Effect of fructose instead of glucose or sucrose on cardiometabolic markers: a systematic review and meta-analysis of isoenergetic intervention trials

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Context: *Free, or added, sugars are considered important determinants in the pandemics of obesity and associated chronic diseases, and fructose has emerged as the sugar of main concern.* ***Objective:*** *The aim of this review was to assess the evidence of the effects of isoenergetic replacement of fructose or high-fructose corn syrup (HFCS) for glucose or sucrose on cardiometabolic markers in controlled dietary intervention trials.* ***Data Sources:*** *The electronic databases PubMed/MEDLINE, the Cochrane Library, and Embase were searched from 1980 to May 5, 2020.* ***Study Selection:*** *Studies were eligible if they measured at least one of the following outcomes: total cholesterol, low- and high-density lipoprotein cholesterol, triacylglycerols, apolipoprotein A1, apolipoprotein B, systolic blood pressure, diastolic blood pressure, fasting glucose, and body weight.* ***Data Extraction:*** *For each outcome, the mean values and the corresponding measure of dispersion were extracted after the intervention or control diet.* ***Data Analysis:*** *Fixed-effects and random-effects models were used to pool study-specific estimates. Between-study heterogeneity was assessed by the χ^2 test and the I^2 statistic and publication bias by the Egger test and funnel plots.* ***Results:*** *Twenty-five studies involving 1744 volunteers were identified. No significant effects were found when fructose or HFCS was substituted for glucose, except for a slight decrease in diastolic blood pressure when fructose was substituted for glucose. Similarly, no effects were found when fructose or HFCS was substituted for sucrose, except for a small increase, of uncertain clinical significance, of apolipoprotein B when HFCS was substituted for sucrose.* ***Conclusions:*** *Isoenergetic substitution of fructose or HFCS for glucose or sucrose has no significant effect on most of the cardiometabolic markers investigated; however, some results were affected by residual between-study heterogeneity and studies with high or unclear risk of bias.* ***Systematic Review Registration:*** *PROSPERO registration number CRD42016042930.*

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INTRODUCTION

Sugars are the smallest and simplest type of carbohydrate and can be classified as either monosaccharides (ie, fructose, glucose, or galactose) or disaccharides (ie, sucrose, lactose, or maltose). Recently, free sugars—defined by the World Health Organization as monosaccharides and disaccharides added to foods and drinks by the manufacturer, cook, or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates—have drawn increasing attention as important determinants in the pandemics of obesity and related chronic diseases.[1] The fructose moiety, in particular, has been suggested as the most harmful component, since it may promote hepatic insulin resistance, dyslipidemia, and hepatic steatosis.[1–11] It has been hypothesized that high fructose consumption increases the levels of its metabolite, methylglyoxal, which—by silencing the AMP-activated protein kinase—leads to de novo hepatic lipogenesis, fatty liver, and insulin resistance.[12] Although fructose is very similar to glucose, it has a completely different metabolic profile. Unlike glucose, it cannot be used directly as an energy source by body cells but needs to be first converted into glucose, lactate, or fatty acids in the liver, intestine, or kidney, which results in lower energy efficiency.[13] In addition, there is less stimulation of insulin and leptin and less suppression of ghrelin with fructose than with glucose, causing less energy expenditure and reduced satiety with fructose compared with glucose intake.[2] Prolonged consumption of diets containing large amounts of fructose could therefore lead to weight gain and obesity as a result of modifications of key signals in the central nervous system that regulate energy balance.[14] If adverse effects of fructose occur at the doses currently consumed by the general population, specific actions to reduce fructose consumption, including reformulation of industrial foods, would be desirable.

Fructose has always been present in the human diet, in fruit, vegetables, and honey, yet fructose consumption has risen drastically since the early 19th century, in part because high-fructose corn syrup (HFCS), a caloric sweetener used by the food industry, has increasingly replaced sucrose. Ecological studies showing a relation between overconsumption of HFCS and increased obesity in the United States have suggested fructose to play a role in weight gain.[2] Other studies, however, have questioned such a role,[15,16] and recent data from the US Department of Agriculture[17] show that, despite a decline in HFCS consumption since the early 2000s, the prevalence of obesity has continued to increase.[18]

Prospective studies assessing the relation between free sugars and health outcomes have generally found positive associations with body weight gain,[1,19,20] cardiovascular diseases,[21,22] and type 2 diabetes.[23–26] However, adjustment for energy intake or body weight generally weakened, or even nullified, the associations. Randomized intervention trials assessing health outcomes, on the other hand, are extremely difficult to conduct and have generally relied on intermediate markers of disease.

In the last 10 years, several systematic reviews and meta-analyses of dietary intervention studies have been conducted on the effect of fructose on body weight and intermediate markers of cardiovascular disease and diabetes.[27–34] However, these meta-analyses differ in their inclusion and exclusion criteria, particularly in relation to the isoenergetic replacement for fructose. In addition, significant residual heterogeneity between studies makes some results nondefinitive. Few meta-analyses have specifically investigated the effect of fructose substitution for glucose,[28,29,31] which is relevant in order to investigate whether fructose is the moiety of concern among the free sugars.

Since several randomized intervention trials on the effect of fructose or HFCS as isocaloric replacement for glucose or sucrose have recently been published,[35–39] this systematic review and meta-analysis includes these latest trials to further investigate whether isoenergetic exchange of fructose or HFCS for glucose or sucrose affects the main cardiometabolic markers. This review is an extension of a previous systematic review and meta-analysis of nutritional intervention trials investigating the effects of free sugars vs complex carbohydrates.[27]

METHODS

Search strategy and selection of studies

The systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[40] (see Appendix S1 in the Supporting Information online) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration no. CRD42016042930). The PICOS (Population, Intervention, Comparison, Outcomes, and Settings)[41] strategy for defining the research question is shown in Table 1. Relevant articles published between 1980 and May 5, 2020, were identified through searches in the PubMed/MEDLINE, Cochrane Library, and Embase databases using strings that included the terms "fructose," "glucose," and "sucrose" (see Table S1 in the Supporting Information online). EndNote software

Table 1 **PICOS criteria for inclusion and exclusion of studies**

P	Population	General population
I	Intervention	Diets containing fructose or high-fructose corn syrup
C	Comparator	Diets containing glucose or sucrose
O	Outcomes	Cardiometabolic markers: total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triacylglycerols, apolipoprotein A1, apolipoprotein B, systolic blood pressure, diastolic blood pressure, fasting blood glucose, and body weight
S	Setting	Isoenergetic controlled nutritional trials

(version X1) was used to assist in the literature search. Potentially relevant reviews and meta-analyses were retrieved and checked to identify additional relevant publications.

Studies were eligible if they met the following criteria: (1) included original data from controlled dietary intervention trials comparing a diet containing a given amount of energy provided by fructose or HFCS with a control diet containing the same amount of energy provided by glucose or sucrose; (2) included interventions lasting at least 1 week; (3) provided mean values after the intervention/control diet for at least one of the parameters of interest, ie, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triacylglycerols (TGs), apolipoprotein AI, apolipoprotein B, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose, and body weight; (4) provided corresponding measures of dispersion or sufficient data to derive them; and (5) were conducted in humans. Abstracts and full-text articles were screened for inclusion by 2 authors independently, and disagreements were resolved by discussion with a third author.

Data collection and quality assessment

For each of the studies selected, the following information was extracted: authors, publication year, country, baseline characteristics of the population (sex, age, body mass index or body weight, and health status), number of individuals involved, study design (crossover, parallel, randomized, blinded), intervention and control diets (including total energy provided by the diet and the percentage of energy exchanged by the specific test sugar), duration of intervention, and source of financial support. For each parameter of interest, the mean was extracted after the intervention/control diet, along with its standard error, standard deviation, or 95%CI and, when available, the mean difference between the 2 groups, along with the corresponding standard error, standard deviation, 95%CI, *P* value, or *t* value. The quality scores of the trials were assigned using the Cochrane Collaboration's risk of bias tool.[42] This tool evaluates possible bias in 7 domains and gives a score of 0 (low risk of bias), 1 (unclear risk of bias), or 2 (high risk of bias). For each study, the scores given for each domain were added together to obtain a final score. Studies were then categorized into 3 groups (low, unclear, or high risk of bias).

Statistical analysis

Diets containing a given amount of energy provided by fructose or HFCS were compared with diets in which the same amount of energy was provided by glucose or sucrose. For the analyses, total cholesterol, LDL-C, HDL-C, TGs, and apolipoproteins were converted into milligrams per deciliter (mg/dL). In each study and for each parameter of interest, when not available in the original study, the mean difference between the intervention and control diet, along with its standard error, was computed. For parallel studies, the standard error was computed using the intervention and control standard errors; for crossover studies, the standard error was computed using the reported *P* value and *t* value.[43,44] A *P* value of 0.5 or of 0.01 was assumed if the difference was reported only as nonsignificant or as significant, respectively. In a few crossover studies that did not report any *P* value or *t* value, this adjustment was not done; in addition, no adjustment was possible when the mean difference was zero.

The study-specific estimates were pooled to calculate the weighted mean difference (WMD) of the parameters of interest between the intervention (fructose or HFCS, overall and separately) and control diets using both fixed-effects and random-effects models.[43] However, only the results from the latter model were presented in order to account for heterogeneity in the estimates (thus providing more conservative assessments). Heterogeneity between studies was assessed using the χ^2 test, defining significant heterogeneity as a *P* value of < 0.10, and was quantified using the I^2 statistic,[45] which gives the percentage of the total variation across studies attributable to heterogeneity rather than to chance.

Subgroup and meta-regression analyses were conducted on the following covariates: health status, body weight, geographical study area, total energy from diet, percentage of energy supplied by the test sugar, and intervention dose. Sensitivity analyses were also conducted by removing one study at a time and by removing nonrandomized trials, studies at higher risk of bias, and studies with only 1 week of intervention.

For each parameter, forest plots were also created by plotting a square for each study. Each square

corresponds to the study-specific mean difference, with the area of the square being proportional to the inverse of the variance of the mean difference, thus giving a measure of the amount of statistical information available. Diamonds were used to plot the summary WMDs and the corresponding 95%CIs. Publication bias was evaluated by visual inspection of the funnel plot and quantified by the Egger test.[46,47] STATA software (release 13) was used for all statistical analyses.[48]

RESULTS

Study selection

The original literature search yielded 2609 records (Figure 1), of which 44 were potentially eligible for inclusion. After closer evaluation, 19 were excluded for different reasons (see Table S2 in the Supporting Information online), thus leaving 25 studies for the present review and meta-analysis.

Trial characteristics

Table 2[35–39,49–68] lists the main characteristics of the 25 studies included in the present meta-analysis. The studies included 1744 individuals (47% female), aged between 13 and 62 years. Four studies included males only,[49–52] while the remaining studies included both sexes. Eighteen studies compared fructose with glucose,[35,36,38,39,49–62] 5 compared HFCS with glucose,[35,36,38,39,58] 10 compared fructose with sucrose,[35,39,50–52,63–67] and 5 compared HFCS with sucrose.[35,37,39,65,66] Thirteen studies had a crossover design[36–38,49–52,54,55,60,63,64,68] and 12 a parallel design.[35,39,53,56–59,61,62,65–67] Five studies were not randomized.[53,54,56,58,64] The duration of intervention ranged between 1 week[36,38,49,53,68] and 12 weeks,[65] with a median of 3 weeks. The fructose dose ranged from 33 g[61] to 250 g,[53] and the intervention dose represented between 6% and 48% of the total daily kilocalories provided by the diets. Three studies were conducted in individuals with diabetes,[54,64,68] 6 in individuals with obesity,[59–62,66,67] and the remainder in healthy

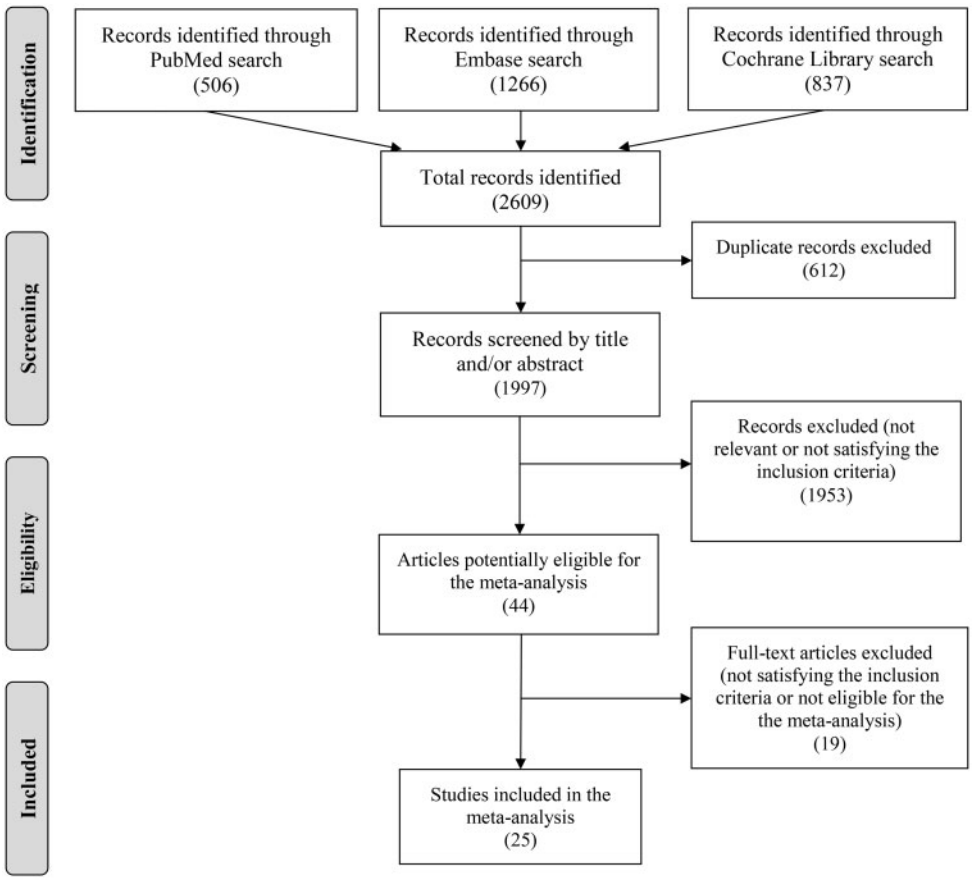

Figure 1 **Flow diagram of the literature search process.** Reasons for exclusion of selected studies are shown in Table S2 in the Supporting Information online.

Table 2 **Main characteristics of the studies included in the review/meta-analysis**

Reference	Country	Study design	No. & sex of participants	Age (years)	Health status	Fructose dose (g/d)	Intervention diet	Control diet	Duration of intervention
Beck-Nielsen et al (1980)[53]	Denmark	Parallel	15 (M, F)	21–35[a]	Healthy	250	High-fructose diet (44% CHO, 38% fat, 18% P), E 2035±190 kcal + 250 g fructose with E 1000 kcal/d	High-glucose diet (44% CHO, 38% fat, 18% P), E 2035±190 kcal + 250 g glucose/d with E 1000 kcal/d	1 wk
Bossetti et al (1984)[63]	USA	Randomized crossover	4 M; 4 F	20–32[a]	Healthy	50–107	Fructose diet [35%–49% CHO (50–107 g/d fructose), 35%–45% fat, 12%–20% P], E 1500–2900 kcal/d	Sucrose diet [35%–49% CHO (50–107 g/d sucrose), 35%–45% fat, 12%–20% P], E 1500–2900 kcal/d	2 wk
Bantle et al (1986)[68]	USA	Randomized crossover	6 M; 6 F 5 M; 7 F	15–32[a] 36–80[a]	T1DM T2DM	85	High-fructose diet [55% CHO (21% fructose), 15% P, 30% fat]	High-sucrose diet [55% CHO (23% sucrose), 15% P, 30% fat]	1 wk
Rizkalla et al (1986)[62]	France	Double-blind, randomized, parallel	7 M; 16 F 7 M; 18 F	22±2[b]	Obese	36	Fructose diet (560 kcal/d) (70 g P, 16 g lipids, 36 g CHO)	Glucose diet (560 kcal/d) (70 g P, 16 g lipids, 36 g CHO)	2 wk
Koh et al (1988)[54]	USA	Crossover	3 M; 6 F 3 M; 6 F	54±6[c] 50±5[c]	IGT NGT	45–83 45–112	Fructose diet [50%–55% CHO (15% fructose), 30%–35% fat, 15%–20% P]	Glucose diet [50%–55% CHO (15% glucose), 30%–35% fat, 15%–20% P]	4 wk
Malerbi et al (1996)[64]	Brazil	Crossover	7 M; 9 F	54.2±2.8[c]	Well-controlled T2DM	63.2	High-fructose diet [55% CHO (1% sucrose + 34% polysaccharides + 20% fructose), 15% P, 30% fat], E 1815 kcal/d	High-sucrose diet [55% CHO (19% sucrose + 35% polysaccharides + 1% fructose), 15% P, 30% fat], E 1815 kcal/d	4 wk
Bantle et al (2000)[55]	USA	Randomized crossover	12 M; 12 F	< 40: 6 M, 6 F ≥ 40: 6 M, 6 F	Healthy	80	Fructose diet [276 g CHO (80 g fructose + 10 g glucose, 134 g starch), 66 g fat, 76 g P]	Glucose diet [276 g CHO (10 g fructose + 80 g glucose), 134 g starch, 66 g fat, 76 g P]	6 wk
Stanhope et al (2009)[56]	USA	Parallel	7 M; 8 F 9 M; 8 F	54±3[c] M; 56±2[c] F 52±4[c] M; 53±2[c] F	Healthy	150	Fructose diet (55% CHO, 20% fat 15% P) + 25% total E as fructose	Glucose diet (55% CHO, 20% fat, 15% P) + 25% total E glucose	8 wk

(continued)

Table 2 **Continued**

Reference	Country	Study design	No. & sex of participants	Age (years)	Health status	Fructose dose (g/d)	Intervention diet	Control diet	Duration of intervention
Ngo Sock et al (2010)[49]	Switzerland	Randomized crossover	9 M; 8 F 11 M	52±4[c] M; 53±2[c] F 24.6±0.6[c]	Healthy	≈ 213	High-fructose diet [55% CHO (11% simple sugars), 30% fat, 15% P] + 3.5 g fructose/kg fat mass/d, corresponding to E increase = 35%	High-glucose diet [55% CHO (11% simple sugars), 30% F, 15% P] + 3.5 g glucose/kg fat mass/d, corresponding to E increase = 35%	1 wk
Aeberli et al (2011)[50]	Switzerland	Double-blind, randomized, crossover	29 M	26.3±6.6[b]	Healthy	40	Moderate-fructose diet [50.9% CHO (85 g/d fructose + 42.5 g/d glucose + 60.1 g/d sucrose), 14.4% P, 34.7% fat], E 2431±671 kcal/d	Moderate-glucose diet [52.5% CHO (49.4 g/d fructose + 86.8 g/d glucose + 65.1 g/d sucrose), 13.1% P, 31.9% fat], E 2505±382 kcal/d	3 wk
						80	High-fructose diet [54.9% CHO (115.9 g/d fructose + 35.8 g/d glucose + 48.6 g/d sucrose), 13.5% P, 31.5% fat], E 2468±559 kcal/d	High-glucose diet [56.5% CHO (46.6 g/d fructose + 122.7 g/d glucose + 59.5 g/d sucrose), 12.8% P, 30.5% fat], E 2533±518 kcal/d High-sucrose diet [54.8% CHO (78.6 g/d fructose + 79.2 g/d glucose + 130.4 g/d sucrose), 13% P, 32.2% fat], E 2596±576 kcal/d	
Silbernagel et al (2011)[57]	Germany	Randomized parallel	5 M; 5 F 6 M; 4 F	32.6±3.4[c] 28.6±2.3[c]	Healthy	150	Fructose diet [50% CHO (150 g fructose), 30% fat, 15% P]	Glucose diet [50% CHO (150 g glucose), 30% fat, 15% P]	4 wk
Stanhope et al (2011)[58]	USA	Parallel	12	27 ±7.2[b]	Healthy	140	Fructose diet [55% CHO (25% fructose + 30% complex CHO), 30% fat, 15% P]	Glucose diet [55% CHO (25% glucose + 30% complex CHO), 30% fat, 15% P]	2 wk

(continued)

Table 2 **Continued**

Reference	Country	Study design	No. & sex of participants	Age (years)	Health status	Fructose dose (g/d)	Intervention diet	Control diet	Duration of intervention
			12 12	28±6.8[b] 28.8±7.6[b]			HFCS diet [55% CHO (25% HFCS + 30% complex CHO), 30% fat, 15% P]		
Lowndes et al (2012)[65]	USA	Double-blind, parallel, randomized, prospective	35 M; 127 F	40.7±10.3[b] 41.7±11.3[b] 41.7±11.1[b] 42.9±11.2[b]	Obese & overweight	55 91	HFCS diet 20%: 234.6 g CHO, 163.2 g total sugars, 46.1 g fat HFCS diet 10%: 241.0 g CHO, 143.9 g total sugars, 88.2 g fat	Sucrose diet 20%: 250.1 g CHO, 163.3 total sugars, 49.0 g fat Sucrose diet 10%: 220.1 g CHO, 125.2 total sugars, 70.5 g fat	12 wk
Aeberli et al (2013)[52]	Switzerland	Randomized crossover	9 M	21–25[a]	Healthy	80	High-fructose diet [56% CHO (80 g/d fructose), 31% fat, 13% P], E 2387 kcal/d	High-glucose diet [54% CHO (80 g/d glucose), 31% fat, 14% P], E 2187 kcal/d High-sucrose diet [54% CHO (80 g/d sucrose), 30% F, 16% P], E 2141 kcal	2 wk
Johnston et al (2013)[59]	UK	Double-blind, randomized, parallel	15 M 17 M	35±11[b] 33±9[b]	Obese & overweight	100	Fructose diet [55 % CHO (25% fructose), 15% P, 30% fat]	Glucose diet [55% CHO (25% glucose), 15% P, 30% fat]	2wk
Heden et al (2014)[60]	USA	Double-blind, randomized, crossover	20 M; 20 F	17.9±0.3[c]	Normal weight & overweight	50	High-fructose diet (50 g fructose + 15 g glucose) in addition to normal diet	High-glucose diet (50 g glucose + 15 g fructose) in addition to normal diet	2wk
Hochuli et al (2014)[51]	Switzerland	Randomized crossover	34 M	20–50[a]	Healthy	80	High-fructose diet [55% CHO (80 g/d fructose), 31% fat, 13% P], E 2444 kcal/d	High-glucose diet [56% CHO (80 g/d glucose), 31% fat, 13% P], E 2457 kcal/d High-sucrose diet [54% CHO (80 g/d sucrose), 32% fat, 14% P], E 2507 kcal/d	3 wk

(continued)

Table 2 **Continued**

Reference	Country	Study design	No. & sex of participants	Age (years)	Health status	Fructose dose (g/d)	Intervention diet	Control diet	Duration of intervention
Jin et al (2014)[61]	USA	Double-blind, randomized, parallel	3 M; 6 F 8 M; 4 F	14.2±0.9[c] 13±0.7[c]	Obese & overweight with NAFLD	33	30 g fructose (114 kcal) added to normal diet	31 g glucose (114 kcal) added to normal diet	4 wk
Lowndes et al (2014)[66]	USA	Double-blind, randomized, parallel	8 M; 9 F	39.3±10.9[b]	Obese & overweight	106	HFCS 20% diet [374.3 g CHO (247.9 g total sugars), 72.2 g fat, 109.1 g P]	Sucrose 20% diet [348.6 g CHO (215.4 g total sugars), 62.2 g fat, 108 g P]	10 wk
			5 M; 8 F	36.5±48[b]		65	HFCS 10% diet [341.6 g CHO (199.6 g total sugars), 86.2 g fat, 122 g P]	Sucrose 10% diet [383 g CHO (218.8 g total sugars), 99.4 g fat, 144.2 g P]	
			9 M; 8 F 12 M; 6 F	39.8±11.6[b] 41.2±12.2[b]					
Lowndes et al (2014)[67]	USA	Double-blind, randomized, parallel	32 M; 26 F	38.6±12.3[b]	Obese & overweight	40	Fructose 8%: 50% CHO (27% sugars)	Sucrose 8%: 48% CHO (26% sugars)	10 wk
			27 M; 26 F	38.9±11.7[b]		91	Fructose 18%: 54% CHO (33% sugars)	Sucrose 18%: 53% CHO (33% sugars)	
			30 M; 30 F	40.4±11.3[b]		145	Fructose 30%: 58% CHO (41% sugars)	Sucrose 30%: 60% CHO (41% sugars)	
			26 M; 38 F 23 M; 28 F 27 M; 26 F	41.3±11.1[b] 43.4±11.3[b] 38.9±11.6[b]					
Kuzma et al (2015)[36]	USA	Double-blind, randomized, crossover	15 M; 9 F	36±12[b]	Healthy	126	Fructose diet [38% CHO + 21.6% (638 g) fructose, 26.7% fat, 14.3% P], E 2970 kcal	Glucose diet [38% CHO + 22% (641 g) glucose, 26.7% fat, 14.3% P], E 2940 kcal/d	1 wk
						70	HFCS diet [38% CHO + 12.1% fructose + 9.9% glucose (640 g HFCS), 26.7% fat, 14.3% P], E 2950 kcal/d		
Lowndes et al (2015)[39]	USA	Partially blinded, randomized, prospective, parallel	11 M; 17 F	36.5±11.3[b]	Healthy	85	HFCS 18% diet: 18% sweetened milk with HFCS (total E, 2384 kcal/d)	Sucrose 18% diet: 18% sweetened milk with sucrose (total E, 2492 kcal/d)	10 wk
						45	Fructose 9% diet: 9% sweetened	Glucose 9% diet: 9% sweetened milk	

(continued)

Table 2 **Continued**

Reference	Country	Study design	No. & sex of participants	Age (years)	Health status	Fructose dose (g/d)	Intervention diet	Control diet	Duration of intervention
			15 M; 18 F	34.1±11.0[b]			milk with fructose (total E, 2198.6 kcal/d)	with glucose (total E, 2189 kcal/d)	
			16 M; 14 F	35.6±10.4[b]					
			17 M; 17 F	37.0±11.7[b]					
Raatz et al (2015)[37]	USA	Randomized crossover	28 (M, F)	38.9±3.6[c]	Healthy	50	HFCS diet (50 g HFCS/d)	Sucrose diet (50 g sucrose/d)	2 wk
			27 (M, F)	52.1±2.7[c]	with IGT				
Angelopoulos et al (2016)[35]	USA	Double-blind, randomized, prospective, parallel	61 (M, F)	36.3[b]	Healthy	87	HFCS-55 18% diet: 18% sweetened milk with HFCS (total E, 2390.1 kcal/d)	Sucrose 18% diet: 18% sweetened milk with sucrose (total E, 2277.5 kcal/d)	10 wk
			64 (M, F)	39.8[b]		47		Glucose 9% diet: 9% sweetened milk with glucose (total E, 2182.2 kcal/d)	
			65 (M, F)	38.7[b]			Fructose 9% diet: 9% sweetened milk with fructose (total E, 2195.4 kcal/d)		
			77 (M, F)	36.1[b]					
Kuzma et al (2018)[38]	USA	Blinded, randomized, crossover	15 M; 9 F	36±12[b]	Healthy	126	Fructose diet [38% CHO + 21.6% (638 g) fructose, 26.7% fat, 14.3% P], E 2970 kcal/d	Glucose diet [38% CHO + 22% (641 g) glucose, 26.7% fat, 14.3% P], E 2940 kcal/d	1 wk
						70	HFCS diet [38% CHO + 12.1% fructose + 9.9% glucose (640 g HFCS), 26.7% fat, 14.3% P], E 2950 kcal/d		

Abbreviations: CHO, carbohydrates; E, energy; F, females; HFCS, high-fructose corn syrup; IGT, impaired glucose tolerance; M, males; NAFLD, nonalcoholic fatty liver disease; NGT, normal glucose tolerance; P, protein; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

aRange.

bMean ± standard deviation.

cMean ± standard error.

individuals. Sixteen studies were conducted in the United States,[35–39,54–56,58,60,61,63,65–68] one in Brazil,[64] and the others in Europe. Only 7 studies were supported by public institutions,[36,38,49,55,57,58,63] with the others being entirely or partially supported by commercial or industrial companies.

A critical appraisal of the 25 studies is provided in the Supporting Information online. Seven studies were classified as having low risk of bias,[36,38,39,50,52,57,59] 6 as having high risk of bias,[51,54–56,63,64] and the remaining 12 as having uncertain risk of bias.[35,37,49,53,58,60–62,65–68] In the studies with high risk of bias, problems in randomization, allocation concealment, blinding of study participants, or outcome assessment were generally identified.

Effects of fructose or HFCS vs glucose or sucrose

Substitution of fructose for glucose did not meaningfully modify total cholesterol, LDL-C, HDL-C, TGs, apolipoprotein B, apolipoprotein AI (Figure 2A–F[49,51,52,54–61]), or SBP (Figure 3A[50,54,56,57]) but significantly decreased DBP (WMD −2.44; 95%CI −4.45 to −0.43; Figure 3B[50,54,56,57]). No meaningful effects were found for fasting blood glucose or body weight (Figure 3C and D[36,38,49–62]).

Significant heterogeneity between studies was detected for the effects on TGs ($I^2 = 48.0\%$; $P = 0.023$; Figure 2D), fasting blood glucose ($I^2 = 47.4\%$; $P = 0.022$; Figure 3C), and body weight ($I^2 = 54.5\%$; $P = 0.002$; Figure 3D).

Subgroup analysis for fructose showed effect modification for fasting blood glucose in studies including only males (WMD −0.41; 95%CI −0.73 to −0.08; see Figure S2 in the Supporting Information online), for body weight in studies exchanging < 20% of kilocalories per day (WMD 0.15; 95%CI 0.06–0.25; see Figure S3 in the Supporting Information online), and in studies with an intervention dose of ≤90 g (WMD 0.15; 95%CI 0.06–0.25; see Figure S4 in the Supporting Information online). In all these subgroups, heterogeneity lost statistical significance. Meta-regression models detected a significant effect of the exchanged intervention energy or the intervention dose on body weight (data not shown).

There were no meaningful effects of the substitution of HFCS for glucose on LDL-C, HDL-C, or TGs (see Figure S5A–C in the Supporting Information online) or on fasting blood glucose or body weight (see Figure S6A and B in the Supporting Information online). There was no heterogeneity between studies.

Substitution of fructose for sucrose did not meaningfully affect total cholesterol, LDL-C, HDL-C, TGs, fasting blood glucose, or body weight (Figure 4A–F[50–52,63,64,68]). There was no heterogeneity in any of the estimates.

Substitution of HFCS for sucrose did not meaningfully affect total cholesterol, LDL-C, HDL-C, or TGs (Figure 5A–D) but significantly increased apolipoprotein B (WMD 11.29; 95%CI 0.80–21.78; Figure 5E). No meaningful effects of HFCS vs sucrose were observed for SBP, DBP, fasting blood glucose, or body weight (Figure 6A–D[35,37,39,65–67]). The estimates were not heterogeneous, except for fasting blood glucose ($I^2 = 64.6\%$; $P = 0.009$; Figure 6C). In particular, 1 study showed a significant increased effect,[39] while 2 studies showed a significant decreased effect[35,67] (Figure 6C). No significant differences were observed for HFCS across strata of dose or percentage of energy exchanged by the test sugar.

No meaningful changes were found in sensitivity analyses when one study at a time, studies at the highest risk of bias, studies not randomized, or studies of less than 2 weeks' duration were removed, except for the effect of fructose on DBP, which lost statistical significance when the study by Koh et al[54] (WMD −1.62; 95%CI −4.15 to 0.16) or the one by Stanhope et al[56] was removed or when studies at the highest risk of bias (see Figure S7 in the Supporting Information online) or those not randomized (WMD 0.37; 95%CI −2.45 to 3.18) were excluded. In addition, when studies at the highest risk of bias were excluded, heterogeneity for the pooled estimates of TGs and fasting glucose lost statistical significance (see Figures S8 and S9 in the Supporting Information online, respectively).

Publication bias

Some evidence of publication bias was found, but only for total cholesterol when fructose was exchanged for glucose, since the funnel plot suggested that small studies reporting a favorable role of fructose may have been missing (Egger test, $P = 0.048$). The trim-and-fill method estimated 3 missing studies, but adjustment for asymmetry did not modify the significance of the estimate (WMD 0.79; 95%CI −3.07 to 1.50; see Figure S10 in the Supporting Information online).

DISCUSSION

This meta-analysis indicates that the isoenergetic substitution of fructose for glucose has no effect on total cholesterol, LDL-C, HDL-C, apolipoprotein B, apolipoprotein AI, or fasting TGs. Results for apolipoprotein B and apolipoprotein AI, however, were based on a few small studies that had either unclear risk of bias[58] or high risk of bias.[55,56] No between-study heterogeneity was found for these markers, except for

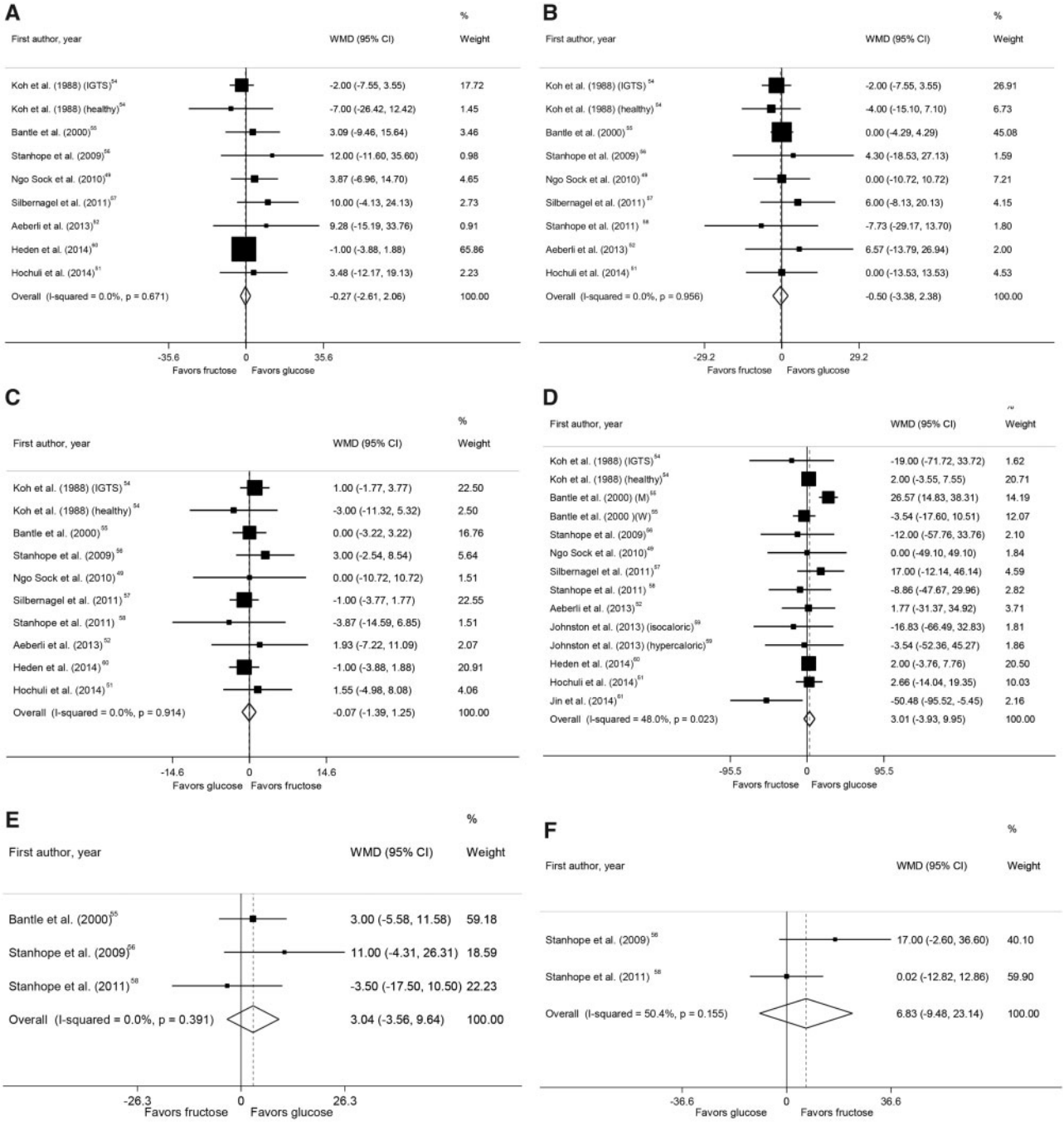

Figure 2 **Forest plots showing the weighted mean difference (WMD) and 95%CI expressed in mg/dL for (A) total cholesterol, (B) LDL cholesterol, (C) HDL cholesterol, (D) triacylglycerols, (E) apolipoprotein B, and (F) apolipoprotein A1 following isoenergetic exchange between fructose and glucose in dietary intervention trials**. WMDs were calculated from random-effects models. *Abbreviations*: IGTS, impaired glucose tolerant subjects; M, men; W, women.

fasting TGs. This heterogeneity persisted after various subgroup analyses and was almost entirely due to 2 studies.[55,61] However, the sensitivity analysis in which trials at the highest risk of bias were excluded confirmed the result of the main analysis, with no heterogeneity detected. Results of subgroup and meta-regression analyses did not support a dose-dependent response for fasting TGs, as has been suggested by other investigations.[69,70] This could be due to the low power to detect this effect, since only few studies included in the present meta-analysis used high doses of fructose[53] or catalytic doses of fructose.[61,62]

Overall, these results do not indicate metabolic differences between fructose and glucose, when consumed isocalorically, on hepatic de novo lipogenesis, which has been observed in animal studies[71–73] and is one of the

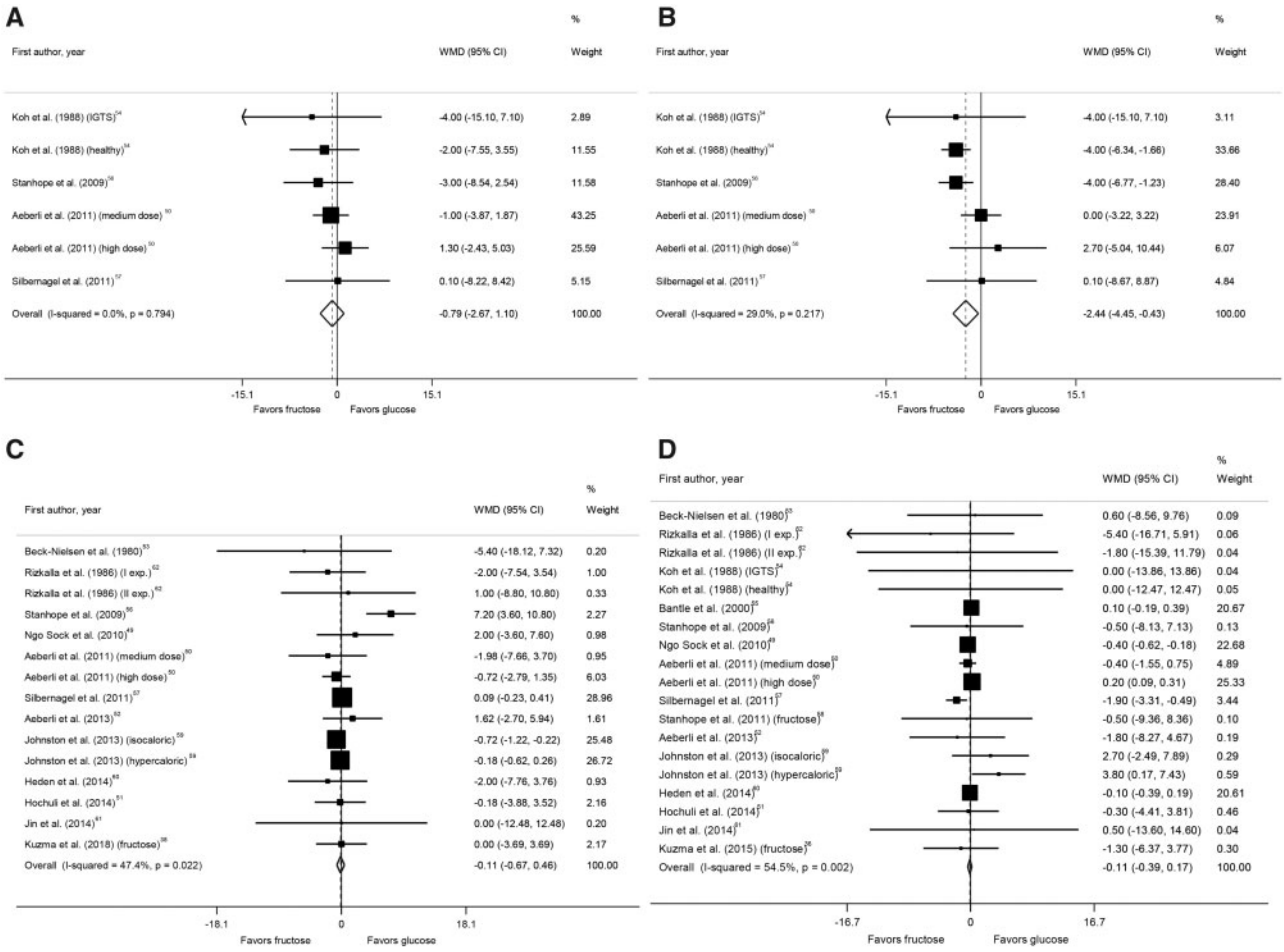

Figure 3 **Forest plots showing the weighted mean difference (WMD) and 95%CI for (A) systolic blood pressure (mmHg), (B) diastolic blood pressure (mmHg), (C) fasting blood glucose (mg/dL), and (D) body weight (kg) following isoenergetic exchange between fructose and glucose in dietary intervention trials**. WMDs were calculated from random-effects models. *Abbreviations*: exp., experiment; IGTS, impaired glucose tolerant subjects.

mechanisms involved in the pathogenesis and progression of nonalcoholic fatty liver disease.[74] They confirm the results for blood lipids reported in a recent meta-analysis that had the same inclusion criteria but a lower number of studies[28]; however, they partially differ from those of another previous meta-analysis that found an increase in total cholesterol, although in the presence of significant heterogeneity.[29]

Fructose substitution for glucose also had no significant effect on SBP, with no heterogeneity between studies. These results differ from those published by Sievenpiper et al,[29] who found a decrease in SBP. In the present review, fructose decreased DBP, although this decrease appears to be driven by 2 trials assessed to have high risk of bias,[54,56] as shown in the sensitivity analysis.

The fasting blood glucose results are slightly different from those reported in the previous meta-analysis, which showed a small but significant reduction when fructose was substituted for glucose [32] and an effect modification by dose.[75] The estimates are affected by significant between-study heterogeneity, explained in part by sex, since the effect on fasting blood glucose in trials involving only males showed a small but significant decrease, with no heterogeneity detected. It was not possible to assess whether this result was due to sex-specific responses to fructose because there were very few trials in females. Sex differences in relation to the metabolism of fructose or sucrose have been observed in animals[76–78] and humans[79]; however, the direction of such results was opposite that found in the present study, since reduced metabolic effects, including lower fasting glucose, were found in females compared with males.

In contrast to the 2 meta-analyses mentioned above,[28,29] which found a small but significant reduction in body weight when fructose was isoenergetically exchanged for glucose, no significant differences were found. These results were significantly heterogeneous, but, as suggested by the sensitivity and subgroup

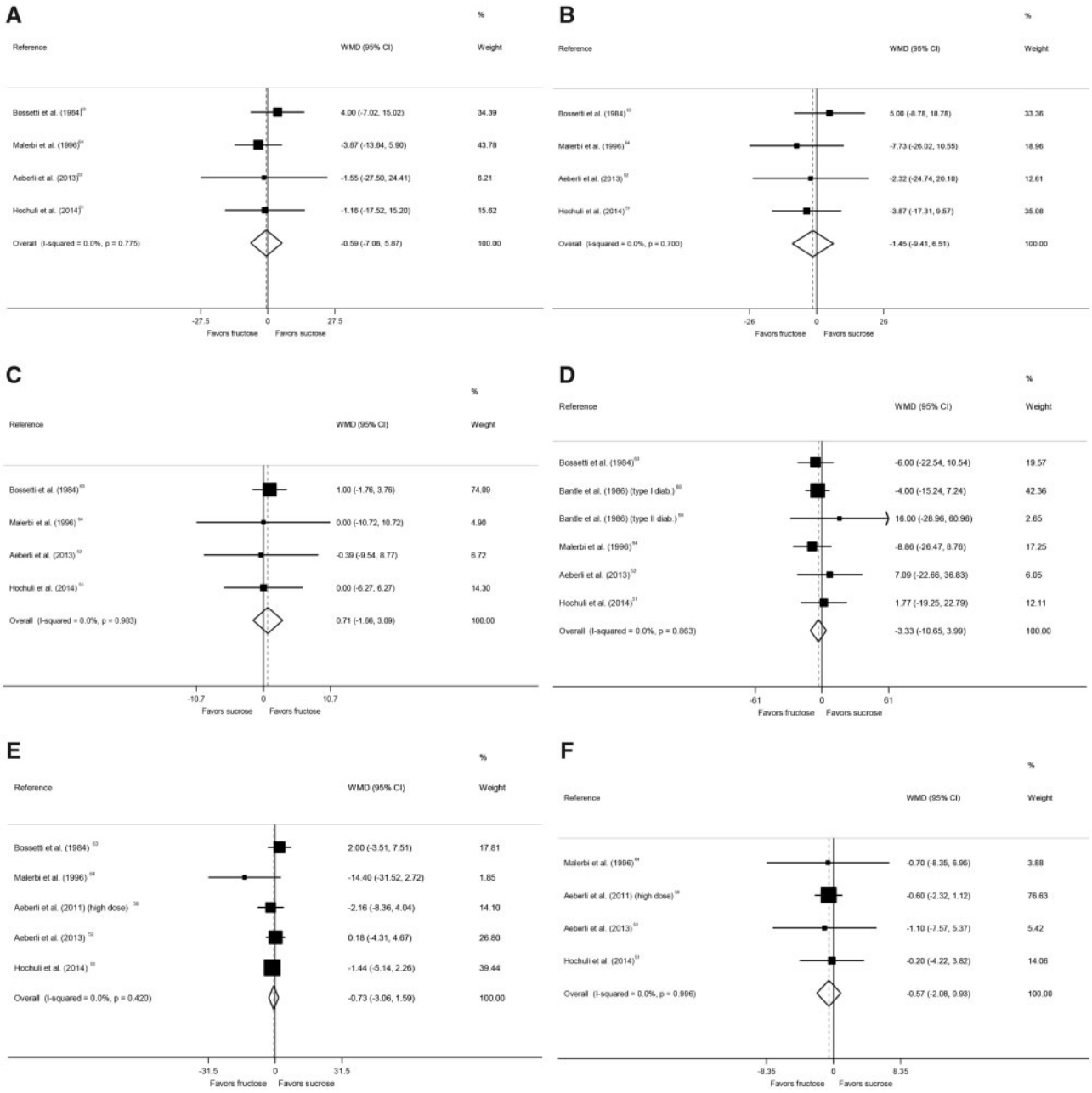

Figure 4 **Forest plots showing the weighted mean difference (WMD) and 95%CI for (A) total cholesterol (mg/dL), (B) LDL cholesterol (mg/dL), (C) HDL cholesterol (mg/dL), (D) triacylglycerols (mg/dL), (E) fasting blood glucose (mg/dL), and (F) body weight (kg) following isoenergetic exchange between fructose and sucrose in dietary intervention trials**. WMDs were calculated from random-effects models. *Abbreviation*: diab., diabetes.

analyses, heterogeneity was attributable almost entirely to the results of the study by Aeberli et al,[50] which had the highest intervention dose but was not included in the previously meta-analyses.[28,29] The significant increases in body weight in trials that investigated doses of $\leq$ 90 g or exchanged $\leq$ 20% of kilocalories per day were also driven by the study of Aeberli et al.[50] Overall, these results indicate that isoenergetic exchange of fructose or HFCS for glucose has no effect on body weight.

Given the chemical structure of sucrose, which is a disaccharide composed of one molecule of glucose and one molecule of fructose, diluted effects were expected when fructose was compared with sucrose instead of glucose, and no effects were expected when HFCS was compared with sucrose. Consistent with this hypothesis, no significant effect on total cholesterol, LDL-C, HDL-C, TGs, SBP, DBP, fasting blood glucose, or body weight were found when fructose or HFCS was substituted for sucrose. These results were in line with

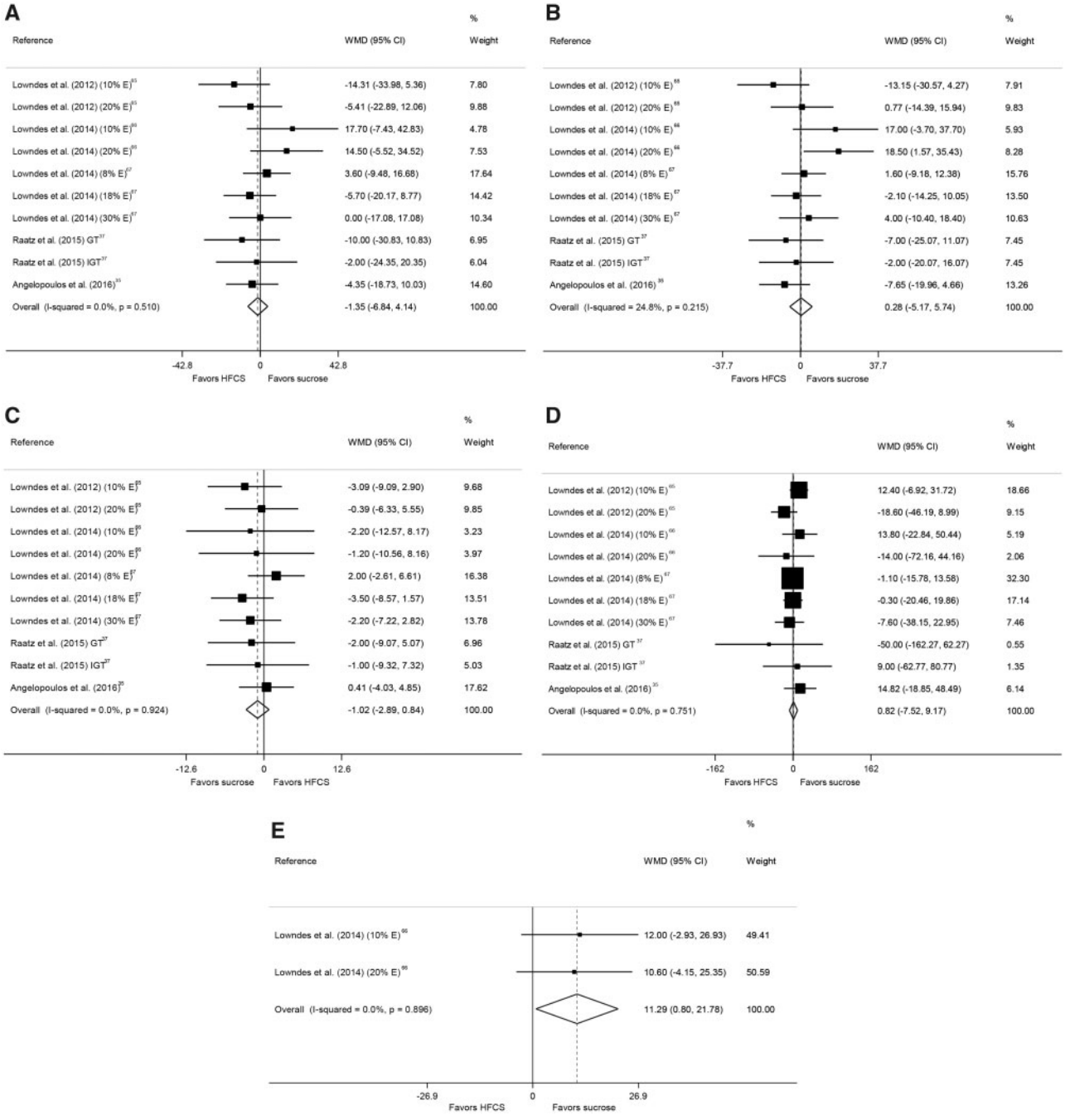

Figure 5 **Forest plots showing the weighted mean difference (WMD) and 95%CI expressed in mg/dL for (A) total cholesterol, (B) LDL cholesterol, (C) HDL cholesterol, (D) triacylglycerols, and (E) apolipoprotein B following isoenergetic exchange between high-fructose corn syrup (HFCS) and sucrose in dietary intervention trials.** WMDs were calculated from random-effects models. *Abbreviations*: E, energy; GT, glucose tolerance; IGT, impaired glucose tolerance.

those of previous meta-analyses,[28,29] with the only difference being that Evans et al[28] found a small but significant decrease in fasting blood TGs when fructose was substituted for sucrose, although that result was based on a smaller number of studies. In the present analysis, substitution of HFCS for sucrose significantly raised apolipoprotein B. This result, however, should be considered with caution because it was based on a single study that was assessed to have an unclear risk of bias. Moreover, the biochemical similarity between HFCS and sucrose, coupled with the absence of an effect on apolipoprotein B when fructose was substituted for glucose, makes it unlikely that HFCS had a causal role in the increase of apolipoprotein B. Moreover, even though apolipoprotein B, among the blood lipids, is considered one of the most reliable risk indicators of

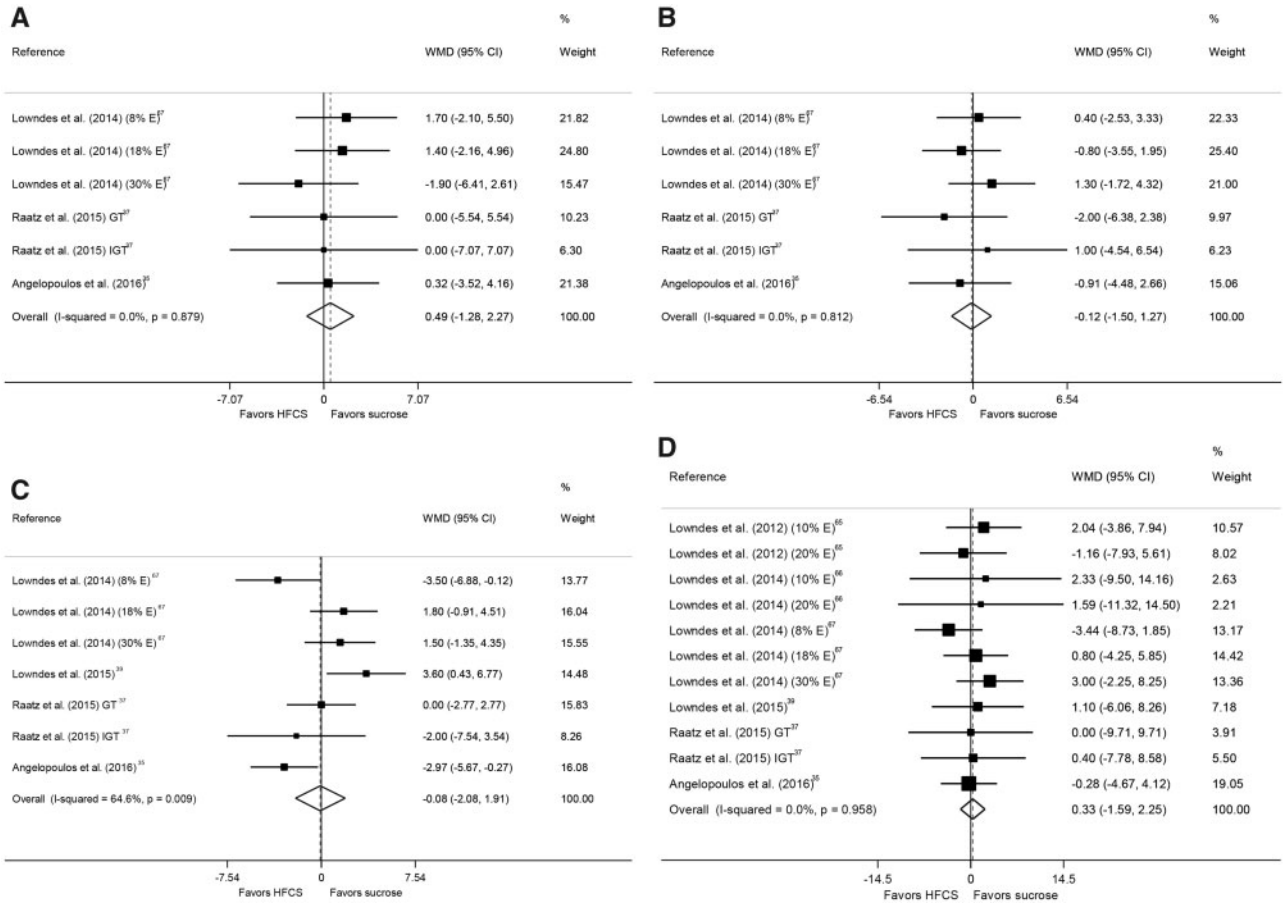

Figure 6 **Forest plots showing the weighted mean difference (WMD) and 95%CI for (A) systolic blood pressure (mmHg), (B) diastolic blood pressure (mmHg), (C) fasting blood glucose (mg/dL), and (D) body weight (kg) following isoenergetic exchange between high-fructose corn syrup (HFCS) and sucrose in dietary intervention trials**. WMDs were calculated from random-effects models. *Abbreviations*: E, energy; GT, glucose tolerance; IGT, impaired glucose tolerance.

cardiovascular disease,[80] the clinical relevance of a such variation, without any variation in other related markers, is questionable.

Overall, when fructose or HFCS was compared with sucrose at the doses used in the studies included in the present meta-analysis, there were no significant variations in cardiometabolic markers, yet alterations in such markers would be expected if fructose were a highly lipogenic sugar that increases the risk of nonalcoholic fatty liver disease, metabolic syndrome, and cardiovascular disease.

Strengths and limitations

A strength of this meta-analysis is its inclusion of new studies that, compared with older studies, had a larger sample size,[35] a longer duration,[35,39] and a lower risk of bias.[36,38,39] Another strength is that it included only studies in which the intervention and control diets were matched for energy, and the intervention diets were similar to diets that would be commonly consumed in western countries. Indeed, the mean dose of fructose in the studies included in this meta-analysis was 86 g/d, which corresponds to 16% of the total energy provided by diet. These figures are similar to the mean intakes of added sugars estimated for the adult population in Europe[81] and the United States,[82] ie, 42 to 106 g/d and 76.7 g/d, respectively. In addition, no evidence of publication bias was detected for any of the cardiometabolic markers analyzed except total cholesterol.

Among the limitations of this review, the most important are those inherent to the original studies, most of which had high or unclear risk of bias and had a low power to detect significant differences. In addition, most of the studies were of short duration (less than 4 weeks), which limits their ability to detect potential small effects following lifetime exposure to fructose. Finally, as already mentioned, all of the included trials measured markers of disease rather than health outcomes, and therefore the clinical relevance of the small differences observed is unclear.

CONCLUSION

The potential harm from the intake of dietary fructose or HFCS on obesity and its related chronic diseases has garnered much attention. However, this systematic review and meta-analysis of nutritional isoenergetic intervention trials found no evidence of a significant effect on the cardiometabolic markers investigated, with the exception of a slight decrease in DBP when fructose was substituted for glucose and a small increase in apolipoprotein B when HFCS was substituted for sucrose. However, some results were affected by residual between-study heterogeneity and by studies assessed to have high or unclear risk of bias

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Declaration of interest. The authors have no relevant interests to declare.

SUPPORTING INFORMATION

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 **PRISMA 2009 checklist.**

Table S1 **Search strategy.**

Table S2 **Studies excluded from the meta-analysis, along with reasons for exclusion.**

Figure S1 **Risk-of-bias assessment of the 25 studies included in the meta-analysis.**

Figure S2 **Forest plots of subgroup analysis by sex, showing weighted mean difference (WMD) and corresponding 95%CI for fasting blood glucose (mg/dL) following isoenergetic exchange between fructose and glucose in dietary intervention trials**. WMDs were calculated from random-effects models.

Figure S3 **Forest plots of subgroup analysis by kilocalories per day exchanged by fructose ($\geq$ 20% or < 20% of total kilocalories per day), showing weighted mean difference (WMD) and corresponding 95%CI for body weight (kg) following isoenergetic exchange between fructose and glucose in dietary intervention trials**. WMDs were calculated from random-effects models. IGTS, impaired glucose tolerant subjects.

Figure S4 **Forest plots of subgroup analysis by intervention dose (> 90 g and $\leq$ 90 g of fructose), showing weighted mean difference (WMD) and corresponding 95%CI for body weight (kg) following isoenergetic exchange between fructose and glucose in dietary intervention trials**. WMDs were calculated from random-effects models. IGTS, impaired glucose tolerant subjects.

Figure S5 **Forest plots showing the weighted mean difference (WMD) and 95%CI expressed in mg/dL for (A) LDL cholesterol, (B) HDL cholesterol, and (C) triacylglycerols following isoenergetic exchange between high-fructose corn syrup (HFCS) and glucose in dietary intervention trials**. WMDs were calculated from random-effects models.

Figure S6 **Forest plots showing the weighted mean difference (WMD) and 95%CI for (A) fasting blood glucose (mg/dL) and (B) body weight (kg) following isoenergetic exchange between high-fructose corn syrup (HFCS) and glucose in dietary intervention trials**. WMDs were calculated from random-effects models.

Figure S7 **Forest plot of sensitivity analysis conducted by removing studies at highest risk of bias, showing weighted mean difference (WMD) and corresponding 95%CI for diastolic blood pressure (mmHg) following isoenergetic exchange between fructose and glucose in dietary intervention trials.** WMDs were calculated from random-effects models.

Figure S8 **Forest plot of sensitivity analysis conducted by removing studies at highest risk of bias, showing weighted mean difference (WMD) and corresponding 95%CI for fasting triacylglycerols (mg/dL) following isoenergetic exchange between fructose and glucose in dietary intervention trials.** WMDs were calculated from random-effects models.

Figure S9 **Forest plot of sensitivity analysis conducted by removing studies at highest risk of bias, showing weighted mean difference (WMD) and corresponding 95%CI for fasting blood glucose (mg/dL) following isoenergetic exchange between fructose and glucose in dietary intervention trials**. WMDs were calculated from random-effects models.

Figure S10 **Funnel plot of dietary intervention trials of isoenergetic exchanges between fructose and glucose for total cholesterol.**

REFERENCES

1. Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ*. 2012;346:e7492.
2. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr*. 2004;79:537–543.
3. Lustig RH. Fructose: metabolic, hedonic, and societal parallels with ethanol. *J Am Diet Assoc*. 2010;110:1307–1321.
4. Lustig RH, Schmidt LA, Brindis CD. Public health: the toxic truth about sugar. *Nature*. 2012;482:27–29.
5. Bremer AA, Lustig RH. Effects of sugar-sweetened beverages on children. *Pediatr Ann*. 2012;41:26–30.
6. Lustig RH. Fructose: it's "alcohol without the buzz". *Adv Nutr*. 2013;4:226–235.
7. Gugliucci A, Lustig RH, Caccavello R, et al. Short-term isocaloric fructose restriction lowers apoC-III levels and yields less atherogenic lipoprotein profiles in children with obesity and metabolic syndrome. *Atherosclerosis*. 2016;253:171–177.
8. Lustig RH. Fructose and nonalcoholic fatty liver disease. *J Calif Dent Assoc*. 2016;44:613–617.
9. Lustig RH, Mulligan K, Noworolski SM, et al. Isocaloric fructose restriction and metabolic improvement in children with obesity and metabolic syndrome. *Obesity*. 2016;24:453–460.
10. Stanhope KL. Sugar consumption, metabolic disease and obesity: the state of the controversy. *Crit Rev Clin Lab Sci*. 2016;53:52–67.
11. Schwarz J-M, Noworolski SM, Erkin-Cakmak A, et al. Effects of dietary fructose restriction on liver fat, de novo lipogenesis, and insulin kinetics in children with obesity. *Gastroenterology*. 2017;153:743–752.
12. Gugliucci A. Fructose surges damage hepatic adenosyl-monophosphate-dependent kinase and lead to increased lipogenesis and hepatic insulin resistance. *Med Hypotheses*. 2016;93:87–92.
13. Campos VC, Tappy L. Physiological handling of dietary fructose-containing sugars: implications for health. *Int J Obes (Lond)*. 2016;40(suppl 1):S6–S11.
14. Stanhope KL, Havel PJ. Endocrine and metabolic effects of consuming beverages sweetened with fructose, glucose, sucrose, or high-fructose corn syrup. *Am J Clin Nutr*. 2008;88:1733S–1737S.
15. White JS. Straight talk about high-fructose corn syrup: what it is and what it ain't. *Am J Clin Nutr*. 2008;88:1716S–1721S.
16. Klurfeld DM, Foreyt J, Angelopoulos TJ, et al. Lack of evidence for high fructose corn syrup as the cause of the obesity epidemic. *Int J Obes (Lond)*. 2013;37:771–773.
17. US Department of Agriculture, Agricultural Research Service. Sugar and sweeteners yearbook tables. US Dept of Agriculture website. https://www.ers.usda.gov/data-products/sugar-and-sweeteners-yearbook-tables.aspx.Accessed November 14, 2019.
18. Centers for Disease Control of Prevention. Overweight & obesity. Centers for Disease Control and Prevention website. https://www.cdc.gov/obesity/index.html. Published September 11, 2019. Accessed November 14, 2019.
19. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr*. 2006;84:274–288.
20. Malik VS, Pan A, Willett WC, et al. Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. *Am J Clin Nutr*. 2013;98:1084–1102.
21. Yang Q, Zhang Z, Gregg EW, et al. Added sugar intake and cardiovascular diseases mortality among US adults. *JAMA Intern Med*. 2014;174:516–524.
22. Malik VS. Sugar sweetened beverages and cardiometabolic health. *Curr Opin Cardiol*. 2017;32:572–579.
23. Montonen J, Järvinen R, Knekt P, et al. Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. *J Nutr*. 2007;137:1447–1454.
24. Malik VS, Popkin BM, Bray GA, et al. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. 2010;33:2477–2483.
25. Malik VS, Hu FB. Sweeteners and risk of obesity and type 2 diabetes: the role of sugar-sweetened beverages. *Curr Diab Rep*. 2012;12:195–203.
26. Imamura F, O'Connor L, Ye Z, 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.
27. Fattore E, Botta F, Agostoni C, et al. Effects of free sugars on blood pressure and lipids: a systematic review and meta-analysis of nutritional isoenergetic intervention trials. *Am J Clin Nutr*. 2017;105:42–56.
28. Evans RA, Frese M, Romero J, et al. Chronic fructose substitution for glucose or sucrose in food or beverages has little effect on fasting blood glucose, insulin, or triglycerides: a systematic review and meta-analysis. *Am J Clin Nutr*. 2017;106:519–529.
29. Sievenpiper JL, de Souza RJ, Cozma AI, et al. Fructose vs. glucose and metabolism: do the metabolic differences matter? *Curr Opin Lipidol*. 2014;25:8–19.
30. Kelishadi R, Mansourian M, Heidari-Beni M. Association of fructose consumption and components of metabolic syndrome in human studies: a systematic review and meta-analysis. *Nutrition*. 2014;30:503–510.
31. Evans RA, Frese M, Romero J, et al. Fructose replacement of glucose or sucrose in food or beverages lowers postprandial glucose and insulin without raising triglycerides: a systematic review and meta-analysis. *Am J Clin Nutr*. 2017;106:506–518.
32. Chiavaroli L, de Souza RJ, Ha V, et al. Effect of fructose on established lipid targets: a systematic review and meta-analysis of controlled feeding trials. *J Am Heart Assoc*. 2015;4:E001700.doi:10.1161/JAHA.114.001700
33. Sievenpiper JL, de Souza RJ, Mirrahimi A, et al. Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156:291–304.
34. Ter Horst KW, Schene MR, Holman R, et al. Effect of fructose consumption on insulin sensitivity in nondiabetic subjects: a systematic review and meta-analysis of diet-intervention trials. *Am J Clin Nutr*. 2016;104:1562–1576.
35. Angelopoulos TJ, Lowndes J, Sinnett S, et al. Fructose containing sugars at normal levels of consumption do not effect adversely components of the metabolic syndrome and risk factors for cardiovascular disease. *Nutrients*. 2016;8:179.
36. Kuzma JN, Cromer G, Hagman DK, et al. No difference in ad libitum energy intake in healthy men and women consuming beverages sweetened with fructose, glucose, or high-fructose corn syrup: a randomized trial. *Am J Clin Nutr*. 2015;102:1373–1380.
37. Raatz SK, Johnson LK, Picklo MJ. Consumption of honey, sucrose, and high-fructose corn syrup produces similar metabolic effects in glucose-tolerant and -intolerant individuals. *J Nutr*. 2015;145:2265–2272.
38. Kuzma JN, Cromer G, Hagman DK, et al. Consuming glucose-sweetened, not fructose-sweetened, beverages increases fasting insulin in healthy humans. *Eur J Clin Nutr* 2019;73:487–490.
39. 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;7:8830–8845.
40. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
41. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. 1996. *Clin Orthop Relat Res*. 2007;455:3–5. PMID: 17340682
42. Higgins JPT, Altman DG, Gøtzsche PC et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
43. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 1st ed. Chichester, UK: John Wiley & Sons; 2008. www.training.cochrane.org/handbook. Accessed October 16, 2018.
44. Elbourne DR, Altman DG, Higgins JPT, et al. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31:140–149.
45. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
46. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
47. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol*. 2000;53:207–216.
48. STATA [statistical software program]. Release 13. College Station, TX: StataCorp LP; 2013.
49. Ngo Sock ET, Lê K-A, Ith M, et al. Effects of a short-term overfeeding with fructose or glucose in healthy young males. *Br J Nutr*. 2010;103:939–943.
50. Aeberli I, Gerber PA, Hochuli M, et al. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. *Am J Clin Nutr*. 2011;94:479–485.
51. Hochuli M, Aeberli I, Weiss A, et al. Sugar-sweetened beverages with moderate amounts of fructose, but not sucrose, induce fatty acid synthesis in healthy young men: a randomized crossover study. *J Clin Endocrinol Metab*. 2014;99:2164–2172.
52. Aeberli I, Hochuli M, Gerber PA, et al. Moderate amounts of fructose consumption impair insulin sensitivity in healthy young men: a randomized controlled trial. *Diabetes Care*. 2013;36:150–156.
53. Beck-Nielsen H, Pedersen O, Lindskov HO. Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects. *Am J Clin Nutr*. 1980;33:273–278.
54. Koh ET, Ard NF, Mendoza F. Effects of fructose feeding on blood parameters and blood pressure in impaired glucose-tolerant subjects. *J Am Diet Assoc*. 1988;88:932–938.
55. Bantle JP, Raatz SK, Thomas W, et al. Effects of dietary fructose on plasma lipids in healthy subjects. *Am J Clin Nutr*. 2000;72:1128–1134.
56. Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest*. 2009;119:1322–1334.
57. Silbernagel G, Machann J, Unmuth S, 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;106:79–86.

58. Stanhope KL, Bremer AA, Medici V, et al. Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women. *J Clin Endocrinol Metab*. 2011;96:E1596–E1605.
59. Johnston RD, Stephenson MC, Crossland H, et al. No difference between high-fructose and high-glucose diets on liver triacylglycerol or biochemistry in healthy overweight men. *Gastroenterology*. 2013;145:1016.e2–1025.e2.
60. Heden TD, Liu Y, Park Y-M, et al. Moderate amounts of fructose- or glucose-sweetened beverages do not differentially alter metabolic health in male and female adolescents. *Am J Clin Nutr*. 2014;100:796–805.
61. Jin R, Welsh JA, Le N-A, et al. Dietary fructose reduction improves markers of cardiovascular disease risk in Hispanic-American adolescents with NAFLD. *Nutrients*. 2014;6:3187–3201.
62. Rizkalla SW, Baigts F, Fumeron F, et al. Comparative effects of several simple carbohydrates on erythrocyte insulin receptors in obese subjects. *Pharmacol Biochem Behav*. 1986;25:681–688.
63. Bossetti BM, Kocher LM, Moranz JF, et al. The effects of physiologic amounts of simple sugars on lipoprotein, glucose, and insulin levels in normal subjects. *Diabetes Care*. 1984;7:309–312.
64. Malerbi DA, Paiva ESA, Duarte AL, et al. Metabolic effects of dietary sucrose and fructose in type II diabetic subjects. *Diabetes Care*. 1996;19:1249–1256.
65. Lowndes J, Kawiecki D, Pardo S, et al. The effects of four hypocaloric diets containing different levels of sucrose or high fructose corn syrup on weight loss and related parameters. *Nutr J*. 2012;11:55.
66. Lowndes J, Sinnett S, Pardo S, et al. The effect of normally consumed amounts of sucrose or high fructose corn syrup on lipid profiles, body composition and related parameters in overweight/obese subjects. *Nutrients*. 2014;6:1128–1144.
67. Lowndes J, Sinnett S, Yu Z, et al. The effects of fructose-containing sugars on weight, body composition and cardiometabolic risk factors when consumed at up to the 90th percentile population consumption level for fructose. *Nutrients*. 2014;6:3153–3168.
68. Bantle JP, Laine DC, Thomas JW. Metabolic effects of dietary fructose and sucrose in types I and II diabetic subjects. *JAMA*. 1986;256:3241–3246.
69. Livesey G, Taylor R. Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies. *Am J Clin Nutr*. 2008;88:1419–1437. doi:10.3945/ajcn.2007.25700
70. Livesey G. Fructose ingestion: dose-dependent responses in health research. *J Nutr*. 2009;139:1246S–1252S.
71. Softic S, Gupta MK, Wang G-X, et al. Divergent effects of glucose and fructose on hepatic lipogenesis and insulin signaling. *J Clin Invest*. 2017;127:4059–4074.
72. Reaven GM. Effects of fructose on lipid metabolism. *Am J Clin Nutr*. 1982;35:627–627.
73. Park OJ, Cesar D, Faix D, et al. Mechanisms of fructose-induced hypertriglyceridaemia in the rat. Activation of hepatic pyruvate dehydrogenase through inhibition of pyruvate dehydrogenase kinase. *Biochem J*. 1992;282(pt 3):753–757.
74. Softic S, Cohen DE, Kahn CR. Role of dietary fructose and hepatic de novo lipogenesis in fatty liver disease. *Dig Dis Sci*. 2016;61:1282–1293.
75. Choo VL, Viguiliouk E, Blanco Mejia S, et al. Food sources of fructose-containing sugars and glycaemic control: systematic review and meta-analysis of controlled intervention studies. *BMJ*. 2018;363:K4644.
76. Galipeau DM, Yao L, McNeill JH. Relationship among hyperinsulinemia, insulin resistance, and hypertension is dependent on sex. *Am J Physiol Heart Circ Physiol*. 2002;283:H562–H567.
77. Horton TJ, Gayles EC, Prach PA, et al. Female rats do not develop sucrose-induced insulin resistance. *Am J Physiol*. 1997;272(5 pt 2):R1571–1576.
78. Pektaş MB, Sadi G, Akar F. Long-term dietary fructose causes gender-different metabolic and vascular dysfunction in rats: modulatory effects of resveratrol. *Cell Physiol Biochem*. 2015;37:1407–1420.
79. Couchepin C, Lê K-A, Bortolotti M, et al. Markedly blunted metabolic effects of fructose in healthy young female subjects compared with male subjects. *Diabetes Care*. 2008;31:1254–1256.
80. Sniderman AD, Pencina M, Thanassoulis G. ApoB. *Circ Res*. 2019;124:1425–1427.
81. Azaïs-Braesco V, Sluik D, Maillot M, et al. A review of total & added sugar intakes and dietary sources in Europe. *Nutr J*. 2017;16:6.
82. Welsh JA, Sharma AJ, Grellinger L, et al. Consumption of added sugars is decreasing in the United States. *Am J Clin Nutr*. 2011;94:726–734.