

Effect of Fructose on Body Weight in Controlled Feeding Trials

A Systematic Review and Meta-analysis

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Background: The contribution of fructose consumption in Western diets to overweight and obesity in populations remains uncertain.

Purpose: To review the effects of fructose on body weight in controlled feeding trials.

Data Sources: MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through 18 November 2011).

Study Selection: At least 3 reviewers identified controlled feeding trials lasting 7 or more days that compared the effect on body weight of free fructose and nonfructose carbohydrate in diets providing similar calories (isocaloric trials) or of diets supplemented with free fructose to provide excess energy and usual or control diets (hypercaloric trials). Trials evaluating high-fructose corn syrup (42% to 55% free fructose) were excluded.

Data Extraction: The reviewers independently reviewed and extracted relevant data; disagreements were reconciled by consensus. The Heyland Methodological Quality Score was used to assess study quality.

Data Synthesis: Thirty-one isocaloric trials (637 participants) and 10 hypercaloric trials (119 participants) were included; studies tended to be small (<15 participants), short (<12 weeks), and of

low quality. Fructose had no overall effect on body weight in isocaloric trials (mean difference, -0.14 kg [95% CI, -0.37 to 0.10 kg] for fructose compared with nonfructose carbohydrate). High doses of fructose in hypercaloric trials ($+104$ to 250 g/d, $+18\%$ to 97% of total daily energy intake) lead to significant increases in weight (mean difference, 0.53 kg [CI, 0.26 to 0.79 kg] with fructose).

Limitations: Most trials had methodological limitations and were of poor quality. The weight-increasing effect of fructose in hypercaloric trials may have been attributable to excess energy rather than fructose itself.

Conclusion: Fructose does not seem to cause weight gain when it is substituted for other carbohydrates in diets providing similar calories. Free fructose at high doses that provided excess calories modestly increased body weight, an effect that may be due to the extra calories rather than the fructose.

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Western health care systems are threatened by rapidly increasing rates of overweight, obesity, and type 2 diabetes (1). The possible contribution of increasing fructose in Western diets to the epidemic of overweight, obesity, and diabetes and, by association, to the burden of cardiometabolic disease in the United States (2, 3), has attracted much attention, especially in relation to children (2, 4). Fructose may be more lipogenic than other carbohydrates, an observation first made early in the past century (5), and animal studies demonstrate that a diet in which fructose comprises 60% of total energy can induce obesity, insulin resistance, hypertriglyceridemia, hypertension, and hyperuricemia (6, 7).

Whether fructose in Western diets induces the same phenotype in humans is unclear. Ecologic analyses have linked high-fructose corn syrup (42% to 55% fructose) with the obesity epidemic in the United States over the past 30 years (8, 9). Evidence from observational studies and controlled feeding trials also suggest a positive association between the consumption of sugar-sweetened beverages, in which high-fructose corn syrup is the main sweetener, and increased energy consumption and weight gain in both pediatric and adult populations (10–12), but not all meta-analyses have supported this conclusion (13, 14).

Several recent reviews and commentaries have concluded that fructose increases body weight (6, 15, 16), but

others have concluded that the evidence for this effect is particular to hypercaloric trials, in which a diet supplemented with excess energy from high doses of fructose is compared with the same diet without the high fructose doses (17, 18). Meta-analyses of trials in which a diet with high doses of fructose is compared with a diet with other sources of carbohydrate in isocaloric substitution have reported no effect on body weight (19).

Recent guidelines reflect these uncertainties. A 2009 American Heart Association statement recommended an upper limit of intake for added sugars equal to one half of the discretionary calorie allowance (≤ 100 kcal/d for women and ≤ 150 kcal/d for men) to achieve and maintain a healthy body weight (20). The 2010 U.S. Department of

See also:

Print

Editors' Notes 292

Web-Only

Appendix Tables

Appendix Figures

CME quiz (preview on page I-26)

Conversion of graphics into slides

Context

Many people suspect that increasing levels of dietary fructose contribute to obesity in developed countries.

Contribution

In this review of feeding trials, pure fructose had no effect on weight compared with diets that provided the same calories using nonfructose carbohydrate. Fructose increased weight in diets when the fructose added extra calories compared with the control diets.

Caution

Most trials followed small numbers of healthy participants for only a short period.

Implication

In small feeding trials, fructose had no clear weight-increasing effect. Weight gain seems to be due to the extra calories that are characteristic of high-fructose diets and not to fructose itself.

—The Editors

Agriculture dietary guidelines were more conservative, recommending a reduction in sugars without set targets and stating that “. . . under isocaloric controlled conditions, added sugars, including sugar-sweetened beverages, are no more likely to cause weight gain than any other source of energy” (21). Although the possible role of fructose was acknowledged, neither the guidelines nor the earlier Dietary Reference Intakes (22) recommend an upper limit for fructose intake.

To provide better evidence-based guidance on the role of fructose in overweight and obesity, we performed a systematic review and meta-analysis of controlled feeding trials investigating the effect of fructose under both isocaloric and hypercaloric conditions on body weight.

METHODS

We followed the Cochrane Handbook for Systematic Reviews of Interventions to plan and conduct this meta-analysis (23) and report our findings according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (24, 25). The review protocol is available at ClinicalTrials.gov (registration number: NCT01363791).

Study Selection

We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library through 18 November 2011. **Appendix Table 1** (available at www.annals.org) shows the search strategy. The search did not have language restrictions. Manual searches of the reference lists of all selected articles and review articles supplemented the electronic search.

We included controlled feeding trials investigating the effect of free (unbound, monosaccharide) fructose com-

pared with other sources of carbohydrate in the diet or diets supplemented with free fructose compared with the same diet alone on body weight in humans. Comparisons were considered isocaloric when fructose in the fructose group was compared with nonfructose carbohydrate providing the same amount of energy in the control group and hypercaloric when fructose in the fructose group was added to the usual or control diet so that the fructose provided excess energy relative to the diet alone. To isolate the effects of fructose, we did not include trials in which fructose was administered exclusively as sucrose (bound fructose) or high-fructose corn syrup (42% to 55% of free fructose), except where these sweeteners were the comparator. We also excluded trials with less than 7 days of follow-up (diet duration) and those that administered intravenous fructose, lacked a control group, or did not provide body weight data. In cases where multiple publications existed for the same study, the article with the most information was included.

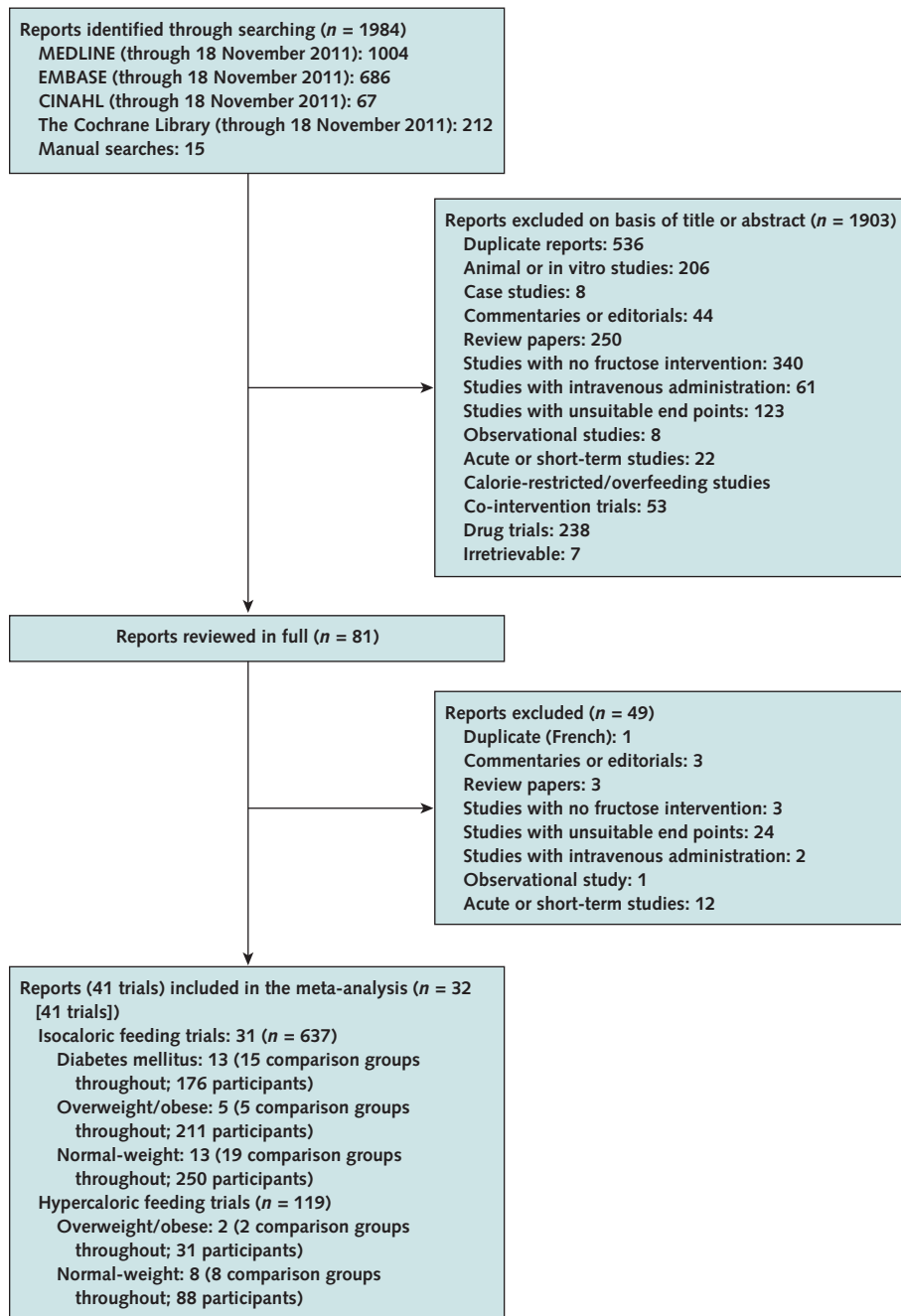
Data Extraction

At least 3 reviewers independently reviewed and extracted relevant data from each report. Non-English-language articles were translated by Dr. Sievenpiper (French) and Ms. Chiavaroli (German). Extracted data included information on study setting, design, randomization, blinding, sample size, and participant characteristics; fructose form, dose, and comparator; follow-up; macro-nutrient profile of the background diet; and funding. The quality of each study was assessed by using the Heyland Methodological Quality Score (MQS) (26). Trials receiving scores of 8 or more were considered to be of higher quality. Disagreements were reconciled by consensus.

Data on mean (SD) body weight were extracted as the primary end point. We used available statistical data to calculate change-from-baseline differences within and between treatments, and end differences between treatments, in trials that did not report either outcome. We calculated missing SDs from available statistics by using standard formulae (23). If these data were not reported, preventing calculation, we imputed SDs by using a pooled correlation coefficient derived from a meta-analysis of correlation coefficients from those trials reporting sufficient data. We derived correlation coefficients for individual trials according to a standard formula (23, 27). We then imputed these values into the meta-analysis as transformed z scores (\pm SEs), from which we derived the pooled correlation coefficient. If SD coefficients still could not be imputed, then we derived the missing SD from the pooled SD imputed for the other trials (28). **Appendix Table 2** (available at www.annals.org) shows how missing data were handled. Selected authors were contacted to request additional information.

Statistical Analysis

We analyzed data by using Review Manager, version 5.1.4 (The Nordic Cochrane Centre, The Cochrane Col-

Figure 1. Summary of evidence search and selection.

laboration, Copenhagen, Denmark), for primary analyses and Stata, version 12 (StataCorp, College Station, Texas), for subgroup analyses. We conducted separate pooled analyses for isocaloric and hypercaloric fructose feeding trials by using the generic inverse variance method, using random-effects models with data expressed as mean differences (MDs) and 95% CIs for the primary end point of body weight. Random-effects models were preferred to

fixed-effects models even where there was no evidence of between-study heterogeneity because the former yield more conservative summary effect estimates in the presence of residual heterogeneity.

We stratified analyses within categories of diabetes, overweight/obese, and normal weight on the basis of trial entry criteria. In the absence of specific overweight/obese entry criteria, we assumed that trials were conducted in

Table. Characteristics of Isocaloric and Hypercaloric Feeding Trials Investigating the Effect of Fructose on Body Weight

Study, Year (Reference)	Participants	Mean Age (SD or Range), y	Mean Body Weight or BMI (SD)*	Setting	Design†	Feeding Control‡
Isocaloric trials						
Diabetes						
Pelkonen et al, 1972 (30)	10 DM1 (5 M, 5 W)	25.5 (19–70)	60.1 kg (6.7)	IP, Finland	C	Met
McAteer et al, 1987 (31)	10 DM2	64.4 (54–71)	59.3 kg (5.4)	OP, Northern Ireland	C	Supp
Osei et al, 1987 (32)	18 DM2 (15 M, 3 W)	57 (9)	Starch, 82.5 kg (12.0); fructose, 82.8 kg (15.6)	OP, USA	P	Supp
Grigosco et al, 1988 (33)	8 DM2 (5 M, 3 W)	40 (20)	74.3 kg (12.4)	OP, France	C	Supp
Thorburn et al, 1989 (34)	8 DM2 (4 M, 4 W)	55 (10)	95.2 kg (23.7)	IP, USA	P	Met
Anderson et al, 1989 (35)	14 DM2 (14 M, 0 W)	60 (15)	81.4 kg (13.6)	IP/OP, USA	C	Supp
Osei and Bossetti, 1989 (36)	13 DM2 (5 M, 8 W)	54 (11)	88.3 kg (20.9)	OP, USA	C	Supp
Thorburn et al, 1990 (37)	6 DM2 (4 M, 2 W)	54 (4)	95.2 kg (23.7)	IP, USA	C	Met
Blayo et al, 1990 (38)						
Starch	6 DM1, 2 DM2	43 (11)	22 kg/m ² (1.6)	OP, France	P	Supp
Sucrose	3 DM1, 3 DM2	51 (12)	23 kg/m ² (2.3)			
Fructose	5 DM1, 1 DM2	48 (17)	23 kg/m ² (2.0)			
Bantle et al, 1992 (39)	12 DM2 (4 M, 8 W)	DM2, 62 (40–72)	80.7 kg (21.2)	OP, USA	C	Met
	6 DM1 (3 M, 3 W)	DM1, 23 (18–34)				
Koivisto and Yki-Järvinen, 1993 (40)	10 DM2 (4 M, 6 W)	61 (10)	81.8 kg (15.8)	IP, Finland	C	Met
Malerbi et al, 1996 (41)	16 DM2 (7 M, 9 W)	54.2 (34–66)	65.7 kg (8.1)	OP, Brazil	C	Supp
Vaisman et al, 2006 (42)	25 DM2	65.4 (10.7)	Starch, 83.4 kg (17.6); fructose, 82.9 kg (10.9)	OP, Israel	P	Supp
Overweight/obese						
Rizkalla et al, 1986 (43) (T1)§§	23	22.2	Glucose, 75.7 kg (9.1); fructose, 69.8 kg (15)	OP, France	P	Met
Rizkalla et al, 1986 (43) (T2)§§	18	22.2	Glucose, 70.4 kg (13); fructose, 75.7 kg (9.1)	OP, France	P	Met
Swarbrick et al, 2008 (44)	7 (0 M, 7 W)	50–72	75.7 kg (24.3)	IP, USA	C	Met
Stanhope et al, 2009 (45)¶¶¶¶	32 (16 M, 16 W)	53	Glucose, 85.9 kg (10.5); fructose, 85.7 kg (10.1)	IP/OP, USA	P	Met/Supp
Madero et al, 2011 (46)§§	131 (29 M, 102 W)	38.8 (8.8)	Starch, 82.7 kg (13.3); fructose, 79.1 kg (13.4)	OP, Mexico	P	DA
Normal weight						
Kaufmann et al, 1966 (47)	5 HTG (3 M, 2 W)*** 4 N (3 M, 1 W)	42.8 (14.2)	66.4 kg (6.4)	IP/OP, Israel	C	Met
Förster and Heller, 1973 (48)	12 N (8 M, 4 W)	20–26	69.1 kg (12.4)	IP, Germany	P/C	Met
Turner et al, 1979 (49) (LC)	6 HTG (6 M, 0 W)***	45.7 (7.7)	80.5 kg (10.2)	IP, USA	C	Met
Turner et al, 1979 (49) (HC)	5 HTG (5 M, 0 W)***	46.8 (8.0)	82.6 kg (9.9)	IP, USA	C	Met
Beck-Nielsen et al, 1980 (50)¶¶	15	21–35	Glucose, 60.9 kg (7.4); fructose, 61.5 kg (9.9)	OP, Denmark	P	Supp
Swanson et al, 1992 (51)	14 (7 M, 7 W)	34 (19–60)	68.5 kg (11.2)	OP, Denmark	C	Met
Bantle et al, 2000 (52)	24 (12 M, 12 W)	M, 42.5; F, 40	74.1 kg (9.8)	OP, USA	C	Met
Ngo Sock et al, 2010 (53)¶¶	11 (11 M, 0 W)	24.6 (2)	71.9 kg (5.3)	OP, Switzerland	C	Met
Aeberli et al, 2011 (54) (LD)	29 (29 M, 0 W)	26.3 (6.6)	73.7 kg (8.8)	OP, Switzerland	C	Supp
Aeberli et al, 2011 (54) (HD)	29 (29 M, 0 W)	26.3 (6.6)	73.7 kg (8.8)	OP, Switzerland	C	Supp
Brymora et al, 2011 (55)	28 CKD (17 M, 11 W)	59 (15)	85.8 kg (11.5)	OP, Poland	C	DA
Silbernagel et al, 2011 (56)¶¶	20 (12 M, 8 W)	30.5	Glucose, 80.3 kg (9.1); fructose, 80.7 kg (7.5)	OP, Germany	P	Supp
Stanhope et al, 2011 (57)¶¶¶¶	48 (27 M, 21 W)	28.0 (27.2)	Glucose, 76.5 kg (14.0); HFCS, 74.3 kg (14.9); fructose, 76.8 kg (10.4)	IP/OP, USA	P	Met/Supp
Hypercaloric trials						
Overweight/obese						
Rizkalla et al, 1986 (58)§§	14	22.2	Diet alone, 75.8 kg (13.7); diet + fructose, 73.3 kg (7.7)	OP, France	P	Met
Stanhope et al, 2009 (45)¶¶¶¶	17	53	85.7 kg (10.7)	IP/OP, USA	C	Met/Supp
Normal weight						
Beck-Nielsen et al, 1980 (50)¶¶	8	21–35	Diet alone, 57 kg; diet + fructose, 61.5 kg (9.9)	OP, Denmark	C	Supp
Lê et al, 2006 (59)	7 (7 M, 0 W)	24.7 (3.4)	69.3 kg (6.9)	OP, Switzerland	C	Supp
Le et al, 2009 (60) (N)	8 (8 M, 0 W)	24 (3)	71.2 kg (5.4)	OP, Switzerland	C	

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Randomization	Fructose Dosage, g/d§	Fructose Form	Comparator¶	Diet**	Energy Balance	Follow-up	MQS††	Funding Source‡‡
No	75 (15% E)	Mixed	Starch	40:40:20	Neutral	10 d	7	Agency
No	50 (11.6% E)	Liquid	Starch	42:38:20	Neutral	4 wk	7	Industry (materials)
Yes	60 (10% E)	Mixed	Starch	50:35:15	Neutral	12 wk	8	Agency
Yes	30 (8% E)	Liquid	Starch	50:30:20	Neutral	8 wk	8	Agency and industry
No	~100 (13% E)	Mixed	Sucrose	55:30:15	Neutral	12 wk	6	Agency and industry
No	~55 (12% E)	Mixed	Starch	55:25:20	Neutral	23 wk	8	Agency and industry
Yes	60 (7.5% E)	Mixed	Starch	50:35:15	Neutral	26 wk	8	Agency (salary award)
No	~138 (13% E)	Mixed	Sucrose	55:30:15	Neutral	100 d	4	Agency and industry
Yes	~25 (~5% E)	Mixed	Starch Sucrose	55:30:15	Neutral	52 wk	7	Agency and industry
Yes	~120 (20% E)	Mixed	Starch	55:30:15	Neutral	4 wk	8	Agency and industry
Yes	~55 (20% E)	Liquid	Starch	50:30:20	Neutral	4 wk	9	Agency and industry
No	63.2 (20% E)	Liquid	Starch Sucrose	55:30:15	Neutral	4 wk	7	Agency and industry
Yes	22.5 (4.5% E)	NA	Starch	-	Neutral	12 wk	5	NR
Yes	36 (25% E)	Liquid	Glucose Galactose	25:50:25	Negative	2 wk	8	Industry
Yes	36 (25% E)	Liquid	Glucose Galactose	25:50:25	Negative	2 wk	8	Industry
No	~125 (25% E)	Liquid	Starch	55:30:15	Neutral	10 wk	7	Agency
No	~182 (+25% E)	Liquid	Glucose	55:30:15	Positive	10 wk	6	Agency
Yes	~60 (13% E)	Solid (fruit)	Starch	55:30:15	Negative	6 wk	9	Agency
No	300 (55% E)	Mixed	Starch Sucrose Glucose	77:5:18	Neutral	~24 d	7	Agency
No	162	Liquid	Sucrose Glucose	90:00:10	Neutral	10 d	7	NR
No	~39.5 (9% E)	Liquid	D-Maltose	45:40:15	Neutral	~2 wk	7	Agency and industry
No	~122 (17% E)	Liquid	D-Maltose	85:00:15	Neutral	~2 wk	4	Agency and industry
Yes	250 (~+50% E)	Liquid	Glucose	55:30:15	Positive	7 d	6	Agency and industry
Yes	~120 (20% E)	Mixed	Starch	55:15:30	Neutral	4 wk	8	Agency and industry
Yes	85 (17% E)	Mixed	Glucose	55:30:15	Neutral	6 wk	9	Agency
Yes	~213 (+35% E)	Liquid	Glucose	55:30:15	Positive	7 d	8	Agency
Yes	40 (~7% E)	Liquid	Glucose Starch	51:14:35	Neutral	3 wk	9	Agency and industry
Yes	80 (~13% E)	Liquid	Glucose Sucrose	55:14:32	Neutral	3 wk	9	Agency and industry
No	53 (9% E)	Mixed	Starch	55:30:15	Neutral	6 wk	8	Agency
Yes	150 (+22% E)	Liquid	Glucose	50:35:15	Positive	4 wk	7	Agency
No	~168 (+25% E)	Liquid	Glucose HFCS	55:30:15	Positive	2 wk	6	Agency
Yes	+100 (+97% E)	Liquid	Diet alone	0:35:65	Negative	2 wk	8	Agency and industry
No	~+182 (+25% E)	Liquid	Diet alone	55:30:15	Positive	10 wk	5	Agency
No	+250 (~+50% E)	Liquid	Diet alone	55:30:15	Positive	7 d	5	Agency and industry
No	~+104 (+18% E)	Liquid	Diet alone	55:30:15	Positive	4 wk	7	Agency and industry
Yes	~+213 (+35% E)	Liquid	Diet alone	55:30:15	Positive	7 d	8	Agency and industry

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Table—Continued

Study, Year (Reference)	Participants	Mean Age (SD or Range), y	Mean Body Weight or BMI (SD)*	Setting	Design†	Feeding Control‡
Le et al, 2009 (60) (ODM2)	16 (16 M, 0 W)	24.7 (5.2)	75 kg (4.4)	OP, Switzerland	C	Supp
Ngo Sock et al, 2010 (53)	11 (11 M, 0 W)	24.6 (2)	71.9 kg (5.3)	OP, Switzerland	C	Met
Sobrecases et al, 2010 (61)	12 (12 M, 0 W)	23.9 (2.2)	22.6 kg/m ² (1.1)	OP, Switzerland	C	Supp
Silbernagel et al, 2011 (56)	10 (7 M, 3 W)	30.5	80.7 kg (7.5)	OP, Germany	C	Supp
Stanhope et al, 2011 (57) ¶¶	16 (9 M, 7 W)	28.0 (27.2)	76.8 kg (10.4)	IP/OP, USA	C	Met/Supp

BMI = body mass index; C = crossover; CKD = chronic kidney disease; DA = dietary advice; DM1 = type 1 diabetes mellitus; DM2 = type 2 diabetes mellitus; E = energy; HC = high carbohydrate; HD = high dose; HTG = hypertriglyceridemia; IP = inpatient; LC = low carbohydrate; LD = low dose; M = men; Met = metabolic; MQS = Heyland Methodological Quality Score; N = normal; NA = not available; NR = not reported; ODM2 = offspring of persons with type 2 diabetes mellitus; OB = obese; OP = outpatient; OW = overweight; P = parallel; Supp = supplement; T1 = trial 1; T2 = trial 2; USA = United States of America; W = women.

* Baseline body weight or weight while receiving the control treatment (comparator) in crossover trials, and baseline body weight in each treatment group in parallel trials. Baseline BMI is reported only when no data on weight were available.

† The study by Förster and Heller (48) had a parallel design for the comparison with sucrose and a crossover design for the comparison with glucose. To mitigate unit-of-analysis error, we combined the 2 groups to create a single pairwise comparison, which we conservatively analyzed as a parallel trial for the overall analysis.

‡ Metabolic feeding control was the provision of all meals, snacks, and study supplements (test sugars and foods) consumed during the study under controlled conditions. Supplement feeding control was the provision of study supplements. Dietary advice is the provision of counseling on the appropriate test and control diets.

§ Doses preceded by “~” represent average doses calculated on the basis of the average reported energy intake or weight of participants. If these data were not available, then the average dose was based on an 2000-kcal intake or 70-kg weight. Plus signs indicate excess energy provided by fructose.

|| Fructose was provided in 1 of 3 forms: 1) liquid, where all or most of the fructose was provided as beverages or crystalline fructose to be added to beverages; 2) solid, where fructose was provided as solid foods (fruit in the one case); or 3) mixed, where all or most of the fructose was provided as a mix of beverages, solid foods (not fruit), and crystalline fructose.

¶ Reference carbohydrate (starch, sucrose, or glucose) in the isocaloric trials and diet alone (weight-maintaining, background diet) in the hypercaloric trials. Fructose was exchanged for the reference carbohydrate, providing an energy-matched comparison in the isocaloric trials, whereas it was added to diet alone to provide excess energy in the hypercaloric trials.

** Energy from carbohydrate:fat:protein.

†† Trials with a score ≥8 were considered to be of higher quality.

‡‡ Agency funding is that from government, university, or not-for-profit health agency sources. None of the trialists declared any conflicts of interest, with the exception of Brymora and colleagues (55); in that study, trialist Dr. Richard Johnson reported being listed as an inventor with the University of Colorado on a patent application for a means of reducing the effects of fructose as a way of slowing diabetic renal disease and authoring a popular book, *The Sugar Fix: The High-Fructose Fallout That Is Making You Fat and Sick* (Rodale and Simon and Schuster, 2008).

§§ Three isocaloric trials (43, 46) and 1 hypercaloric trial (58) provided energy-restricted background diets (negative energy balance) while maintaining the isocaloric and hypercaloric comparisons, respectively.

||| Five reports (45, 50, 53, 56, 57) contained both isocaloric and hypercaloric trials. In the isocaloric trials, there was overfeeding (positive energy balance) in both the fructose and comparator groups, such that the comparisons were energy-matched. The MQS was higher for the isocaloric parallel trials than the hypercaloric crossover trials of Stanhope and colleagues (56) and Silbernagel and colleagues (57) because the hypercaloric trials were not blinded and randomized, respectively.

¶¶ The fructose and comparator (glucose) groups in the 2 isocaloric, parallel trials by Stanhope and colleagues (45, 57) featured an outpatient ad libitum, overfeeding period (8 wk and 10 d, respectively) followed by a shorter inpatient energy-balanced, weight-maintaining period (2 wk and 3.5 d, respectively). The same fructose group was compared with diet alone given over a shorter inpatient energy-balanced, weight-maintaining period (2 wk and 3.5 d, respectively) in the hypercaloric crossover trials.

*** Some participants with HTG had other comorbid conditions: coronary artery disease ($n = 2$) in the trial by Kaufmann and associates (47), hypertension plus diabetes ($n = 1$) and coronary artery disease plus peripheral vascular disease ($n = 1$) in the LC and HC trials by Turner and coworkers (49), and diabetes ($n = 1$) in the LC trial by Turner and coworkers (49).

largely normal-weight participants. Where data for both change-from-baseline differences and end differences in weight were equally available, we used the difference in change from baseline weight as the primary end point for analyses.

We applied paired analyses to all crossover trials according to the methods of Elbourne and colleagues (27); owing to insufficient data, we could not use the more robust techniques that Curtin and colleagues (29) developed. To investigate the effect of imputed correlation coefficients on paired analyses, we performed sensitivity analyses across a range of possible correlation coefficients (0, 0.33, 0.66, and 0.99). To mitigate the unit-of-analysis error from including trials with multiple intervention groups, we combined groups to create single pairwise comparisons (23).

Interstudy heterogeneity was tested by using the Cochran Q statistic (chi-square value), with the significance level set at a P value less than 0.10, and was quantified by using the I² statistic, where a value of 50% or greater indicates substantial heterogeneity (23). We investigated potential sources of clin-

ical and methodological heterogeneity by using sensitivity analyses and a priori subgroup analyses of comparator, fructose form (solid, liquid, or mixed), dose (American Heart Association threshold ≤37.5 g/d or >37.5 g/d [≤150 kcal/d or >150 kcal/d]) (20), follow-up (≤4 weeks or >4 weeks), study quality (Heyland MQS <8 or ≥8) (26), randomization (yes or no), and baseline body weight (≤70 kg or >70 kg). Additional post hoc subgroup analyses were undertaken for study design (parallel or crossover) and energy balance (negative, neutral, or positive).

To increase the statistical power of subgroup analyses, we combined the effects of fructose on body weight across categories of weight and diabetes. We used meta-regression analyses to assess the significance of subgroup effects. We investigated publication bias by inspection of funnel plots and by Egger and Begg tests.

Role of the Funding Source

This work was funded by a Canadian Institutes of Health Research Knowledge Synthesis grant and a grant

Table—Continued

Randomization	Fructose Dosage, g/d§	Fructose Form	Comparator¶	Diet**	Energy Balance	Follow-up	MQS††	Funding Source‡‡
Yes	+220 (+35% E)	Liquid	Diet alone	55:30:15	Positive	7 d	8	Agency and industry
Yes	~+213 (+35% E)	Liquid	Diet alone	55:30:15	Positive	7 d	8	Agency
No	~+175 (+35% E)	Liquid	Diet alone	55:30:15	Positive	7 d	6	Agency
No	+150 (+22% E)	Liquid	Diet alone	50:35:15	Positive	4 wk	6	Agency
No	~+168 (+25% E)	Liquid	Diet alone	55:30:15	Positive	2 wk	6	Agency

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RESULTS

Search Results

Figure 1 shows the trial selection process. Of the 1984 eligible reports identified by the search, 1903 were determined to be irrelevant on review of the titles and abstracts; the remaining 81 reports were retrieved and reviewed in full, of which 49 were excluded. Thus, a total of 32 reports providing data for 41 trials (31 isocaloric and 10 hypercaloric feeding trials) were selected for analyses (30–61). Five of the reports contained both isocaloric and hypercaloric comparisons (45, 50, 53, 56, 57).

Trial Characteristics

Trial characteristics are detailed in the Table. There were 31 isocaloric trials involving 637 participants in diabetic (13 trials), overweight/obese (5 trials), and normal-weight (13 trials) populations and 10 hypercaloric trials involving 119 participants in overweight/obese (2 trials) and normal-weight (8 trials) populations. Participants in isocaloric trials tended to be middle-aged men (median age, 43.0 years [interquartile range {IQR}, 28.0 to 54.6 years; median male–female ratio, 1.5:1), whereas those in hypercaloric trials were mostly younger men (median age, 24.7 years [IQR, 24.2 to 28.0 years]; median male–female ratio, 8:1). Median baseline body weight was 76.7 kg (IQR, 70.4 to 82.7 kg) in isocaloric trials and 72.6 kg (IQR, 67.4 to 70.1 kg) in hypercaloric trials. Participants were generally healthy, although some normal-weight participants in isocaloric trials had comorbid conditions (hypertriglyceridemia with mixed comorbid conditions in 3 trials and nondiabetic chronic kidney disease in 1 trial).

Normal-weight participants in 1 hypercaloric trial were the offspring of parents with type 2 diabetes.

Isocaloric and hypercaloric trials tended to be small (median number of participants, 14 [IQR, 8 to 21] and 12 [IQR, 8 to 21], respectively) and to be conducted in European countries (48% and 80%) and in outpatient settings (61% and 80%). Follow-up was short: Median follow-up was 4 weeks [IQR, 2 to 10 weeks] for isocaloric trials and 1.5 weeks [IQR, 1 to 3.5 weeks] for hypercaloric trials.

Eighteen (58%) isocaloric and 5 hypercaloric (50%) trials were randomized. Nineteen isocaloric (63%) and 9 hypercaloric (90%) trials used crossover designs; 1 isocaloric trial used a crossover design for one group and a parallel design for the other. Comparators in isocaloric trials were starch (18 trial groups), sucrose (7 trial groups), glucose (12 trial groups), high-fructose corn syrup (1 trial group), dextromaltose (2 trial groups), and galactose (2 trials); diet alone was the comparator in all hypercaloric trials. Fructose was administered in fluid (53%), solid (3%), and mixed (43%) forms in the isocaloric trials and in fluid form in all hypercaloric trials. Median fructose doses were 69.1 g/d (IQR, 50.8 to 124.3 g/d; 17% energy [IQR, 10.8% to 25% energy]) in the isocaloric trials and 182 g/d (IQR, 153.5 to 201 g/d; 37.5% energy [IQR, 31.3% to 43.8% energy]) in the hypercaloric trials.

The diets provided a range of energy and macronutrient profiles. Most isocaloric trials provided energy under weight-maintaining conditions (neutral energy balance), but 5 (16%) provided excess energy in both trial groups (positive energy balance) (45, 50, 53, 56, 57). Three (10%) isocaloric trials (10%) tested weight-loss diets, restricting energy in both trial groups (negative energy balance) (43, 46), as did 1 of the hypercaloric trials (58). Macronutrient profiles varied considerably across the isocaloric and hypercaloric trials: 40% to 90% and 0% to 55% carbohydrate energy, 5% to 40% and 30% to 65% fat energy, and 10% to 21% and 15% to 35% protein energy, respectively. Fifteen (48%) of the isocaloric trials and 2 (20%) of the hypercaloric trials used metabolic feeding control exclusively.

The Heyland MQS (maximum possible score, 13) ranged from 4 to 9 in the isocaloric trials and 5 to 8 in the

hypercaloric trials; 12 isocaloric trials (39%) and 4 hypercaloric trials (40%) were considered high-quality (Heyland MQS ≥ 8) (Appendix Table 3, available at www.annals.org). Elements that contributed to low scores were lack of or poor description of randomization, nonconsecutive or poorly described patient selection, and absence of double-blinding. Only 19% to 31% and 22% of the total Heyland MQS points were achieved in the isocaloric and hypercaloric trials, respectively. However, most of the trials had well-matched participants across treatment groups, 100% follow-up, reproducibly described protocols, and well-controlled co-interventions, achieving 70% or more of the total points for these elements.

The majority of trials reported research funding from a combination of agency and industry (55%) or agency alone (34%); only 10% were funded by industry alone. Only 1 trial reported a potential conflict of interest. Other sources of bias were difficult to assess, given the poor quality of reporting; all but 2 of the trials (46, 56) failed to satisfy most of the Consolidated Standards of Reporting Trials (CONSORT) requirements for trials of nonpharmacologic interventions (62).

Isocaloric Feeding Trials

Figure 2 and Appendix Table 4 (available at www.annals.org) show the effect of fructose on body weight in isocaloric comparisons. Fructose had no effect overall or in subsamples of normal-weight participants or those with diabetes. However, statistically significant weight loss (MD, -0.55 kg [95% CI, -1.09 to -0.02 kg]) was seen in the 5 trials that enrolled overweight/obese persons, 3 of which tested diets with negative energy balance.

There was evidence of statistically significant interstudy heterogeneity overall. Sensitivity analyses in which each trial was systematically removed did not change the statistical significance of the interstudy heterogeneity or the body weight effects in the overall analysis. However, within the overweight/obese subpopulation, systematic removal of each trial eliminated the weight loss effect of fructose in the subgroup, except for the study by Rizkalla and colleagues (43) (trial 2 in Table 1 and Figure 2); because the point estimate for weight change in that trial suggested weight gain, its removal did not alter the apparent weight loss effect. The use of more conservative correlation coefficients (0.66, 0.33, and 0) for paired analyses of crossover trials with imputed SD for between-intervention end differences broadened the CIs of these trials, decreasing their weight in the analyses. The effect was to eliminate evidence of interstudy heterogeneity (I^2 value) and increase the relative weighting of effects detected in parallel trials so that the body weight–decreasing effect of fructose then became statistically significant in the overall analysis; for example, with a correlation coefficient of 0.66, the MD was -0.36 kg (CI, -0.60 to -0.12 kg) and the I^2 value was 0%. However, a formal test of interaction of weight change by

study design was not statistically significant (Appendix Figure 1, available at www.annals.org).

Appendix Figure 1 shows subgroup analyses in the isocaloric trials. No evidence of effect modification was seen in any of the subgroup analyses on meta-regression analyses except for fructose form. The weight-decreasing effect of fructose in solid (fruit) and fluid form differed statistically from the weight-increasing effect of fructose in mixed form ($P < 0.05$). Statistically significant unexplained interstudy heterogeneity, however, remained in at least 1 level of all subgroup analyses.

Hypercaloric Feeding Trials

Figure 3 shows the effect of a control diet supplemented with excess energy from high dosages of fructose (104 to 250 g/d; 18% to 97% energy) on body weight. A body weight–increasing effect was seen overall (MD, 0.53 kg [CI, 0.26 to 0.79 kg]), without evidence of interstudy heterogeneity. Sensitivity analyses in which each trial was systematically removed did not alter the significance of the effect. The use of more conservative correlation coefficients for paired analyses of crossover trials with imputed SD broadened the CIs but did not alter the statistical significance of the effect estimates or interstudy heterogeneity (data not shown).

Appendix Figure 2 (available at www.annals.org) shows subgroup analyses in the hypercaloric trials. None of the subgroups was statistically significant in meta-regression analyses. Statistically significant unexplained interstudy heterogeneity, however, remained in at least 1 level of most of the subgroup analyses.

Publication Bias

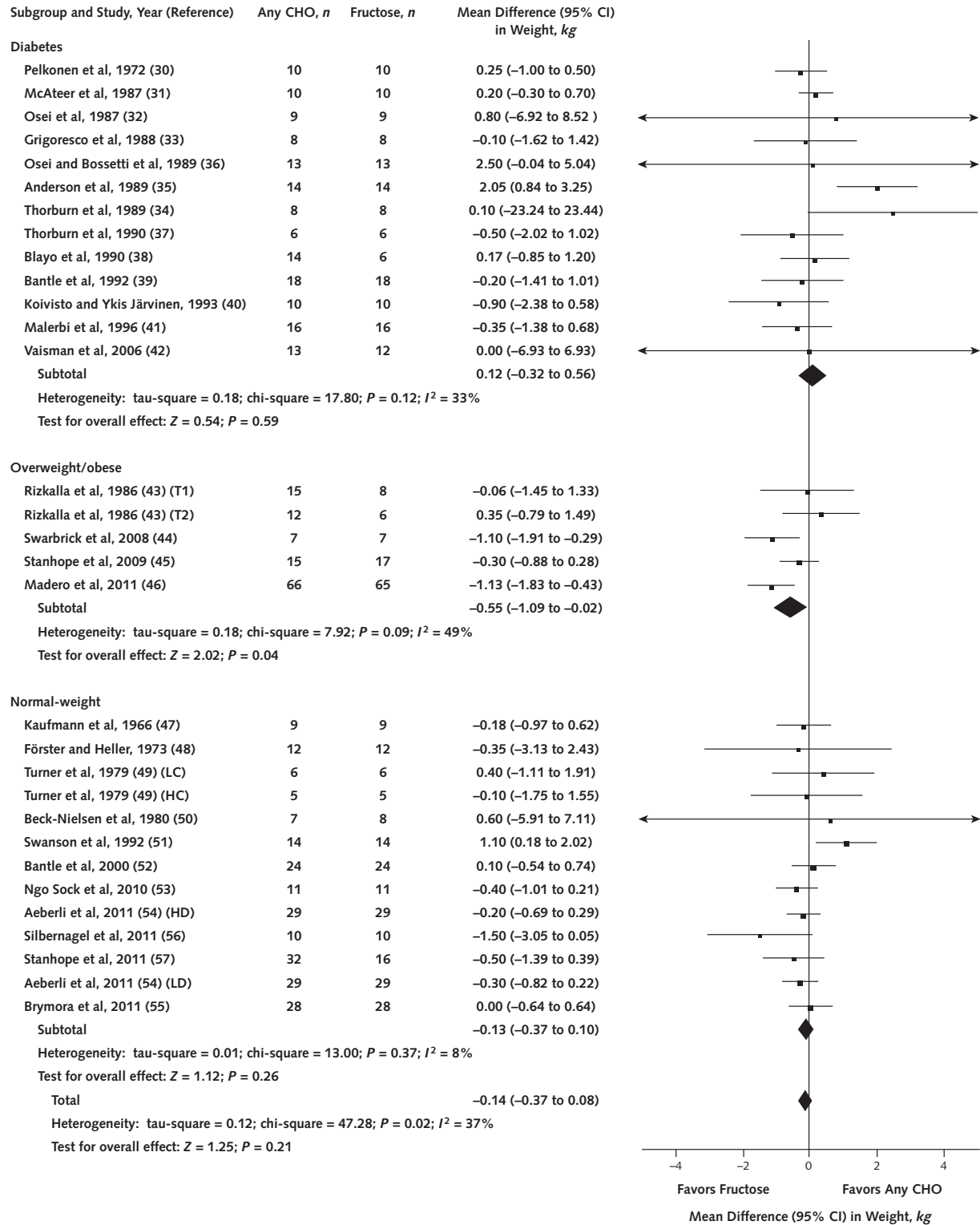
We inspected funnel plots for evidence of publication bias (Appendix Figure 3, available at www.annals.org). No asymmetry or small-study effects were detected among the isocaloric and hypercaloric trials; the Egger and Begg tests were not statistically significant ($P > 0.05$). However, 5 of the hypercaloric trials were conducted by the same group of investigators (with the same senior author).

DISCUSSION

Our aggregate analyses of the effects of fructose in 31 trials with isocaloric comparisons (637 participants) and 10 trials with hypercaloric comparisons (119 participants) showed divergent results. The isocaloric trials did not provide consistent evidence for a body weight–increasing effect of fructose, whereas the hypercaloric trials did. The weight gain when the diet was supplemented with excess energy from high doses of fructose was 0.53 kg (CI, 0.26 to 0.79) over a median follow-up of 1.5 weeks.

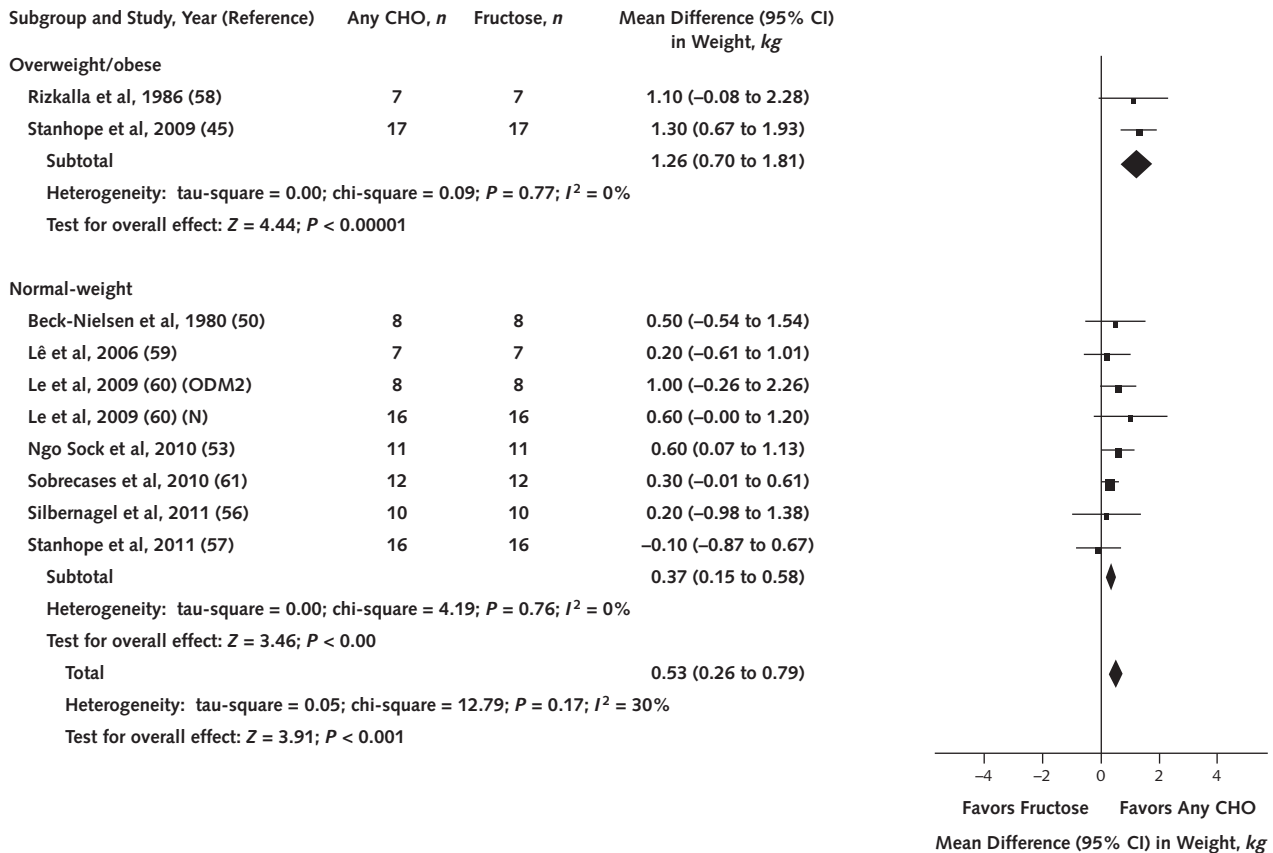
Energy remains an important complicating factor in the interpretation of these analyses. In the hypercaloric trials, weight gain is similar to that which would be predicted with consumption of a 2000-kcal diet supplemented with a similar amount of excess energy. In this context, it becomes

Figure 2. Forest plots of isocaloric feeding trials investigating the effect of isocaloric exchange of fructose for carbohydrate on body weight in diabetic, overweight/obese, and normal-weight people.



Four pooled effect estimates (*diamonds*) are shown: one each for trials in diabetes, overweight/obesity, normal weight, and their combination (total). Paired analyses were applied to all crossover trials (27). Data are expressed as weighted mean differences with 95% CIs, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochran Q statistic (chi-square) at a significance level of $P < 0.10$. Any CHO = any carbohydrate comparator; HC = high-carbohydrate diet; HD = high dose; LC = low-carbohydrate diet; LD = low dose; T1 = trial 1; T2 = trial 2.

Figure 3. Forest plots of hypercaloric feeding trials investigating the effect of a control diet supplemented with 18% to 97% (104 to 250 g/d) excess energy from fructose on body weight in overweight/obese and normal-weight people.



Three pooled effect estimates (*diamonds*) are shown: one each for trials in overweight/obesity, normal weight, and their combination (total). Paired analyses were applied to all crossover trials (27). Data are expressed as weighted mean differences with 95% CIs, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochran *Q* statistic (chi-square) at a significance level of *P* < 0.10. N = normal; ODM2 = offspring of persons with type 2 diabetes mellitus.

difficult to disentangle the relative contributions of fructose, excess energy, and their interaction in the body weight-increasing effect of fructose in the hypercaloric trials.

The mechanisms linking fructose more than other sources of carbohydrate to weight gain are not well-understood. Although fructose, unlike glucose, may bypass phosphofructokinase—allowing it to enter glycolysis as an unregulated substrate, with related increases in lipogenic enzymes (16, 63) that increase *de novo* lipogenesis (45)—whether this mechanism is quantitatively significant under energy-matched conditions is unclear.

Five reports contained both isocaloric and hypercaloric comparisons (45, 50, 53, 56, 57). The 5 isocaloric feeding trials in these reports used excess-energy diets (positive energy balance) in both trial groups and thus had designs that permitted the effect of fructose to be isolated from that of energy. Although an increasing effect on *de novo* lipogenesis and transcription of lipogenic enzymes was seen in 1 trial (45), none of the 5 trials showed a differential effect of fructose on body weight in the excess energy diets. When

we combined these trials in a post hoc subgroup analysis exploring effect modification by energy balance, no differences were seen within or between conditions of negative, neutral, or positive energy balance. These data suggest that the effect of fructose on body weight may not differ from that of other carbohydrates when diets providing equal amounts of energy are compared.

Other levels of evidence support this suggestion. High-precision estimates of energy expenditure, fat oxidation, and carbohydrate oxidation using whole-body calorimetry showed no differences among fructose, glucose, or sucrose fed under conditions of 50% excess energy (64). A meta-analysis of large prospective observational studies also showed that after adjustment for energy, the increasing effect of sugar-sweetened beverages on body weight in children was lost (65). Taken together, excess energy may be a more important consideration than the type of sugar for weight gain.

Other modifiers of the effect of fructose on body weight need to be considered. In their meta-analysis of the

effect of fructose in isocaloric exchange for other carbohydrate, Livesey and Taylor (19) showed no effect on body weight and no subgroup effect modification. They did, however, report dose thresholds of 100 g/d and 50 g/d, respectively, for a triglyceride-increasing effect of fructose on fasting and postprandial triglyceride levels. We also reported that dosage (>60 g/d), comparator (starch), and duration of follow-up (≤ 4 weeks) modified the effect of fructose on triglycerides in a meta-analysis of trials in type 2 diabetes (66). We did not see any similar signals across our subgroup analyses.

We detected significant weight loss when analyses were restricted to overweight/obese participants. A weight loss-inducing effect of fructose, however, seems unlikely: The findings disappeared with sensitivity analyses; no effect was seen in participants with diabetes, most of whom shared an overweight/obese phenotype; and 3 of the trials in the subgroup comprise the only isocaloric comparisons on a background diet with a negative energy balance that was designed to promote weight loss independent of fructose. The finding of a statistically significant effect modification by fructose form (a weight-loss effect with solid fructose) is probably also attributable to the negative energy balance of the background diets in this trial or possibly to the use of fruit to deliver fructose, because fruit intake has been linked to weight loss in large prospective cohorts (67). The weight-loss effect of liquid fructose, however, was surprising, given the evidence linking sugar-sweetened beverages and weight gain (10–12). The remaining subgroup analyses were not statistically significant, although they may have been underpowered and the strategy of combining data across categories of weight and diabetes may have contributed to excess heterogeneity.

Our study has limitations. First, the trials enrolled more younger and middle-aged men than older women.

Second, the durability of the effects remains a concern; only 5 of the isocaloric trials and none of the hypercaloric trials lasted 12 weeks or longer. It is uncertain whether the body weight-increasing effect of fructose in the hypercaloric trials and the null effect in the isocaloric trials will persist over the longer term.

Third, end differences in weight rather than differences in weight change between trial groups were used almost exclusively, owing to the data reported. There was, however, no evidence of baseline differences among trials (data not shown) or of effect modification by randomization in subgroup analyses.

Fourth, study quality was poor (Heyland MQS 8) for at least 60% of the trials. Most of the low quality scores were attributable to a lack of or poor description of randomization, nonconsecutive or poorly described patient selection, and absence of blinding. However no effect modification by study quality (higher vs. lower Heyland MQS score) was seen in subgroup analyses.

Fifth, most of the trials used crossover designs. Although parallel trials have shown a nonsignificant trend for

more conservative effect estimates than crossover trials (68), we did not see effect modification by design. The overall analysis of isocaloric trials, however, was sensitive to the imputation of SD in crossover trials, where the down-weighting of crossover trials rendered the body weight-decreasing effect of fructose statistically significant. The same result would be achieved if we had restricted the isocaloric analysis to parallel trials. This situation creates some uncertainty about the true effects of fructose among the available trials.

Finally, publication bias remains an issue, given the large number of small trials (the majority involved <15 participants). Although neither analysis showed evidence of small-study effects, 50% of the hypercaloric trials were drawn from a single group of investigators in Switzerland, limiting the generalizability of results.

The implications of our findings for real-world dietary advice are unclear. The most important source of added fructose in the U.S. diet according to NHANES III (Third National and Health and Nutrition Examination Survey) (69)—“non-alcoholic beverages” (54.3%)—was well-represented among the included trials (53%). However, our analysis included only 1 trial in which the most important source of naturally occurring fructose, “fruit and fruit products” (72.5%) (69), was tested (46). Because this trial was 1 of only 2 to show statistically significant weight loss, the lack of trials using fruit may be a source of unrealized heterogeneity.

The use of fructose as a sweetener in the included trials is also not representative. Whereas sucrose and high-fructose corn syrup are the primary fructose-containing sweeteners in the U.S. diet, accounting for 44% and 42% of all sweeteners, respectively (69), we excluded trials in which fructose was administered exclusively as sucrose or high-fructose corn syrup to isolate the effect of fructose.

Another issue is the generalizability of the amount of fructose intake tested. More than 75% of the isocaloric trials tested fructose intakes above the 50th percentile (49 g/d), and all of the hypercaloric trials tested intakes above the 95th percentile (87 g/d) (69).

Overall, the evidence from our analysis is too preliminary to guide food choices in the context of real-world intake patterns. Trials using more representative fructose sources and levels of exposure are needed. Given the important contribution of fruit to fructose intake, a possible benefit of fructose as fruit also merits further investigation.

In conclusion, aggregate data analyses of controlled feeding trials do not support a body weight-increasing effect of fructose in isocaloric exchange for other sources of carbohydrate in the diet. However, evidence indicates that added fructose providing excess energy at extreme levels of intake may have a body weight-increasing effect over the short term, although confounding from excess energy cannot be excluded. The short follow-up and poor quality of the majority of trials, as well as the sensitivity to imputations in crossover trials, are sources of uncertainty in our analysis.

To clarify the role of fructose in the obesity epidemic, data from larger, high-quality, long-term (≥ 6 months) feeding trials with fructose in the most commonly consumed forms at generalizable doses are required. Because current dietary guidelines are recommending reductions in the intake of sugar-sweetened beverages and at the same time encouraging consumption of fruits and vegetables (21), it will be equally important to have high-quality feeding trials that reconcile differences in effect between added fructose in sugar-sweetened beverages and naturally occurring fructose in fruits and vegetables. These future trials will be necessary for answering the question of whether the consumption of fructose under real-world conditions leads to overconsumption of calories and weight gain.

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Appendix Table 1. Search Strategy for Studies Assessing the Effect of Fructose on Body Weight in Controlled Feeding Trials*

Database	Search Period	Search
MEDLINE	1948 to week 2 of November 2011	<ol style="list-style-type: none"> 1. Fructose/ 2. body weight.mp. or exp Body Weight/ 3. exp Body Mass Index/ or BMI.mp. 4. body fat.mp. or exp Fat Body/ 5. waist circumference.mp. or exp Waist Circumference/ 6. waist-to-hip ratio.mp. or exp Waist-Hip Ratio/ 7. 2 or 3 or 4 or 5 or 6 8 1 and 7 9. limit 8 to humanst
EMBASE	1980 to week 46 of 2011	<ol style="list-style-type: none"> 1. Fructose/ 2. body weight.mp. or exp Body Weight/ 3. exp Body Mass/ or BMI.mp. 4. body fat.mp. or exp Fat Body/ 5. waist circumference.mp. or exp Waist Circumference/ 6. waist-to-hip ratio.mp. or exp Waist-Hip Ratio/ 7. 2 or 3 or 4 or 5 or 6 8 1 and 7 9. limit 8 to humanst
CINAHL	1982 to 18 November 2011	<ol style="list-style-type: none"> 1. (MH "Fructose") 2. (MH "Body Weight+") OR "body weight" OR (MH "Body Mass Index") OR "bmi" OR "body fat" OR (MH "waist circumference") OR (MH "Waist-Hip Ratio") OR "waist-to-hip ratio" 3. 1 and 2 4. limit 3 to humanst
The Cochrane Library	Issue 4 of 4, October 2011	<ol style="list-style-type: none"> 1. fructose AND (body weight OR body mass index OR BMI OR body fat OR waist circumference OR waist-to-hip ratio) 2. Limit 1 to clinical trials

* For all databases, the original search date was 21 June 2010; updated searches were performed on 13 January, 21 June, 21 September, 1 November, and 18 November 2011.

† Searches were limited to human(s) for each of the updates. The original search was not limited.

Appendix Table 2. Data Calculations and Imputations for Missing Data in Each Included Trial

Study, Year (Reference)	Design	Comparator	Comparison	Within Intervention			Between Interventions			
				Missing Data	Calculations	Imputations	Correlation Coefficient*	Missing Data	Calculations	Imputations
Isocaloric trials										
Diabetes										
Pelkonen et al, 1972 (30)	C	Starch	ED	-	-	-	SD	-	Pooled correlation	[0.989]
McAteer et al, 1987 (31)	C	Starch	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Osei et al, 1987 (32)	P	Starch	ED	-	-	-	SD	-	Standard formula	-
Grigosco et al, 1988 (33)	C	Starch	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Thorburn et al, 1989 (34)	P	Sucrose	ED	-	-	-	SD	-	Standard formula	-
Anderson et al, 1989 (35)	C	Starch	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Osei and Bossetti, 1989 (36)	C	Starch	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Thorburn et al, 1990 (37)	C	Sucrose	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Blayo et al, 1990 (38)	P	Starch	Change from baseline	SD	-	-	SD	-	Standard formula	-
Bantle et al, 1992 (39)	P	Sucrose	Change from baseline	SD	-	-	SD	-	Standard formula	-
Koivisto and Yki-Järvinen, 1993 (40)	C	Starch	ED	-	-	-	SD	-	P value (t test)	0.993
Koivisto and Yki-Järvinen, 1993 (40)	C	Starch	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Malerbi et al, 1996 (41)	C	Starch	ED	-	-	-	SD	-	P value (t test)	0.969
Malerbi et al, 1996 (41)	C	Sucrose	ED	-	-	-	SD	-	P value (t test)	(0.969)
Vaisman et al, 2006 (42)	P	Starch	ED	-	-	-	SD	-	Standard formula	-
Overweight/obese										
Rizkalla et al, 1986 (43) (T1)	P	Glucose	Change from baseline	-	-	-	SD	-	P value (t test)	0.955/0.990
Rizkalla et al, 1986 (43) (T2)	P	Galactose	Change from baseline	-	-	-	SD	-	P value (t test)	0.757/0.990
Rizkalla et al, 1986 (43) (T2)	P	Glucose	Change from baseline	-	-	-	SD	-	P value (t test)	0.990/0.994
Rizkalla et al, 1986 (43) (T2)	P	Galactose	Change from baseline	-	-	-	SD	-	P value (t test)	0.943/0.994
Swarbrick et al, 2008 (44)	C	Starch	ED	-	-	-	SD	-	P value (F test)	0.9999
Stanhope et al, 2009 (45)†	P	Glucose	Change from baseline	-	-	-	SD	-	P value (F test)	-
Madero et al, 2011 (46)	P	Starch	Change from baseline	-	-	-	SD	-	P value (t test)	-
Normal weight										
Kaufmann et al, 1967 (47)†	C	Starch	Change from baseline	-	-	-	SD	-	Pooled correlation	-
Kaufmann et al, 1967 (47)†	C	Starch	ED	-	-	-	SD	-	P value (t test)	0.386
Kaufmann et al, 1967 (47)†	C	Glucose	Change from baseline	-	-	-	SD	-	P value (t test)	0.979
Kaufmann et al, 1967 (47)†	C	Glucose	Change from baseline	-	-	-	SD	-	P value (t test)	0.994
Kaufmann et al, 1967 (47)†	C	Glucose	Change from baseline	-	-	-	SD	-	P value (t test)	0.9999
Kaufmann et al, 1967 (47)†	C	Sucrose	Change from baseline	-	-	-	SD	-	P value (t test)	0.043
Kaufmann et al, 1967 (47)†	C	Sucrose	ED	-	-	-	SD	-	P value (t test)	0.981
Förster and Heller, 1973 (48)§	P	Sucrose	ED	-	-	-	SD	-	Standard formula	-
Turner et al, 1979 (49) (LC)	C	Glucose	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Turner et al, 1979 (49) (HC)	C	D-maltose	Change from baseline	SD	-	-	SD	-	Pooled correlation	[0.349]
Beck-Nielsen et al, 1980 (50)‡	P	Glucose	Change from baseline	SD	-	-	SD	-	Pooled correlation	[0.349]
Beck-Nielsen et al, 1980 (50)‡	P	Glucose	ED	-	-	-	SD	-	Standard formula	-
Swanson et al, 1992 (51)	C	Starch	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Bantle et al, 2000 (52)	C	Glucose	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Ngo Sock et al, 2010 (53)†	C	Glucose	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Aeberli et al, 2011 (54) (LD)	C	Starch	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Aeberli et al, 2011 (54) (HD)	C	Glucose	ED	-	-	-	SD	-	Pooled correlation	[0.989]
Aeberli et al, 2011 (54) (HD)	C	Sucrose	ED	-	-	-	SD	-	Pooled correlation	[0.989]

Continued on following page

Appendix Table 2—Continued

Study, Year (Reference)	Design	Comparator	Comparison	Within Intervention			Between Interventions						
				Missing Data	Calculations	Imputations	Correlation Coefficient*	Missing Data	Calculations	Imputations	Correlation Coefficient*		
Bymora et al, 2011 (55)	C	Starch	ED	—	—	—	—	SD	—	—	Pooled correlation	[0.989]	
Silbemagel et al, 2011 (56)†	P	Glucose	Change from baseline	—	—	—	—	—	—	—	—	—	
Stanhope et al, 2011 (57)†	P	Glucose	Change from baseline	SD	—	Pooled correlation	[0.976/0.982]	SD	—	P value (F test)	—	—	
	P	HFCS	Change from baseline	SD	—	Pooled correlation	[0.976/0.982]	SD	—	—	—	—	
Hypercaloric trials													
Overweight/obese													
Rizkalla et al, 1986 (58)	P	Diet alone	Change from baseline	—	—	—	—	—	—	—	—	—	—
Stanhope et al, 2009 (45)†	C	Diet alone	ED	—	—	—	—	SD	—	P value (t test)	—	—	0.992
Normal weight													
Beck-Nielsen et al, 1980 (50)‡	C	Diet alone	ED	—	—	—	—	SD	—	—	Pooled correlation	[0.989]	
Lé et al, 2006 (59)	C	Diet alone	ED	—	—	—	—	SD	—	—	Pooled correlation	[0.989]	
Le et al, 2009 (60) (N)	C	Diet alone	ED	—	—	—	—	SD	—	—	Pooled correlation	0.993	
Le et al, 2009 (60) (ODM2)	C	Diet alone	ED	—	—	—	—	SD	—	P value (F test)	—	—	0.816
Ngo Sock et al, 2010 (53)†	C	Diet alone	ED	—	—	—	—	SD	—	P value (F test)	—	—	0.989
Sobrecases et al, 2010 (61)	C	Diet alone	ED	—	—	—	—	SD	—	—	Pooled correlation	—	0.991
Silbemagel et al, 2011 (56)†	C	Diet alone	Change from baseline	—	—	—	—	—	—	—	—	—	—
Stanhope et al, 2011 (57)†	C	Diet alone	ED	—	—	—	—	SD	—	—	Pooled correlation	[0.989]	

C = crossover; ED = end difference; HC = high-carbohydrate diet; HD = high dose; HFCS = high-fructose corn syrup; LC = low-carbohydrate diet; LD = low dose; N = normal; ODM2 = offspring of persons with type 2 diabetes mellitus; P = parallel; T1 = trial 1; T2 = trial 2.

* Correlation coefficients without parentheses or square brackets were calculated from the individual trials by using the observed or calculated within and between-treatment SDs according to standard formulae (23, 27). Correlation coefficients in parentheses were borrowed from another group of the same trial. Repeating values of correlation coefficients with square brackets (0.976/0.982) for within treatment and [0.989] for between treatment represent pooled correlation coefficients derived from a meta-analysis of the individual trial-level correlation coefficients. To conduct the meta-analysis, individual trial-level correlation coefficients were inputted into a meta-analysis as transformed z scores with their SEs. The pooled effect estimate from the z scores was then back-transformed to derive the pooled correlation coefficient, which was applied to trials with insufficient data for calculation of the missing between-treatment SDs. The within-treatment correlation coefficients are all for change from baseline. These correlation coefficients were calculated even where end differences are specified as the end point to permit inclusion in the meta-analysis of pooled correlation coefficients. Two within-treatment correlation coefficients are shown, separated by a slash; the first value is for any carbohydrate comparator and the second value is for fructose.

† Five reports (45, 50, 53, 56, 57) contained both isocaloric and hypercaloric trials.

‡ Kaufmann and colleagues (47) provided individual-level patient data, allowing calculation of correlation coefficients for both change-from-baseline and end-difference comparisons.

§ Förster and Heller's study (48) contained a parallel design for the comparison with sucrose and a crossover design for the comparison with glucose.

Appendix Table 3. Study Quality Assessment by Using the Heyland MQS*

Study	Design†				Sample‡			Intervention§		MQS (n/13)
	Randomization (n/2)	Blinding (n/1)	Analysis (n/2)	Selection (n/1)	Comparability (n/1)	Follow-up (n/1)	Protocol (n/1)	Co-interventions (n/2)	Crossovers (n/2)	
Isocaloric trials										
Diabetes										
Pelkonen et al, 1972 (30)	0	0	2	0	1	1	1	2	0	7
McAteer et al, 1987 (31)	0	0	2	0	1	1	1	2	0	7
Osei et al, 1987 (32)	1	0	2	0	1	1	1	2	0	8
Grigoresco et al, 1988 (33)	1	0	2	0	1	1	1	2	0	8
Thorburn et al, 1989 (34)	0	0	2	0	0	1	1	2	0	6
Anderson et al, 1989 (35)	0	0	2	1	1	1	1	2	0	8
Osei and Bossetti, 1989 (36)	1	0	2	0	1	1	1	2	0	8
Thorburn et al, 1990 (37)	0	0	0	0	1	0	1	2	0	4
Blayo et al, 1990 (38)	1	0	2	0	0	1	1	2	0	7
Bantle et al, 1992 (39)	1	0	2	0	1	1	1	2	0	8
Koivisto et al, 1993 (40)	1	1	2	0	1	1	1	2	0	9
Malerbi et al, 1996 (41)	0	0	2	0	1	1	1	2	0	7
Vaisman et al, 2006 (42)	1	1	0	0	1	0	0	2	0	5
Overweight/obese										
Rizkalla et al, 1986 (43) (T1)	1	1	2	0	0	1	1	2	0	8
Rizkalla et al, 1986 (43) (T2)	1	1	2	0	0	1	1	2	0	8
Swarbrick et al, 2008 (44)	0	0	2	0	1	1	1	2	0	7
Stanhope et al, 2009 (45)	0	1	0	1	1	0	1	2	0	6
Madero et al, 2011 (46)	2	0	2	1	1	0	1	2	0	9
Normal weight										
Kaufmann et al, 1966 (47)	0	0	2	0	1	1	1	2	0	7
Förster and Heller, 1973 (48)	0	0	2	1	1	1	0	2	0	7
Turner et al, 1979 (49) (LC)	0	0	2	0	1	1	1	2	0	7
Turner et al, 1979 (49) (HC)	0	0	0	0	1	1	1	2	0	4
Beck-Nielsen et al, 1980 (50)¶	1	0	2	0	0	1	1	1	0	6
Swanson et al, 1992 (51)	1	0	2	0	1	1	1	2	0	8
Bantle et al, 2000 (52)	1	0	2	1	1	1	1	2	0	9
Ngo Sock et al, 2010 (53)	1	0	2	0	1	1	1	2	0	8
Aeberli et al, 2011 (54) (LD)	1	0	2	1	1	1	1	2	0	9
Aeberli et al, 2011 (54) (HD)	1	0	2	1	1	1	1	2	0	9
Brymora et al, 2011 (55)	0	0	2	1	1	1	1	2	0	8
Silbernagel et al, 2011 (56)	2	0	0	1	1	0	1	2	0	7
Stanhope et al, 2011 (57)	0	1	0	1	1	0	1	2	0	6
Hypercaloric trials										
Overweight/obese										
Rizkalla et al, 1986 (58)	1	1	2	0	0	1	1	2	0	8
Stanhope et al, 2009 (45)	0	0	0	1	1	0	1	2	0	5
Normal weight										
Beck-Nielsen et al, 1980 (50)¶	0	0	2	0	0	1	1	1	0	5
Lê et al, 2006 (59)	0	0	2	0	1	1	1	2	0	7
Le et al, 2009 (60) (N)	1	0	2	0	1	1	1	2	0	8
Le et al, 2009 (60) (ODM2)	1	0	2	0	1	1	1	2	0	8
Ngo Sock et al, 2010 (53)	1	0	2	0	1	1	1	2	0	8
Sobrecases et al, 2010 (61)	0	0	2	0	1	1	0	2	0	6
Silbernagel et al, 2011 (56)	0	0	0	1	1	0	1	2	0	5
Stanhope et al, 2011 (57)	0	1	0	1	1	0	1	2	0	6

HC = high-carbohydrate diet; HD = high dose; LC = low-carbohydrate diet; LD = low dose; MQS = Heyland Methodological Quality Score; N = normal; ODM2 = offspring of persons with type 2 diabetes mellitus; T1 = trial 1; T2 = trial 2.

* The Heyland MQS assigns a score of 0 or 1 or from 0 to 2 over 9 categories of quality related to study design, sampling procedures, and interventions, for a total of 13 points. Trials that scored ≥8 were considered to be of higher quality (26).

† Randomization was scored 2 points for being randomized with the methods described, 1 point for being randomized without the methods described, or 0 points for being neither randomized nor having the methods described. Blinding was scored 1 point for being double-blind or 0 points for “other.” Analysis was scored 2 points for being intention-to-treat; all other types of analyses scored 0 points.

‡ Sample selection was scored 1 point for being consecutive eligible or 0 points for being preselected or indeterminate. Sample comparability was scored 1 point for being comparable or 0 points for not being comparable at baseline. Follow-up was scored 1 point for being 100% or 0 points for <100%.

§ Treatment protocol was scored 1 point for being reproducibly described or 0 points for being poorly described. Co-interventions were scored 2 points for being described and equal, 1 point for being described but unequal or indeterminate, or 0 points for not being described. Treatment crossovers (where participants were switched from the control treatment to the experimental treatment) were scored 2 points for being <10%, 1 point for being >10%, and 0 points for not being described.

|| Five reports (45, 50, 53, 56, 57) contained both isocaloric and hypercaloric trials. The MQS was higher for the isocaloric parallel trials than the hypercaloric crossover trials of Stanhope and colleagues (56) and Silbernagel and coworkers (57) because their hypercaloric trials were not blinded and randomized, respectively.

Appendix Table 4. Body Weight Data From Each Trial in the Meta-analysis

Study, Year (Reference)	Design	Comparator	Comparison	Any CHO Comparator				Fructose				Between Interventions						
				Sample Size, n	Start	SD(Start)	End	SD(End)	Δ	SD(Δ)*	Sample Size, n	Start	SD(Start)	End	SD(End)	Δ	SD(Δ)*	MD
Isocaloric trials																		
Diabetes																		
Pelkonen et al, 1972 (30)	C	Starch	ED	10	-	60.05	7.56	-	-	-	59.80	7.91	-	-	-	-0.25	(0.39)	
McAteer et al, 1987 (31)	C	Starch	ED	10	-	59.30	5.08	-	-	-	59.50	5.38	-	-	-	0.20	(0.26)	
Osei et al, 1987 (32)	P	Starch	ED	9	82.50	12.00	6.00	-	-	-	83.80	15.60	-	-	-	0.80	(3.94)	
Grigosco et al, 1988 (33)	C	Starch	ED	8	74.30	12.40	12.80	-	-	-	74.30	12.40	-	-	-	-0.10	(0.78)	
Thorburn et al, 1989 (34)	P	Sucrose	ED	3	-	-	23.70	-	-	-	95.30	23.93	-	-	-	0.10	(1.91)	
Anderson et al, 1989 (35)	C	Starch	ED	14	82.27	14.24	15.11	-	-	-	80.00	15.31	-	-	-	2.05	(0.62)	
Osei and Bossetti, 1989 (36)	C	Starch	ED	13	88.30	20.91	21.63	-	-	-	87.70	27.40	-	-	-	2.50	(1.30)	
Thorburn et al, 1990 (37)	C	Sucrose	ED	6	-	98.93	23.23	-	-	-	98.43	22.70	-	-	-	-0.50	(0.78)	
Blayo et al, 1990 (38)	P	Starch	Change from baseline	8	-	-	-	1.70	(1.64)	-	-	-	-	1.70	(1.67)	0.00	(0.63)	
	P	Sucrose	Change from baseline	6	-	-	-	1.30	(1.64)	-	-	-	-	1.70	(1.67)	0.40	(0.68)	
	P	Combined†	Change from baseline	14	-	-	-	1.53	(1.64)	-	-	-	-	1.70	(1.67)	0.17	(0.52)	
Bantle et al, 1992 (39)	C	Starch	ED	18	80.70	21.21	79.90	21.21	-	-	79.70	20.36	-	-	-	-0.20	0.62	
Koivisto and Yki-Jarvinen, 1993 (40)	C	Starch	ED	10	81.80	15.81	81.50	15.81	-	-	82.00	15.81	-	-	-	-0.90	(0.76)	
Malerbi et al, 1996 (41)	C	Starch	ED	16	65.50	8.40	65.30	8.00	-	-	65.90	8.00	-	-	-	0.00	0.02	
	C	Sucrose	ED	16	65.90	8.00	66.00	8.40	-	-	65.90	8.00	-	-	-	-0.70	0.53	
	C	Combined†	ED	16	65.70	8.07	65.65	8.08	-	-	65.90	8.00	-	-	-	-0.35	0.52	
Vaisman et al, 2006 (42)	P	Starch	ED	13	83.40	17.60	83.40	12.50	-	-	82.90	10.90	-	-	-	0.00	(3.54)	
Overweight/obese																		
Rizkalla et al, 1986 (43) (T1)	P	Glucose	Change from baseline	8	75.70	9.05	70.40	9.05	-5.30	2.72	69.80	14.99	-	-	-4.80	2.465296	0.50	0.92
	P	Galactose	Change from baseline	7	64.00	2.70	59.90	2.30	-4.10	1.78	69.80	14.99	-	-	-4.80	2.465296	-0.70	0.79
	P	Combined†	Change from baseline	15	70.24	8.98	65.50	8.52	-4.74	2.34	69.80	14.99	-	-	-4.80	2.465296	-0.06	0.71
Rizkalla et al, 1986 (43) (T2)	P	Glucose	Change from baseline	6	71.90	13.23	67.20	12.49	-4.80	1.96	70.40	12.98	-	-	-5	1.959592	-0.20	0.80
	P	Galactose	Change from baseline	6	69.50	5.88	63.50	5.63	-6.00	0.49	70.40	12.98	-	-	-5	1.959592	1.00	0.58
	P	Combined†	Change from baseline	12	70.70	9.84	65.35	9.44	-5.35	1.50	70.40	12.98	-	-	-5	1.959592	0.35	0.58
Swarbrick et al, 2008 (44)	C	Starch	ED	7	-	-	75.70	24.34	-	-	-	-	-	-	-	-1.10	0.42	
Stanhope et al, 2009 (45)†	P	Glucose	Change from baseline	15	85.90	10.46	87.50	11.23	1.60	2.05	85.70	10.07	-	-	1.30	1.31851	-0.30	0.30
Madero et al, 2011 (46)	P	Starch	Change from baseline	66	82.74	13.32	-	-	-2.94	2.18	79.07	13.38	-	-	-4.07	2.39	-1.13	0.36
Normal weight																		
Kaufmann et al, 1967 (47)	C	Starch	Change from baseline	8	66.40	6.41	65.70	5.80	-0.70	0.89	66.07	5.39	-	-	-0.68	1.34	0.02	0.46
	C	Sucrose	Change from baseline	8	66.59	5.98	66.35	5.50	-0.23	0.78	67.87	4.70	-	-	-1.10	0.84	-0.87	0.39
	C	Glucose	Change from baseline	3	62.96	7.82	62.50	7.03	-0.46	0.90	65.24	5.58	-	-	-0.79	1.02	-0.33	0.09
	C	Combined†	Change from baseline	9	66.39	6.43	65.80	5.92	-0.58	0.65	66.78	5.48	-	-	-0.76	1.28	-0.18	0.41
Forster and Heller, 1973 (48)§	C	Sucrose	ED	6	69.00	10.00	69.00	9.60	-	-	68.00	15.10	-	-	-	-1.10	(1.10)	
	P	Glucose	ED	6	69.20	15.50	67.50	14.90	-	-	68.00	15.10	-	-	-	0.40	(0.92)	

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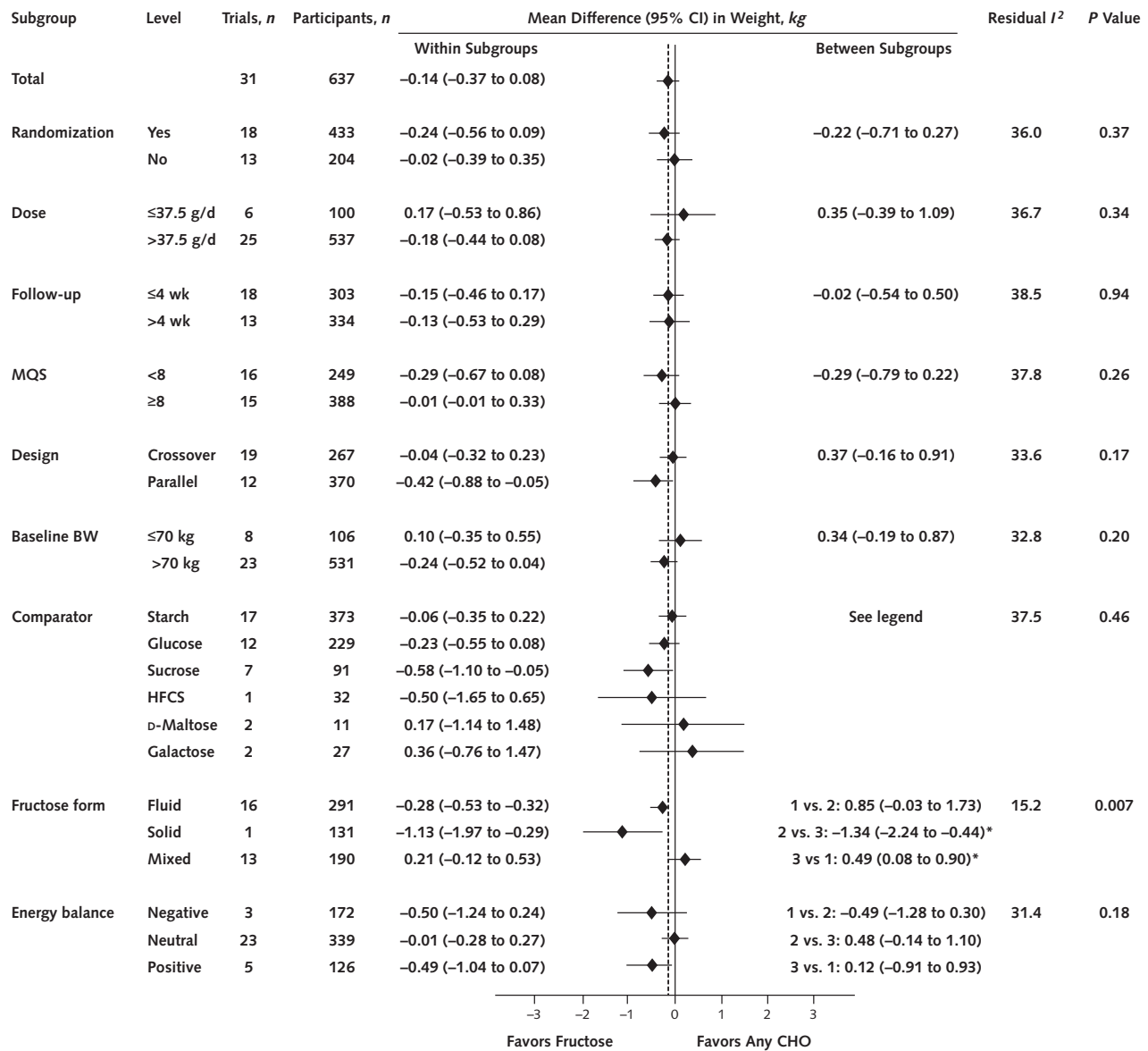
Study, Year (Reference)	Design	Comparator	Comparison	Any CHO Comparator				Fructose				Between Interventions							
				Sample Size, n	Start	SD(Start)	End	SD(End)	Δ	SD(Δ)*	Sample Size, n	Start	SD(Start)	End	SD(End)	Δ	SD(Δ)*	MD	SE(MD)*
Turner et al, 1979 (49) (LC)	P	Combined†	ED	12	69.10	12.44	68.25	11.98	-	-	6	68.00	15.10	67.90	14.90	-	-	-0.35 (0.96)	
Turner et al, 1979 (49) (HC)	C	β-maltose	Change from baseline	6	-	-	-	-	-0.70 (1.64)	-	6	-	-	-	-0.30 (1.67)	-	-	0.40 (0.77)	
Turner et al, 1979 (49) (HC)	C	β-maltose	Change from baseline	5	-	-	-	-	-0.50 (1.64)	-	5	-	-	-	-0.60 (1.67)	-	-	-0.10 (0.84)	
Beck-Nielsen et al, 1980 (50)§	C	Glucose	ED	7	60.90	7.41	61.40	8.20	-	-	8	61.50	9.90	62.00	9.90	-	-	0.60 (3.32)	
Swanson et al, 1992 (51)	C	Starch	ED	14	68.50	11.22	67.40	11.60	-	-	14	68.60	11.60	68.50	11.60	-	-	1.10 (0.47)	
Bantle et al, 2000 (52)	C	Glucose	ED	24	74.10	9.80	72.70	9.80	0.00	1.80	24	74.10	10.29	72.80	10.29	0.00	1.67	0.10 (0.33)	
Ngo Sock et al, 2010 (53)†	C	Glucose	ED	11	-	-	72.90	4.97	-	-	11	-	-	72.50	5.64	-	-	-0.40 (0.31)	
Aeberli et al, 2011 (54) (LD)	C	Starch	ED	29	-	-	74.10	8.70	-	-	29	-	-	73.90	9.10	-	-	-0.20 (0.26)	
Aeberli et al, 2011 (54) (LD)	C	Glucose	ED	29	-	-	74.30	9.10	-	-	29	-	-	73.90	9.10	-	-	-0.40 (0.26)	
Aeberli et al, 2011 (54) (HD)	C	Combined†	ED	29	-	-	74.20	8.62	-	-	29	-	-	73.90	9.10	-	-	-0.30 (0.26)	
Aeberli et al, 2011 (54) (HD)	C	Glucose	ED	29	-	-	73.60	9.20	-	-	29	-	-	73.80	8.90	-	-	0.20 (0.26)	
Aeberli et al, 2011 (54) (HD)	C	Sucrose	ED	29	-	-	74.40	8.60	-	-	29	-	-	73.80	8.90	-	-	-0.60 (0.25)	
Brymora et al, 2011 (55)	C	Combined†	ED	29	-	-	74.00	8.84	-	-	29	-	-	73.80	8.90	-	-	-0.20 (0.25)	
Silbernagel et al, 2011 (56)‡	P	Starch	ED	28	-	-	84.30	10.90	-	-	28	-	-	84.30	11.30	-	-	0.00 (0.33)	
Silbernagel et al, 2011 (56)‡	C	Glucose	Change from baseline	10	80.30	9.17	-	-	1.70	1.26	10	80.70	7.59	-	-	0.20	1.90	-1.50 (0.79)	
Stanhope et al, 2011 (57)‡	P	Glucose	Change from baseline	16	76.80	14.00	77.20	14.80	0.40	(2.87)	16	76.80	10.40	76.70	10.40	-0.10	(2.27)	-0.50	0.44
Stanhope et al, 2011 (57)‡	C	HFCS	Change from baseline	16	74.30	14.80	74.70	14.80	0.40	(2.84)	16	76.80	10.40	76.70	10.40	-0.10	(2.27)	-0.50	0.44
Stanhope et al, 2011 (57)‡	P	Combined†	Change from baseline	32	75.55	14.23	75.95	14.61	0.40	(2.79)	16	76.80	10.40	76.70	10.40	-0.10	(2.27)	-0.50	0.46
Stanhope et al, 2009 (45)‡	C	Diet alone	ED	17	-	-	85.70	10.72	-	-	17	85.90	11.13	87.00	10.72	-	-	1.30	0.32
Stanhope et al, 2009 (45)‡	C	Diet alone	ED	8	-	-	61.50	9.90	-	-	8	-	-	62.00	9.90	-	-	0.50	(4.43)
Beck-Nielsen et al, 1980 (50)§	C	Diet alone	ED	7	-	-	69.30	6.88	-	-	7	-	-	69.50	7.14	-	-	0.20	(0.41)
Le et al, 2006 (59)	C	Diet alone	ED	16	-	-	75.00	4.40	-	-	16	-	-	76.00	4.00	-	-	1.00	0.64
Le et al, 2009 (60) (N)	C	Diet alone	ED	8	-	-	71.20	5.37	-	-	8	-	-	71.80	5.94	-	-	0.60	0.31
Le et al, 2009 (60) (ODM2)	C	Diet alone	ED	11	-	-	71.90	5.31	-	-	11	-	-	72.50	5.64	-	-	0.60	(0.27)
Ngo Sock et al, 2010 (53)‡	C	Diet alone	ED	12	-	-	73.80	6.84	-	-	12	-	-	73.94	7.73	-	-	0.14	0.47
Sobrecases et al, 2010 (61)	C	Diet alone	Change from baseline	10	-	-	80.30	9.17	-	-	10	-	-	-	-	-	-	0.20	0.60
Stanhope et al, 2011 (57)‡	C	Diet alone	ED	16	-	-	76.80	10.40	-	-	16	-	-	76.70	10.40	-	-	-0.10	(0.39)

C = crossover; CHO = carbohydrate; ED = end difference; HC = high-carbohydrate diet; HD = high dose; HFCS = high-fructose corn syrup; LC = low-carbohydrate diet; LD = low dose; MD = mean difference; N = normal; ODM2 = offspring of persons with type 2 diabetes mellitus; P = parallel; T1 = trial 1; T2 = trial 2.
 * SD and SE values in parentheses were borrowed from another group of the same trial or derived from pooled correlation coefficients from a meta-analysis of the individual trial-level correlation coefficients. Data without parentheses were observed or calculated from the individual trials by using the observed or calculated within and between-treatment SDs according to standard formulae (23, 27). Appendix Table 1 provides further details.
 † To mitigate the unit-of-analysis error from including trials with multiple intervention groups, we combined multiple trial groups for any CHO comparator into a single group for pairwise comparison with fructose by using standard formulae (23). Two sample sizes were combined according to the formulae $N_{combined} = N_1 + N_2$ for parallel trials and $N_{combined} = N_1 = N_2$ for crossover trials. Two means were combined according to the formula $M_{combined} = ((N_1 \times M_1) + (N_2 \times M_2)) / (N_1 + N_2)$. Two SDs were combined according to the formula:

$$\sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2} (M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}}$$

If there were 3 groups to combine, we applied the above formulae sequentially combining group 1 and group 2 to create combined group 1 + 2, then combining group 1 + 2 and group 3 to create combined group 1 + 2 + 3.
 ‡ Five reports (45, 50, 53, 56, 57) contained both isocaloric and hypercaloric trials.
 § Förster and Heller's study (48) contained a parallel design for the comparison with sucrose and a crossover design for the comparison with glucose.

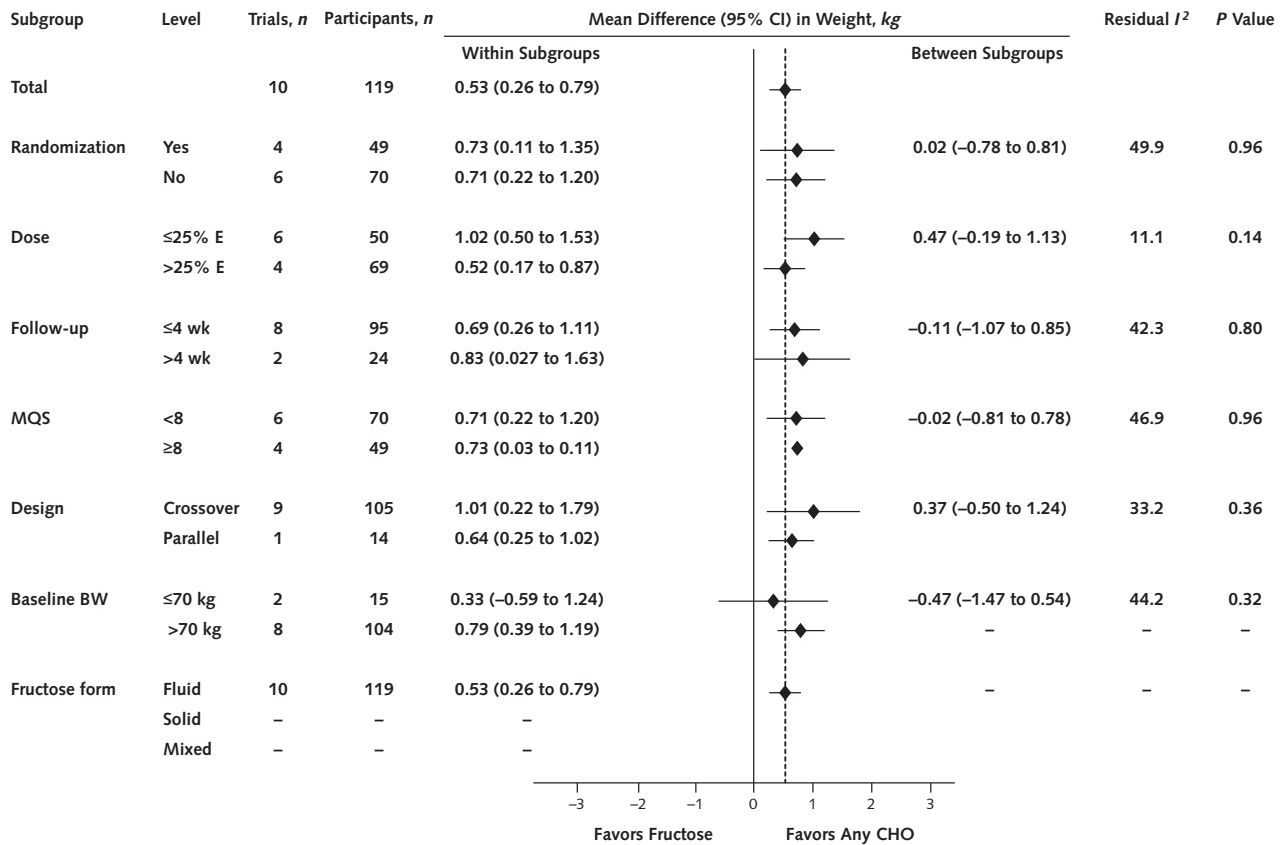
Appendix Figure 1. Subgroup analyses in the isocaloric feeding trials investigating the effect of isocaloric exchange of fructose for carbohydrate on body weight in diabetes, overweight/obese, and normal weight.



Point estimates for each subgroup level (*diamonds*) are the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual *I*² value indicates the interstudy heterogeneity unexplained by the subgroup. Pairwise between-subgroup mean differences (95% CIs) for comparators were as follows: 0.17 kg (-0.25 to 0.59 kg) (1 vs. 2) to 0.51 kg (-0.08 to 1.11 kg) (1 vs. 3) to 0.44 kg (-0.75 to 1.63 kg) (1 vs. 4) to -0.23 kg (-1.57 to 1.11 kg) (1 vs. 5) to -0.42 kg (-1.57 to 0.73 kg) (1 vs. 6) to 0.34 kg (-0.27 to 0.95 kg) (2 vs. 3) to 0.27 kg (-0.93 to 1.46 kg) (2 vs. 4) to -0.40 kg (-1.75 to 0.95 kg) (2 vs. 5) to -0.59 kg (-1.75 to 0.57 kg) (2 vs. 6) to -0.08 kg (-1.34 to 1.19 kg) (3 vs. 4) to -0.75 kg (-2.16 to 0.67 kg) (3 vs. 5) to -0.93 kg (-2.17 to 0.30 kg) (3 vs. 6) to -0.67 kg (-2.42 to 1.08 kg) (4 vs. 5) to -0.86 kg (-2.45 to 0.75 kg) (4 vs. 6) to and -0.19 kg (-1.91 to 1.53 kg) (5 vs. 6). Any CHO = any carbohydrate comparator; BW = body weight; HFCS = high-fructose corn syrup; MQS = Heyland Methodological Quality Score.

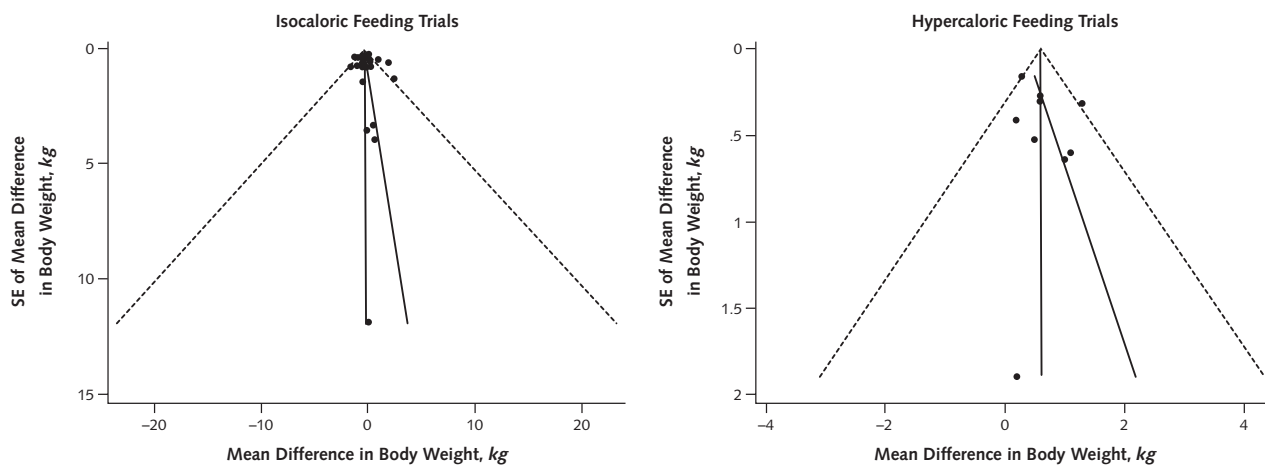
* Statistically significant pairwise subgroup effect modification by meta-regression analyses (*P* < 0.05).

Appendix Figure 2. Subgroup analyses in the hypercaloric feeding trials investigating the effect of a control diet supplemented with 18% to 97% excess energy from fructose on body weight in overweight/obese and normal-weight people.



No subgroup analysis was done by comparator because all trials used diet alone. Point estimates for each subgroup level (*diamonds*) are the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual *I*² value indicates the interstudy heterogeneity unexplained by the subgroup. Significant subgroup effect modification was assessed by meta-regression analyses (*P* < 0.05). Any CHO = any carbohydrate comparator; BW = body weight; E = energy; MQS = Heyland Methodological Quality Score.

Appendix Figure 3. Funnel plots for the effect of fructose on body weight in the isocaloric and hypercaloric feeding trials.



The solid line represents the pooled effect estimate expressed as the weighted mean difference for each analysis. The fitted line corresponds to the best-fit regression of the standard normal deviate of the fructose effect estimate against its precision (Egger test). Dashed lines represent pseudo-95% confidence limits.