ORIGINAL RESEARCH

Effect of Fructose on Established Lipid Targets: A Systematic Review and Meta-Analysis of Controlled Feeding Trials

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***Background*—**Debate over the role of fructose in mediating cardiovascular risk remains active. To update the evidence on the effect of fructose on established therapeutic lipid targets for cardiovascular disease (low-density lipoprotein cholesterol [LDL]-C, apolipoprotein B, non-high-density lipoprotein cholesterol [HDL-C]), and metabolic syndrome (triglycerides and HDL-C), we conducted a systematic review and meta-analysis of controlled feeding trials.

***Methods and Results*—**MEDLINE, EMBASE, CINHAL, and the Cochrane Library were searched through July 7, 2015 for controlled feeding trials with follow-up ≥7 days, which investigated the effect of oral fructose compared to a control carbohydrate on lipids (LDL-C, apolipoprotein B, non-HDL-C, triglycerides, and HDL-C) in participants of all health backgrounds. Two independent reviewers extracted relevant data. Data were pooled using random effects models and expressed as mean difference with 95% CI. Interstudy heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 statistic). Eligibility criteria were met by 51 isocaloric trials (n=943), in which fructose was provided in isocaloric exchange for other carbohydrates, and 8 hypercaloric trials (n=125), in which fructose supplemented control diets with excess calories compared to the control diets alone without the excess calories. Fructose had no effect on LDL-C, non-HDL-C, apolipoprotein B, triglycerides, or HDL-C in isocaloric trials. However, in hypercaloric trials, fructose increased apolipoprotein B (n=2 trials; mean difference = 0.18 mmol/L; 95% CI: 0.05, 0.30; P=0.005) and triglycerides (n=8 trials; mean difference = 0.26 mmol/L; 95% CI: 0.11, 0.41; P<0.001). The study is limited by small sample sizes, limited follow-up, and low quality scores of the included trials.

***Conclusions*—**Pooled analyses showed that fructose only had an adverse effect on established lipid targets when added to existing diets so as to provide excess calories (+21% to 35% energy). When isocalorically exchanged for other carbohydrates, fructose had no adverse effects on blood lipids. More trials that are larger, longer, and higher quality are required.

***Clinical Trials Registration*—**URL: https://www.clinicaltrials.gov/. Unique Identifier: NCT01363791. **(*J Am Heart Assoc.* 2015;4:e001700 doi: 10.1161/JAHA.114.001700)**

Key Words: lipids • meta-analysis • nutrition

With the global rise in obesity, diabetes, and cardiovascular disease, there is growing concern about the role played by fructose-containing sugars (fructose, sucrose, and high fructose corn syrup [HFCS]).[1,2] In response, various heart and diabetes associations have set strict upper limits for added fructose based on achieving and maintaining healthy

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Accompanying Tables S1 through S3 and Figures S1 through S13 are available at http://jaha.ahajournals.org/content/4/9/e001700/suppl/DC1

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blood lipids. For example, the American Heart Association[3] in their statement on triglycerides and cardiovascular disease has recommended reducing intake of fructose to <100 g/day, 50 to 100 g/day, and <50 g/day in people with borderline, high, and very high triglycerides, respectively, while the Canadian Diabetes Association[4] recommends limiting added fructose to <10% of total energy in people with diabetes.

The evidence on which these recommendations are based comes chiefly from 2 earlier systematic reviews and meta-analyses of controlled feeding on the effect of fructose on lipids. Livesey and Taylor in 2008[5] identified a threshold of ≥100 g/day for fasting triglyceride effects in different participant types, while Sievenpiper et al in 2009[6] identified a dose threshold of >60 g/day or 10% of total energy in people with diabetes. Since these systematic reviews[5,6] were published, numerous additional controlled feeding trials on the effect of fructose on fasting lipids have been published.[7–18] More recent systematic reviews and meta-analyses of the effect of fructose on other related cardiometabolic risk factors have suggested that fructose only has adverse effects on body weight, postprandial triglycerides, glycemic control, uric acid, and markers of nonalcoholic fatty liver disease insofar as it contributes to excess calories.[19–24] Whether these dose thresholds for the effect of fructose on lipids remain in isocaloric comparisons or are confined to comparisons with fructose provided as excess energy is unclear. To address these issues, we undertook an updated systematic review and meta-analysis of controlled clinical trials to assess the effect of fructose on established therapeutic lipid targets for cardiovascular disease (low density lipoprotein cholesterol [LDL-C], apolipoprotein B [apo B], non–high density lipoprotein cholesterol [HDL-C]) and metabolic syndrome (triglycerides and HDL-C).

Subjects and Methods

Design

We followed the Cochrane Handbook for Systematic Reviews of Interventions[25] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[26] The review protocol is available at ClinicalTrials.gov (registration number: NCT01363791).

Study Selection

We searched the databases MEDLINE, EMBASE, CINAHL, and the Cochrane Library through July 7, 2015 for relevant articles and supplemented with manual searches. The full search term used in this study is presented in Table S1. No restrictions were placed on language. Controlled trials that investigated the effect of oral fructose on lipids (LDL-C, apo B, non-HDL, triglycerides, and HDL-C) in participants of all health backgrounds were included. We defined controlled trials as clinical intervention studies using a crossover or parallel design in which a group of participants is allocated to a fructose and/or a control diet intervention with or without randomization. A comparison was considered isocaloric when the amount of fructose was exchanged for an equal amount of a carbohydrate comparator. If the trial involved overfeeding of fructose so that the fructose provided excess energy resulting in a positive energy balance, then the comparison was still considered isocaloric as long as the carbohydrate comparator was matched for the excess energy resulting in the same positive energy balance. A comparison was considered hypercaloric when a control diet was supplemented with excess energy from fructose compared with the same control diet alone without the excess energy. Trials that involved a follow-up of <7 days, administered intravenous fructose, lacked a control diet, or did not provide suitable end-point data were excluded.

Data Extraction

Four reviewers (L.C., V.H., A.I.C., D.D.W.) independently reviewed and extracted relevant data from each report. The quality of each study was assessed using the Heyland methodological quality score (MQS).[27] Disagreements were reconciled by consensus. Mean±SD differences between fructose and control arms were extracted as the main end points. In those trials where the data were included in figures and not provided numerically, we used the software program Plot Digitizer (http://plotdigitizer.sourceforge.net/) to extract the data. Additional information was requested from the authors of all included trials.

Access to Study

All authors had access to the study data and reviewed and approved the final manuscript.

Statistical Analysis

Data analyses were conducted using Review Manager version 5.1.6 (RevMan) (Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for primary analyses and Stata version 13 (College Station, TX: StataCorp LP) for subgroup analyses. Separate analyses were conducted for the isocaloric and hypercaloric trials using the generic inverse variance method with random effects weighting. Data were expressed as mean differences (MD) with 95% CI. Trials that did not report standard error (SE) values had these computed from the available statistics using standard

formulae.[25,28] To generate SE for included crossover trials, we assumed paired analyses as described by Elbourne,[28] where the SDs for the means of the treatment arms were used along with the sample size and correlation coefficient to calculate the SD of the mean difference, which was then converted to a SE. If insufficient data were available for computations in crossover trials, SE values were imputed using a conservative correlation coefficient of 0.5, which was chosen since there no more than 10 isocaloric trials with available data for calculated correlations (7 for LDL, 0 for non-HDL-C and apo B; 10 for triglycerides, and 2 for HDL-C). Sensitivity analyses were performed using correlation coefficients of 0.25 and 0.75.

Non-HDL-C was determined using studies that reported both total cholesterol and HDL-C by calculating the difference between the means. The SDs for non-HDL-C were calculated using a standard formula using the SDs of total cholesterol and HDL-C as has been previously published.[29]

Inter-trial heterogeneity was assessed by the Cochran Q statistic, where $P<0.10$ is considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ indicates substantial heterogeneity.[25] Sources of heterogeneity were investigated by sensitivity analyses in which each individual trial was removed from the analysis and through a priori subgroup analyses by comparator (starch, glucose, sucrose or HFCS), fructose dose (≤60 g/day or >60 g/day[6]; <100 g/day or ≥100 g/day[5]), fructose form (solid, liquid or mixed), follow-up (≤4-weeks or >4-weeks), MQS (<8 or ≥8), randomization (yes or no), design (crossover or parallel), feeding control (metabolic or non-metabolic) and energy balance (negative, neutral or positive). Meta-regression analyses assessed the significance of subgroup effects. Multivariate meta-regression analyses assessed dose response models were also performed using the covariates comparator, patient type, follow-up, design, and fructose form. Each covariate was included in the model individually and then added one at a time in order of decreasing R^2 as obtained from the individual models. When a dose response model for a lipid outcome was significant, it was further explored using an interaction model. If the interaction term was significant, then the dose response was explored separately at each level of the covariate. Publication bias was evaluated via visual inspection of funnel plots and Egger[30] and Begg[31] tests.

Results

Search Results

The flow of the literature is shown in Figure 1. Our search identified 1918 reports, of which 43 reports including data for 59 trials met the eligibility criteria.[7–18,32–62]

Trial Characteristics

Trial characteristics are shown in Table. A total of 51 isocaloric trials (26 trials for LDL, 8 for apo B, 27 for non-HDL-C, 51 for triglycerides, and 28 for HDL-C) in 943 participants and 8 hypercaloric trials (4 trials for LDL, 2 for non-HDL-C, 2 for apo B, 8 for triglycerides, and 4 for HDL-C) in 125 participants were included in the analyses. The majority of the studies were conducted in an outpatient setting in the United States or Europe and tended to be small (median, interquartile range ([IQR]) sample size, 11.0 (7.0 to 16.0) and 15.5 (10.25 to 23), in isocaloric and hypercaloric trials, respectively).

About half of the participants were healthy, 16% had hypertriglyceridemia or insulin resistance, and 20% had diabetes (the majority of which were type 2 diabetes). Patients tended to be young and middle aged (median [IQR] age=40.0 years [24.6 to 53.5 years] and 26.4 years [24.7 to 31.6 years]) in isocaloric and hypercaloric trials, respectively, with equal numbers of males and females (median male: female ratio=50:50) in isocaloric trials and were all males (median male:female ratio=100:0) in hypercaloric trials.

Crossover designs were used in 78% of isocaloric and in 88% of hypercaloric trials. Forty-seven percent of isocaloric and 50% of hypercaloric trials were randomized. Starch was the most common comparator (57%) while sucrose was used in 20%, glucose in 31%, maltose in 4%, and high fructose corn syrup in 2% of other comparisons in isocaloric trials. The control diet alone without added energy from fructose was the comparator in all hypercaloric trials. The diets provided a range of energy and macronutrient profiles. Comparisons made in the isocaloric trials were matched for energy and were provided under conditions of neutral energy balance (that is, both arms provided energy to maintain body weight) in the majority of comparisons. However, in 6 comparisons, both fructose and the comparator were provided under conditions of positive energy, and only 1 comparison had both fructose and the comparator provided under conditions of negative energy balance. Fructose was administered in fluid form in 45%, mixed in 45%, and solid in 10% of isocaloric trials, and at a median (IQR) dose of 97.0 g/day (60.8 to 151.0 g/day). In all hypercaloric trials, fructose was administered in fluid form at a median (IQR) dose of 193.0 g/day (163.5 to 213.0 g/day). The median (IQR) excess energy provided by the hypercaloric trials was +25% (+24% to 35%). A metabolic feeding control was used in 57% of isocaloric and 13% of hypercaloric trials; partial-metabolic feeding control was used in 8% and 13% and the remainder provided fructose as a supplement. The median (IQR) dietary follow-up was 4 weeks (2 to 5 weeks) for isocaloric and 2 weeks (1 to 4 weeks) for hypercaloric trials.

The majority of trials were of poor quality. The Heyland MQS was considered low (MQS<8) in 53% of isocaloric and 50% of hypercaloric trials. Lack of or poor description of

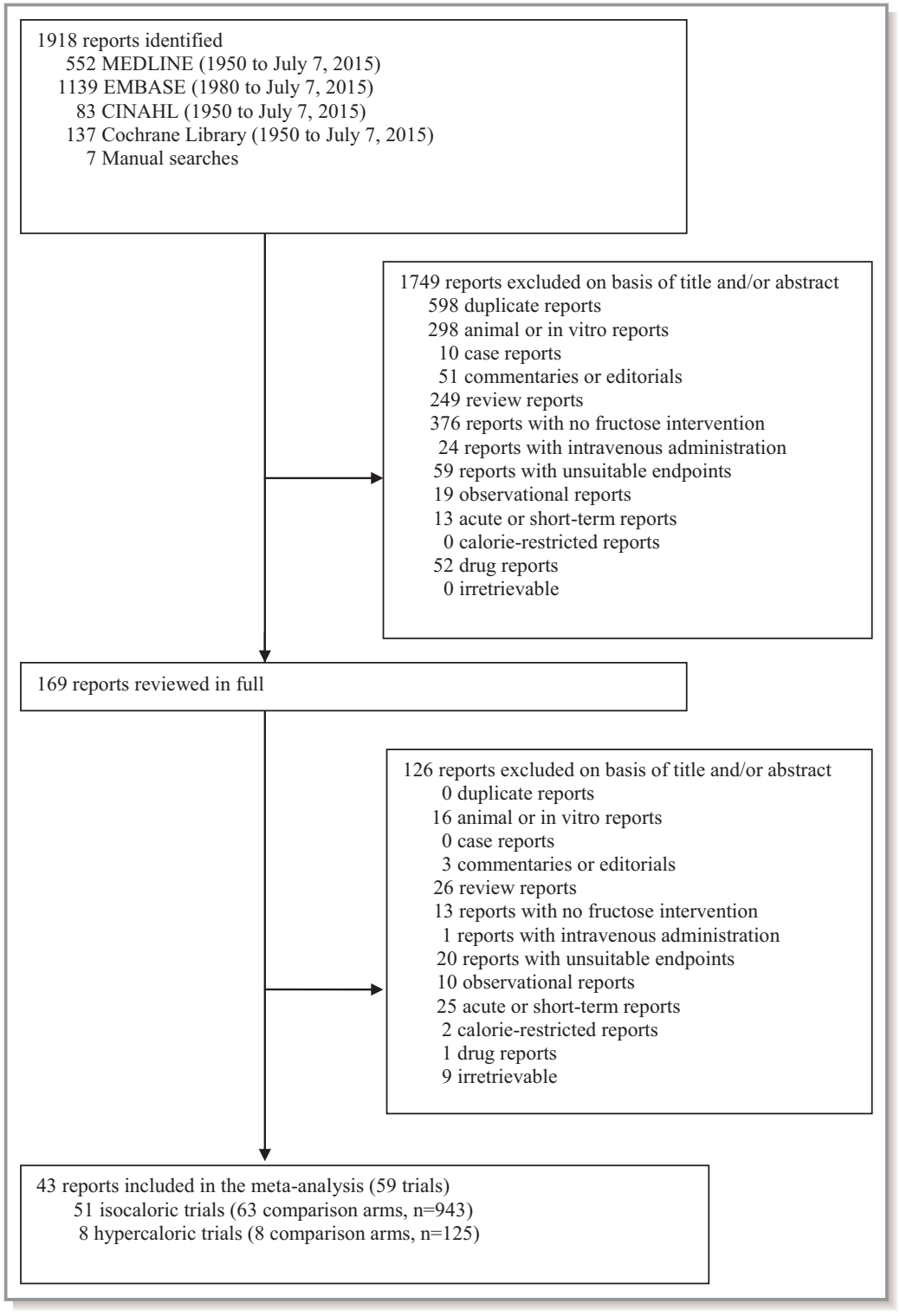

Figure 1. Flow of the literature.

randomization, nonconsecutive or poorly described patient selection, and absence of double-blinding contributed to lower scores. Funding of trials came from a combination of agency alone (47%), agency-industry sources (29%), industry alone (4%), or was not reported (20%).

Isocaloric Feeding Trials

Effect of fructose on LDL-C

Twenty-four reports (26 trials) provided data on the effect of fructose intake on LDL-C (Figure 2). Primary pooled analyses

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Table. Characteristics of Controlled Feeding Trials Investigating the Effect of Fructose on Lipids

Study, Year (Reference)	Participants	Mean Age (SD or Range), y	Setting	Design	Feeding Control	Randomization	Fructose Dose*	Fructose Form†	Comparator‡	Diet§	Energy Balance	Follow-Up	MQS‖	Funding Source¶
Isocaloric feeding trials														
Diabetes														
Akerblom et al 1972 (39)	16 T1DM	10 (2 to 16)	OP, Finland	C	Supp	No	≈40 g/day (20% E)	Mixed	Starch	45:35:20	Neutral	1 week	4	Industry (materials)
Pelkonen et al 1972 (32)	8 T1DM	25.2 (19 to 70)#	IP, Finland	C	Met	No	75 g/day (15% E)	Liquid	Starch	40:40:20	Neutral	10 days	7	Agency
Bantle et al 1986 (44)	12 T1DM (6M:6F)	23 (15 to 32)	IP, USA	C	Met	Yes	≈97 g/day (21% E)	Mixed	Starch	55:30:15	Neutral	8 days	8	Agency
Bantle et al 1986 (44)	12 T2DM (5M:7F)	62 (36 to 84)	IP, USA	C	Met	Yes	≈97 g/day (21% E)	Mixed	Starch	55:30:15	Neutral	8 days	8	Agency
Crapo et al 1986 (38)	7 T2DM (3M:4F)	51 (3)	IP/OP, USA	C	Met	No	≈98 g/day (13.2% E)	Mixed	Sucrose	55:30:15	Neutral	2 weeks	7	Agency, industry
Mcateer et al 1987 (37)	10 T2DM	64.4 (54 to 71)	OP, Northern Ireland	C	Supp	No	50 g/day (11.6% E)	Liquid	Starch	42:38:20	Neutral	4 weeks	7	Industry (materials)
Osei et al 1987 (42)	18 T2DM (15M:3F)	57 (9)	OP, USA	P	Supp	Yes	60 g/day (10% E)	Liquid	Starch	50:35:15	Neutral	12 weeks	8	Agency
Grigoresco et al 1988 (43)	8 T2DM (5M:3F)	40 (20)	OP, France	C	Supp	Yes	30 g/day (8% E)	Liquid	Starch	50:30:20	Neutral	8 weeks	8	Agency, industry
Anderson et al 1989 (36)	14 T2DM (14M:0F)	60 (15)	IP/OP, USA	C	Supp	No	≈55 g/day (12% E)	Mixed	Starch	55:25:20	Neutral	23 weeks	8	Agency, industry
Thorburn et al 1989 (34)	8 T2DM (4M:4F)	55 (10)	IP, USA	P	Met	No	≈100 g/day (13% E)	Mixed	Sucrose	55:30:15	Neutral	12 weeks	6	Agency, industry
Osei et al 1989 (41)	13 T2DM (5M:8F)	54 (11)	OP, USA	C	Supp	Yes	60 g/day (7.5% E)	Mixed	Starch	50:35:15	Neutral	26 weeks	8	Agency (salary award)
Blayo et al 1990 (35)														
Starch	6 T1DM, 2 T2DM	43 (11)	OP, France	P	Supp	Yes	≈ 25 (~5% E)	Mixed	Starch	55:30:15	Neutral	52 weeks	7	Agency, industry
Sucrose	3 T1DM, 3 T2DM	51 (12)							Sucrose					
Fructose	5 T1DM, 1 T2DM	48 (17)												

Continued

Table. Continued

Study, Year (Reference)	Participants	Mean Age (SD or Range), y	Setting	Design	Feeding Control	Randomization	Fructose Dose*	Fructose Form†	Comparator‡	Diet§	Energy Balance	Follow-Up	MQS‖	Funding Source¶
Bantle et al 1992 (40)	6 T1DM (3M:3F)	23 (18 to 23)	OP, USA	C	Met	Yes	≈120 (20% E)	Mixed	Starch	55:30:15	Neutral	4 weeks	8	Agency, industry
Bantle et al 1992 (40)	12 T2DM (4M:8F)	62 (40 to 72)	OP, USA	C	Met	Yes	≈120 (20% E)	Mixed	Starch	55:30:15	Neutral	4 weeks	8	Agency, industry
Koivisto and Yki-Jarvinen 1993 (33)	10 T2DM (4M:6F)	61 (10)	IP, Finland	C	Met	Yes	≈55 (20% E)	Liquid	Starch	50:30:20	Neutral	4 weeks	9	Agency, industry
Malerbi et al 1996 (46)	16 T2DM (7M:9F)	54.2 (34 to 66)	OP, Brazil	C	Supp	No	63.2 (20% E)	Liquid	Starch	55:30:15	Neutral	4 weeks	7	Agency, industry
Hypertriglyceridemia & insulin resistance														
Kaufmann et al 1966 (51)	5 HTG (3M:2F) **	42.8 (14.2)	IP/OP, Israel	C	Met	No	300 g/day (55% E)	Mixed	Starch	77:5:18	Neutral	~24-days	7	Agency
	3 HTG (2M:1F)								Sucrose					
Nestel et al 1970—Study1 (50)	3 HTG	19 (0)	IP, Australia	C	Met	No	50% to 52% E	Mixed	Glucose	77:9:14	Neutral	1-week	6	Agency
Nestel et al 1970—Study 2 (50)	2 HTG	19 (0)	IP, Australia	C	Met	No	52% to 55% E	Mixed	Glucose	77:9:14	Neutral	1-week	6	Agency
Nikkila and Kekki 1972 (49)	10 Type 4 HTG (5DM2)	53.5 (26 to 67)	IP, Finland	C	Met	Yes	≈77.5 (~17% E)	Liquid	Starch	45:35:20	Neutral	10 to 20-days	6	Agency
									Sucrose					
Turner et al 1979 (LC) (53)	6 HTG (6M:0F) **	45.7 (7.7)	IP, USA	C	Met	No	≈39.5 g/day (9% E)	Liquid	D-Maltose	45:40:15	Neutral	~2-weeks	7	Agency, industry
Turner et al 1979 (HC) (53)	5 HTG (5M:0F) **	46.8 (8.0)	IP, USA	C	Met	No	≈122 g/day (17% E)	Liquid	D-Maltose	85:00:15	Neutral	~2-weeks	4	Agency, industry
Cybulska and Naruszewicz 1982 (55)	16 Type 4 HTG	57 (38 to 80)	OP, Poland	C	Supp	No	80 g/day	Liquid	Starch	45:40:15	Neutral	28-days	7	NR
Hallfrisch et al 1983 (56)	12 IR (12M:0F)	39.5 (2.1)	IP/OP, USA	C	Met	No	50 g/day (7.5% E)	Solid	Starch	43:42:15	Neutral	5-weeks	8	NR
							100 g/day (15% E)							

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Table. Continued

Study, Year (Reference)	Participants	Mean Age (SD or Range), y	Setting	Design	Feeding Control	Randomization	Fructose Dose*	Fructose Form†	Comparator‡	Diet§	Energy Balance	Follow-Up	MQS‖	Funding Source¶
Koh et al 1988 (54)	9 IGT (3M, 6F)	54 (18)	OP, USA	C	Supp	No	≈64 (15% E)	Mixed	Glucose	50 to 55:30 to 35:15 to 20	Neutral	4-weeks	8	NR
Reiser et al 1989 (58)	10 IR (10M:0F)	47	IP, USA	C	Met	No	167 (20% E)	Solid	Starch	51:36:13	Neutral	5-weeks	4	NR
Normal														
Kaufmann et al 1966 (51)	4 N (3M:1F)	42.8 (14.2)	IP/OP, Israel	C	Met	No	300 (55% E)	Mixed	Starch	77:5:18	Neutral	~24-days	7	Agency
									Sucrose					
Forster and Heller 1973 (60)	12 N (8M:4F)	20 to 26	IP, Germany	C	Met	No	162 g/day	Liquid	Glucose	90:00:10	Neutral	10-days	7	NR
Forster and Heller 1973 (60)	6 N (4M:2F)	20 to 26	IP, Germany	C	Met	No	162 g/day	Liquid	Glucose	90:00:10	Neutral	10-days	7	NR
Huttunen et al 1976 (48)	68 N	28 (7)	OP, Finland	P	Supp	No	69 (14% E)	Mixed	Sucrose	—	Neutral	95-weeks	5	NR
Hallfrisch et al 1983 (56)	12 N (12M:0F)	39.8	IP/OP, USA	C	Met	No	50 g/day (7.5% E)	Solid	Starch	43:42:15	Neutral	5-weeks	8	NR
							100 g/day (15% E)							
Bossetti et al 1984 (57)	8 N (4M:4F)	26.7 (20 to 32)	OP, USA	C	Met	Yes	≈78.5	Liquid	Sucrose	35 to 49:35 to 45:12 to 20	Neutral	2-weeks	8	Agency
Koh et al 1988 (54)	9 N (3M, 6F)	50 (15)	OP, USA	C	Supp	No	≈78.5 (15% E)	Mixed	Glucose	50 to 55:30 to 35:15 to 20	Neutral	4-weeks	8	NR
Reiser et al 1989 (58)	11 N (11M:0F)	38	IP, USA	C	Met	No	167 (20% E)	Solid	Starch	51:36:13	Neutral	5-weeks	4	NR
Swanson et al 1992 (59)	14 N (7M:7F)	34 (19 to 60)	OP, Denmark	C	Met	Yes	≈120 (20% E)	Mixed	Starch	55:15:30	Neutral	4-weeks	8	Agency, industry
Bantle et al 2000 (45)	24 N (12M:12F)	M, 42.5; F, 40	OP, USA	C	Met	Yes	85 (17% E)	Mixed	Glucose	55:30:15	Neutral	6-weeks	9	Agency
Sunehag et al 2002 (47)	12 N (6M:6F)	M, 15 (1.2); F, 14.5 (1.5)	IP/OP, USA	C	Met	Yes	74.4 (12% E)	Mixed	Starch	60:25:15	Neutral	1-week	9	Agency, industry
							151.32 (24% E)							
Treuth et al 2003 (52)	6 N (6M:0F)	15.3 (0.8)	OP, USA	C	Met	Yes	128.5 (40% E)	Mixed	Starch	60:25:15	Neutral	8-days	9	Agency, industry
	6 N (0M:6F)	14.7 (1.2)												

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DOI: 10.1161/JAHA.114.001700

Table. Continued

Study, Year (Reference)	Participants	Mean Age (SD or Range), y	Setting	Design	Feeding Control	Randomization	Fructose Dose*	Fructose Form†	Comparator‡	Diet§	Energy Balance	Follow-Up	MQS‖	Funding Source¶
Sunehag et al 2008 (7)	6 N (3M:3F)	15.2 (1.2)	IP/OP, USA	C	Met	Yes	≈149 (24% E)	Mixed	Starch	60:25:15	Neutral	7-days	9	Agency, industry
Swarbrick et al 2008 (8)	7 OW/OB (0M:7F)	50 to 72	IP, USA	C	Met	No	≈125 (25% E)	Liquid	Starch	55:30:15	Neutral	10-weeks	7	Agency
Stanhope et al 2009 (9)	32 OW/OB (16M:16F)	53	IP/OP, USA	P	Met/ Supp	No	≈182 (+25% E)	Liquid	Glucose	55:30:15	Positive	10-weeks	6	Agency
Ngo Sock et al 2010 (10)	11 N (11M:0F)	24.6 (2)	OP, Switzerland	C	Met	Yes	≈213 (+35% E)	Liquid	Glucose	55:30:15	Positive	7-days	8	Agency
Brymora 2012 (11)	28 CKD (17M:11F)	59 (15)	OP, Poland	C	DA	No	53 (9% E)	Mixed	Starch	55:30:15	Neutral	6-weeks	8	Agency
Madero et al 2011 (12)	131 OB (29M: 102F)	38.8 (8.8)	OP, Mexico	P	DA	Yes	≈60 (13% to 14% E)	Solid (fruit)	Starch	55:30:15	Negative	6-weeks	7	Agency
Silbernagel et al 2011 (13)	20 N (12M:8F)	30.5	OP, Germany	P	Supp	Yes	150 (+22% E)	Liquid	Glucose	50:35:15	Positive	4-weeks	7	Agency
Stanhope et al 2011 (16)	48 N (27M:21F)	28.0 (27.2)	IP/OP, USA	P	Met/ Supp	No	≈168 (+25% E)	Liquid	Glucose	55:30:15	Positive	2-weeks	6	Agency
									HFCS					
Aeberli et al 2013 (14)	9 N (9M)	22.8 (21 to 25)	OP, Switzerland	C	Supp	Yes	80 (≈14%)	Liquid	Glucose	47 to 56:29 to 31:13 to 16	Neutral	3-weeks	10	Agency
									Sucrose					
Johnston et al 2013—A (15)	32 OW (32M:0F)	33.9 (10.0)	OP, UK	P	Met/ Supp	Yes	≈204 (25% E)	Liquid	Glucose	55:30:15	Neutral	2-weeks	10	Agency
Johnston et al 2013—B (15)	32 OW (32M:0F)	33.9 (10.0)	OP, UK	P	Met/ Supp	Yes	≈204 (25% E)	Liquid	Glucose	55:30:15	Positive	2-weeks	10	Agency
Heden et al 2014 (17)	40 N (20M:20F)	17.9 (1.9)	OP, USA	C	Supp	Yes	50 (≈10% E)	Liquid	Glucose	50:34:16	Positive	2-weeks	5	Agency
Jin et al 2014 (18)	21 OW (11M:10F)	13.6 (2.5)	OP, USA	P	Supp	Yes	99 (≈20% E)	Liquid	Glucose	N/A	Neutral	4-weeks	7	Agency
Hypercaloric feeding trials														
Le et al 2006 (61)	7 N (7M:0F)	24.7 (3.4)	OP, Switzerland	C	Supp	No	≈+104 g/ day (+18% E)	Liquid	Diet alone	55:30:15	Positive	4-weeks	7	Agency, industry

Continued

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Table. Continued

Study, Year (Reference)	Participants	Mean Age (SD or Range), y	Setting	Design	Feeding Control	Randomization	Fructose Dose*	Fructose Form†	Comparator‡	Diet§	Energy Balance	Follow-Up	MQS‖	Funding Source¶
Le et al 2009 (62)	8 N (8M:0F)	24 (3)	OP, Switzerland	C	Supp	Yes	≈+213 g/day (+35% E)	Liquid	Diet alone	55:30:15	Positive	7-days	8	Agency, industry
	16 Off-T2DM (16M:0F)	24.7 (5.2)	OP, Switzerland	C	Supp	Yes	≈+213 g/day (+35% E)	Liquid	Diet alone	55:30:15	Positive	7-days	8	Agency, industry
Stanhope et al 2009 (9)**	32 OW/OB (16M:16F)	53	IP/OP, USA	P	Supp	No	≈182 g/day (25% E)	Liquid	Diet alone	55:30:15	Positive	10-weeks	5	Agency
Ngo Sock et al 2010 (10)**	11 N (11M:0F)	24.6	OP, Switzerland	C	Met	Yes	≈213 g/day (+35% E)	Liquid	Diet alone	55:30:15	Positive	7-days	8	Agency
Silbernagel et al 2011 (13)	20 N (12M:8F)	30.5	OP, Germany	C	Supp	Yes	150 (21% to 25% E)	Liquid	Diet alone	50:35:15	Positive	4-weeks	7	Agency
Stanhope et al 2011 (16)	16 N (9M:7F)	28	IP/OP, USA	C	Partial	No	≈168 (25% E)	Liquid	Diet alone	55:30:15	Positive	2-weeks	6	Agency
Johnston et al 2013 (15)	15 OW (15M:0F)	35	OP, UK	C	Supp	No	≈204 (25% E)	Liquid	Diet alone	55:30:15	Positive	2-weeks	10	Agency

C indicates crossover; CKD, chronic kidney disease; DA, dietary advice; E, energy; F, female; HFCS, high fructose corn syrup; HTG, hypertriglyceridemic; IGT, impaired glucose tolerance; IP, inpatient; IR, insulin resistant; M, male; Met, metabolic; MQS, methodological quality score; N, normal; N/A, not available; NR, not reported; Off-T2DM, offspring of persons with type 2 diabetes mellitus; OP, outpatient; OW/OB, overweight/obese; P, parallel; Supp; supplemented; T1DM, type 1 diabetes mellitus.

*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 a 2000-kcal intake. Plus signs indicate excess energy provided by fructose.

†Fructose was provided as beverages or crystalline fructose to be added to beverages (Liquid), added to foods or consumed within the context of foods (Solid), or was a mixture of both liquid and solid forms (Mixed).

‡Comparators were the reference carbohydrate in the isocaloric trials and the control diet (weight-maintaining, background diet) alone without the added energy from fructose in the hypercaloric trials. Fructose was exchanged for the reference carbohydrate, providing an energy-matched comparison in the isocaloric trials, while it supplemented the control diet 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 according to the Heyland MQS.[27]

¶Agency funding is that from government, university, or not-for-profit health agency sources.

#Pelkonen et al[32] age was based on 10 participants.

**Four trials[9,10,13,16] featured both isocaloric and hypercaloric comparisons. The isocaloric comparisons were balanced yet under hypercaloric conditions, in that both the fructose and glucose arms were matched for energy but fed under conditions of excess energy. In the hypercaloric comparisons, the fructose arm was fed under hypercaloric conditions whereas the background diet was fed under eucaloric, weight-maintaining conditions.

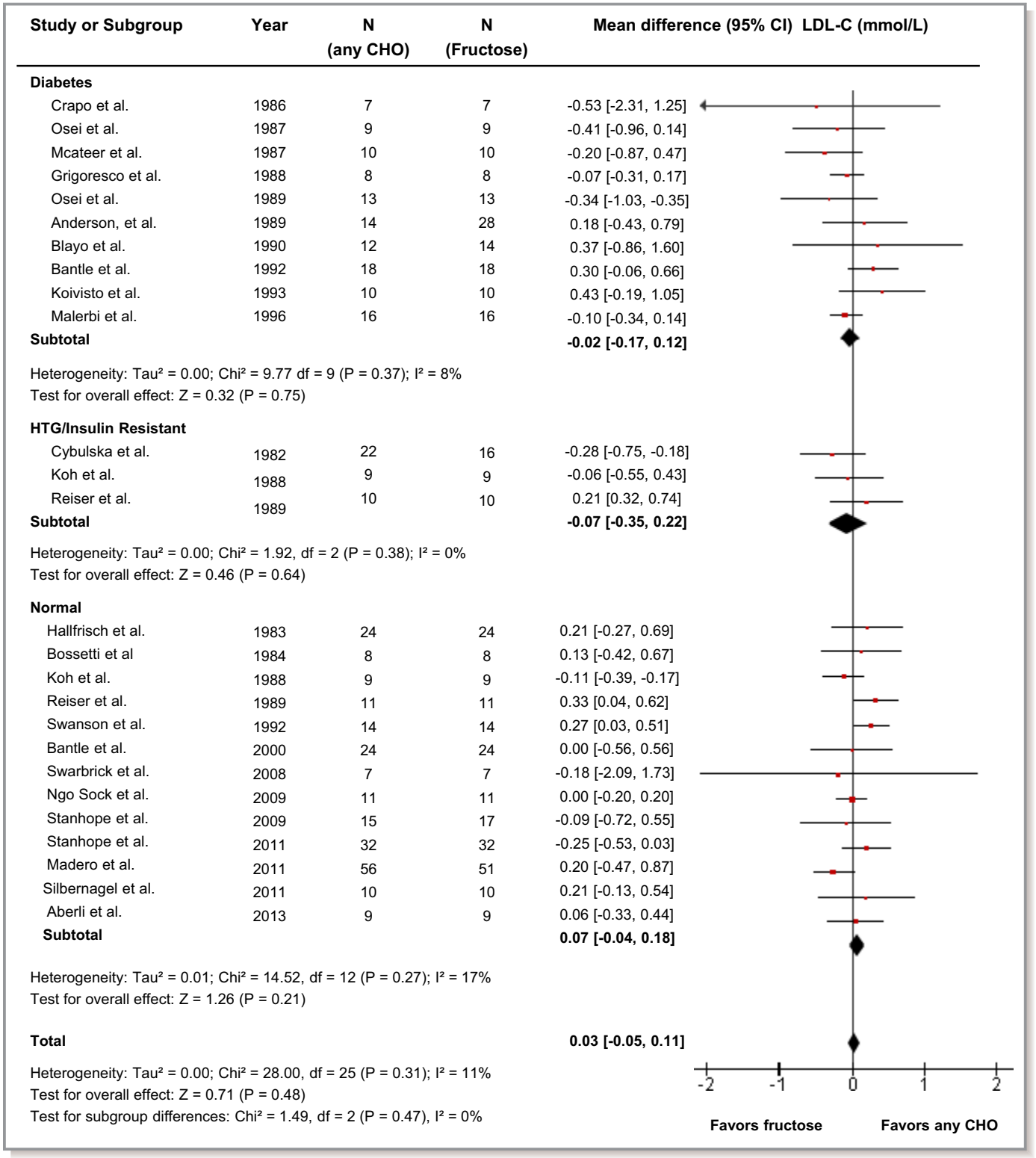

Figure 2. Forest plots of the effect of fructose on LDL-C in isocaloric feeding trials. Pooled effect estimates are shown as diamonds. Data are expressed as MD with 95% CI using generic inverse variance random effects models. Interstudy heterogeneity was tested the Cochran Q statistic at a significance level of $P<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and $\geq 75\%$ considerable heterogeneity. Any CHO denotes any carbohydrate comparator. HTG indicates hypertriglyceridemic; LDL-C, low density lipoprotein; MD, mean difference.

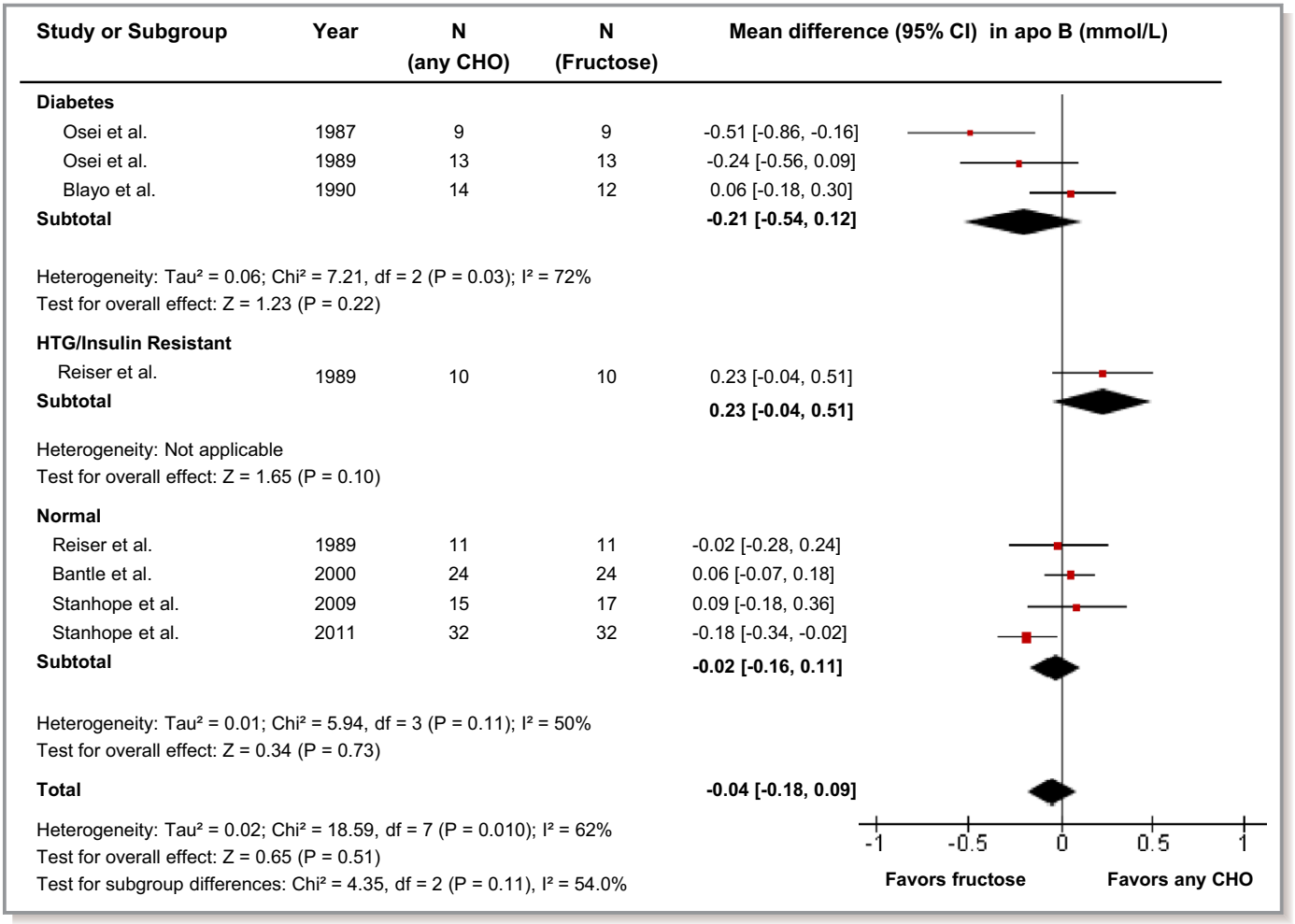

Figure 3. Forest plots of the effect of fructose on apo B in isocaloric feeding trials. Pooled effect estimates are shown as diamonds. Data are expressed as MD with 95% CI using generic inverse variance random effects models. Interstudy heterogeneity was tested by the Cochran Q statistic at a significance level of $P<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and ≥75% considerable heterogeneity. Any CHO denotes any carbohydrate comparator. apo B indicates apolipoprotein B; HTG, hypertriglyceridemic; MD, mean difference.

showed that isocaloric exchange of fructose for other carbohydrate did not affect LDL (MD=0.03 mmol/L [95% CI: −0.05, 0.11], P=0.48). There was no evidence of statistically significant interstudy heterogeneity overall (I^2=11%, P=0.31). Sensitivity analyses in which each study was removed or when correlation coefficients of 0.25 and 0.75 were used did not alter the results. Categorical subgroup analyses using metaregression analyses found significant effect modification by feeding control and fructose form (Figure S1). Neither categorical subgroup analyses at 60 g/day nor at 100 g/day found a significant effect modification by dose, and continuous dose response metaregression analyses did not reveal a significant dose response or threshold (Figures S1 and S10, Table S2). Dose response metaregression analyses explored with multivariate models confirmed the significant effect of fructose form found in categorical subgroup analyses; however, dose was not found to be dependent on fructose form (Table S2).

Effect of fructose on apo B

Seven reports (8 trials) provided data on the effect of fructose intake on apo B (Figure 3). Primary pooled analyses showed no effect of fructose on apo B (MD=−0.04 mmol/L [95% CI: −0.18, 0.09], P=0.51) with evidence of statistically significant interstudy heterogeneity overall (I^2=62%, P=0.01). Sensitivity analyses in which each study was removed or when correlation coefficients of 0.25 and 0.75 were used did not alter the results. Neither categorical subgroup analyses nor continuous multivariate metaregression analyses to investigate a dose response or threshold were significant (Figure S2 and Table S2).

Effect of fructose on non-HDL-C

Twenty-five reports (27 trials) provided data on the effect of fructose intake on non-HDL-C (Figure 4). Primary pooled

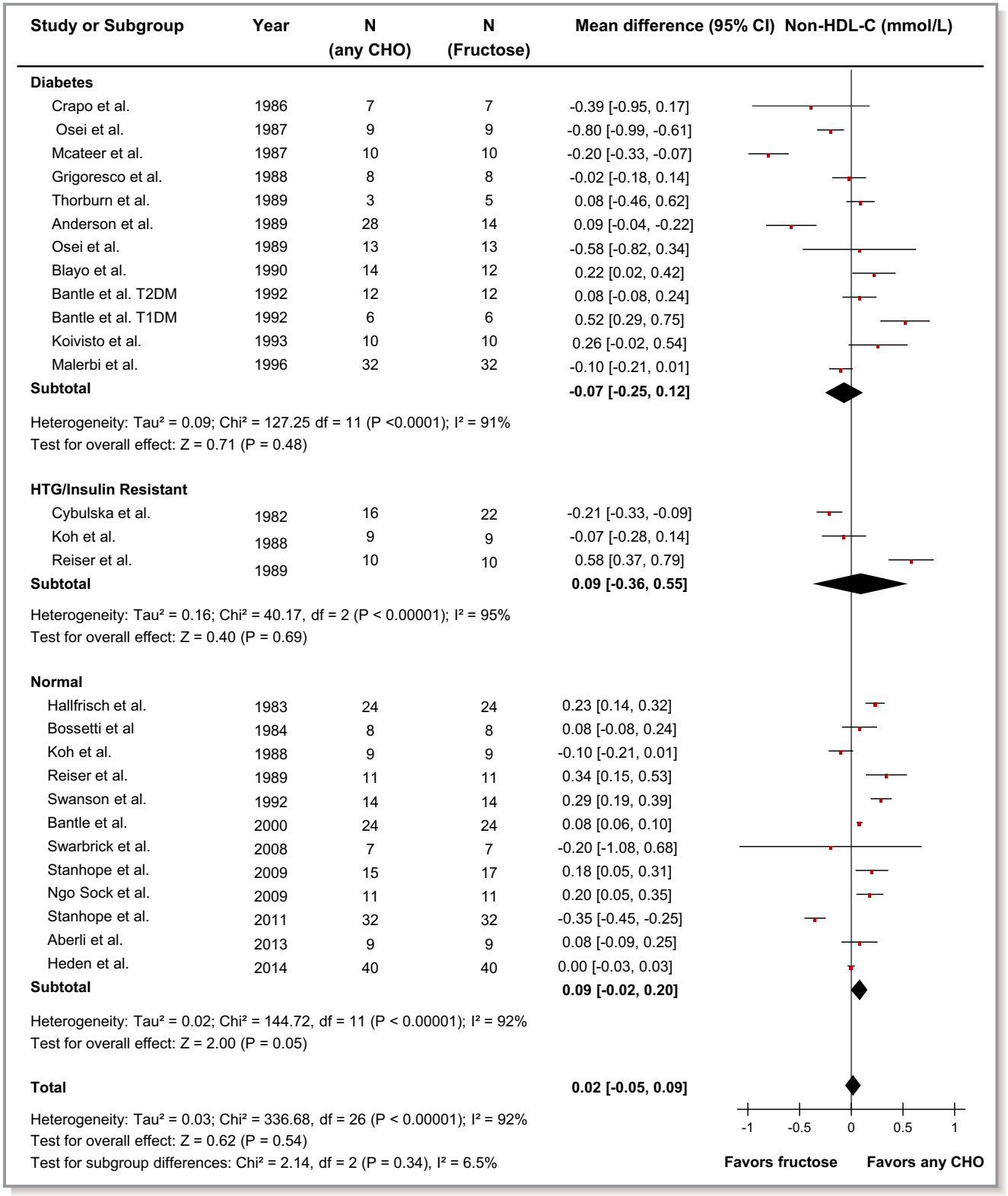

Figure 4. Forest plots of the effect of fructose on non-HDL-C in isocaloric feeding trials. Pooled effect estimates are shown as diamonds. Data are expressed as MD with 95% CI using generic inverse variance random effects models. Interstudy heterogeneity was tested by the Cochran Q statistic at a significance level of $P<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and ≥75% considerable heterogeneity. Any CHO denotes any carbohydrate comparator. HDL-C indicates high density lipoprotein; HTG, hypertriglyceridemic; MD, mean difference; T2DM, type 2 diabetes mellitus.

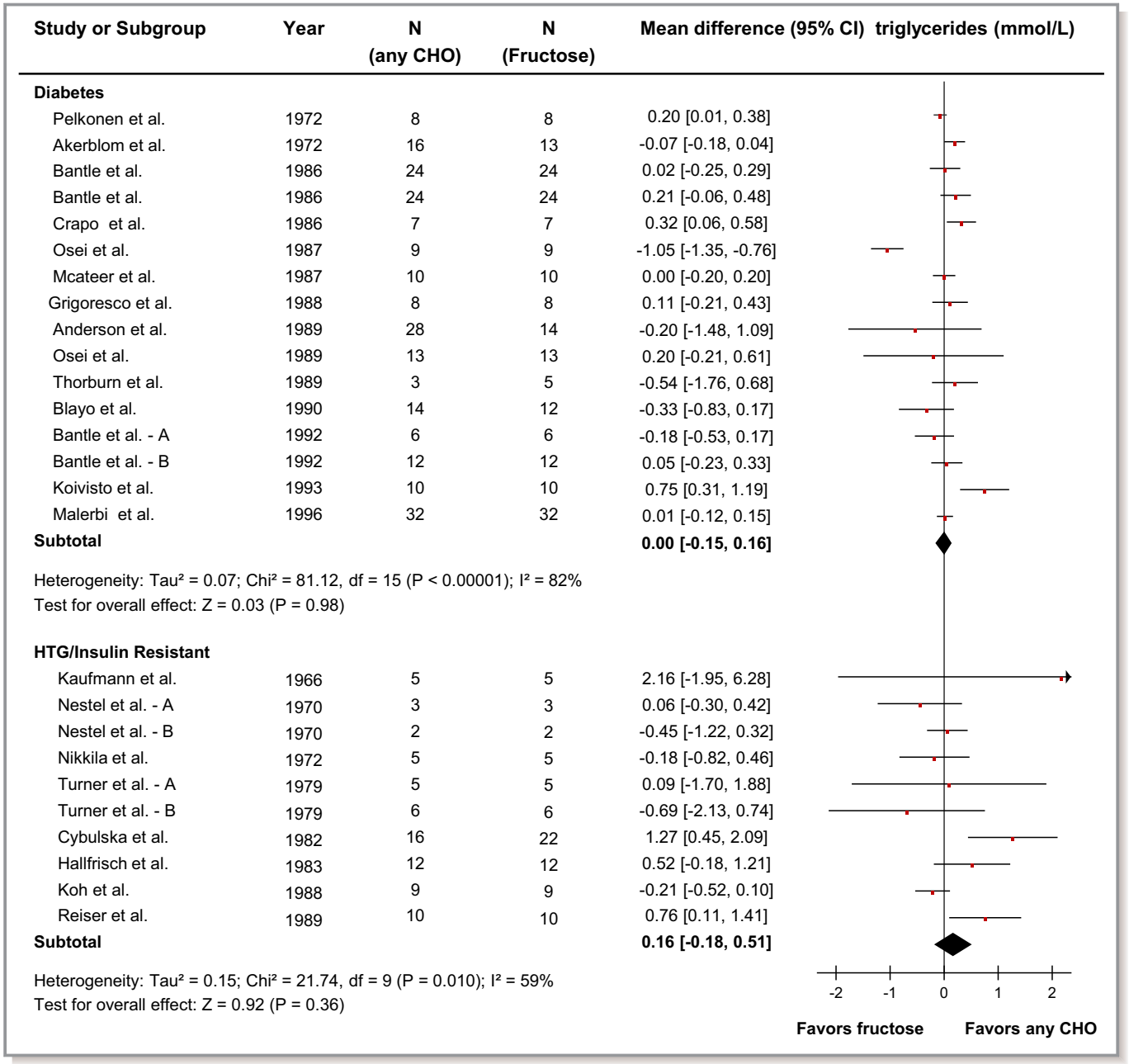

Figure 5. Forest plots of the effect of fructose on triglycerides in isocaloric feeding trials. Pooled effect estimates are shown as diamonds. Data are expressed as MD with 95% CI using generic inverse variance random effects models. Inter-study heterogeneity was tested by the Cochran Q statistic at a significance level of $P<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and ≥75% considerable heterogeneity. A, B refers to study A and study B (two separate trials) within the same report. Any CHO denotes any carbohydrate comparator. HTG indicates hypertriglyceridemic; MD, mean difference.

analyses showed no effect of fructose on non-HDL-C (MD=0.02 mmol/L [95% CI: −0.05, 0.09], P=0.54) with evidence of statistically significant interstudy heterogeneity overall (I^2=92%, P<0.01). Sensitivity analyses in which each study was removed or when correlation coefficients of 0.25 and 0.75 were used did not alter the results. Categorical subgroup analyses did not reveal evidence of effect modification in any subgroup except for metabolic feeding control and fructose form (Figure S3). Metaregression analyses showed that relative to other carbohydrates, fructose raised non-HDL-C under metabolic feeding conditions, or when the fructose was given in solid form. Neither categorical subgroup analyses at 60 g/day nor at 100 g/day found a significant effect modification by dose, and continuous dose response metaregression analyses did not reveal a significant dose response or threshold (Figures S3 and S10,

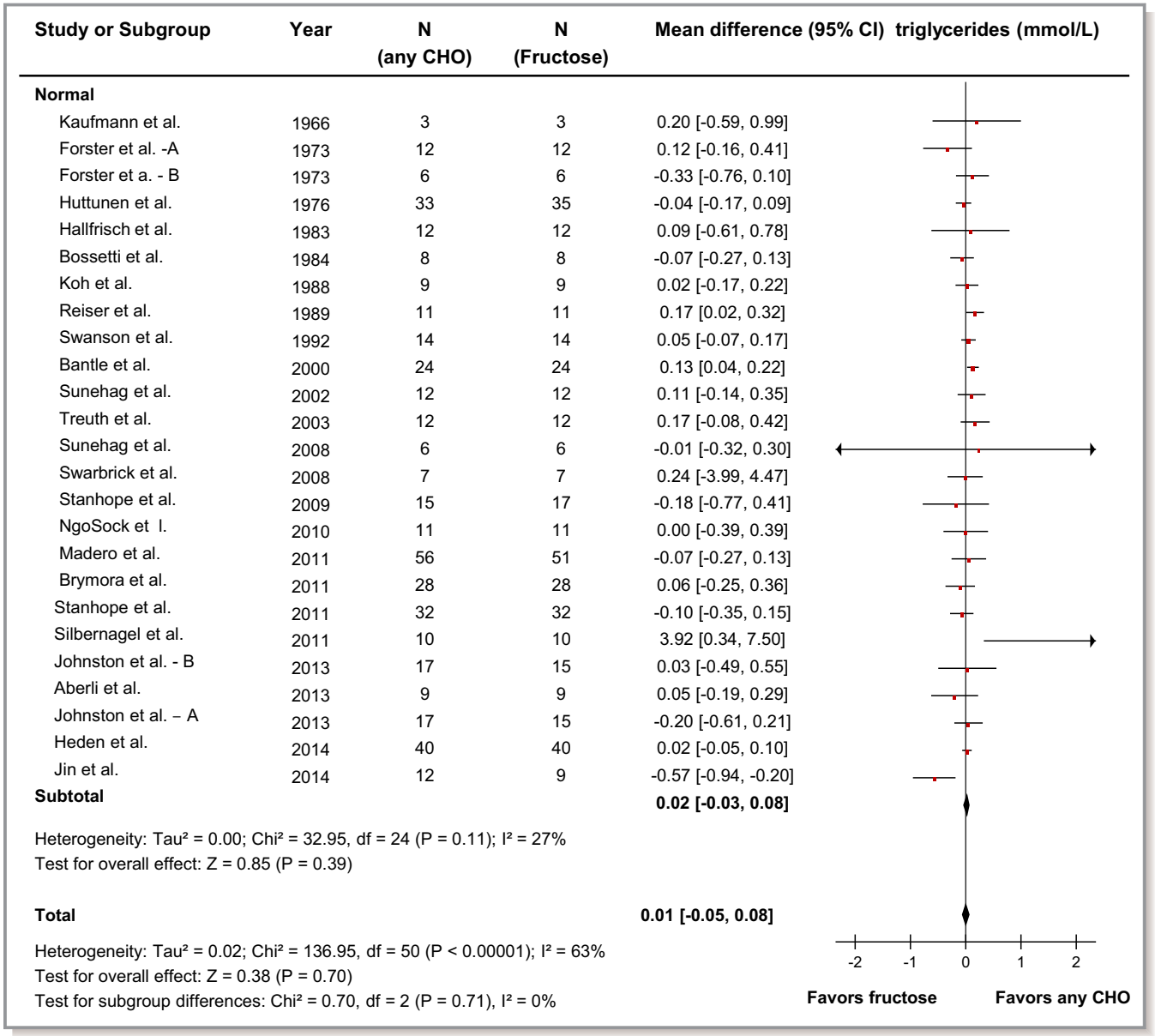

Figure 5. Continued.

Table S2). Dose response metaregression analyses explored with multivariate models confirmed the significant effect of fructose form found in categorical subgroup analyses; however, dose was not found to be dependent on fructose form (Table S2).

Effect of fructose on triglycerides

Forty-one reports (51 trials) provided data on the effect of fructose intake on triglycerides (Figure 5). Primary pooled analyses showed no effect of fructose on triglycerides (MD=0.01 mmol/L [95% CI: −0.05, 0.08], *P*=0.70) with evidence of statistically significant interstudy heterogeneity overall (I^2=63%, *P*<0.01). Sensitivity analyses in which each study was removed or when correlation coefficients of 0.25 and 0.75 were used did not alter the results. Categorical subgroup analyses found that relative to other carbohydrates, fructose raised triglycerides under metabolic feeding control conditions and in trials with a crossover design (Figure S4). Neither categorical subgroup analyses at 60 g/day nor at 100 g/day found a significant effect modification by dose, and continuous dose response meta-regression analyses did not reveal a significant dose response or threshold (Figures S4 and S10, Table S2). Dose response metaregression analyses explored with multivariate models confirmed the significant effect of design found in categorical subgroup analyses; however, dose was not found to be dependent on design (Table S2).

Study or Subgroup	Year	N (any CHO)	N (Fructose)	Mean difference (95% CI) HDL-C (mmol/L)
Diabetes				
Crapo et al.	1986	7	7	0.00 [-0.51, 0.51]
Osei et al.	1987	9	9	0.03 [-0.38, 0.44]
Mcateer et al.	1987	10	10	0.00 [-0.06, 0.06]
Grigoresco et al.	1988	8	8	-0.08 [-1.80, 1.64]
Anderson et al.	1989	28	14	-0.00 [-0.23, 0.23]
Osei et al.	1989	13	13	0.18 [-0.08, 0.44]
Thorburn et al.	1989	3	5	0.02 [-0.24, 0.28]
Blayo et al.	1990	14	12	0.07 [-0.19, 0.34]
Bantle et al. - A	1992	12	12	0.24 [-0.10, 0.58]
Bantle et al. - B	1992	6	6	-0.23 [-0.47, 0.01]
Koivisto et al.	1993	10	10	0.04 [-0.21, 0.29]
Malerbi et al.	1996	32	32	0.00 [-0.14, 0.14]
Subtotal				**0.01 [-0.04, 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 7.79, df = 11 (P = 0.73); I² = 0%				
Test for overall effect: Z = 0.26 (P = 0.79)				
HTG/Insulin Resistant				
Cybulska et al.	1982	16	22	-0.08 [-0.20, 0.04]
Koh et al.	1988	9	9	0.02 [-0.18, 0.22]
Reiser et al.	1989	10	10	0.01 [-0.21, 0.23]
Subtotal				**-0.04 [-0.13, 0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%				
Test for overall effect: Z = 0.83 (P = 0.40)				
Normal				
Hallfrisch et al.	1983	24	24	0.05 [-0.16, 0.25]
Bossetti et al	1984	8	8	0.03 [-0.16, 0.21]
Koh et al.	1988	9	9	-0.08 [-0.25, 0.09]
Reiser et al.	1989	11	11	0.05 [-0.16, 0.26]
Swanson et al.	1992	14	14	0.08 [0.02, 0.14]
Bantle et al.	2000	24	24	0.00 [-0.04, 0.05]
Swarbrick et al.	2008	7	7	-0.03 [-0.58, 0.52]
Ngo Sock et al.	2009	11	11	-0.10 [-0.44, 0.24]
Stanhope et al.	2009	15	17	0.10 [0.01, 0.20]
Silbernagel et al.	2011	10	10	-0.03 [-0.09, 0.04]
Stanhope et al.	2011	32	32	-0.95 [-1.30, -0.60]
Aberli et al.	2013	9	9	0.02 [-0.14, 0.18]
Heden et al.	2014	40	40	-0.03 [-0.13, 0.08]
Subtotal				**-0.01 [-0.07, 0.05]**
Heterogeneity: Tau² = 0.01; Chi² = 41.27, df = 12 (P < 0.0001); I² = 71%				
Test for overall effect: Z = 0.27 (P = 0.79)				
Total				**0.00 [-0.04, 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 51.08, df = 27 (P = 0.003); I² = 47%				
Test for overall effect: Z = 0.02 (P = 0.98)				
Test for subgroup differences: Chi² = 0.76, df = 2 (P = 0.68), I² = 0%				

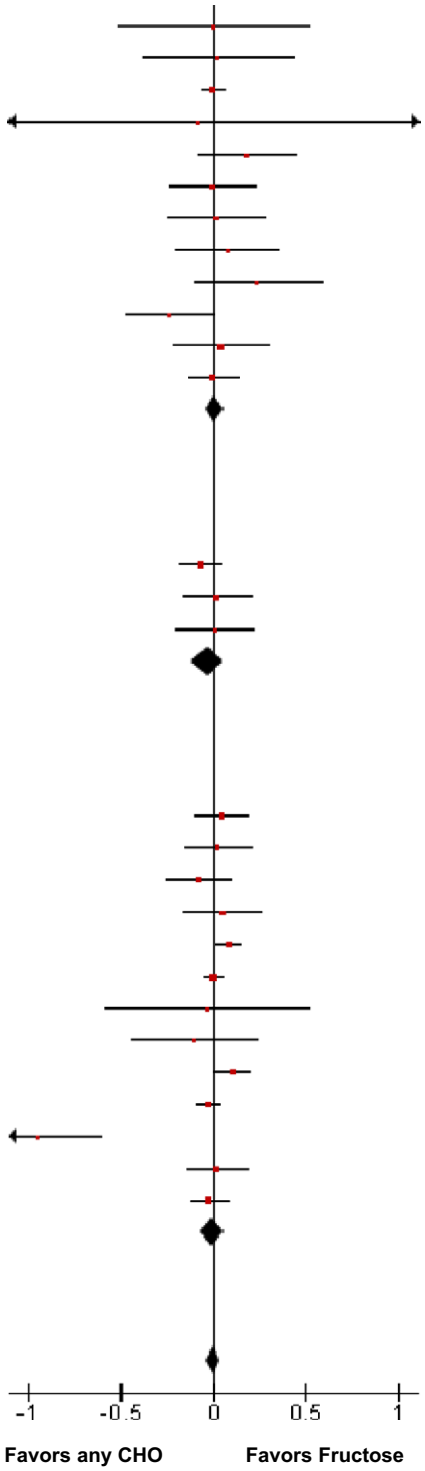

Figure 6. Forest plots of the effect of fructose on HDL-C in isocaloric feeding trials. Pooled effect estimates are shown as diamonds. Data are expressed as MD with 95% CI using generic inverse variance random effects models. Interstudy heterogeneity was tested by the Cochran Q statistic at a significance level of $P<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and ≥75% considerable heterogeneity. Any CHO denotes any carbohydrate comparator. HDL-C indicates high density lipoprotein; HTG, hypertriglyceridemic; MD, mean difference.

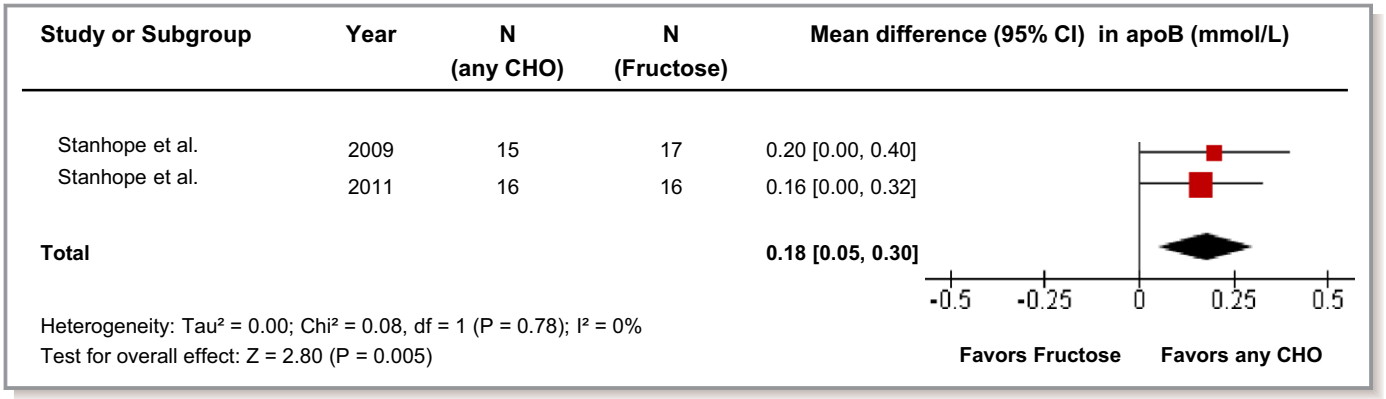

Figure 7. Forest plots of the effect of fructose on apo B in hypercaloric feeding trials. Pooled effect estimates are shown as diamonds. Data are expressed as MD with 95% CI using generic inverse variance random effects models. Interstudy heterogeneity was tested by the Cochran Q statistic at a significance level of $P<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and ≥75% considerable heterogeneity. Any CHO denotes any carbohydrate comparator. apo B indicates apolipoprotein B; MD, mean difference.

Effect of fructose on HDL-C

Twenty-four reports (28 trials) provided data on the effect of fructose intake on HDL-C (Figure 6). Primary pooled analyses showed no effect of fructose on HDL-C (MD=0.00 [95% CI: −0.04, 0.04], P=0.98) with evidence of statistically significant interstudy heterogeneity overall (I^2=47%, P=0.003). Sensitivity analyses in which each study was removed or when correlation coefficients of 0.25 and 0.75 were used did not alter the results. Categorical subgroup analyses showed that relative to other carbohydrates, fructose increased HDL-C when the comparator was starch and lowered HDL-C when the comparator was high fructose corn syrup, although there was only 1 study with high fructose corn syrup as comparator, or when both arms were designed to be isocaloric (ie, neutral energy balance) (Figure S5). Neither categorical subgroup analyses at 60 g/day nor at 100 g/day found a significant effect modification by dose, and continuous dose response metaregression analyses did not reveal a significant dose response or threshold (Figures S5 and S11, Table S2). Dose response metaregression analyses explored with multivariate models confirmed the significant effect of comparator found in categorical subgroup analyses, by showing a significant interaction between fructose and non-fructose-containing comparators. We then further explored the dose response relationship within each level of the covariate independently (non-fructose-containing or fructose-containing comparators). Although there was no significant dose response within trials using non-fructose-containing comparators (P=0.952) (Figure S11), there was a significant dose response within trials using fructose-containing comparators (P=0.014) (Figure S11). However, when an extreme outlier was removed, it was no longer significant (P=0.802).

Hypercaloric Feeding Trials

Effect of fructose on LDL-C

Primary pooled analyses of the effect of fructose on LDL-C in 4 hypercaloric trials (Figure S6) showed no effect (MD=0.08 (95% CI: −0.22, 0.38), P=0.60) with evidence of statistically significant interstudy heterogeneity overall (I^2=77%, P<0.01). Sensitivity analyses revealed that removal of Ngo Sock et al[10] resulted in a significant LDL-C increasing effect of fructose with no evidence of significant interstudy heterogeneity. However, Ngo Sock et al was the only 1 out of 4 trials with a high quality score (MQS=8) and that was metabolically controlled and was 1 of the 2 of the 4 trials that was randomized. Sensitivity analyses where correlation coefficients of 0.25 and 0.75 were used did not alter the results. Categorical subgroup analyses and continuous multivariate metaregression analyses were not undertaken owing to the small number of trials.

Effect of fructose on apo B

Primary pooled analyses of the effect of fructose on apo B in 2 hypercaloric trials (Figure 7) showed an apo B–increasing effect of fructose (MD=0.18 [95% CI: 0.05, 0.30], P=0.005) with no evidence of statistically significant interstudy heterogeneity overall (I^2=0%, P=0.78). Sensitivity analyses in which each study was removed or when correlation coefficients of 0.25 and 0.75 were used did not alter the results. Categorical subgroup analyses and continuous multivariate metaregression analyses were not undertaken owing to the small number of trials.

Effect of fructose on non-HDL-C

Primary pooled analyses of the effect of fructose on non-HDL-C in 2 hypercaloric trials (Figure S7) showed no effect

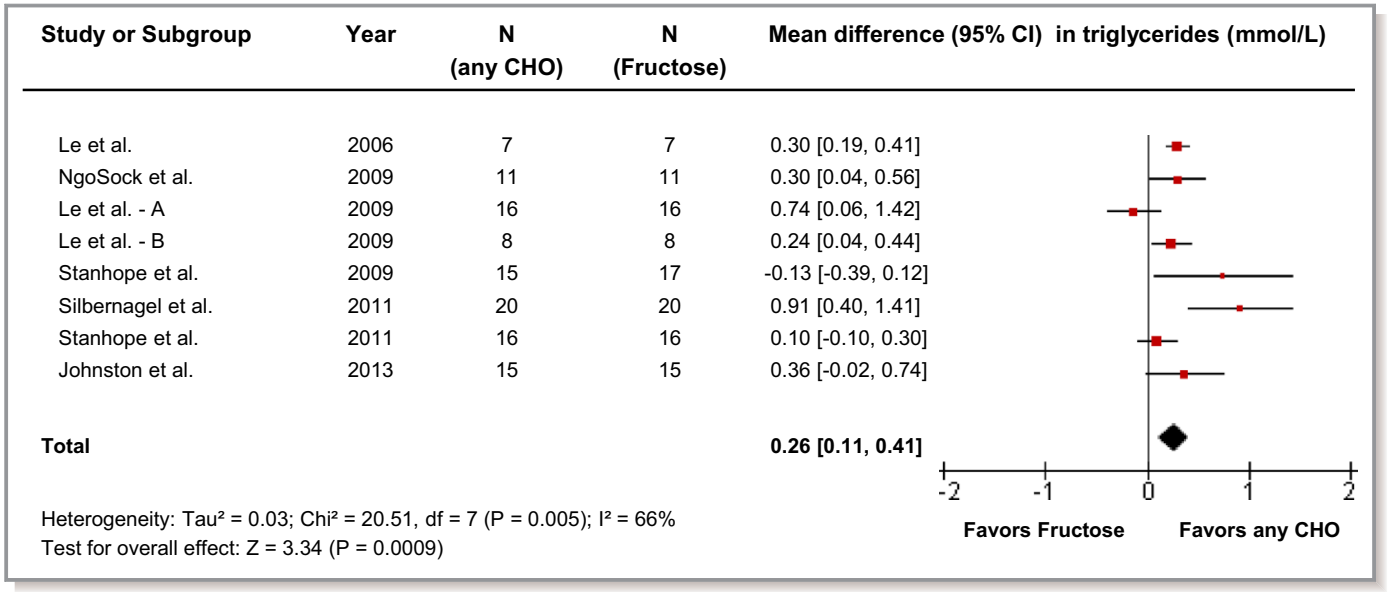

Figure 8. Forest plots of the effect of fructose on triglycerides in hypercaloric feeding trials. Pooled effect estimates are shown as diamonds. Data are expressed as mean difference with 95% CI using generic inverse variance random effects models. Interstudy heterogeneity was tested by the Cochran Q statistic at a significance level of $P<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and ≥75% considerable heterogeneity. Any CHO denotes any carbohydrate comparator.

(MD=0.07 [95% CI: −0.26, 0.39], $P=0.69$), with evidence of statistically significant interstudy heterogeneity overall ($I^2=93\%$, $P<0.01$). Sensitivity analyses in which each study was removed or when correlation coefficients of 0.25 and 0.75 were used did not alter the results. Categorical subgroup analyses and continuous multivariate metaregression analyses were not undertaken owing to the small number of trials.

Effect of fructose on triglycerides

Primary pooled analyses of the effect of fructose on triglycerides in 8 hypercaloric trials (Figure 8) showed a triglyceride-increasing effect of fructose (MD=0.26 [95% CI: 0.11, 0.41], $P<0.01$) with evidence of statistically significant interstudy heterogeneity overall ($I^2=66\%$, $P<0.01$). Sensitivity analyses in which each study was removed or when correlation coefficients of 0.25 and 0.75 were used did not alter the results. Neither categorical subgroup analyses nor continuous multivariate metaregression analyses to investigate a dose response or threshold were significant; however, since the number of trials was small (<10), the analyses were likely underpowered (Figure S8 and Table S3).

Effect of fructose on HDL-C

Primary pooled analyses on the effect of fructose on HDL-C in 4 hypercaloric trials (Figure S9) showed no effect of fructose on HDL-C (MD=0.05 [95% CI: −0.07, 0.17], $P=0.43$) with no evidence of statistically significant interstudy heterogeneity overall ($I^2=0\%$, $P=0.89$). Sensitivity analyses in which each study was removed or when correlation coefficients of 0.25 and 0.75 were used did not alter the results. Categorical subgroup analyses and continuous multivariate metaregression analyses were not undertaken owing to the small number of trials.

Publication Bias

Funnel plots were examined for evidence of publication bias (Figures S12 and S13). There was no evidence of asymmetry or small study effects in either of the isocaloric or hypercaloric feeding trials for each lipid end point assessed by the Begg and Egger tests.

Discussion

This systematic review and meta-analysis assessed the effect of fructose on established lipid targets for cardiovascular disease (LDL-C, apo B, non-HDL-C) and metabolic syndrome (triglycerides and HDL-C) in 59 controlled feeding trials involving 1068 participants with varying metabolic phenotypes. Fructose in isocaloric trial comparisons, in which the amount of fructose was exchanged for an equal amount of a carbohydrate comparator, did not alter any of the lipid end points. However, fructose in hypercaloric trial comparisons, in which fructose supplemented control diets with excess calories compared with the same diets alone with the excess energy, did increase apo B and triglycerides. There was significant effect modification by several factors including study design, metabolic feeding control, comparator, fructose

form, and energy balance, which modified the effect across certain end points.

Relation of Findings to Other Lines of Evidence

Although none of the previous systematic reviews and meta-analyses of the effect of fructose on lipids showed an overall effect of fructose in isocaloric exchange for other carbohydrates, they have demonstrated variable results. A dose response has been identified across all of the meta-analyses in this area. A recent meta-analysis by Zhang et al[63] found no effect of fructose on LDL or HDL-C; however, it found that at doses >100 g/day, there was an LDL-increasing effect of fructose. We, however, published a letter of concern as the authors missed data from 11 trials and miscategorized the doses for 2 trials.[64] Earlier meta-analyses of the effect of fructose on lipids found a fasting triglyceride-increasing effect of fructose only at >60 g/day[6] in people with diabetes and of ≥100 g/day across individuals with different metabolic phenotypes.[5] In the current meta-analysis, which includes 13 new additional trials, we were unable to reproduce these dose thresholds for harm, using both univariate and multivariate models.

Effect modification has also been seen for other subgroups in previous meta-analyses. Significant subgroup effects have been reported for fructose form for body weight,[19] metabolic phenotype for postprandial triglycerides,[20] and comparator, duration of follow-up, and design for triglycerides in those with diabetes.[6] In the current meta-analysis, effect modification was observed by some of the same subgroups (fructose form and comparator) and several other subgroups (metabolic feeding control, study design, and energy balance) for specific end points. None adequately explained heterogeneity. Although the subgroups tend to be underpowered with few trials within each level, the inability of subgroups to explain heterogeneity and the lack of consistency in subgroups across end points suggests other factors may be contributing to the observed heterogeneity.

Limitations

Our systematic review and meta-analysis has several limitations. First, the durability of the effects is a concern since the median follow-up was 4-weeks for isocaloric trials and 2-weeks in hypercaloric trials, so the longstanding effects are unknown. Second, the median fructose dose administered was 96.8 g/day in isocaloric trials, which is well beyond the 95th percentile of intake, so the generalizability of the results is limited.[65] Third, there were a limited number of subjects in the included studies, the majority of which were also of poor design and poor study quality (MQS<8 in 51% of 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 was seen in subgroup analyses. Fourth, end differences in the lipid end points rather than differences in lipid changes between trials groups were used owing to the data reported. Additionally, there was no evidence of baseline differences among trials (data not shown) or effect modification by randomization in subgroup analyses for any of the lipid end points. Fifth, imputations were required for both SDs or SEs of end values (11.5% of trials for LDL-C, 23.1% of trials for non-HDL-C, 37.5% of trials for apo B, 8.2% of trials for triglycerides, and 14.8% of trails for HDL-C) and of differences between end values due to missing study data (42.3% of trials for LDL-C, 100% of trials for non-HDL-C, 50% of trials for apo B, 65.3% of trials for triglycerides, and 63% of trials for HDL-C). Sixth, only one trial was identified that used high fructose corn syrup as a comparator, which is surprising since it is a dominant sweetener in the United States.[66] Seventh, the subgroup analyses were underpowered. Although we did attempt to explore the relative contribution of the subgroups with meta-regression models, there are limitations performing these with so few studies. Seventh, since only published studies were included, publication bias may be a possibility, although there was no bias noted upon inspection of funnel plots and no evidence as assessed by the Begg and Egger tests. However, for the analysis of isocaloric trials of apo B and for all end points in the hypercaloric trial analyses, the number of trials was small (<10), and therefore the possibility of publication bias is difficult to determine. Finally, there was considerable heterogeneity in the analysis of apoB, non-HDL-C, triglycerides, and HDL-C, which was unexplained by sensitivity analyses or any of the subgroup analyses. It is possible that there may be other dietary factors contributing to the large heterogeneity, including viscous soluble dietary fiber,[67,68] dietary pulses,[29] nuts,[69] garlic,[70] or combination of these in some dietary patterns, such as the dietary portfolio,[71] all of which have been shown to modify lipid responses. Overall, there remains a need for larger, longer, higher quality trials to address the sources of uncertainty that remain across the different analyses to date related to feeding control, fructose form, study design, and comparator.

Implications and Clinical Relevance

The American Heart Association[3] and Canadian Diabetes Association [4] in their most recent guidance have taken a harm reduction approach with fructose, setting upper limits for intake based on its ability to raise fasting and postprandial triglycerides. The thresholds for intake were based on earlier meta-analyses by Livesey and Taylor[5] from 2008 (100 g/day) and Sievenpiper[6] from 2009 (60 g/day). The present systematic

review and meta-analysis serves to update these earlier meta-analyses and improve on their eligibility criteria by extending the minimum follow-up (diet duration) requirement. Unlike Livesey and Taylor, where there was no restriction on length of follow-up and thus permitted the inclusion of acute and very short-term trials, we only considered trials ≥7 days. Since their analysis, we identified an additional 13 new trials that met these eligibility criteria. The advantage of including more trials is that it improves the precision of the summary estimates of the effect of fructose on lipids. The inclusion of more recent trials also allows for the control of energy in the analyses, as hypercaloric trials were only published after the census date of the Livesey and Taylor systematic review and meta-analysis (June 2006).[5] As a result of this update, our systematic review and meta-analysis has arrived at a different set of conclusions. Fructose in isocaloric exchange for other carbohydrates did not show a triglyceride-raising effect across a wide dose range (median, 97.0 g/day; IQR, 60.8 to 151.0 g/day). Continuous univariate and multivariate meta-regression models also failed to identify thresholds for either fasting triglycerides, as presented in the current analysis, or postprandial triglycerides, as we have recently published.[20] This lack of effect extended to established lipid targets (LDL-C, apo B, non-HDL-C, and HDL-C), as long as the comparisons were matched for calories. Therefore, based on the most up to date evidence, it appears unwarranted to set specific restrictions on the intake of fructose in the context of lipid effects. In our analyses, we did, however, show that fructose supplementing diets with excess calories (IQR, 24% to 35%) at high doses (IQR, 163.5 to 213.0 g/day) do increase both fasting and postprandial triglycerides, as well as apo B. This effect, however, is no different than what would be expected when overfeeding any other carbohydrate that might replace fructose. A subset of 5 of the isocaloric trials included in our systematic reviews and meta-analyses[9,10,13,15,16] used diets providing excess energy (positive energy balance) in both the added fructose and carbohydrate comparator (starch or glucose) arms, thus permitting the effect of added fructose to be isolated from that of energy under matched yet excess energy feeding conditions. When we restricted our meta-analyses to these trials, there was no evidence of harm with added fructose providing excess energy as long as the comparison with the carbohydrate comparator (starch and glucose) was matched for the excess energy. As a result, there was no significant effect modification by energy balance in post hoc subgroup analyses of the isocaloric trials. Future guideline development may wish to focus on the provision of excess calories whether it be from fructose or any other high glycemic index carbohydrate (starch or glucose) as opposed to a specific dose. There is also a need to focus on other nutritional factors, foods, and dietary patterns that may modify lipid responses.[29,67–71]

Conclusions

Overall, the updated evidence for the effect of fructose on established lipid targets for cardiovascular disease risk reduction does not support earlier identified thresholds on which current clinical practice guidelines are based. There was no significant effect of fructose on LDL-C, non-HDL-C, apo B, triglycerides, or HDL-C in isocaloric comparisons with other carbohydrates across individuals with different metabolic phenotypes. There was, however, evidence of a significant triglyceride and apo B–raising effect in hypercaloric comparisons in which fructose supplemented diets with excess calories. In the absence of an effect in isocaloric comparisons, the effect of fructose seen in hypercaloric comparisons appears more attributable to the calories rather than fructose per se. Clinical practice guidelines, which are currently based on earlier meta-analyses, may wish to consider these current findings in their updates. There remains a need for larger, longer, higher quality trials that assess whether fructose has a meaningful effect on established lipid targets under ad libitum conditions, where fructose-containing sugars freely replace other sources of calories at real-world levels of exposure.

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