [-3.62, 0.07]	
Conceição et al. 2003	26	9	1.2%	-0.07 [-0.35, 0.20]	+
Hegde et al. 2013	60	63	0.3%	-1.10 [-1.73, -0.47]	<u> </u>
Kanellos et al. 2014	26	22	0.2%	0.17 [-0.76, 1.10]	
Kolehmainen et al. 2012	15	12	0.7%	0.10 [-0.29, 0.49]	+
Lehtonen et al. 2010	28	22	1.0%	0.10 [-0.22, 0.42]	+
Madero et al. 2011	65	66	3.0%	-0.05 [-0.09, 0.00]	•
Moazen et al. 2013	19	17	0.4%	0.06 [-0.50, 0.62]	- <b>-</b> -
Rodriguez et al. 2005	7	8	0.9%	0.00 [-0.34, 0.34]	+
Singh et al. 1997	52	49	2.1%	-0.40 [-0.55, -0.25]	-
Subtotal (95% CI)	371	317	11.2%	-0.10 [-0.26, 0.06]	•
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup>		1 (P < 0.0	001); I² = 71%		
Test for overall effect: Z = 1.23 (	(P = 0.22)				
SARS-SWEETENED BEVERAGES	20	20	2 49/	1000100010001	Ļ
Aeberli et al. 2011 (HD) Aeberli et al. 2011 (MD)	29 29	29 29	2.4% 2.5%	0.08 [-0.04, 0.20] -0.13 [-0.24, -0.01]	1
Aeberli et al. 2011 (MD) Aeberli et al. 2013	29	29	2.5%	0.09 [-0.09, 0.26]	1
Beck-Nielsen et al. 1980	15	15	0.5%	-0.30 [-0.81, 0.21]	
Heden et al. 2014 (AJCN-H)	20	20	1.4%	-0.25 [-0.49, -0.01]	_
Heden et al. 2014 (AJCN-OW/OB		20	1.4%	-0.06 [-0.25, 0.14]	4
Heden et al. 2014 (JPAH)	7	7	0.8%	0.17 [-0.21, 0.54]	+-
Jin et al. 2014	9	12	0.3%	-0.52 [-1.26, 0.22]	_ <del></del>
Johnston et al. 2013 (T1)	15	17	1.3%	0.21 [-0.05, 0.47]	<del> -</del> -
Johnston et al. 2013 (T2)	15	17	1.2%	0.24 [-0.04, 0.52]	<u></u> +
Koivisto and Yki-Järvinen 1993	10	10	0.2%	-1.10 [-2.05, -0.15]	— <b>—</b> –
Maersk et al. 2012	10	12	2.5%	-0.12 [-0.23, -0.02]	-
Mark et al. 2014	35	38	1.7%	0.05 [-0.14, 0.24]	+
McAteer et al. 1987	10	10	0.2%	-0.08 [-0.98, 0.82]	-+
Ngo Sock et al. 2010	11	11	2.1%	0.11 [-0.04, 0.26]	t i i i i i i i i i i i i i i i i i i i
Schwarz et al. 2015	8	8	2.0%	0.12 [-0.05, 0.28]	F
Silbernagel et al. 2011	10	10	1.0%	0.02 [-0.30, 0.34]	+
Stanhope et al. 2011 (AJCN)	17	15	3.1%	0.02 [0.01, 0.02]	
Stanhope et al. 2011 (JCEM)	32	16	2.6%	0.15 [0.06, 0.24]	<u> </u>
Swarbrick et al. 2008	7	7	2.4%	0.38 [0.26, 0.50]	
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup>	318 2 = 79 92 df = 1	312 9 (P < 0 0)	31.7%	0.05 [-0.02, 0.11]	ľ
Test for overall effect: Z = 1.33 (			5501),I - 707		
UID MEAL REPLACEMENTS					
Hendler et al. 1990	9	7	1.1%	0.92 [0.63, 1.21]	<del>-</del>
Johnson et al. 2015	24	27	1.4%	-0.02 [-0.27, 0.23]	+
Rizkalla et al. 1986 (EXP1)	8	15	1.2%	-0.14 [-0.41, 0.14]	-
Rizkalla et al. 1986 (EXP2)	6	12	1.2%	0.22 [-0.05, 0.49]	<del> -</del> -
Turner et al. 1979 (HC)	4	4	1.3%	-0.15 [-0.41, 0.10]	-
Turner et al. 1979 (LC DM)	2	2	0.0%	-1.17 [-3.27, 0.92]	
Turner et al. 1979 (LC Non-DM)	4	4	1.2%	0.24 [-0.03, 0.51]	
Subtotal (95% CI)	57	71	7.5%	0.15 [-0.15, 0.45]	◆
Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup>		6 (P < 0.00	001); l² = 85%		
Test for overall effect: Z = 0.97 (	(P = 0.33)				
		~~	4 004	0.401.000.000	
RY PRODUCTS	~~	65	1.8%	-0.10 [-0.28, 0.08]	7
RY PRODUCTS Lowndes et al.2015	30			0 4 0 1 0 00 0 001	
RY PRODUCTS Lowndes et al.2015 Subtotal (95% CI)	30 <b>30</b>	65	1.8%	-0.10 [-0.28, 0.08]	•
RY PRODUCTS Lowndes et al.2015 Subtotal (95% CI) Heterogeneity: Not applicable	30		1.8%	-0.10 [-0.28, 0.08]	•
RY PRODUCTS Lowndes et al.2015 Subtotal (95% CI)	30		1.8%	-0.10 [-0.28, 0.08]	•
RY PRODUCTS Lowndes et al.2015 Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 (	30		1.8%	-0.10 [-0.28, 0.08]	•
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS	30 (P = 0.28)	65			
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC)	<b>30</b> (P = 0.28) 6	<b>65</b> 6	0.9%	0.07 [-0.28, 0.42]	
RY PRODUCTS Lowndes et al.2015 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al.1980 (non-OC) Behall et al.1980 (OC)	<b>30</b> (P = 0.28) 6 6	<b>65</b> 6	0.9% 0.6%	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50]	• ÷
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (OC) Claesson et al. 2009	<b>30</b> (P = 0.28) 6 6 12	65 6 13	0.9% 0.6% 1.7%	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.00 [-0.20, 0.20]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (noC) Claesson et al. 2009 Hallfrisch et al. 1983 (HI)	<b>30</b> (P = 0.28) 6 6 12 12	65 6 13 12	0.9% 0.6% 1.7% 0.2%	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.00 [-0.20, 0.20] 0.16 [-0.73, 1.05]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (nor-OC) Behall et al. 2009 Hallfrisch et al. 1983 (H) Hallfrisch et al. 1983 (H)	<b>30</b> (P = 0.28) 6 6 12 12 12 12	65 6 13 12 12	0.9% 0.6% 1.7% 0.2% 0.2%	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.00 [-0.20, 0.20] 0.16 [-0.73, 1.05] 0.15 [-0.74, 1.04]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (OC) Claesson et al. 2009 Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (H) Jones et al. 2014	<b>30</b> (P = 0.28) 6 6 12 12 12 12 25	65 6 13 12 12 25	0.9% 0.6% 1.7% 0.2% 0.2% 1.3%	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.00 [-0.20, 0.20] 0.16 [-0.73, 1.05] 0.15 [-0.74, 1.04] -0.09 [-0.34, 0.16]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (OC) Behall et al. 1980 (OC) Claesson et al. 2009 Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Jones et al. 2014 Kelsay et al. 1974	30 (P = 0.28) 6 6 12 12 12 12 25 8	65 6 13 12 12 25 8	0.9% 0.6% 1.7% 0.2% 0.2% 1.3% 0.5%	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.00 [-0.20, 0.20] 0.16 [-0.73, 1.05] 0.15 [-0.74, 1.04] -0.09 [-0.34, 0.16] 0.33 [-0.14, 0.81]	
RY PRODUCTS Lowndes et al.2015 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al.1980 (non-OC) Behall et al.1980 (non-OC) Behall et al.1980 (non-OC) Hallfrisch et al.1983 (HI) Hallfrisch et al.1983 (HI) Hallfrisch et al.1983 (HI) Jones et al.2014 Kelsay et al.2014 Malerbi et al.1966	<b>30</b> (P = 0.28) 6 12 12 12 25 8 16	65 6 13 12 12 25 8 16	0.9% 0.6% 1.7% 0.2% 1.3% 0.5% 0.4%	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.00 [-0.20, 0.20] 0.16 [-0.73, 1.05] 0.15 [-0.74, 1.04] -0.09 [-0.34, 0.16] 0.33 [-0.14, 0.81] -0.50 [-1.09, 0.09]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (OC) Claesson et al. 2009 Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1974 Kelsay et al. 1974 Malerbi et al. 1966 Reiser et al. 1986 (HI)	<b>30</b> (P = 0.28) 6 12 12 12 12 25 8 16 10	6 6 13 12 25 8 16 10	0.9% 0.6% 1.7% 0.2% 1.3% 0.5% 0.4% 0.1%	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.00 [-0.20, 0.20] 0.15 [-0.73, 1.05] 0.15 [-0.74, 1.04] -0.09 [-0.34, 0.16] 0.33 [-0.14, 0.81] -0.50 [-1.09, 0.09] 0.30 [-0.68, 1.28]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( CED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (OC) Claesson et al. 2009 Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Jones et al. 2014 Kelsay et al. 1974 Malerbi et al. 1966 Reiser et al. 1989 (HI) Reiser et al. 1989 (HI)	30 (P = 0.28) 6 6 12 12 12 25 8 16 10 11	6 6 13 12 25 8 16 10 11	0.9% 0.6% 1.7% 0.2% 0.2% 1.3% 0.5% 0.4% 0.1% 0.2%	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.01 [-0.20, 0.20] 0.15 [-0.74, 1.04] 0.09 [-0.34, 0.16] 0.33 [-0.14, 0.81] -0.50 [-1.09, 0.09] 0.30 [-0.68, 1.28] 0.10 [-0.83, 1.03]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( CED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (NOC) Claesson et al. 2009 Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Jones et al. 2014 Kelsay et al. 2014 Kelsay et al. 1974 Malerbi et al. 1966 Reiser et al. 1989 (HI) Reiser et al. 1989 (HI) Subtotal (95% CI)	30 (P = 0.28) 6 6 12 12 12 25 8 16 10 11 118	65 6 13 12 25 8 16 10 11 <b>119</b>	0.9% 0.6% 1.7% 0.2% 0.2% 0.5% 0.4% 0.1% 0.2% <b>6.1%</b>	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.00 [-0.20, 0.20] 0.15 [-0.73, 1.05] 0.15 [-0.74, 1.04] -0.09 [-0.34, 0.16] 0.33 [-0.14, 0.81] -0.50 [-1.09, 0.09] 0.30 [-0.68, 1.28]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (nOC) Claesson et al. 2009 Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Reiser et al. 1989 (HI) Reiser et al. 1989 (HI) Reiser et al. 1989 (HI) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	30 (P = 0.28) 6 6 12 12 12 25 8 16 10 11 118 2 = 5.98, off = 9	65 6 13 12 25 8 16 10 11 <b>119</b>	0.9% 0.6% 1.7% 0.2% 0.2% 0.5% 0.4% 0.1% 0.2% <b>6.1%</b>	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.01 [-0.20, 0.20] 0.15 [-0.74, 1.04] 0.09 [-0.34, 0.16] 0.33 [-0.14, 0.81] -0.50 [-1.09, 0.09] 0.30 [-0.68, 1.28] 0.10 [-0.83, 1.03]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (non-OC) Behall et al. 1980 (non-OC) Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Jones et al. 2014 Kelsay et al. 1974 Malerbi et al. 1966 Reiser et al. 1989 (HI) Reiser et al. 1989 (HI) Subtotal (95% CI)	30 (P = 0.28) 6 6 12 12 12 25 8 16 10 11 118 2 = 5.98, off = 9	65 6 13 12 25 8 16 10 11 <b>119</b>	0.9% 0.6% 1.7% 0.2% 0.2% 0.5% 0.4% 0.1% 0.2% <b>6.1%</b>	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.01 [-0.20, 0.20] 0.15 [-0.74, 1.04] 0.09 [-0.34, 0.16] 0.33 [-0.14, 0.81] -0.50 [-1.09, 0.09] 0.30 [-0.68, 1.28] 0.10 [-0.83, 1.03]	
RY PRODUCTS Lowndes et al. 2015 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( KED GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (nOC) Claesson et al. 2009 Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Reiser et al. 1989 (HI) Reiser et al. 1989 (HI) Reiser et al. 1989 (HI) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	30 (P = 0.28) 6 6 12 12 12 25 8 16 10 11 118 2 = 5.98, off = 9	65 6 13 12 25 8 16 10 11 <b>119</b>	0.9% 0.6% 1.7% 0.2% 0.2% 0.5% 0.4% 0.1% 0.2% <b>6.1%</b>	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.01 [-0.20, 0.20] 0.15 [-0.74, 1.04] 0.09 [-0.34, 0.16] 0.33 [-0.14, 0.81] -0.50 [-1.09, 0.09] 0.30 [-0.68, 1.28] 0.10 [-0.83, 1.03]	
PRODUCTS Lowndes et al. 2015 Subtotal (95% Cl) Heterogeneity: Not applicable Test for overall effect: Z = 0.81 ( GOODS, SWEETS AND DESSERTS Behall et al. 1980 (non-OC) Behall et al. 1980 (non-OC) Claesson et al. 2009 Hallfrisch et al. 1983 (HI) Hallfrisch et al. 1983 (HI) Jones et al. 2014 Kelsay et al. 1974 Malerbi et al. 1989 (HI) Reiser et al. 1989 (HI) Reiser et al. 1989 (HI) Subtotal (95% Cl)	30 (P = 0.28) 6 6 12 12 12 25 8 16 10 11 118 2 = 5.98, off = 9	65 6 13 12 25 8 16 10 11 <b>119</b>	0.9% 0.6% 1.7% 0.2% 0.2% 0.5% 0.4% 0.1% 0.2% <b>6.1%</b>	0.07 [-0.28, 0.42] 0.06 [-0.38, 0.50] 0.01 [-0.20, 0.20] 0.15 [-0.74, 1.04] 0.09 [-0.34, 0.16] 0.33 [-0.14, 0.81] -0.50 [-1.09, 0.09] 0.30 [-0.68, 1.28] 0.10 [-0.83, 1.03]	-4 -2 0 2 4 Favors Fructose-

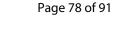
Supplementary Figure 9. Forest plot for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood glucose (continues next page).

1	MIXED SOURCES					1
2	Abraira et al. 1988	9	9	0.0%	-0.89 [-3.68, 1.90]	
	Anderson et al. 1989	14	14	0.0%	-0.36 [-2.46, 1.74]	
3	Bantle et al. 1986 (DM1)	12	12	0.0%	0.46 [-2.05, 2.98]	
4	Bantle et al. 1986 (DM2)	12	12	0.1%	0.45 [-0.78, 1.68]	- <del></del>
-	Bantle et al. 1992 (DM1)	6	6	0.0%	-2.60 [-7.67, 2.47]	· · · · · · · · · · · · · · · · · · ·
5	Bantle et al. 1992 (DM2) Bantle et al. 1993	12 12	12 12	0.0%	-1.08 [-2.85, 0.69]	
6	Bantle et al. 1993	24	24	0.1% 2.3%	-0.62 [-2.01, 0.77] 0.08 [-0.05, 0.20]	
	Black et al. 2006	13	13	1.7%	0.00 [-0.20, 0.20]	1
7	Blayo et al. 1990	8	6	0.1%	-1.14 [-2.11, -0.16]	
8	Brunner et al. 2012	49	52	0.4%	0.32 [-0.27, 0.90]	
	Brymora et al. 2012	28	28	1.5%	0.11 [-0.12, 0.34]	+
9	Brynes et al. 2003	17	17	1.2%	0.05 [-0.22, 0.32]	+
10	Cooper et al. 1988	17	17	0.1%	0.30 [-1.04, 1.64]	<del></del>
	Coulston et al. 1985	11	11	0.3%	-0.49 [-1.20, 0.23]	
11	Dunnigan et al. 1970 Emanuele et al. 1986	9 5	9 5	2.6% 0.0%	0.22 [0.13, 0.32] -1.55 [-3.93, 0.84]	<b>_</b>
12	Fry et al. 1972	19	19	2.0%	0.17 [0.00, 0.33]	
12	Grigoresco et al. 1988	8	8	0.0%	-0.40 [-2.26, 1.46]	
13	Jellish et al. 1984	18	8	0.0%	-0.40 [-2.58, 1.78]	
14	Koh et al. 1988 (IGT)	9	9	0.1%	-0.54 [-1.57, 0.49]	— <del></del>
14	Koh et al. 1988 (NGT)	9	9	0.1%	-0.62 [-1.65, 0.41]	
15	Lewis et al. 2013	13	13	1.3%	0.40 [0.15, 0.65]	-
16	Liu et al. 1983	5	5	0.4%	0.62 [0.04, 1.20]	
16	Lock et al. 1980	18	18	2.5%	-0.08 [-0.18, 0.03]	1
17	Maki et al. 2015 Malerbi et al. 1966	34 16	34 16	2.2%	0.11 [-0.03, 0.25]	Ē
10	Osei et al. 1987	16	9	0.1%	0.30 [-0.02, 0.62] -1.89 [-3.30, -0.47]	
18	Osei et al. 1989	13	13	0.0%	-3.40 [-6.44, -0.36]	
19	Paineau et al. 2008	297	298	2.5%	0.00 [-0.11, 0.11]	Ļ
	Pelkonen et al. 1972	10	10	0.1%	0.80 [-0.63, 2.23]	
20	Peterson 1986 (DM1)	12	12	0.0%	-0.20 [-3.47, 3.07]	
21	Peterson 1986 (DM2)	11	11	0.1%	-0.20 [-1.77, 1.37]	
	Pinheiro et al. 2007 (G1)	5	5	1.7%	-0.25 [-0.45, -0.05]	-
22	Pinheiro et al. 2007 (G2) Porta et al. 1989	5 8	5 8	1.4% 0.1%	0.11 [-0.13, 0.36]	+
23	Rath et al. 1989	6	6	2.0%	1.60 [0.10, 3.10] -0.33 [-0.50, -0.16]	
	Reiser et al. 1986 (W)	9	9	1.0%	0.34 [0.02, 0.67]	
24	Reiser et al. 1986 (M)	10	10	0.8%	0.18 [-0.17, 0.54]	
25	Souto et al. 2013	15	18	0.0%	-2.27 [-4.70, 0.16]	
	Sunehag et al. 2002 (P1-AD)	12	12	1.7%	-0.10 [-0.30, 0.10]	-
26	Sunehag et al. 2002 (P1-PP)	12	12	0.9%	0.00 [-0.34, 0.34]	+
27	Sunehag et al. 2002 P2	12	12	1.7%	0.20 [0.00, 0.40]	-
	Sunehag et al.2008 Surwit et al.1997	6 20	6 22	1.7% 0.4%	-0.10 [-0.30, 0.10]	4
28	Swanson et al. 1997	20 14	14	0.4%	0.17 [-0.37, 0.71] 0.00 [-0.34, 0.34]	Ŧ
29	Szanto et al. 1969	19	19	0.3%	0.00 [-0.71, 0.71]	
	Van Meijl et al. 2011	35	35	2.5%	-0.01 [-0.11, 0.09]	Ļ
30	Volp et al. 2008 (G1)	6	6	0.0%	-0.26 [-4.39, 3.86]	
31	Volp et al. 2008 (G2)	6	6	0.0%	0.13 [-4.03, 4.29]	
	Vrolix et al. 2010	15	15	1.5%	0.06 [-0.16, 0.28]	+
32	Subtotal (95% CI)	974	971	41.7%	0.04 [-0.03, 0.11]	
33	Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup>		: 50 (P < 0.0	0001);	1%	
	Test for overall effect: Z = 1.03 (F	= 0.31)				
34	Total (95% CI)	1868	1824	100.0%	0.03 [-0.01, 0.07]	
35	Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 302.86					
	Test for overall effect: Z = 1.52 (P = 0.13)					-4 -2 0 2 4
36	Test for subgroup differences: Chi <sup>2</sup> = 4.60	, df = 5 (P = 0	.47), I <sup>2</sup> = 0%			
37						Favors Fructose- Favors Comparator Containing Sugar
						containing sugar
38						

Supplementary Figure 9. Forest plot for substitution trials investigating the effect of isocaloric exchange of 39 40 fructose-containing food sources for other macronutrients on fasting blood glucose (continued). AJCN = 41 American Journal of Clinical Nutrition; DM= diabetes mellitus; EXP1= experiment 1; EXP2= experiment 2; 42 H=healthy; HC= high carbohydrate; HD= high dose; HI=hyperinsulinemic; JPAH= Journal of Physical Activity 43 and Health; JCEM= Journal of Clinical Endocrinology and Metabolism; LC= low carbohydrate; MD= moderate 44 45 dose; N= number of participants; OC= oral contraceptive users; OW/OB= overweight/obese participants; T1= 46 trial 1; T2=Trial 2. Pooled effect estimates for each subgroup and overall effect are represented by the 47 diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the 48 generic inverse-variance method with random effects models. Paired analyses were applied to all crossover 49 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p < 0.10 and 50 51 quantified by  $l^2$ , levels  $\leq$  50% represent moderate heterogeneity,  $\geq$  50% representing substantial 52 heterogeneity and  $\geq$  75%, considerable heterogeneity. 53

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Basue al. 2010 (BB) 25 23 2.1 AM 0.20 (-0.19, 0.03) 1 Basue al. 2010 (BL ALL ALL ALL ALL ALL ALL ALL ALL ALL A	Subgroup and Study, Year Inte FRUITS	rvention, N	Control, N	weight	incui bi	Terence	ce [95% CI] in Fasting Blood Glucose, mmol/L
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Hence and the set of							Τ.
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NUMAR-SWETTEND BYERNES       6       6       3.4%       0.10 [0.30, 0.10]         Beck-Needer at J.2008       6       6       3.4%       0.20 [0.34, 0.51]         Beck-Needer at J.2008       6       6       3.4%       0.20 [0.34, 0.51]         Well-Stand       1.300       1.5       5       2.3%       0.40 [0.27, 0.53]         Well-Stand       1.5       5       2.3%       0.26 [0.27, 0.25]       1         Magretat J.2011       1.5       5       2.3%       0.21 [0.27, 0.47, 0.07]       1         Niker at J.2011       3       3.1       4.4%       0.21 [0.27, 0.01]       1         Submoper et al.2010       8       8       3.3%       0.02 [0.40, 0.01]       1         Submoper et al.2011       10       10       3.9%       0.02 [0.40, 0.01]       1       1         Submoper et al.2011       10       10       1.9%       0.02 [0.40, 0.23]       1       1       1       1       10	Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =	14.16, df = 1			0.03 [-0.04, 0.10]		
Model Sayed et al. 2008       6       6       3.4%       -0.10 [0.30, 0.10]         Beck-Niews et al. 1980       12       12       3.4%       -0.20 [0.40, 0.10]         Holi set al. 2001       12       12       3.4%       -0.21 [0.40, 0.10]         Holi set al. 2006       7       7       2.9%       0.28 [0.22, 0.31]         Het al. 2006       16       16       3.9%       0.28 [0.22, 0.31]         Maget al. 2011       10       1.25       4.3%       0.15 [0.64, 0.26]         Maget al. 2011       10       1.25       4.3%       0.15 [0.64, 0.26]         Maget al. 2011       10       1.24       0.38 [0.17, 0.66]	Test for overall effect: Z = 0.81 (P	= 0.42)					
BeckNielsen et al. 1990       8       2       0.6%       -0.20 [0.94, 0.54]         Bilis et al. 2009       26       25       2.6%       0.25 [0.40, 0.53]         Mediate al. 2010       15       5       2.3%       0.21 [0.40, 0.53]         Mediate al. 2010       15       5       2.3%       0.21 [0.40, 0.53]         Merick et al. 2010       10       2.5       2.3%       0.31 [0.15, 0.64]         Merick et al. 2011       10       10       3.2%       3.3 [0.47, 0.07]         Miscour et al. 2011       10       10       3.2%       0.33 [0.17, 0.06]         Nikeet al. 2011       10       10       3.9%       0.23 [0.47, 0.07]	SUGARS-SWEETENED BEVERAGES	6	c	2 40/	0 10 [ 0 20 0 10]		
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$ \begin{array}{c} \text{Koppman ct al. 2014} & \text{if } 5 & \text{c. } 238 & 0.04 (-0.27, 0.35) \\ \text{if } \text{ct al. } 2009 (DM2) & \text{if } 6 & \text{if } 6 & \text{if } 88 & 0.31 (0.35, 0.46) \\ \text{Marske al. } 2009 (DM2) & \text{if } 16 & \text{if } 398 & 0.31 (0.35, 0.46) \\ \text{Marske al. } 2011 & 10 & 23 & 31 & 3.48 & 0.27 (-0.47, 0.07) \\ \text{Marske al. } 2011 & 10 & 10 & 398 & 938 & 0.06 (-0.27, 0.35) \\ \text{Subbranglet al. } 2011 & 10 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 10 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 10 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 10 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 10 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 10 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 10 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 10 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 100 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 100 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2011 & 100 & 10 & 398 & 0.28 (-0.47, 0.07) \\ \text{Subbranglet al. } 2009 & 0.7 & 7.1 & 158 & 5.51 & 0.08 (-0.03, 0.07) \\ \text{Subbranglet al. } 2009 & 25 & 25 & 2.38 & 0.26 (-0.05, 0.57) \\ \text{Subbranglet al. } 2009 & 0.53 & 3.38 & 6.38 & 0.31 (-0.02, 0.26) \\ \text{Hettrogenetity: Nat applicable \\ \text{Test for overall effect: 2 + 1.96 (P = 0.00)} \\ \text{Subbranglet: Nat applicable \\ \text{Test for overall effect: 2 + 2.94 (P = 0.003)} \\ \text{Subbranglet: Nat applicable \\ \text{Test for overall effect: 2 + 2.94 (P = 0.003)} \\ \text{Subbranglet: Nat applicable \\ \text{Test for overall effect: 2 + 2.38 (f = 0.0007); P = 238 \\ \text{Subbrand et al. } 2013 & 20 & 0 & 10.5 & 0.09 (-0.02, 0.20) \\ \text{Metrogenety: Nat applicable \\ \text{Test for overall effect: 2 + 2.28 (f = 0.0003); P = 725 \\ \text{Subbrand et al. } 2013 & 20 & 0 & 10.5 & 0.09 (-0.02, 0.20) \\ \text{Subbrand et al. } 2013 & 20 & 0 & 10.5 & 0.09 (-0.02, 0.20) \\ \text{Subbrand et al. } 2013 & 20 & 0 & 10.5 & 0.09 (-0.02, 0.20) \\ \text{Subbrand et al. } 2013 & 20 & 0 & 10.5 & 0.09 (-0.02, 0.20) \\ Subbrand $							<u> </u>
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Niket al. 2011 3 39 39 30 30% -0.23 [0.47, 0.00] Siberages et al. 2011 10 10 3.95% 0.24 [0.69, 0.40] Sobreases et al. 2010 8 8 8 3.35% 0.02 [0.18, 0.23] Stambope et al. 2011 (JCM FRU) 16 16 3.5% 0.00 [0.20, 0.19] Stambope et al. 2011 (JCM FRU) 16 16 3.5% 0.00 [0.20, 0.07] Subtotal (95% C1) 2.248 2.248 3.24% 0.01 [0.00, 0.07] Subtotal (95% C1) 2.5 25 2.5 2.3% 0.01 [0.00, 0.26] Hetrogenetic; Tau' = 0.05; Ch' = 12.2 8.5, dt = 21 [P = 0.36]; t <sup>2</sup> = 0.0% Test for overall effect: 2 = 1.50 (P = 0.00) Subtotal (95% C1) 53 35 36 6.3% 0.01 [0.00, 0.26] Hetrogenetic; Tau' = 0.00; Ch' = 0.36]; t <sup>2</sup> = 0.0% Test for overall effect: 2 = 0.40 (P = 0.11) WKEM Subtata (95% C1) 51 41 (P = 0.36]; t <sup>2</sup> = 0.0% Test for overall effect: 2 = 0.40 (P = 0.11) WKEM Subtata (195% C1) 51 41 (20 = 0.000); t <sup>2</sup> = 7.3% Test for overall effect: 2 = 0.40 (P = 0.11) WKEM Subtata (195% C1) 52 20 10% -0.86 [1.43, -0.30] Bahrang et al. 2001 2.5 ch' = 12.2.85, dt = 31 4.4% 0.09 [-0.02, 0.20] Hetrogenetic; Not applicable Test for overall effect: 2 = 0.40 (P = 0.11) WKEM Subtata (195% C1) 52 20 10% -0.86 [1.43, -0.30] Bahrang et al. 2001 2.5 ch' = 12.2.85, dt = 31 0.00% 0.027 [0.002, 0.21] Hetrogenetic; Tau' = 0.02; ch' = 12.2.85, dt = 24 (P - 0.000); t <sup>2</sup> = 83% Test for overall effect: 2 = 0.40 (P = 0.000); t <sup>2</sup> = 83% Test for overall effect: 2 = 0.40 (P = 0.000); t <sup>2</sup> = 7.2% Test for overall effect: 2 = 0.40 (P = 0.000); t <sup>2</sup> = 5.5% Test for overall effect: 2 = 0.40 (P = 0.000); t <sup>2</sup> = 5.5% Supplementary Figure 10. For est plot for addition trials investigating the effect of adding excess call the diet in the form of fructose-containing food sources on fasting blood glucose. AJCN = American . Clinical Nutrition; BB= blueberries; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructor						Ì	
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Surhope et al. 2011 (CEM FRU) 16 16 3.5% 0.000 [0.20, 0.20] Surhope et al. 2011 (CEM FRU) 26 16 4.7% 0.001 (0.09, 0.07] Subtotal (55% C) 248 245 53.1% 0.08 (-0.01, 0.18] Heterogeneity: Tat" = 0.03; Ch" = 7.21.1, df = 15 (P = 0.0001); P = 79% Test for overall effect: 2 = 1.26 (P = 0.10) FRUT JUCE Holl (set al. 2009 25 25 2.3% 0.26 (-0.05, 0.57] Subtotal (55% C) 28 33, df = 1 (P = 0.36); P = 0% Test for overall effect: 2 = 1.36 (P = 0.06) IQUID MEAL REPLACEMENTS Rickalia et al. 2015 61 31 4.4% 0.09 (-0.0, 0.26] Heterogeneity: Tat" = 0.09; Ch" = 0.33, df = 1 (P = 0.36); P = 0% Test for overall effect: 2 = 0.39 (P = 0.06) JOUNTES LOWING stal. 2015 61 31 4.4% 0.09 (-0.02, 0.20] Meterogeneity: Tat" = 0.02; Ch" = 1.23, fd = 1 (P = 0.36); P = 0% Test for overall effect: 2 = 0.39 (P = 0.01) WEED SOURCES Abdurfman et al. 2013 20 20 10% -0.36 (-1.43, -0.30) Heterogeneity: Tat" = 0.02; Ch" = 1.23, fd = 3 (P = 0.0007); P = 83% Test for overall effect: 2 = 0.04) Heterogeneity: Tat" = 0.02; Ch" = 1.22, 5, df = 1.21, 5, df = 3 (P = 0.0007); P = 83% Test for overall effect: 2 = 0.04) Heterogeneity: Tat" = 0.02; Ch" = 1.23, fd = 3 (P = 0.0007); P = 83% Test for overall effect: 2 = 0.04) Favors Fructose- Containing Sugar Supplementary Figure 10. Forest plot for addition trials investigating the effect of adding excess call the diet in the form of fructose-containing food sources on fasting blood glucose. AJCN = American Clinical Nutrition; BB= blueberries; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructo	Sobrecases et al. 2010	8	8	3.3%	0.02 [-0.18, 0.23]	i	+
Subtool (95% C) 248 245 53.14 Heterogeneity: Tau* = 0.03; Ch* = 7.21, df = 15 ( $P < 0.0001$ ); $P = 79\%$ Test for overall effect: Z = 1.66 ( $P = 0.0$ ) FRUT JUCE Holliset al. 2009 25 25 2.3% 0.26 ( $+ 0.05, 0.57$ ) Silver at 2.001 ( $+ 0.05, 0.57$ ) Silver at 1.906 ( $P = 0.05$ ) Heterogeneity: Tau* = 0.00; Ch* = 0.03, ( $+ 0 = 0.65$ ) Heterogeneity: Tau* = 0.00; Ch* = 0.03, ( $+ 0 = 0.65$ ) Heterogeneity: Tau* = 0.00; Ch* = 0.00; Ch* = 0.00; Ch* = 0.00; Ch* = 1.19, ( $P = 0.36$ ; $P = 0.05$ Subtool (95% C) 7 7 1.1% 0.83 (0.28, 1.39) Subtool (95% C) 7 7 1.1% 0.83 (0.28, 1.39) Subtool (95% C) 61 31 4.4% 0.09 ( $-0.02, 0.20$ ) Subtool (95% C) 61 31 4.4% 0.09 ( $-0.02, 0.20$ ) Subtool (95% C) 61 31 4.4% 0.09 ( $-0.02, 0.20$ ) Subtool (95% C) 61 31 4.4% 0.09 ( $-0.02, 0.20$ ) Subtool (95% C) 61 31 4.4% 0.09 ( $-0.02, 0.20$ ) Heterogeneity: Not applicable Test for overall effect: $2 = 0.49$ ( $P = 0.11$ ) WIKED SOURCES Abdulthman et al. 2013 20 20 1.0% $-0.86$ ( $-1.43, -0.30$ ) Bahrami et al. 2003 25 23 0.4% $-1.39$ ( $2.40, -0.38$ ) Subtool (95% C) 70 616 100.0% 0.07 ( $0.002, 0.31$ ) Heterogeneity: Tau* = 0.02; Ch* = 1.22.8, df = 4.000001); $P = 7.2\%$ Test for overall effect: $2 = 0.24$ ( $P = 0.000$ ); $P = 8.3\%$ Test for overall effect: $2 = 0.24$ ( $P = 0.000$ ); $P = 56.5\%$ Supplementary Figure 10. Forest plot for addition trials investigating the effect of adding excess call the diet in the form of fructose-containing food sources on fasting blood glucose. AJCN = American . Clinical Nutrition; BB= blueberries; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructo	Stanhope et al. 2011 (AJCN)	17	17	4.6%	0.27 [0.18, 0.37]	i	+
Subtorial (95% C) 248 245 53.1% 0.08 [0.01, 0.18] Heterogeneity: Ta <sup>4</sup> = 0.02; Ch <sup>2</sup> = 22.1, (d = 15 (P < 0.00001); P = 79% First for overall effect: Z = 1.66 (P = 0.10) FNUT JUCE Hollistei al. 2009 25 25 2.3% 0.26 [0.05, 0.57] Subtorial (95% C) 53 53 6.3% 0.13 [-0.00, 0.26] Heterogeneity: Ta <sup>4</sup> = 0.00; Ch <sup>2</sup> = 0.36; P = 0.36]; P = 0% Test for overall effect: Z = 1.90 (P = 0.36); P = 0.36; P = 0% Test for overall effect: Z = 1.90 (P = 0.36); P = 0.36; P = 0% Test for overall effect: Z = 2.94 (P = 0.36); P = 0.36] Subtorial (95% C) 7 7 1.1% 0.83 [0.28, 1.39] Heterogeneity: Not applicable Test for overall effect: Z = 2.94 (P = 0.003) DARY PRODUCTS Subtorial (95% C) 61 31 4.4% 0.09 [-0.02, 0.20] Heterogeneity: Not applicable Test for overall effect: Z = 2.94 (P = 0.01) WIED SOURCES Abdulthman et al. 2013 20 20 1.0% -0.86 [-1.43, -0.30] Baltramit et al. 2009 25 23 0.4% -1.39 [2.40, -0.36] Colleguine tal. 2013 20 20 1.0% -0.85 [-1.44, 0.31] Heterogeneity: Not applicable Test for overall effect: Z = 1.24 (P = 0.21) VIEE SOURCES Abdulthman et al. 2013 20 20 1.0% -0.85 [-1.44, 0.31] Heterogeneity: Not applicable Test for overall effect: Z = 1.24 (P = 0.21) For overall effect: Z = 1.24 (P = 0.24), P = 56.5% Supplementary Figure 10. For est plot for addition trials investigating the effect of adding excess call the diet in the form of fructose-containing food sources on fasting blood glucose. AJCN = American Clinical Nutrition; BB= blueberries; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructo	Stanhope et al. 2011 (JCEM FRU)	16	16	3.5%		i	+
Heterogeneity: Tau" = 0.03; Ch <sup>2</sup> = 7.211, df = 15 ( $p < 0.00001$ ); $p = 79\%$ Test for overall effect: $2 = 1.66 (p = 0.10)$ FRUIT JUCE Holliset al. 2009 25 25 2.3% 0.26 (-0.05, 0.57) Silver al. 2001 25 25 2.3% 0.13 (-0.05, 0.25) Subtotal (95% C) 53 53 6.3% 0.13 (-0.00, 0.26) Heterogeneity: Tau" = 0.00; Ch <sup>2</sup> = 0.36; p <sup>1</sup> = 0.36; p <sup>1</sup> = 0.% Test for overall effect: $2 = 1.90 (p = 0.06)$ ICUID MCAL REPLACEMENTS Bixlail actil 1.986 (SP2) 7 7 1.1% 0.83 (0.28, 1.39) Subtotal (95% C) 7 7 1.1% 0.83 (0.28, 1.39) Heterogeneity: Not applicable Test for overall effect: $2 = 2.94 (p = 0.003)$ DARIV PRODUCTS Lowndes et al. 2015 61 31 4.4% 0.09 [-0.02, 0.20] Subtotal (95% C) 61 31 4.4% 0.09 [-0.02, 0.20] Mike a competity: Not applicable Test for overall effect: $2 = 0.49 (p = 0.11)$ WIKED SOURCES Abdulthman et al. 2013 20 20 1.0% -0.86 [-1.43, -0.30] Bahrami et al. 2009 25 23 0.4% -1.39 [2.40, -0.38] Collagiure 1.1989 9 9 0.15 [-0.09, 0.39] Subtotal (95% C) 700 615 100.0% 0.07 (0.002, 0.13] Heterogeneity: Tau" = 0.52; Ch <sup>2</sup> = 7.15, df = 3 (P = 0.0007); P = 83% Test for overall effect: $2 = 2.04 (p = 0.21)$ Total (95% C) 700 615 100.0% 0.07 (0.002, 0.13] Heterogeneity: Tau" = 0.02; Ch <sup>2</sup> = 3.4 (P = 0.0007); P = 85.5% Supplementary Figure 10. Forest plot for addition trials investigating the effect of adding excess call the diet in the form of fructose-containing food sources on fasting blood glucose. AJCN = American Clinical Nutrition; BB= blueberries; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructo	Stanhope et al.2011 (JCEM HFCS)	16	16	4.7%		i	+
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RUT JUCE         Hollis et al. 2019       25       25       2.3%       0.26 [+0.05, 0.57]         Subrotal (95% C)       53       53       6.3%       0.13 [-0.00, 0.26]         Heterogeneity: Tou" = 0.00; Ch" = 0.33, dif = (P = 0.36); P = 0%       7       1.1%       0.83 [0.28, 1.39]         JQUD MEAL REPLACEMENTS       Rizkall setal. 1986 (CMP2)       7       7       1.1%       0.83 [0.28, 1.39]         Subrotal (95% C)       61       31       4.4%       0.09 [-0.02, 0.20]       1000000000000000000000000000000000000			5 (P < 0.000	01); I <sup>2</sup> = 799	%		
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Subtotal (95% C) 53 53 63% 0.10 [-0.05, 0.25] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.36]; l <sup>2</sup> = 0.% East for overall effect: Z = 1.90 (P = 0.06) IQUID MEAL REPLACEMENTS Rizkali et al. 1996 (P20) 7 7 1.1% 0.83 [0.28, 1.39] Subtotal (95% C) 7 7 1.1% 0.83 [0.28, 1.39] Heterogeneity: Nat applicable Test for overall effect: Z = 2.94 (P = 0.003) DARY PRODUCTS Lownodes et al. 2015 61 31 4.4% 0.09 [-0.02, 0.20] Subtotal (95% C) 61 31 4.4% 0.09 [-0.02, 0.20] Heterogeneity: Nat applicable Test for overall effect: Z = 0.49 (P = 0.11) WIKED SOURCES Addulrhman et al. 2013 20 20 1.0% -0.86 [-1.43, -0.30] Bahrami et al. 2013 20 20 1.0% -0.86 [-1.43, -0.30] Bahrami et al. 2013 20 20 1.0% -0.86 [-1.41, 0.31] Heterogeneity: Tau <sup>2</sup> = 0.02; Ch <sup>2</sup> = 1.71.5, df = 3 (P = 0.0007); P <sup>2</sup> = 83% Test for overall effect: Z = 1.24 (P = 0.21) Fortal (95% C) 700 616 100.0% 0.07 (0.002, 0.13] Heterogeneity: Tau <sup>2</sup> = 0.02; Ch <sup>2</sup> = 1.22.85, df = 34 (P = 0.0007); P <sup>2</sup> = 83% Test for overall effect: Z = 1.24 (P = 0.21) Fortal (95% C) 700 616 100.0% 0.07 (0.002, 0.13] Heterogeneity: Tau <sup>2</sup> = 0.02; Ch <sup>2</sup> = 1.22.85, df = 34 (P = 0.0007); P <sup>2</sup> = 83% Test for overall effect: Z = 1.24 (P = 0.24) Total (95% C) 50 Forest plot for addition trials investigating the effect of adding excess call the diet in the form of fructose-containing food sources on fasting blood glucose. AJCN = American . Clinical Nutrition; BB= blueberries; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructo		25	25	<b>n</b> 20/	0.26 [ 0.05 0.57]		
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				,		-	



with type 2 diabetes; SB= strawberries. Pooled effect estimates for each subgroup and overall effect are

significance level of p < 0.10 and quantified by  $I^2$ , levels  $\leq$  50% represent moderate heterogeneity,  $\geq$  50 %

intervals (CIs), using the generic inverse-variance method with random effects models. Paired analyses were

represented by the diamonds. Data are expressed as weighted mean differences with 95% confidence

applied to all crossover trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a

representing substantial heterogeneity and  $\geq$  75%, considerable heterogeneity.

BMJ

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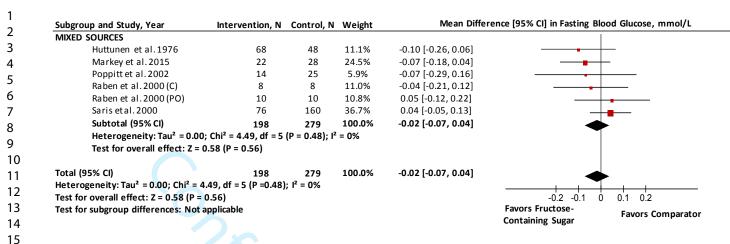
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2							
3	Subgroup and Study, Year	Intervention, N	Control, N	Weight	Mean Diffe	rence [95% CI] in Fasting Blo	od Glucose, mmol/L
5	SUGARS-SWEETENED BEVERAGES						
4	Campos et al. 2015 (G1)	6	6	4.9%	-0.10 [-0.49, 0.29]		
5	Campos et al. 2015 (G2)	7	8	8.2%	-0.40 [-0.70, -0.10]		
6	Hernandez Cordero et al. 201	4 120	120	6.3%	-0.02 [-0.37, 0.32]		
0	Tate et al. 2012	213	105	80.6%	0.03 [-0.06, 0.13]	-	<b>—</b>
7	Subtotal (95% CI)	346	239	100.0%	-0.01 [-0.10, 0.07]		
8	Heterogeneity: Chi <sup>2</sup> = 7.32, d	f = 3 (P = 0.06); I <sup>2</sup>	= 59%				
9	Test for overall effect: Z = 0.2	27 (P = 0.79)					
10	Total (95% CI)	346	239	100.0%	-0.01 [-0.10, 0.07]	-	
11	Heterogeneity: Chi <sup>2</sup> = 7.32, df = 3 (P =					+ <del>`</del>	
12	Test for overall effect: Z = 0.27 (P = 0.	79)				-0.5 -0.25 0	0.25 0.5
	Test for subgroup differences: Not ap	plicable				Favors Comparator	Favors Fructose-
13						· · · · · · · · · · · · · · · · · · ·	Containing Sugar
14							

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  $l^2$ , levels  $\leq$  50% represent moderate heterogeneity,  $\geq$  50% representing substantial heterogeneity and  $\geq$  75%, considerable heterogeneity. The Review Only



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 % ι, .rable he. significance level of p < 0.10 and quantified by  $l^2$ , levels  $\leq$  50% represent moderate heterogeneity,  $\geq$  50 % representing substantial heterogeneity and  $\geq$  75%, considerable heterogeneity.

Subgroup	Level	Trials	N	Within subgroups		Between subgroups	Residual I <sup>2</sup>	P-value
Total		101	2948	0.03 (-0.01 to 0.07)	<b> </b>	5.		
Food Source	Fruit (1)	12	697	-0.10 (-0.26 to 0.06)		See legend	65.87%	0.45
	SSB (2)	20	455	0.04 (0.47 to -0.06)				
	LMR (3)	7	118	0.16 (-0.03 to 0.35)				
	Dairy (4)	1	95	-0.10 (-0.51 to 0.31)	+			
	Sweets (5)	10	156	0.02 (-0.18 to 0.22)	<b>+</b>			
	Mixed (6)	51	1427	0.04 (-0.05 to 0.12)				
Energy Balan		80	1668	0.03 (-0.04 to 0.09)	- <b>-</b> -	1 vs 2:-0.02 (-0.18 to 0.14)	66.44%	0.58
	Positive (2) Negative (3)	11 10	322 958	0.01 (-0.14 to 0.16) 0.08 (-0.07 to 0.23)	_ <b>_</b>	1 vs 3:0.06 (-0.11 to 0.22) 2 vs 3:-0.07 (-0.28 to 0.14)		
	Negative (5)	10	956	0.08 (-0.07 to 0.23)	+	2 vs 3:-0.07 (-0.28 (0 0.14)		
Comparator	Starch (1)	46	1353	0.09 (0.005 to 0.17)	<b></b>	See legend	64.38%	0.25
Form	Glucose (2)	25	573	0.02 (-0.07 to 0.10)	_ <b>+</b> -			
	Mixed (3) Fat (4)	14 9	552 170	-0.17 (-0.31 to -0.02) 0.09 (-0.09 to 0.26)				
	Lactose (5)	5	515	-0.01 (-0.20 to 0.19)				
	D-maltose (6)	3	10	0.02 (-0.28 to 0.32)	<b>_</b>			
	Galactose (7)	2	13	0.11 (-0.25 to 0.47)	<b>_</b>			
	Isomaltulose (8)	2	116	0.12 (-0.23 to 0.47)				
Fructose Form		48	829	0.01 (-0.07 to 0.09)		See legend	65.21%	0.17
	Sucrose (2)	46	1429	0.09 (0.01 to 0.17)	<b>⊢</b> ←			
	Fruit (3) HFCS (4)	12 1	697 16	-0.10 (-0.26 to 0.06) 0.15 (-0.23 to 0.53)				
Fructose Dos	e ≤ 10% E > 10% E	30 73	942 1985	-0.06 (-0.17 to 0.04) 0.06 (0.002 to 0.12)	-+-	0.12 (0.0006 to 0.04)	64.71%	0.05
	> 10% E	75	1965	0.06 (0.002 (0 0.12)				
Baseline Fast	ng ≤6.1 mmol/L	47	1291	0.07 (0.01 to 0.14)	<b></b>	-0.40 (-0.61 to -0.18)	65.25%	< 0.05
Blood Glucos	e >6.1 mmol/L	24	725	-0.32 (-0.52 to -0.12)	<b>_</b>			
Age	≤18	6	83	-0.04 (-0.23 to 0.16)		0.07 (-0.13 to 0.27)	67.31%	0.50
	>18	95	2865	0.03 (-0.02 to 0.09)	· · · · · · · · · · · · · · · · · · ·			
Study Design	Crossover	61	779	0.05 (-0.02 to 0.11)		-0.03 (-0.14 to 0.08)	65.72%	0.46
,	Parallel	40	2169	0.01 (-0.07 to 0.10)	<b>—</b>			
							/	
Follow-Up	<8 weeks ≥8 weeks	72 29	1256 1692	0.05 (-0.01 to 0.12) -0.02 (-0.12 to 0.08)		-0.07 (-0.19 to 0.04)	66.39%	0.15
	20 WEEKS		1092	-0.02 (-0.12 (0 0.08)				
Randomizatio		70	2432	-0.001 (-0.07 to 0.06)	+	-0.09 (-0.21 to 0.02)	66.32%	0.11
	No	31	516	0.09 (-0.004 to 0.19)	-			
Underlying	Otherwise Healthy (1)	33	1142	0.01 (-0.07 to 0.09)		See legend	67.15%	0.13
Health Status		31	728	-0.11 (-0.30 to 0.09)				
	Overweight/ Obese (3) MetS Criteria (4)	25 12	802 276	0.08 (-0.08 to 0.17) 0.04 (-0.11 to 0.19)				
	wiets criteria (4)	14	270	0.04 (-0.11 (0 0.19)		7		
					-0.6 -0.3 0 0.3 0	0.6		
					Favours Fructose- Favours Con			
					Containing Sugar			

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<sup>2</sup> 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).

				Mean difference	(95% CI) in fast	ting blood gl	ucose (mmol/L)	in addition trials	-	
Subgroup	Level	Trials	Ν	Within subgroups		6		Between subgroups	Residual I <sup>2</sup>	P-value
Total		35	985	0.03 (-0.12, 0.17)		<b>•</b> -				
Energy Balance	Positive (1)	23	500	0.05 (-0.07 to 0.17)		- <b> </b>	1	vs 2: -0.05 (-0.26 to 0.16)	72.96%	0.52
	Neutral (2)	9	358	0.002 (-0.17 to 0.18)		- <b>+</b> -		vs 3: 0.15 (-0.18 to 0.48)		
	Negative (3)	3	127	0.20 (-0.10 to 0.51)		<b>†</b> ◆──	2	vs 3: -0.20 (-0.56 to 0.15)		
Comparator	Diet alone (1)	25	647	0.03 (-0.08 to 0.13)		+		vs 2: 0.12 (-0.01 to 034)	75.25%	0.55
Form	Water (2)	7	252	0.14 (-0.05 to 0.33)				vs 3: 0.05 (-0.26 to 0.35)		
	Sweetener (3)	4	91	0.07 (-0.21 to 0.35)			2	vs 3: 0.07 (-0.27 to 0.41)		
Fructose Form	Fruit (1)	13	433	0.06 (-0.05 to 0.17)		-		See legend	67.55%	0.01
	Fructose (2) Sucrose (3)	9 9	104 273	0.17 (0.05 to 0.30) 0.08 (-0.06 to 0.21)						
	Honey (4)	3	131	-0.47 (-0.78 to -0.16)	<b>_</b>	-				
	HFCS (5)	2	75	0.09 (-0.13 to 0.31)		- <u> </u> +				
Fructose Dose	≤ 10% E	16	444	0.002 (-0.13 to 0.13)		<b>_</b>		0.09 (-0.08 to 0.26)	72.76%	0.28
Tructose Dose	> 10% E	20	572	0.09 (-0.02 to 0.20)		•-		0.05 (-0.08 (0 0.20)	72.70%	0.20
Baseline Fasting	≤5.10 mmol/L	17	532	0.11 (-0.01 to 0.24)		i.		-0.20 (-0.44 to -0.04)	74.27%	0.09
Glucose	>5.10 mmol/L	10	266	-0.09 (-0.30 to 0.11)		•		,		
Age	≤18	1	20	-0.86 (-1.59 to -0.13) 🗲	+	_∔		0.94 (0.21 to1.67)	70.66%	0.01
	>18	34	965	0.08 (0.004 to 015)		┣-				
Study Design	Parallel	18	675	0.06 (-0.07 to 0.19)		<b>-</b>		0.02 (-0.16 to 0.20)	74.91%	0.83
	Crossover	17	310	0.04 (-0.08 to 0.17)		- <b>†</b>				
Follow-Up	<8 weeks	18	375	0.02 (-0.10 to 0.15)				0.06 (-0.11 to 0.24)	71.27%	0.48
	≥8 weeks	17	610	0.08 (-0.04 to 0.21)		<b>+</b>				
Randomization	Yes	23	796	0.07 (-0.05 to 0.18)		<b>_</b>		0.04 (-0.15 to 0.22)	74.58%	0.70
	No	12	189	0.03 (-0.12 to 0.18)		- <b>-</b> -				
Underlying	Overweight/Obese (1)	15	580	0.11 (0.02 to 0.20)		i.		See legend	68.79%	0.004
Health Status	Otherwise Healthy (2)	12	209	0.03 (-0.08 to 0.14)		- <b> </b> -				
	Diabetes (3)	4	92	-0.91 (-1.44 to -0.38) —	<b></b>	i				
	MetS Criteria (4)	4	104	0.15 (-0.05 to 0.36)		+				
				-1.5	-0.75	0 0	.75 1.5			
				Favou	rs Fructose-	Favour	s Comparator			
					ning Sugar	ravour	5 comparator			
					5.0					

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<sup>2</sup> 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).

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2	Subgroup	Level	Trials	- N	Mean Within subgroups	difference (95% CI) in fasti	ing blood glucose (mm	nol/L) in substitution trials Between subgroups	Residual <i>i</i> <sup>2</sup>	P-value
3 4		LEVEI					L	Between subgroups		
5	Total Sequence Generation	Unclear Risk of Bias	101 69	2948 1336	0.03[-0.01,0.07]			URB Vs. HRB=0.05[-0.10,0.19]	67.00% 66.94%	0.13 0.80
6 7	sequence Generation	Low Risk of Bias High Risk of Bias	16 16	1249 363	0.02[-0.05,0.09] 0.07[-0.06,0.19] 0.02[-0.10,0.13]	-	-	URB Vs. LRB=-0.00[-0.14,0.13] HRB Vs. LRB= 0.05[-0.12,0.22]	66.94%	0.80
8 9	Allocation Concealment	Unclear Risk of Bias Low Risk of Bias High Risk of Bias	77 6 18	2287 239 422	0.01[-0.06,0.08] 0.07[-0.12,0.25] 0.07[-0.05,0.19]	-	► 	URB Vs. HRB= 0.06[-0.06,0.08] URB Vs. LRB=0.06[-0.14,0.25] HRB Vs. LRB=-0.00[-0.22,0.22]	67.83%	0.64
10 11 12	Blinding of Participants, Personnel, and Outcome Assessors	Unclear Risk of Bias Low Risk of Bias High Risk of Bias	41 58 2	1629 1227 92	-0.04[-0.13,0.04] 0.07[0.00,0.14] -0.32[-1.29,0.65]		•	URB Vs. HRB=0.28[-0.70,1.25] URB Vs. LRB=-0.12[-0.23,-0.00] HRB Vs. LRB=-0.39[-1.37,0.58]	66.20%	0.09
13 14	Incomplete Outcome Data	Unclear Risk of Bias Low Risk of Bias High Risk of Bias	60 35 6	1188 1522 238	0.04[-0.04,0.11] 0.03[-0.06,0.13] -0.07[-0.26,0.13]		•	URB Vs. HRB=-0.10[-0.31,0.11] URB Vs. LRB=-0.00[-0.12,0.12] HRB Vs. LRB= 0.10[-0.12,0.32]	67.26%	0.61
15 16 17	Selective Outcome Reporting	Unclear Risk of Bias Low Risk of Bias High Risk of Bias	48 53 0	841 2107 0	0.06[-0.03,0.15] 0.01[-0.06,0.08] *		•	URB Vs. HRB=* URB Vs. LRB=0.05[-0.07,0.16] HRB Vs. LRB=*	66.27%	0.40
17 18						-1.5 -0.5	0.5	1.5		
19						Favors Fructose- Containing Sugars	Favours Comparate			
20										
21	Supplementa	ry Figure 15.	Risk o	f bias	(using The	Cochrane Coll	aboration 1	Fool) subgroup anal	ysis for	
22 23	substitution t	rials investiga	ating tl	he eff	ect of isocal	oric exchange	e of fructos	e-containing food so	ources for	other
23 24	macronutrien	ts on fasting	blood	gluco	se. Point es	timates for ea	ach subgrou	ip level are the pool	ed effect	
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27				-		· · ·		available for respect	-	
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2	Subgroup	Level	Trials	N	Mean differer	nce (95% CI) in fasting blood glucose (m	mol/L) in addition trials	Residual I <sup>2</sup>	P-value
3					Within subgroups		Between subgroups		
4	Total		35	985	0.07[0.00,0.13]	<b></b>		72.00%	0.04
5 6 7	Sequence Generation	Unclear Risk of Bias Low Risk of Bias High Risk of Bias	17 7 11	498 347 140	0.11[-0.01,0.23] -0.05[-0.22,0.11] 0.09[-0.04,0.22]		URB Vs. HRB=-0.02[-0.19,0.16] URB Vs. LRB=-0.17[-0.37,0.04] HRB Vs. LRB=0.15[-0.06,0.36]	72.83%	0.24
8 9 10	Allocation Concealment	Unclear Risk of Bias Low Risk of Bias High Risk of Bias	22 1 12	733 92 160	0.05[-0.06,0.16] 0.09[-0.31,0.49] 0.09[-0.04,0.22]	 	URB Vs. HRB= 0.04[-0.13,0.21] URB Vs. LRB=0.04[-0.37,0.46] HRB Vs. LRB=0.00[-0.42,0.42]	73.00%	0.89
11 12	Blinding of Participants, Personnel, and Outcome Assessors	Unclear Risk of Bias Low Risk of Bias High Risk of Bias	22 13 0	529 456 0	0.04[-0.06,0.14] 0.11[-0.02,0.24] *	+	URB Vs. HRB=* URB Vs. LRB=-0.07[-0.10,0.23] HRB Vs. LRB=-*	72.20%	0.41
13 14 15	Incomplete Outcome Data	Unclear Risk of Blas Low Risk of Blas High Risk of Blas	17 16 2	391 452 142	0.10[ 0.01,0.21] 0.02[-0.11,0.15] 0.12[-0.21,0.45]		URB Vs. HRB= 0.03[ 0.32,0.38] URB Vs. LRB=-0.08[-0.25,0.09] HRB Vs. LRB=-0.10[-0.46,0.25]	73.61%	0.61
16 17	Selective Outcome Reporting	Unclear Risk of Bias Low Risk of Bias High Risk of Bias	15 20 0	354 631 0	0.04[-0.10,0.17] 0.09[-0.02,0.19] *		URB Vs. HRB=* URB Vs. LRB=-0.05[-0.21,0.12] HRB Vs. LRB=*	72.98%	0.57
18 19 20					-0.5 Favors fructose	-0.3 -0.1 0.1 0.3			

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<sup>2</sup> 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). 

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	ntervention, N	Control, N	weight	Mean Difference	[95% CI] in Fasting Blood Insulin, mmol/L
FRUITS Agebratt et al. 2016	15	15	2.2%	-1.74 [-14.39, 10.92]	
Conceição et al. 2003	26	9	0.3%	-15.28 [-60.28, 29.72]	
Kolehmainen et al. 2012	15	12	0.3%	-14.58 [-44.04, 14.87]	
Lehtonen et al.2010	28	22	4.3%	0.69 [-2.08, 3.46]	
Madero et al. 2011	65	66	1.6%	-16.19 [-32.98, 0.60]	
Rodriguez et al. 2005	7	8	1.7%	-1.39 [-17.21, 14.43]	
Subtotal (95% Cl)	156	132	10.6%	-0.81 [-4.58, 2.97]	
Heterogeneity: Tau <sup>2</sup> = 2.70; Ch				0.01 [ 1.00, 1.07]	
Test for overall effect: Z = 0.42		. "			
SUGARS-SWEETENED BEVERAGES					
Aeberli et al. 2013	9	9	1.1%	4.05 [-17.75, 25.85]	
Beck-Nielsen et al. 1980	15	15	1.1%	-27.78 [-48.87, -6.69]	
Heden et al. 2014 (AJCN-H)	20	20	1.8%	-4.15 [-19.30, 11.00]	<b>_</b> _
Heden et al. 2014 (AJCN-OW/O		20	0.8%	-5.90 [-31.17, 19.37]	
Heden et al. 2014 (JPAH)	7	7	0.3%	7.00 [-40.57, 54.57]	
Jin et al. 2014	9	12	0.0%	149.32 [-250.31, 548.95]	•
Johnston et al. 2013 (T1)	15	17	1.5%	14.58 [-2.77, 31.94]	
Johnston et al. 2013 (T2)	15	17	0.9%	-2.78 [-26.50, 20.94]	
Koivisto and Yki-Järvinen 1993		10	0.5%	0.00 [-34.84, 34.84]	
Maersk et al. 2012	10	12	2.5%	-21.04 [-31.97, -10.11]	_
Market al. 2012	35	38	2.1%	2.86 [-9.94, 15.66]	
Ngo Sock et al. 2010	11	11	3.4%	1.80 [-5.02, 8.62]	<u> </u>
Schwarz et al. 2015	8	8	2.0%	1.39 [-12.48, 15.26]	
Silbernagel et al. 2011	10	10	1.1%	-4.90 [-26.05, 16.25]	
Stanhope et al. 2011 (AJCN)	10	10	2.6%	9.73 [-0.83, 20.29]	
Stanhope et al. 2011 (JCEM)	32	16	3.2%	-4.04 [-11.79, 3.70]	
Swarbrick et al. 2008	7	7	2.5%	3.57 [-7.42, 14.57]	
Subtotal (95% Cl)	250	244	27.3%	-1.47 [-6.56, 3.62]	4
Heterogeneity: Tau <sup>2</sup> = 43.71; C					T
Test for overall effect: Z = 0.56	,	- 10 (1 -0.02	,, 1 = <b>40</b> ,		
	,				
LIQUID MEAL REPLACEMENTS					
Hendler et al. 1990	9	7	0.9%	23.70 [-0.50, 47.90]	
Johnson et al. 2015	24	27	0.4%	-17.00 [-53.90, 19.90]	
Rizkalla et al. 1986 (EXP1)	8	15	0.6%	-7.36 [-37.33, 22.61]	
Rizkalla et al. 1986 (EXP2)	6	12	0.9%	3.82 [-20.10, 27.74]	<b>_</b>
Turner et al. 1979 (HC)	4	4	0.3%	-19.47 [-66.59, 27.65]	
Turner et al. 1979 (LC DM)	2	2	0.0%	-20.30 [-183.01, 142.41]	+
Turner et al. 1979 (LC Non-DM)		4	0.8%	-19.48 [-45.25, 6.30]	
Subtotal (95% CI)	57	71	4.0%	-2.64 [-16.40, 11.13]	<b>•</b>
Heterogeneity: Tau <sup>2</sup> = 73.22; C		6 (P=0.26); I	² = 22%		
Test for overall effect: Z = 0.38	(P = 0.71)				
DAIRY PRODUCTS					
Lowndes et al. 2015	30	65	1.5%	26.59 [9.51, 43.68]	<del></del>
Subtotal (95% CI)	30	65	1.5%	26.59 [9.51, 43.68]	
Heterogeneity: Not applicable					-
Test for overall effect: Z = 1.98	(P = 0.002)				
BAKED GOODS, SWEETS AND DESSERTS					
Behall et al. 1980 (non-OC)	6	6	0.1%	-34.03 [-100.94, 32.88]	
Behall et al. 1980 (OC)	6	6	0.4%	37.50 [0.05, 74.95]	
Claesson et al. 2009	12	13	2.6%	9.00 [-1.29, 19.29]	
Hallfrisch et al. 1983 (HI)	12	12	0.7%	26.39 [-3.26, 56.04]	
Hallfrisch et al. 1983 (H)	12	12	0.7%	1.39 [-28.26, 31.04]	
Jones et al. 2014	25	25	1.7%	0.91 [-14.69, 16.50]	
Kelsay et al. 1974	8	8	0.5%	0.00 [-36.01, 36.01]	
Malerbi et al. 1966	16	16	1.6%	-15.60 [-31.88, 0.68]	
Reiser et al. 1989 (HI)	10	10	0.6%	10.00 [-22.48, 42.48]	
Reiser et al. 1989 (H)	10	10	0.6%	2.00 [-28.97, 32.97]	
	118	11 119			
Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 63.35; C			9.4% 1 <sup>2</sup> = 33%	3.97 [-5.26, 13.20]	₹
Test for overall effect: Z = 0.84		J (1 - 0.13)	, - 33%		
					-100 -50 0 50 10
					Favors Fructose- Favors Compa
					Containing Sugar

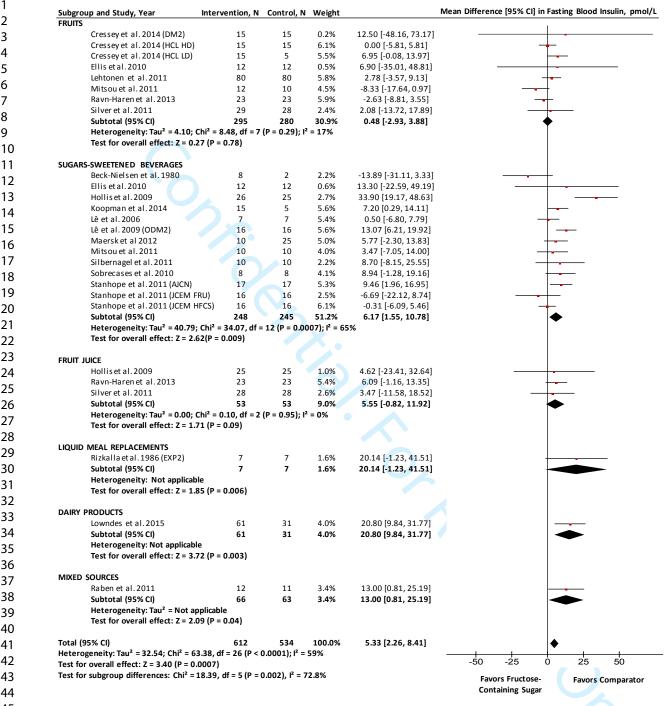
**Supplementary Figure 17.** Forest plot for substitution trials investigating the effect of isocaloric exchange of fructose-containing food sources for other macronutrients on fasting blood insulin (Continues next page).

1	MIXED SOURCES					
2	Abraira et al. 1988	9	9	0.1%	13.89 [-82.36, 110.14]	
3	Bantle et al. 2000	24	24	3.2%	-4.92 [-12.84, 3.00]	
	Black et al. 2006	13	13	1.4%	6.95 [-10.91, 24.80]	
4	Brunner et al. 2012	49	52	1.1%	12.15 [-9.03, 33.34]	
5	Brymora et al.2012	28	28	2.2%	10.70 [-2.00, 23.40]	
6	Brynes et al. 2003	17	17	0.9%	13.25 [-11.24, 37.74]	
7	Cooper et al. 1988	17	17	1.0%	-5.56 [-28.46, 17.35]	
	Coulston et al. 1985	11	11	2.9%	-4.97 [-13.76, 3.82]	
8	Dunnigan et al. 1970	9	9	2.0%	6.95 [-6.67, 20.56]	+
9	Emanuele et al. 1986	5	5	0.4%	49.33 [9.59, 89.07]	· · · · · · · · · · · · · · · · · · ·
10	Grigoresco et al. 1988	8	8	0.1%	-2.08 [-91.53, 87.36]	
	Hendler et al. 1986	6	6	0.9%	6.95 [-16.63, 30.52]	
11	Jellish et al. 1984	18	8	0.3%	25.43 [-22.18, 73.05]	
12	Koh et al. 1988 (IGT) Koh et al. 1988 (NGT)	9 9	9 9	0.5% 0.5%	-52.23 [-86.47, -17.99]	
13	Lewis et al. 2013	9 13	9 13	0.5%	-83.36 [-117.60, -49.12] 28.47 [2.86, 54.09]	
	Liu et al. 1983	5	5	0.8%	11.15 [-44.92, 67.21]	
14	Maki et al. 2015	34	34	2.4%	12.85 [1.33, 24.37]	<u> </u>
15	Malerbi et al. 1966	16	34 16	2.4 <i>%</i> 4.4%	0.70 [-0.47, 1.87]	
16	Paineau et al. 2008	297	298	2.1%	-3.06 [-15.90, 9.79]	
	Pinheiro et al. 2007 (G1)	5	5	0.4%	43.55 [6.02, 81.07]	
17	Pinheiro et al. 2007 (G2)	5	5	0.8%	31.53 [5.72, 57.34]	
18	Reiser et al. 1986 (W)	9	9	1.9%	-6.25 [-20.66, 8.16]	
19	Reiser et al. 1986 (M)	10	10	1.2%	-8.33 [-28.93, 12.26]	
	Sunehag et al. 2002 (P1-AD)	12	12	2.6%	8.33 [-1.94, 18.61]	· · · · · · · · · · · · · · · · · · ·
20	Sunehag et al. 2002 (P1-PP)	12	12	3.4%	11.81 [5.00, 18.61]	<b>-</b>
21	Sunehag et al. 2002 P2	12	12	2.0%	-2.08 [-15.70, 11.53]	
22	Sunehag et al. 2008	6	6	0.7%	-10.42 [-39.71, 18.87]	
	Szanto et al. 1969	19	19	0.9%	41.67 [18.10, 65.24]	
23	Van Meijl et al. 2011	35	35 🤇	3.2%	3.47 [-4.03, 10.98]	
24	Volp et al. 2008 (G1)	6	6 🧹	0.4%	37.88 [-1.61, 77.38]	
25	Volp et al. 2008 (G2)	6	6	0.1%	30.99 [-62.61, 124.60]	
	Vrolix et al. 2010	15	15	1.4%	-10.42 [-29.01, 8.17]	
26	Yudkin et al. 1972	11	11	0.6%	34.73 [4.34, 65.11]	
27	Subtotal (95% CI)	974	971	47.1%	4.71 [0.25, 9.18]	◆
28	Heterogeneity: Tau <sup>2</sup> = 72.40; Chi	-	f = 33(P < 0.00	0001); l² =	= 68%	
	Test for overall effect: Z = 2.07 (F	' = 0.04)				
29	T + 1 (0.50/ 01)			400.00/		
30	Total (95% CI)	1371	1354	100.0%	1.72 [-0.84, 4.29]	•
31	Heterogeneity: Tau <sup>2</sup> = 37.03; Chi <sup>2</sup> = 167.8	1, af = 74 (P <	< 0.00001); [*	= 56%		-100 -50 0 50 100
	Test for overall effect: Z = 1.32 (P = 0.19) Test for subgroup differences: Chi <sup>2</sup> = 8.66	df - 5 (D - 0	12) 12 - 12 3	0/		Favors Fructose- Favors Comparator
32	rest for subgroup unterences. Chi" = 8.00	, ui – 5 (F = 0	.12],1 - 42.3	/0		Containing Sugar
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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  $\leq$  50% represent moderate heterogeneity,  $\geq$  50 % representing substantial heterogeneity and  $\geq$  75%, considerable heterogeneity. 

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45 Supplementary Figure 18. Forest plot for addition trials investigating the effect of adding excess calories to 46 47 the diet in the form of fructose-containing food sources on fasting blood insulin. AJCN = American Journal of 48 Clinical Nutrition; DM2= type 2 diabetes mellitus; EXP2= experiment 2; FRU=fructose; HCL= 49 hypercholesterolemic; HD= high dose; HFCS= high fructose corn syrup; JCEM= Journal of Clinical 50 Endocrinology and Metabolism; LD= low dose; N= number of participants; ODM2= offspring of people with 51 type 2 diabetes. Pooled effect estimates for each subgroup and overall effect are represented by the 52 53 diamonds. Data are expressed as weighted mean differences with 95% confidence intervals (CIs), using the 54 generic inverse-variance method with random effects models. Paired analyses were applied to all crossover 55 trials. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p < 0.10 and 56 quantified by  $I^2$ , levels  $\leq$  50% represent moderate heterogeneity,  $\geq$  50% representing substantial 57 heterogeneity and  $\geq$  75%, considerable heterogeneity. 58

Mean Difference [95% CI] in Fasting Blood insulin, pmol/L Subgroup and Study, Year Intervention, N Control, N Weight SUGARS-SWEETENED BEVERAGES Campos et al. 2015 (G1) 6 6 39.4% 30.56 [-9.01.70.13] Campos et al. 2015 (G2) 7 8 51.0% -34.03 [-68.79, 0.73] Subtotal (95% CI) 13 90.4% -5.89 [-32.01, 20.22] 14 Heterogeneity: Chi<sup>2</sup> = 5.78, df = 1 (P = 0.02); l<sup>2</sup> = 83% Test for overall effect: Z = 0.44 (P = 0.66) MIXED SOURCES 9.6% 76.39 [-3.75, 156.54] Friedman et al. 1970 6 6 Subtotal (95% CI) 6 9.6% 76.39 [-3.75, 156.54] 6 10 Heterogeneity: Not Applicable 0.25 -0.5 -0.25 0.5 Test for overall effect: Z = 1.87 (P = 0.06) 11 **Favors Comparator** Favors Fructose-Total (95% CI) 100.0% 2.00 [-22.83, 26.83] 12 19 20 **Containing Sugar** Heterogeneity: Chi<sup>2</sup> = 9.44, df = 2 (P =0.009); l<sup>2</sup> = 79% 13 Test for overall effect: Z = 0.16 (P = 0.87) 14

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Test for subgroup differences: 3.66, df = 1 (P=0.06),  $I^2 = 72.7\%$ 

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 < nete. 0.10 and quantified by  $l^2$ , levels  $\leq$  50% represent moderate heterogeneity,  $\geq$  50% representing substantial heterogeneity and  $\geq$  75%, considerable heterogeneity.

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Subgroup and Study, Year	Intervention, N	Control, N	Weight	Mean Dif	ference [95%	CI] in Fas	ting Blo	od Insulin	, pmol/L
MIXED SOURCES									
Markey et al. 2015	22	28	71.9%	1.10 [-3.85, 6.05]					
Raben et al.2000 (C)	8	8	5.2%	17.00 [-1.45, 35.45]			-		
Raben et al. 2000 (PO)	10	10	4.6%	0.50 [-19.17, 20.17]			<u>-</u>		
Saris et al. 2000	76	160	18.4%	9.63 [-0.17, 19.42]				_	
Subtotal (95% CI)	116	206	100.0%	3.46 [-0.73, 7.66]			$\bullet$		
Heterogeneity: Chi <sup>2</sup> = 4.55,		= 34%							
Test for overall effect: Z = 1	62 (P = 0.11)								
		200	100.0%						
Total (95% Cl) Heterogeneity: Chi <sup>2</sup> = 4.55, df = 3 (P	116 -0 21): 1 <sup>2</sup> - 34%	206	100.0%	3.46 [-0.73, 7.66]					
Test for overall effect: $Z = 1.62$ (P = 0					-0.5	-0.25	ò	0.25	0.5
Test for subgroup differences: Not a	•				Favors F	ructose-			
						ng Sugar		Favors C	Comparator
						00			
						~ ·			
Supplementary Figure 20.	Forest plot fo	or ad libit	tum trial	s investigating the	effect of	freely	replac	cing cal	ories
from fructose-containing f	ood sources v	with othe	er dietar	v sources on fastin	g blood ir	nsulin.	C=con	trol: N	=
•				•	0			-	
number of participants; PC	= post-obese	e. Pooled	enecte	sumates for each	subgroup	and ov	erall	enecta	ire
represented by the diamor	nds. Data are	expresse	ed as we	ighted mean differ	ences wit	th 95%	confi	dence	
intervals (CIs), using the ge		•		•					woro
intervals (CIS), using the ge	ment inverse	-variatice	emetho	u with random ene	ects mode	eis. Pai	reu a	naiyses	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  $\leq$  50% represent moderate heterogeneity,  $\geq$  50 % representing substantial heterogeneity and  $\geq$  75%, considerable heterogeneity. 

					Mean difference (95% CI) in fasting blood insulin (pmol/L) in addition trials								
	Subgroup	Level	Trials	N	Within subgroups						Between subgroups	Residual I <sup>2</sup>	P-value
	Total		27	760	5.33 (2.26 to 8.41)			-					
	Energy Balance	Positive (1)	17	318	6.25 (1.50 to 10.99)			_	i.		vs 2: -2.60 (-10.48 to 5.29)	60.42%	0.77
		Neutral (2)	7	315	3.65 (-2.65 to 9.95)				+		vs 3: 0.81 (-13.31 to 14.94)		
		Negative (3)	3	127	7.06 (-6.24 to 20.37)			_	֥	▶ 2	vs 3: -3.41 (-18.13to 11.31)		
	Comparator	Diet alone (1)	21	549	6.04 (2.23 to 9.85)			_	<u>i</u>	1	vs 2: -6.85 (-15.60 to 1.89)	56.45%	0.12
	Form	Water (2)	5	176	-0.81 (-8.69 to 7.06)			-			L vs 3: 7.27 (-5.36 to 19.89)		
		Sweetener (3)	2	45	13.31 (1.27 to 25.35)				1	<b></b> 2	vs 3: -14.12 (-28.50 to 0.26)		
<b>、</b>	Fructose Form	Fruit (1)	11	365	1.52 (-4.21 to 7.26)		_	_ <b>_</b>			See legend	55.38%	0.24
)		Fructose (2)	9	159	7.23 (0.79 to 13.67)				+ •	_			
		Sucrose (3)	7	223	10.42 (3.31 to 17.53)			-	+ +				
		HFCS (4)	2	75	8.06 (-4.21 to 20.32)		_	-	<u>.</u>				
2	Fructose Dose	≤ 10% E	12	386	1.12 (-3.95 to 6.18)		-	_ <b>_</b> _	<u>i                                    </u>		6.59 (0.19 to 12.99)	49.75%	0.04
3		> 10% E	17	436	7.70 (3.79 to 11.61)			-	++	-	. ,		
ł	Baseline Fasting	≤53.5 pmol/L	11	146	3.15 (-2.52 to 8.82)				<u> </u>		4.45 (-4.49 to 13.90)	64.92%	0.31
5	Insulin	>53.5 pmol/L	10	353	7.60 (3.79 to 11.6)				<u>.</u>				
5	Age	≤18	0	0	-				1		-	-	-
		>18	27	760	5.33 (2.26 to 8.41)			-	÷				
7	Study Design	Crossover	15	285	4.12 (-0.43 to 8.67)				į		3.21 (-3.97 to 10.39)	58.92%	0.37
3		Parallel	12	475	7.33 (1.77 to 12.89)				<b>—</b>	_			
9	Follow-Up	<8 weeks	15	282	3.80 (-1.02 to 8.61)						3.45 (-3.59 to 10.49)	59.49%	0.32
)		≥8 weeks	12	478	7.25 (2.11 to 12.38)				+	-			
	Randomization	Yes	16	547	6.85 (2.27 to 11.42)			_	<u>.</u>		3.50 (-3.62 to 10.63)	58.60%	0.32
		No	11	213	3.34 (-2.12 to 8.81)			++	<u>+</u>				
2	Underlying	Overweight/Obese (1)	14	566	8.32 (2.95 to 13.70)			_	<u>;</u>	_	See legend	61.34%	0.52
3	Health Status	Otherwise Healthy (2)	10	149	2.98 (-2.43 to 8.39)			<b>_</b>	<u> </u>		0		
		MetS Criteria (3)	2	30	3.34 (-7.55 to 14.24)				<u> </u>				
1		Diabetes (4)	1	15	12.50 (-53.10 to 78.10)	•			÷	••			
5						-15	-7.5	0	7.5	15			
5					_								
7						vours Fr ntaining	uctose-	Fav	ours Co	mparat	or		
3					col		Sugar						

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**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<sup>2</sup> 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).

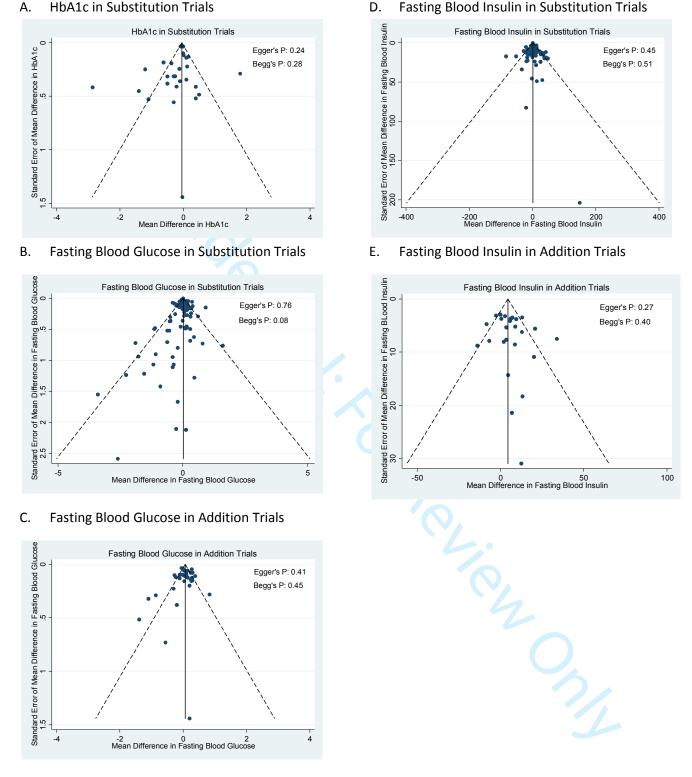
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2					Mean differe					
3	Subgroup	Level	Trials	N	Within subgroups			Between subgroups	Residual I <sup>2</sup>	P-value
4	Total		75	2194	1.89 (-0.69 to 4.48)		++-			
5	Energy Balance	Neutral (1)	56	1106	3.29 (-1.22 to 7.80)			1 vs 2: -4.48 (-15.12 to 6.17)	57.38%	0.54
6		Positive (2)	10	199	-1.19 (-10.82 to 8.45	,	•	1 vs 3: -5.13 (-17.46 to 7.20)		
7		Negative (3)	9	889	-1.84 (-13.31 to 9.63	)		2 vs 3: 0.65 (-14.33 to 15.64)		
	Comparator	Starch (1)	30	1119	2.01 (-3.84 to 7.85)		-++	See legend	55.19%	0.21
8	Form	Glucose (2)	21	492	-3.31 (-10.17 to 3.55		► <del> </del>			
9		Fat (3) Mixed (4)	8 7	140 163	17.97 (5.75 to 30.18 8.73 (-2.30 to 19.76					
		Lactose (5)	3	91	-1.46 (-15.22 to 12.30					
10		D-maltose (6)	3	10	-19.50 (-48.87 to 9.8)					
11		Galactose (7)	2	27	-5.73 (-34.85 to 23.40					
		Isomaltulose (8)	2	116	0.12 (-21.31 to 21.54					
12		Protein (9)	1	6	6.95 (-26.40 to 40.29	) 🖣				
13	Fructose Form	Fructose (1)	35	636	-1.47 (-7.00 to 4.06)		→Li	See legend	56.74%	0.13
14		Sucrose (2)	35	1222	6.73 (1.32 to 12.13)		<u>+</u> → −	0		
		Fruit (3)	5	268	-6.34 (-19.67 to 6.99					
15		HFCS (4)	1	32	-0.12 (-22.00 to 21.7	5)				
16	Fructose Dose	≤ 10% E	20	481	2.01 (-5.84 to 9.87)	_		0.31 (-8.64 to 9.26)	56.15%	0.89
17		> 10% E	57	1686	2.32 (-1.96 to 6.61)			0.51 ( 0.04 (0 5.20)	50.1570	0.05
18	Baseline Fasting	≤89.1 pmol/L	23	600	0.22 (-5.35 to 5.80)	_		4.75 (-4.67 to 14.18)	53.28%	0.34
	Insulin	>89.1 pmol/L	23	534	4.98 (-2.62 to 12.58		_ <u>_</u>	4.75 (-4.07 (0 14.18)	55.26%	0.54
19										
20	Age	≤18 >18	6 69	83 2111	3.53 (-9.16 to 16.23)			-1.70 (-15.02 to 11.61)	55.17%	0.82
21		>10	69	2111	1.83 (-2.18 to 5.84)		li			
	Study Design	Crossover	46	595	2.36 (-2.51 to 7.22)		-+ <u>+</u>	-0.97 (8.84 to 6.91)	56.97%	0.85
22		Parallel	29	1599	1.39 (-4.80 to 7.58)	-	- <u> </u>			
23	Follow-Up	<8 weeks	59	1058	2.84 (-1.54 to 7.23)			-3.48 (-12.32 to 5.37)	56.96%	0.49
24		≥8 weeks	16	1136	-0.63 (-8.32 to 7.05)					
25	Randomization	Yes	49	1865	2.54 (-2.24 to 7.32)			1.54 (-6.46 to 9.54)	56.79%	0.68
26		No	26	329	1.00 (-5.41 to 7.42)	-				
	Underlying	Otherwise Healthy (1)	28	1016	1.17 (-4.92 to 7.27)	_		See legend	58.03%	0.92
27	Health Status	Overweight/Obese (2)	25	752	3.07 (-7.47 to 13.61	)				
28		Diabetes (3)	12	264	3.28 (-3.50 to 10.05					
29		MetS Criteria (4)	11	131	0.07 (-11.49 to 11.63	)	- <u>+</u> ;			
						-25 -12.5	0 12.5 25			
30						-25 -12.5 Favours Fructose-		tor		
31						Containing Sugar	Favours Compara			
32						5.5				

Supplementary Figure 22. Subgroup analyses for substitution trials investigating the effect of isocaloric 33 34 exchange of fructose-containing food sources for other macronutrients on fasting blood insulin. E= energy; 35 HFCS= high fructose corn syrup; MetS= metabolic syndrome; N= number of participants.Pooled effect 36 estimates for each subgroup are represented by the diamonds. The dashed line represents the pooled 37 effect estimate for the overall analysis. The residual  $I^2$  value represents unexplained heterogeneity for each 38 subgroup. Pairwise between-subgroup mean differences (95% CI) for comparator form are as follows: 1 vs 39 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 40 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: 41 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 42 43 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:-44 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 45 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: 46 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 47 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: -48 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 49 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 50 9: -6.83 (-46.46 to 32.80). Pairwise between-subgroup mean differences (95% CI) for fructose form are as 51 52 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: -53 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-54 subgroup mean differences (95% CI) for underlying disease status are as follows: 1 vs 2: 2.10 (-7.01 to 55 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: -56 3.21 (-16.61 to 10.19); 3 vs 4: -3.00 (-19.01 to 13.00). 57



**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.