

Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids^{1–3}

Lisa A Te Morenga, Alex J Howatson, Rhiannon M Jones, and Jim Mann

ABSTRACT

Background: Dietary sugars have been suggested as a cause of obesity, several chronic diseases, and a range of cardiometabolic risk factors, but there is no convincing evidence of a causal relation between sugars and risk factors other than body weight.

Objective: We conducted a systematic review and meta-analysis of randomized controlled trials that examined effects of the modification of dietary free sugars on blood pressure and lipids.

Design: Systematic searches were conducted in OVID Medline, Embase, Scopus, Cumulative Index to Nursing and Allied Health Literature, and Web of Science databases (to August 2013) to identify studies that reported intakes of free sugars and at least one lipid or blood pressure outcome. The minimum trial duration was 2 wk. We pooled data by using inverse-variance methods with random-effects models.

Results: A total of 39 of 11,517 trials identified were included; 37 trials reported lipid outcomes, and 12 trials reported blood pressure outcomes. Higher compared with lower sugar intakes significantly raised triglyceride concentrations [mean difference (MD): 0.11 mmol/L; 95% CI: 0.07, 0.15 mmol/L; $P < 0.0001$], total cholesterol (MD: 0.16 mmol/L; 95% CI: 0.10, 0.24 mmol/L; $P < 0.0001$), low-density lipoprotein cholesterol (0.12 mmol/L; 95% CI: 0.05, 0.19 mmol/L; $P = 0.0001$), and high-density lipoprotein cholesterol (MD: 0.02 mmol/L; 95% CI: 0.00, 0.03 mmol/L; $P = 0.03$). Subgroup analyses showed the most marked relation between sugar intakes and lipids in studies in which efforts were made to ensure an energy balance and when no difference in weight change was reported. Potential explanatory factors, including a weight change, in most instances explained $<15\%$ of the heterogeneity between studies ($I^2 = 36\text{--}75\%$). The effect of sugar intake on blood pressure was greatest in trials ≥ 8 wk in duration [MD: 6.9 mm Hg (95% CI: 3.4, 10.3 mm Hg; $P < 0.001$) for systolic blood pressure and 5.6 mm Hg (95% CI: 2.5, 8.8 mm Hg; $P = 0.0005$) for diastolic blood pressure].

Conclusions: Dietary sugars influence blood pressure and serum lipids. The relation is independent of effects of sugars on body weight. Protocols for this review were registered separately for effects of sugars on blood pressure and lipids in the PROSPERO International prospective register of systematic reviews as PROSPERO 2012: CRD42012002379 and 2012: CRD42012002437, respectively. *Am J Clin Nutr* doi: 10.3945/ajcn.113.081521.

INTRODUCTION

Dietary sugars have been suggested as a cause of obesity, several chronic diseases, and a range of cardiometabolic risk factors (1). The association between free sugars and dental caries,

although attenuated by fluoride, has been established beyond reasonable doubt (2), and a recent meta-analysis has confirmed the relation between sugar intake and body weight (3). The effect of dietary sugars on weight appears to result from the extent to which increasing or decreasing intakes in free-living individuals influence energy intakes because no change in weight is apparent when proportions of total energy derived from sugar are altered in the context of strict energy balance. These observations appear to apply regardless of whether sugars are consumed in a liquid (eg, sugar-sweetened beverages) or solid form (3). There is no convincing evidence of a causal relation between sugars and other disease outcomes; hence, there has been a high degree of interest of effects on blood pressure, blood lipids, urate, and, most recently, hepatic lipid metabolism and deposition (4, 5). An appreciable body of data is available that relate to effects of sugars on blood pressure and lipids. In this article, we report a systematic review and meta-analysis of randomized controlled trials that compared higher with lower dietary free-sugar intakes in adults or children free of acute illnesses, and reported fasting lipid or blood pressure outcomes. Because our aim was to provide an indication of what might be achieved by population changes in intake of dietary sugars, we included studies in which energy intakes were not strictly controlled as well as controlled feeding studies.

METHODS

Search strategy

Separate electronic searches were conducted to identify randomized trials related to effects of dietary sugars on blood lipids and

¹ From the Departments of Human Nutrition (LATM, AJH, RMJ, and JM) and Medicine (JM), the Riddet Institute (LATM, AJH, RMJ, and JM), and the Edgar National Centre for Diabetes and Obesity Research (LATM and JM), University of Otago, Dunedin, New Zealand.

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³ Address reprint requests and correspondence to LA Te Morenga, Department of Human Nutrition, University of Otago, PO Box 56, Dunedin 9054, New Zealand. E-mail: lisa.temorenga@otago.ac.nz.

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blood pressure in humans according to Cochrane Collaboration guidelines (6). OVID Medline (<http://www.nlm.nih.gov/bsd/pmrresources.html>) and Embase (<http://www.embase.com/>), Scopus (www.scopus.com), Web of Science (<http://thomsonreuters.com/web-of-science/>), and the Cumulative Index to Nursing and Allied Health Literature (<http://www.ebscohost.com/academic/the-cinahl-database>) were searched for English-language trials published between 1960 and August 2013. We applied a modified search strategy on the basis of Cochrane Collaboration methods to identify randomized controlled trials (6). Gray literature databases including Bioline, Clinicaltrials.gov, Directory of Open Access Journals, SCIRUS, OpenDOAR, OpenGrey, Google, and DocuTicker were also searched. Hand searches of reference lists of included studies and published meta-analyses were also undertaken. See Online Supplementary Material under “Supplemental data” in the online issue for the OVID Medline search strategy used.

Study selection

Two reviewers assessed titles and abstracts of all identified studies. Discrepancies in opinion as to whether a study should be included for a full review were adjudicated by a third reviewer. A similar process was undertaken to determine which studies should be included in the formal analysis.

We included randomized trials, including crossover trials, parallel trials, and cluster-randomized trials with a duration >2 wk, which compared dietary interventions intended to alter intake of sugar (sucrose) or other free sugars in one arm compared with another arm of the study. The term free sugars refers to all monosaccharides and disaccharides added to foods by the manufacturer, cook, or consumer plus sugars naturally present in honey, syrups, and fruit juices (7).

Trials that involved direct comparisons, behavioral interventions, or multifactorial lifestyle interventions in which effects of sugars could be analyzed separately from other diet or lifestyle factors were included. Comparison groups could include a control diet (on the basis of usual or unmodified dietary intakes) or an intervention in which sugar intake was quantifiably different from sugar intake in the experimental group. Animal and observational studies were excluded. Studies were required to report differences between treatment groups in intake of free sugars or intake of a component of total sugars (expressed in absolute amounts or a percentage of the total energy) and at least one measure of blood pressure [systolic blood pressure (SBP)⁴, diastolic blood pressure (DBP), or average blood pressure] or one measure of blood lipids (triglycerides; total, LDL, or HDL cholesterol). Participants included adults and children free from acute illness, but subjects with diabetes or other noncommunicable diseases in whom conditions were regarded as stable could be included. Trials could include studies in which participants in the intervention arm were advised to either increase or decrease free sugars or foods and drinks that contained sugars. We included both trials in which there was an isocaloric substitution of sugars with other forms of carbohydrate to control weight and studies in which there was no strict control of energy intake.

Data extraction and quality assessment

Data extraction and a validity assessment were carried out independently by 2 reviewers, and any discrepancies were resolved by discussion with a third reviewer. Data that were related to participant characteristics, study settings and designs, outcomes, exposures or interventions, and potential effect modifiers, such as the degree of weight loss, were extracted by using a piloted data-extraction form. For outcome data, we extracted data related to the difference in changes during the intervention and the SE, 95% CI, or *P* value for the mean difference (MD). Cochrane Collaboration criteria (8) were used to examine the validity and risk of bias of each trial including sequence generation, blinding of participants, personal and outcome assessors, completeness of outcome data, and selective outcome reporting. Additional review-specific criteria included whether studies were funded by industries with potential vested interests.

Statistical analysis

Individual trial data for each outcome measure were pooled to obtain estimates for MDs in each outcome measure between intervention and control groups with Review Manager (RevMan) 5.1 software (9) by using the generic inverse-variance method (10) with DerSimonian and Laird random-effects models to account for heterogeneity that could not be explained by differences in study characteristics (10).

Estimates for the SE of differences in means for treatment groups in crossover studies were derived from reported *P* values when the SEM of the MD was not reported. If *P* values were reported simply as not significant, a conservative estimate of *P* = 0.5 was imputed. Adjustment was made if the imputed *P* value produced a very small or large SE that resulted in a disproportionate weighting in meta-analyses.

As in our previous systematic review of effects of sugars on body weight (3), for main analyses, we have presented forest plot analyses by subgroups relating to whether energy intake was prescribed. One group included studies that attempted to achieve an isocaloric replacement of sugars with other forms of carbohydrate, which are referred to as isocaloric trials. The other group included studies in which participants in the intervention arm were advised to decrease or increase sugars or foods and drinks that contained sugars. Although such advice was generally accompanied by the recommendation to increase or decrease other forms of carbohydrate, there was no strict attempt at weight control. In some of these trials, some foods or drinks were provided to participants. These are referred to as ad libitum trials. Additional subgroup analyses involved the examination of data according to whether weight changes differed in intervention and control groups. An additional post hoc analysis of ad libitum trials examined the effect on outcomes of whether sugars were reduced or increased relative to usual intakes in the intervention group.

The heterogeneity of studies was assessed by using a combination of measures. We ascertained visually whether CIs of each study in the forest plot overlapped. The chi-square test and *I*² statistics were used to quantify heterogeneity (10). We conducted metaregression analyses [with Stata/IC 11.2 software for Mac (StataCorp)] to further examine effects of prespecified explanatory factors, including weight change, diabetes status, metabolic syndrome status, and study design (crossover- or

⁴Abbreviations used: DBP, diastolic blood pressure; MD, mean difference; SBP, systolic blood pressure.

parallel-designed trials), and the study duration on outcome variables. Sensitivity analyses were conducted to examine the effect of study quality by excluding trials considered to have high risk of bias. A 2-sided $P < 0.05$ was considered significant for all analyses.

RESULTS

Study identification

A total of 11,514 articles were initially identified after electronic searching. After deduplication and the exclusion of clearly irrelevant articles, 102 articles remained for which full-text papers were obtained for detailed inspection. Thirty-eight studies were considered to meet the inclusion criteria. Hand searches through article reference lists identified an additional 2 articles that met the inclusion criteria. In total, 40 studies were included in the systematic review and meta-analysis involving 1699 subjects (1217 subjects in parallel-designed trials and 482 subjects in crossover-designed trials) (11–51). Of these studies, 39 trials reported lipid outcomes (11–14, 16–20, 22–51), and 12 trials reported blood pressure outcomes (11–22). The study identification process is shown in **Figure 1**, and characteristics of included studies are described in **Table 1**. See Online Supplementary Table 1 under “Supplemental data” in the online issue for a description of the 62 excluded experimental trials.

Lipids

Of included trials, 38 studies reported on outcomes for triglycerides ($n = 1660$ subjects) (11–14, 16–20, 22–49, 51), 36 studies reported on total cholesterol ($n = 1596$) (11–14, 17–20, 22–34, 36–44, 46–50), 22 studies reported on LDL cholesterol

($n = 1395$) (11–14, 17, 19, 20, 22, 24–26, 33, 34, 36–38, 40, 42, 43, 46, 49), and 29 studies reported on HDL cholesterol ($n = 1515$) (11–14, 17–20, 22, 24–26, 28, 29, 31, 33, 34, 36–40, 42–44, 46, 48, 49). A total of 28 trials involved a crossover design (11–14, 16, 17, 19, 23, 25–32, 34–38, 40–42, 46–49), 16 trials involved interventions for which energy intakes were not strictly controlled (11, 18–20, 24, 28, 36, 38, 39, 43–45, 47–49, 51), and 11 trials had durations >8 wk (18, 20, 24, 31, 33, 37, 39, 43–45, 51). Participants included adults described as being of healthy normal weight (11, 12, 18, 30, 40, 41, 46, 47, 50, 51) or overweight (22, 33, 36, 43–46, 51) or with various cardiovascular risk factors (14, 20, 23, 27, 42, 44) or gallstones (49) or adults with diabetes (13, 16, 24–26, 28, 29, 31, 34, 37–39, 48) (Table 1).

The overall mean effect of higher sugars was 0.11 mmol/L (95% CI: 0.07, 0.15 mmol/L; $P < 0.0001$) for triglycerides, 0.16 mmol/L (95% CI: 0.09, 0.24 mmol/L; $P < 0.0001$) for total cholesterol, 0.12 mmol/L (95% CI: 0.05, 0.19 mmol/L; $P = 0.001$) for LDL cholesterol, and 0.02 mmol/L (95% CI: 0.00, 0.03 mmol/L; $P = 0.02$) for HDL cholesterol (**Figures 2–5**). The effect of altering sugar intake on triglyceride concentrations was similar in studies in which an attempt was made to achieve isocaloric comparisons and studies in which ad libitum diets were consumed (Figure 2). For total, LDL, and HDL cholesterol (Figures 3–5), the effect of higher sugar intakes was significant only in isocaloric trials; however, the differences between subgroup effect estimates were NS.

Subgroup analyses according to whether weight change occurred (*see* online supplementary Figures 1–4 under “Supplemental data” in the online issue) showed that the greatest effects of sugars on each outcome occurred in trials in which no difference in weight change was reported between intervention and control groups. Similar, less striking, but still significant trends were apparent for triglycerides and total cholesterol when we

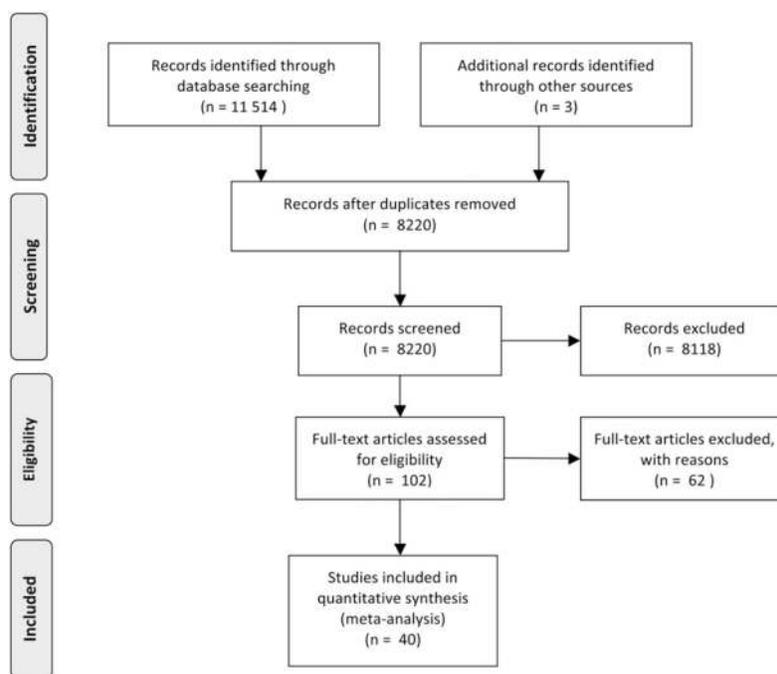


FIGURE 1. PRISMA flow diagram illustrating the study identification and selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

TABLE 1
Characteristics of included trials⁷

First author, year of publication (ref)	Type of study	Participants	Higher-sugar intervention	Lower-sugar comparison intervention or control	Duration	Ad libitum or isocaloric ²	Weight difference ³
Aeberli, 2011 (11)	Randomized crossover trial	29 healthy normal weight men aged 20–50 y, living in and around Zurich, Switzerland	High sugars (fructose, glucose, or sucrose), providing 80 g/d; provided daily in three 200-mL beverages	Moderate sugars (fructose or glucose), providing 40 g/d; provided daily in 3 200-mL beverages	3 wk/treatment, 4-wk washout	Ad libitum	kg −0.17
Antar, 1970 (23)	Randomized crossover trial with controlled feeding	15 hyperlipoproteinemic patients	High-sucrose diet; 40% of energy from sucrose. 96% of food was given as a formula, and 4% of food was given as supplements of raw fruit and vegetables	High-starch diet; 40% of energy from starch; 96% of food was given as a formula, and 4% of foods given as supplements of raw fruit and vegetables	4 wk/treatment, 1–2-wk washout	Isocaloric	0.1
Bahrami, 2009 (24)	Randomized controlled trial	48 Iranian adults with type 2 diabetes but otherwise healthy	Oral honey supplements (first 2 wk, 1.5 g · kg ^{−1} · d ^{−1} ; second 2 wk, 1.5 g · kg ^{−1} · d ^{−1} ; third 2 wk, 2 g · kg ^{−1} · d ^{−1} ; and last 2 wk, 2.5 g · kg ^{−1} · d ^{−1}) in addition to usual diet	Usual diet	8 wk	Ad libitum	−1.8
Bantle, 1992 (25)	Randomized crossover trial with controlled feeding	12 men and women with type 2 diabetes	High-fructose, high-carbohydrate diet; 20% of energy from sucrose	High-starch, low-sugar, high-carbohydrate diet; <3% of energy from fructose	4 wk; >2-d washout	Isocaloric	−0.2
Bantle, 1993 (26)	Randomized crossover trial with controlled feeding	12 men and women with type 2 diabetes; 6 subjects with type 1 diabetes	High-sucrose, high-carbohydrate diet; 19% of energy from sucrose	High-starch, low-sugar, high-carbohydrate diet; <3% of energy from sucrose	4 wk; >2-d washout	Isocaloric	−0.2
Birchwood, 1970 (27)	Randomized crossover trial with controlled feeding	11 hyperlipoproteinemic patients (5 patients with CHD and 1 child)	Therapeutic liquid-formula-based diet for hyperlipidemia but with 40% of total energy from sucrose	Therapeutic liquid-formula-based diet for hyperlipidemia but with 40% of total energy from starch	4 wk; 1–2-wk washout	Isocaloric	−0.2
Black, 2006 (12)	Randomized crossover trial with controlled feeding	13 healthy men	25% of total energy (205 g/d) of diet given as sucrose	10% of total dietary energy (82 g/d) as sucrose	6 wk with 4-wk washout	Isocaloric	0.4
Chantelau, 1985 (28)	Randomized crossover trial	10 type adults with type 1 diabetes and without comorbidities	24 g sucrose	10 g sucrose	4 wk	Ad libitum	−0.8
Colagiuri, 1989 (29)	Randomized crossover trial with controlled feeding of sweeteners	9 adults (8 men) with type 2 diabetes and without comorbidities	Usual diet supplemented with 45 g sucrose/d	Aspartame added to provide similar sweetness as in sucrose intervention	6 wk	Ad libitum	0.6
Cooper, 1988 (13)	Randomized crossover trial	17 adults with type 2 diabetes and without comorbidities	Usual diet with 28 g sucrose supplement/d	Usual diet with saccharin-sweetened starch used to match the sweetness of the sucrose-supplemented diet	6 wk	Isocaloric	0.4
Grande, 1974 (30)	Randomized crossover trial with controlled feeding	12 healthy, male, university students	Identical weight-maintaining experimental diet except providing 500 kcal as sucrose	Identical weight-maintaining experimental diet except providing 500 kcal as wheat flour	2 wk	Isocaloric	0

(Continued)

TABLE 1 (Continued)

First author, year of publication (ref)	Type of study	Participants	Higher-sugar intervention	Lower-sugar comparison intervention or control	Duration	Ad libitum or isocaloric ²	Weight difference ³
Grigoreso, 1988 (31)	Randomized crossover comparing energy-controlled, free-living diets	8 well-controlled adults with type 2 diabetes	Isoglucidic diet replacing 30 g starch/d with 30 g fructose/d	Isoglucidic starch diet	2 mo	Isocaloric	-0.1
Groen, 1996 (50)	Crossover trial	15 men and women	Very-high-sucrose diet providing 231 g (46% of energy) monosaccharides and disaccharides/d	High-bread diet providing 39 g (9% of energy) monosaccharides and disaccharides/d	5 wk	Isocaloric	-0.9
Hallfrisch, 1983 (14)	Randomized crossover trial with controlled feeding	24 hyperinsulinemic men without comorbidities	High-fructose diet; 15% of energy as fructose as a fructose wafer	Low-fructose diet; 0% of energy as fructose; 15% of energy from starch as a starch wafer	5 wk	Isocaloric	0.9
Israel, 1983 (15)	Randomized crossover trial with controlled feeding	24 "carbohydrate-sensitive" adults (12 men, 12 women) without comorbidities	Typical US diet with 30% of energy provided as sucrose in a sucrose/starch patty	Typical US diet with 2% of energy provided as sucrose in a sucrose/starch patty	6 wk	Isocaloric	0
Koivisto, 1993 (16)	Double-blind, randomized, hospital-inpatient, crossover study	10 adults with type 2 diabetes	High-carbohydrate diet supplemented with crystalline fructose; 10% of (55 g/d) energy as fructose	High-carbohydrate diet; 10% of energy as starch	4 wk	Isocaloric	-0.9
Lewis, 2012 (17)	Randomized crossover trial with controlled feeding	17 healthy overweight or obese adults with BMI (in kg/m ²) from 25 to 35	Weight-maintaining diet providing 15% of energy from sucrose	Weight-maintaining diet providing 5% of energy from sucrose (sucrose substituted with starch)	6 wk with 4-wk washout	Isocaloric	0
Little, 1970 (32)	Randomized crossover trial with controlled feeding	9 hyperlipoproteinemic adults and 1 child	High-sucrose diet	High-starch diet	3 wk with >1-wk washout	Isocaloric	0.3
Lowndes, 2012 (33)	Randomized, double-blind, controlled trial	247 healthy overweight and obese adults (162 completers)	Hypoenergetic diet (-500 kcal) providing 20% of energy from high-fructose corn syrup or sucrose	Hypoenergetic diet (-500 kcal) providing 10% of energy from high-fructose corn syrup or sucrose	12 wk	Isocaloric	1.6
Maersk, 2012 (18)	Randomized controlled trial	35 healthy adults	Usual diet supplemented with 1 L sugar-sweetened soft drink/d providing 106 g sucrose/d	Usual diet supplemented with 1 L artificial-sweetened soft drink or H ₂ O/d (0 g sucrose/d)	6 mo	Ad libitum	1.8
Malerbi, 1996 (34)	Randomized crossover trial with controlled feeding	16 adults with well-controlled type 2 diabetes	Standard diet for diabetes but with 20% of energy as fructose or sucrose (with 85% given in a papaya sorbet)	Standard high-starch diet for diabetes; 4% of energy from sucrose/fructose	4 wk with 2-wk washout	Isocaloric	0.5
Mann, 1972 (35)	Randomized crossover trial with controlled feeding	9 normolipemic men aged 30-40 y previously admitted to hospital for nonmetabolic conditions	Typical Western diet with ~70 g sucrose/d, adjusted for each individual's energy needs	Typical Western diet with sucrose replaced by starchy foods (potato and rice)	2 wk	Isocaloric	0.1

(Continued)

TABLE 1 (Continued)

First author, year of publication (ref)	Type of study	Participants	Higher-sugar intervention	Lower-sugar comparison intervention or control	Duration	Ad libitum or isocaloric ²	Weight difference ³
Marckmann, 2000 (36)	Randomized crossover trial	20 postobese adult women; controls matched by age, height, and weight	Ad libitum, high-sucrose diet; 25% of energy (129 g/d) as sucrose	Ad libitum, high-starch diet; 2.5% of energy (14 g/d) as sucrose	2 wk	Ad libitum	
Njike, 2011 (19)	Randomized double-blind crossover trial	44 overweight, but otherwise healthy, US men and women.	Usual diet plus a sugar-sweetened cocoa beverage (22 g cocoa/d and 91 g sugar/d)	Usual diet plus a sugar-free cocoa beverage (22 g cocoa/d)	6 wk with 4-wk washout	Ad libitum	0.2
Osei, 1989 (37)	Randomized crossover trial	13 men and women with type 2 diabetes (outpatients)	Weight-maintaining, diabetic, high-carbohydrate (50% of energy) diet with 60 g crystalline fructose supplement/d	Weight-maintaining diabetic diet, high in complex carbohydrates (50% of energy)	6 mo	Isocaloric	0.8
Paineau, 2008 (51)	Randomized controlled trial	554 parents from the general population	Advice to reduce dietary fats (<35% of total energy intake) and increase complex carbohydrates (>50% of total energy intake)	Advice to reduce dietary fats (<35% of total energy intake) and sugars (-25% of initial crude intake) and increase complex carbohydrates (>50% of total energy intake)	8 mo	Ad libitum	0.4
Peterson, 1986 (38)	Randomized crossover trial	23 nonobese men and women with type 1 and type 2 diabetes, otherwise healthy	High-fiber, high-carbohydrate diet with 45 g sucrose/d replacing complex carbohydrate	High-fiber, high-carbohydrate diet	6 wk	Ad libitum	0.2
Poppitt, 2002 (20)	Randomized controlled trial	28 overweight adults with 3 or more metabolic risk factors	Ad libitum, low-fat, high-simple-carbohydrate diet; 134 g simple sugars/d	Ad libitum, low-fat, high-complex-carbohydrate diet; 47 g simple sugars/d	6 mo	Ad libitum	4.0
Porta, 1989 (39)	Randomized controlled trial	8 matched pairs (n = 16) of adults with type 2 diabetes	Traditional diabetic diet providing 1200–1800 kcal/d with 10% of energy from sucrose replacing starch	Traditional diabetic diet providing 1200–1800 kcal/d (sucrose free)	6 mo	Ad libitum	-0.8
Raben, 2002 (21); Sorensen, 2005 (45)	Randomized controlled trial	41 healthy overweight adults (BMI 25–30) aged 20–50 y	Ad libitum diet supplemented with sucrose-containing foods and beverages providing 27% (177 g/d) of energy as sucrose	Ad libitum diet supplemented with artificially sweetened foods and beverages providing 4% (24 g/d) of energy as sucrose	10 wk	Ad libitum	2.6
Reiser, 1979 (41)	Randomized, crossover, controlled-feeding trial	19 healthy adults (10 men, 9 women)	Typical US diet with 30% (210 g/d) of energy provided as a sucrose patty; 227 g sucrose/d	Typical US diet with 30% (210 g/d) of energy provided as a starch wafer; 17 g sucrose/d	6 wk with 4-wk washout	Isocaloric	0.5
Reiser, 1981 (40)	Randomized crossover, controlled feeding trial	24 carbohydrate-sensitive, healthy men and women	Typical US diet with 30% of energy provided as sucrose in a sucrose/starch patty	Typical US diet with 2% of energy provided as sucrose in a sucrose/starch patty	6 wk	Isocaloric	0
Reiser, 1989 (42)	Crossover, controlled-feeding trial	21 disease-free men of whom 11 subjects were hyperinsulinemic	High-fructose diet; 20% of energy from fructose	High-cornstarch diet; 20% of energy from high-amylase cornstarch	5 wk	Isocaloric	0

(Continued)

TABLE 1 (Continued)

First author, year of publication (ref)	Type of study	Participants	Higher-sugar intervention	Lower-sugar comparison intervention or control	Duration	Ad libitum or isocaloric ²	Weight difference ³
Saris, 2000 (43)	Randomized controlled trial	159 healthy, overweight, and obese (BMI: 25–35) adults aged 20–55 y	Ad libitum diet high in SCHO (ie, sugars); 183 g simple sugars/d	Ad libitum diet high in complex carbohydrates; 106 g simple sugars/d	6 mo	Ad libitum	1.8
Smith, 1996 (44)	Randomized controlled trial	32 middle-aged and overweight men with hypertriglyceridemia	Usual diet; 66 g simple sugars/d	Ad libitum, sugar-free diet; 18 g simple sugars/d	6 mo	Ad libitum	0.5
Surwit, 1997 (22)	Randomized controlled trial with controlled feeding	42 healthy overweight women	Low-kilojoule diet high in sucrose; 121 g sucrose/d	Low-kilojoule diet high in starch; 12 g sucrose/d	6 wk	Isocaloric	1.0
Swanson, 1992 (46)	Randomized crossover trial with controlled feeding	14 healthy, normal weight to overweight men and women	High-fructose diet; 20% (100 g/d) as fructose	Low-fructose, high-starch diet; <3% (14 g/d) as fructose	4 wk	Isocaloric	0
Szanto, 1969 (47)	Crossover trial	19 healthy men	High-sucrose diet (substituting sucrose for starch); 438 g sucrose/d	Low-sucrose diet; 10 g sucrose/d	2 wk with 2-wk washout	Ad libitum	0.4
Venhaus, 1988 (48)	Randomized crossover trial	10 adults with type 1 diabetes	Refined-carbohydrate diet avoiding whole-grain products and limiting fruit and vegetables providing 96 g/d (14% of energy) from simple sugars	Unrefined carbohydrate diet avoiding refined fiber-depleted carbohydrates such as sucrose, white bread, white rice, mashed potatoes, and other highly-processed foods and juices providing 69 g/d (12% of energy) from simple sugars	4 wk	Ad libitum	1.2
Wemer, 1984 (49)	Randomized crossover trial	12 adults with radiolucent gallstones and bile supersaturated with cholesterol but with normal liver function, insulin, and glucose status	Ad libitum, high-sucrose (>100 g/d), fiber-depleted diet; 112 g refined sugar/d	Ad libitum, low-sucrose, fiber-depleted diet; 16 g refined sugar/d	6 wk	Ad libitum	1.4

¹ CHD, coronary heart disease; ref, reference; SCHO, simple carbohydrate.² Ad libitum trials were studies in which an attempt was made to control sugar intakes, but there was no strict prescription regarding total energy intake in either the intervention or control group; foods and beverages high and low in free sugars may have been provided. Isocaloric trials were studies in which energy intakes were intended to be equivalent in intervention and control groups with the only difference being proportions of free sugars or other carbohydrates.³ Difference in reported weight changes in intervention and control groups that occurred during the trial.

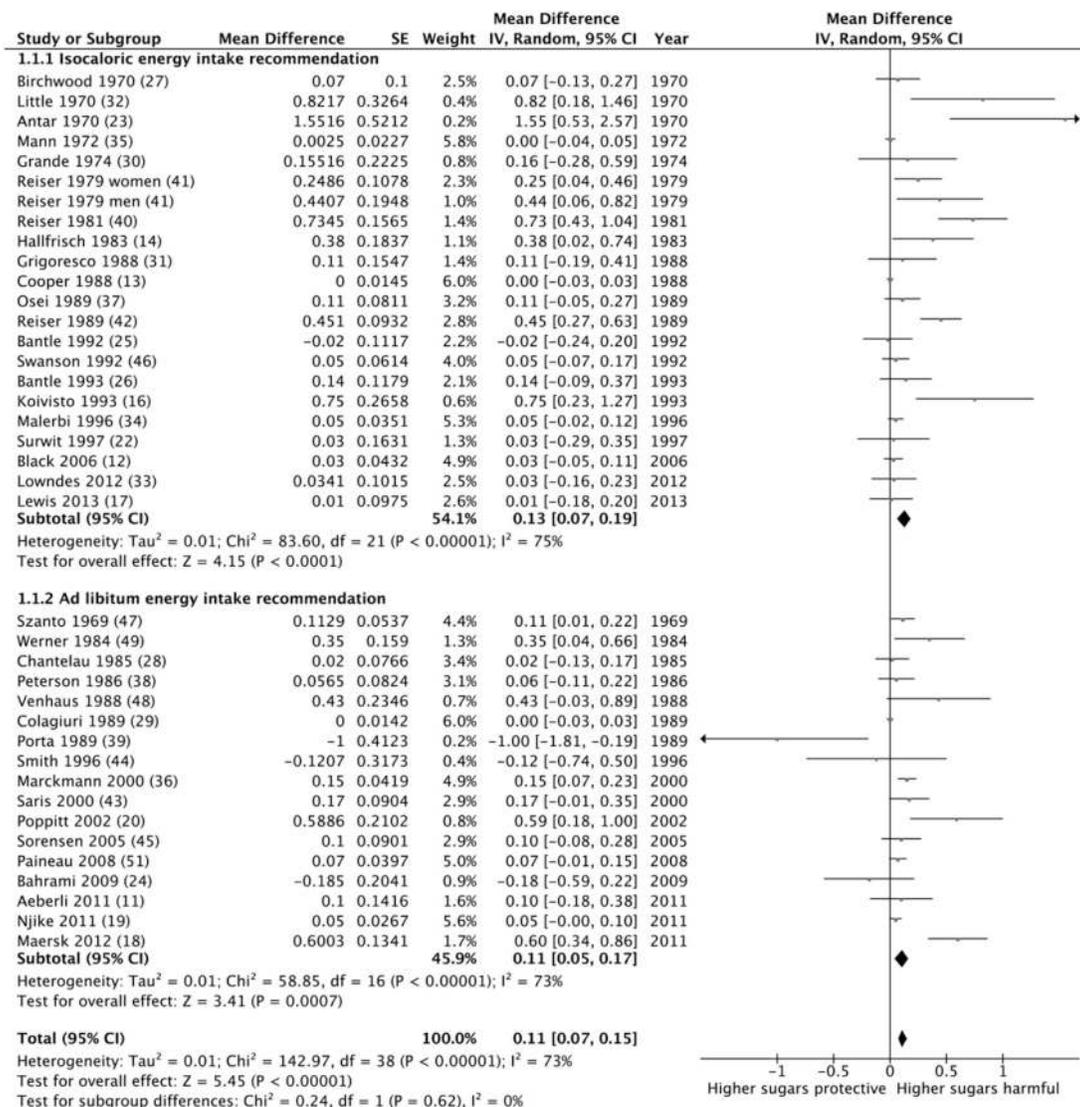


FIGURE 2. Meta-analysis of weighted mean (95% CI) differences (mmol/L) in effects on blood triglyceride concentrations in randomized controlled trials that compared higher with lower free-sugar intakes on blood triglyceride concentrations by subgroups relating to energy intake prescription. Black diamonds denote the weighted mean difference for the two subgroup analyses and the overall effect. For individual studies, the black square denotes the mean study effect, and the bars represent the 95% CI. Data were estimated by using generic IV methods with a DerSimonian and Laird random-effects model. IV, inverse variance.

considered trials in which weight gain was reported in intervention compared with control groups. In contrast, the effect of sugars on triglycerides and total cholesterol was attenuated and no longer significant when we considered trials in which greater weight reduction was reported in higher-sugar groups.

See online supplementary Figures 5–8 under “Supplemental data” in the online issue for post hoc subgroup analyses according to whether the intervention group involved a reduction or increase in sugar intakes relative to usual intakes. Eleven trials involved increased sugar intakes, and 2 trials involved reduced sugar intakes in intervention relative to control arms. Four trials involved an increase in sugars in one arm and a decrease in sugars in the comparison arm. The greatest effect of higher sugar intakes on lipids was shown in trials that compared an increase in sugars in one arm compared with a decrease in sugars in the other arm, but this effect was only significant for

triglycerides [MD: 0.17 mmol/L (95% CI: 0.06, 0.27 mmol/L; $P = 0.001$) for triglycerides, 0.14 mmol/L (95% CI: -0.13, 0.41 mmol/L; $P = 0.31$) for total cholesterol, and 0.16 mmol/L (95% CI: -0.10, 0.42 mmol/L; $P = 0.23$) for LDL cholesterol]. The effect of sugars was not significant for other trial types.

Heterogeneity in trials was high and significant for each outcome ($I^2 = 73%$ for triglycerides, 74% for total cholesterol, 73% for LDL cholesterol, and 36% for HDL cholesterol). Little of the heterogeneity for triglyceride and total- and LDL-cholesterol outcomes ($<15%$) was explained by differences in study designs, study durations, diabetes status, or types of sugars compared. There was a positive effect of the difference in sugar intakes between intervention and control groups on LDL cholesterol only ($P = 0.005$); this factor explained 54% of between-study heterogeneity. The effect of sugars on total cholesterol was reduced in trials ≥ 8 compared with <8 wk duration ($P = 0.009$),

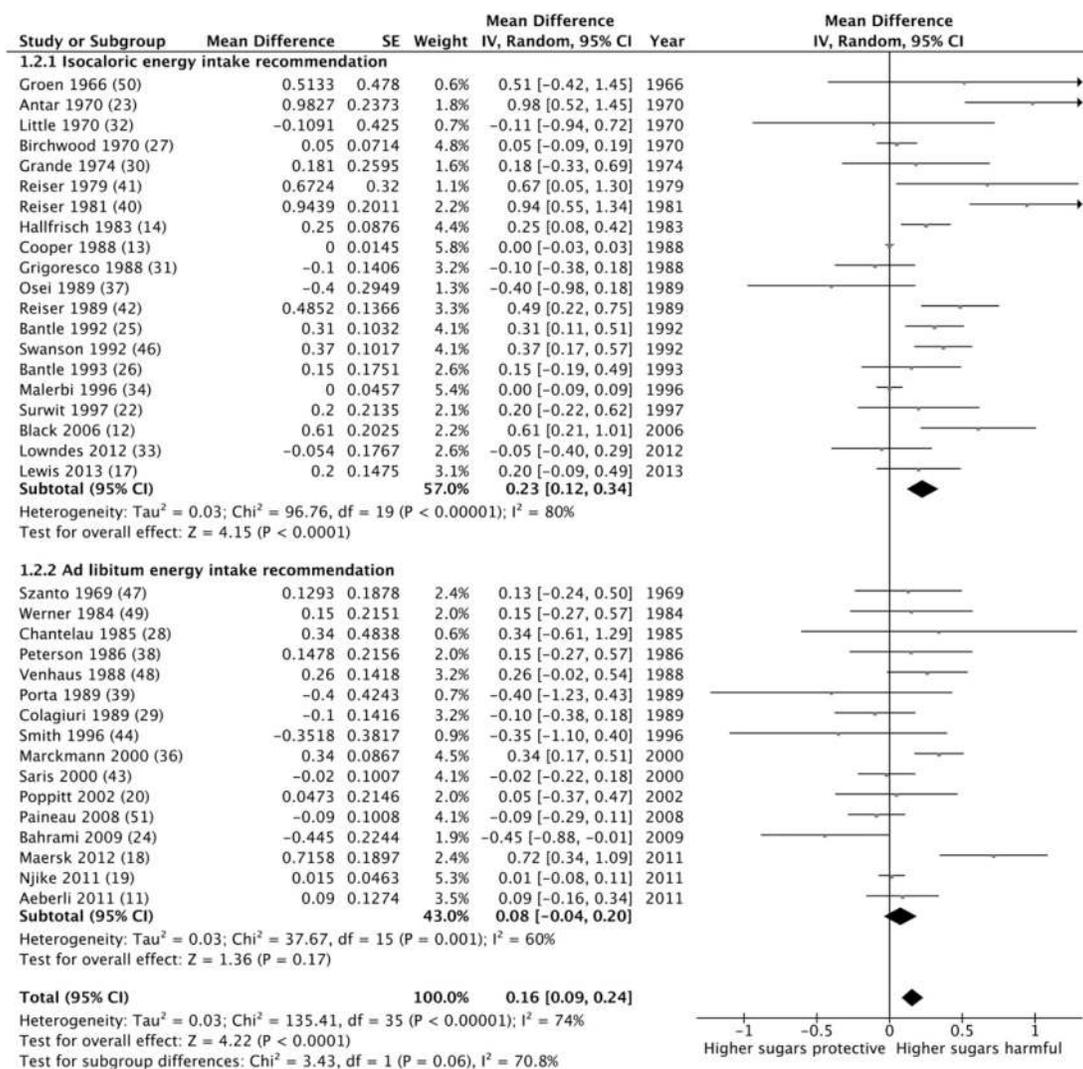


FIGURE 3. Meta-analysis of weighted mean (95% CI) differences (mmol/L) in effects on total cholesterol concentrations in randomized controlled trials that compared higher with lower free-sugar intakes on blood triglyceride concentrations by subgroups relating to energy intake prescription. Black diamonds denote the weighted mean difference for the two subgroup analyses and the overall effect. For individual studies, the black square denotes the mean study effect, and the bars represent the 95% CI. Data were estimated by using generic IV methods with a DerSimonian and Laird random-effects model. IV, inverse variance.

but this factor explained only 14% of the heterogeneity. See online supplementary Table 2 under “Supplemental data” in the online issue for results of meta-regression analyses.

Blood pressure

Twelve trials reported blood pressure outcomes ($n = 324$) (11–22). Participants included those described as healthy but overweight (19–22), hyperinsulinemic (14), with type 2 diabetes (13, 16), or with the metabolic syndrome (20) (Table 1).

There was no significant effect of higher sugar intakes on SBP overall (MD: 1.1 mm Hg; 95% CI: $-1.0, 3.2$ mm Hg; $P = 0.32$); however, there was significant heterogeneity in results of individual trials ($P = 0.0005$, $I^2 = 67\%$) (Figure 6). Subgroup analyses showed a significant interaction with the study duration but no significant difference between isocaloric and ad libitum trials ($P = 0.0002$). In trials of <8 wk duration, there was no evidence of an effect of a higher-sugar diet on SBP, whereas in 3

trials of >8 wk duration (18, 20, 21), the mean effect was 6.9 mm Hg (95% CI: 3.4, 10.3 mm Hg; $P < 0.0001$) (see online supplementary Figure 9 under “Supplemental data” in the online issue). Two of these longer-term trials resulted in significantly higher body weight after the higher-sugar intervention (20, 21). Poppitt et al (20) showed that a higher-sugar intervention resulted in a 0.28-kg weight loss compared with a 4.25-kg loss in the lower-sugar diet group, and Raben et al (21) reported an increase in weight with the high-sugar diet and a decrease in weight with the low-sugar diet.

Heterogeneity was also largely explained by the trial design because 8 of 9 short-term trials had a crossover design (11–17, 19). See online supplementary Table 2 under “Supplemental data” in the online issue for findings of the meta-regression that explored causes for the heterogeneity.

A higher sugar intake was associated with significantly greater DBP of 1.4 mm Hg (95% CI: 0.3, 2.5 mm Hg; $P = 0.02$) overall (Figure 7). This effect was greater for ad libitum trials (MD: 3.7

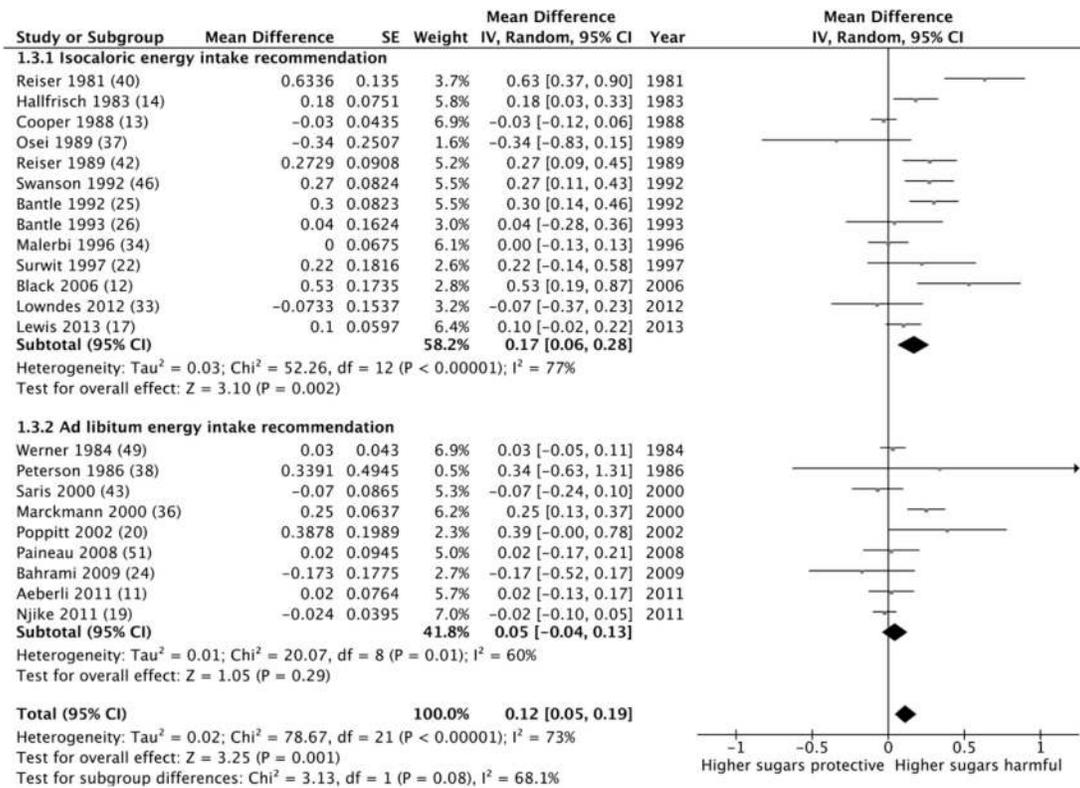


FIGURE 4. Meta-analysis of weighted mean (95% CI) differences (mmol/L) in effects on LDL-cholesterol concentrations in randomized controlled trials that compared higher with lower free-sugar intakes on blood triglyceride concentrations by subgroups relating to energy intake prescription. Black diamonds denote the weighted mean difference for the two subgroup analyses and the overall effect. For individual studies, the black square denotes the mean study effect, and the bars represent the 95% CI. Data were estimated by using generic IV methods with a DerSimonian and Laird random-effects model. IV, inverse variance.

mm Hg; 95% CI: 0.3, 7.1 mm Hg; $P = 0.03$). There was a significant interaction with the study duration ($P = 0.002$) with a stronger association in trials of >8 wk duration (18, 20, 21) of 5.6 mm Hg (95% CI: 2.5, 8.8 mm Hg; $P = 0.0005$) (see online supplementary Figure 10 under “Supplemental data” in the online issue).

Subgroup analyses according to whether a weight change occurred (see online supplementary Figures 11–12 under “Supplemental data” in the online issue) showed a significant effect of sugars on both SBP (MD: 2.7 mm Hg; 95% CI: 0.2, 5.2 mm Hg; $P = 0.03$) and DBP (MD: 3.2 mm Hg; 95% CI: 0.6, 5.77 mm Hg; $P = 0.01$) in 2 trials in which no difference in weight change was reported between intervention and control groups. However, subgroup differences were not statistically significant ($P = 0.61$ for SBP and 0.37 for DBP).

See online supplementary Figures 13–14 under “Supplemental data” in the online issue for post hoc subgroup analyses according to whether the intervention group involved a reduction or increase in sugar intakes relative to usual intakes. There was a significant effect of higher sugar intakes on blood pressure only in 2 trials that compared an increase in sugars in one arm compared with a decrease in sugar in the other arm (MD: 6.0 mm Hg; 95% CI: 1.7, 10.2 mm Hg; $P = 0.006$ for SBP; and 4.9 mm Hg; 95% CI: 1.2, 8.6 mm Hg; $P = 0.01$ for DBP). No trials were identified that involved reduced sugar intakes in the intervention arm compared with usual sugar intakes in the comparison arm.

Risk of bias

See online supplementary Figures 15 and 16 under “Supplemental data” in the online issue for a summary of risk of bias assessment. Although the blinding of participants and researchers to treatment was not explicitly stated in most studies, risk of bias was considered low in crossover trials because participants completed both high- and low-sugar interventions. Moreover, the blinding to treatment was not possible in studies that involved free-living participants and in which the intervention involved a provision of dietary advice.

Fourteen studies included in lipid analyses were considered at high risk of bias because of the reporting of nonsignificant findings as “NS” or “not significant,” and thus, we were required to impute a P value to generate an estimate for the SE (11–14, 16, 27–31, 37, 38, 47, 49). However, the omission of these studies would have resulted in an overestimate of effects of higher sugar intakes on lipid outcomes. Fourteen studies received financial support from the sugar industry (12, 13, 17, 20, 25, 26, 33–36, 43, 46, 48, 51). We considered the risk of bias from such funding as unclear. The exclusion of these studies from the analysis strengthened the effect of sugars on triglycerides (MD: 0.19 mmol/L; 95% CI: 0.11, 0.27 mmol/L; $P < 0.0001$), total cholesterol (MD: 0.18 mmol/L; 95% CI: 0.05, 0.31 mmol/L; $P = 0.008$), and HDL cholesterol (MD: 0.03 mmol/L; 95% CI: 0.00, 0.06 mmol/L; $P = 0.03$).

In trials included in blood pressure analyses, one study was considered to be at high risk of bias because of the reporting of

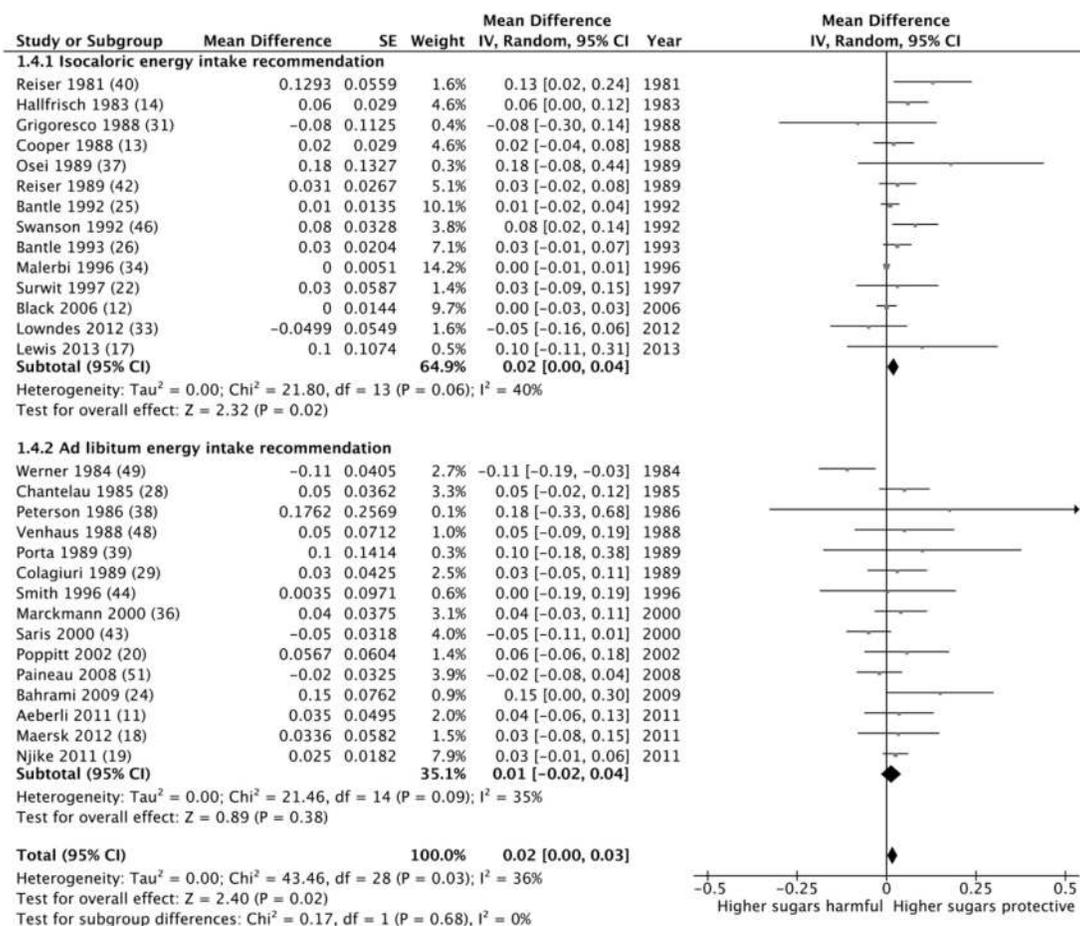


FIGURE 5. Meta-analysis of weighted mean (95% CI) differences (mmol/L) in effects on HDL-cholesterol concentrations in randomized controlled trials that compared higher with lower free-sugar intakes on blood triglyceride concentrations by subgroups relating to energy intake prescription. Black diamonds denote the weighted mean difference for the two subgroup analyses and the overall effect. For individual studies, the black square denotes the mean study effect, and the bars represent the 95% CI. Data were estimated by using generic IV methods with a DerSimonian and Laird random-effects model. IV, inverse variance.

incomplete outcome data because there were substantially more dropouts in the intervention than control groups (28% compared with 8%, respectively) (22). Three crossover trials had no washout period (13–15), and one trial received funding from food-and sugar-manufacturing companies (22). Sensitivity analyses that examined effects of the exclusion of studies with potentially important biases did not alter the significance of the association between higher sugar intakes and blood pressure. The exclusion of the 5 studies that received funding from sugar industries (12, 13, 17, 20, 22) strengthened associations between sugars and SBP (MD: 7.6 mm Hg; 95% CI: 3.9, 11.2 mm Hg; $P < 0.001$) and DBP (MD: 6.1 mm Hg; 95% CI: 2.6, 9.5 mm Hg; $P = 0.0006$) in longer-term trials and overall for DBP (MD: 1.84 mm Hg; 95% CI: 0.1, 3.6 mm Hg; $P = 0.04$).

Publication bias

SEs for mean effects were imputed for 15 crossover studies included in meta-analyses (11–14, 16, 27–31, 37, 38, 47–49) whereby differences in effects on one or more outcomes of interest between higher- and lower-sugar interventions were reported simply as “not significant” and without an estimate of the SEM difference. The resulting SE estimates lacked sufficient

precision to enable meaningful funnel plot analyses or statistical tests for publication bias such as Egger’s test (8). However, the inclusion of a relatively large number of trials that reported nonsignificant effects suggested low risk of publication bias.

DISCUSSION

This systematic review and meta-analyses of randomized controlled trials provides evidence that higher compared with lower intakes of sugars are associated with increased concentrations of triglycerides, total and LDL cholesterol, and blood pressure, although for SBP, this effect was only significant in studies of a longer duration. The study duration was the only important determinant of the heterogeneity in studies with regard to blood pressure outcomes. When we considered lipid outcomes, the significant heterogeneity in studies was not explained by any of the potentially confounding variables. However, because 40% of studies involved free-living individuals who consumed ad libitum diets for which energy intakes were not strictly controlled, and many of the trials that were intended to compare isocaloric diets did not include adequate measures of compliance, it seems likely that a varying adherence to dietary advice explained at least some of the variation.

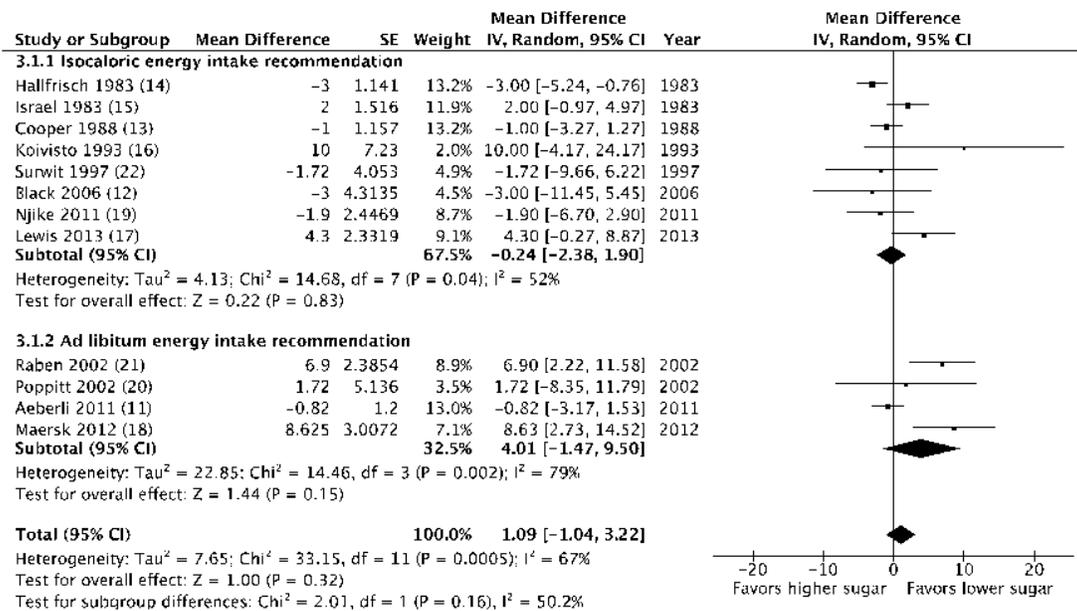


FIGURE 6. Meta-analysis of weighted mean (95% CI) differences (mmol/L) in effects of systolic blood pressure in randomized controlled trials that compared higher with lower free-sugar intakes on blood triglyceride concentrations by subgroups relating to energy intake prescription. Black diamonds denote the weighted mean difference for the two subgroup analyses and the overall effect. For individual studies, the black square denotes the mean study effect, and the bars represent the 95% CI. Data were estimated by using generic IV methods with a DerSimonian and Laird random-effects model. IV, inverse variance.

Because of the powerful association between adiposity and both lipid and blood pressure (52–54) and the potential for change in intakes of free sugars to influence body weight in free-living individuals (3), it might be assumed that altered energy intakes and weight loss explained the present set of observations. However, a subgroup analysis showed that, for triglycerides and total and LDL cholesterol, the most-consistent

associations between higher intakes of sugars and higher concentrations were seen in studies in which attempts were made to achieve an isocaloric exchange or when no difference in weight change between interventions was reported. Higher triglyceride concentrations were also observed in ad libitum studies and when weight increases were reported with the higher-sugar intervention. Effects of sugars on triglycerides appeared to be

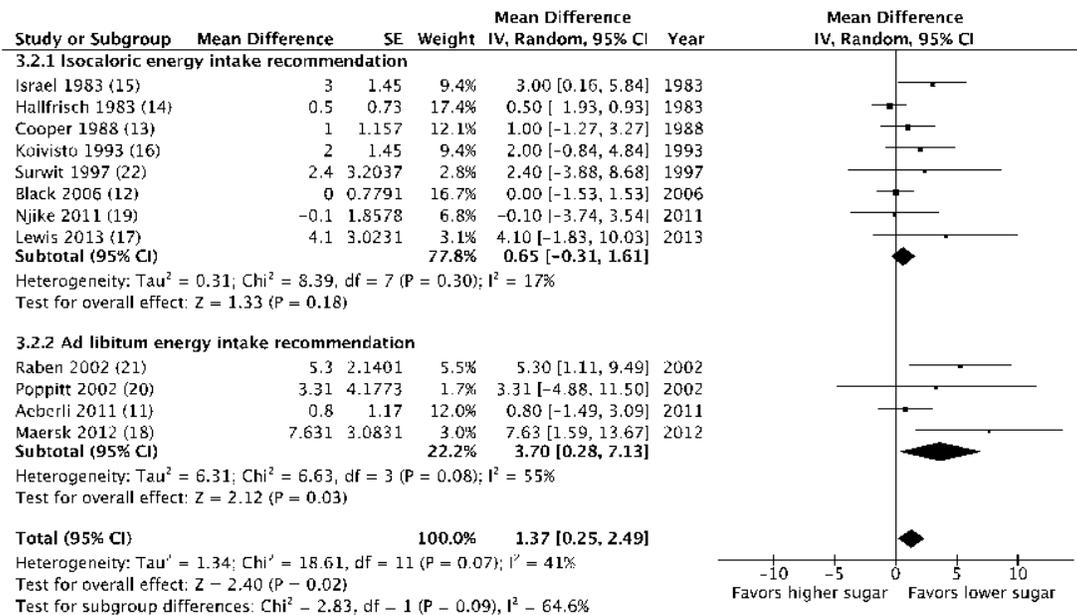


FIGURE 7. Meta-analysis of weighted mean (95% CI) differences (mmol/L) in effects of diastolic blood pressure in randomized controlled trials that compared higher with lower free-sugar intakes on blood triglyceride concentrations by subgroups relating to energy intake prescription. Black diamonds denote the weighted mean difference for the two subgroup analyses and the overall effect. For individual studies, the black square denotes the mean study effect, and the bars represent the 95% CI. Data were estimated by using generic IV methods with a DerSimonian and Laird random-effects model. IV, inverse variance.

attenuated in studies in which, for whatever reason, weight loss occurred. In the absence of an important contribution of an energy imbalance, the most likely explanation for the effect of free sugars on blood pressure and lipids is in the fructose component, which is present in sucrose (sugar), high-fructose corn syrup, honey, and fruit (55).

Excessive intake of dietary fructose, particularly from sugar-sweetened beverages, has been shown to increase hepatic fat synthesis, which results in increased concentrations of circulating triglycerides and cholesterol (1). In addition, unregulated hepatic fructose metabolism may lead to increased urate synthesis. Urate has been shown to decrease nitrous oxide synthesis and impairs the function of endothelial cells resulting in vasoconstriction (1) and may directly stimulate the renin-angiotensin system to increase blood pressure (55, 56). Regardless of the precise mechanism, high serum urate has been linked with hypertension and increased cardiovascular risk (57).

Our findings are compatible with epidemiologic observations and experimental studies in animals that have consistently suggested an association between high dietary sugar or fructose intakes and increased lipids (triglycerides), blood pressure, body fat, and cardiovascular mortality (1, 18, 58–73).

However, our findings contrast with findings of 2 recent systematic reviews and meta-analyses that specifically examined metabolic effects of fructose consumption compared with other carbohydrates (including other sugars), which suggested no unique lipid- or blood pressure-raising effects of fructose unless intakes were very high (>100 g/d) (74) or fructose was exchanged for starch (75). This difference may have resulted because we did not include studies that exchanged fructose for other sugars because our aim was to examine the effect of total free sugars to further inform recommendations. Most trials included in our meta-analysis involved different intakes of sugar (sucrose) and other monosaccharides and disaccharides, or “free sugars” as defined by the WHO (7), in control and intervention arms. We examined effects of total sugars as well as various subcategories of sugars but showed no difference by the type of sugars.

Although effects of sugars on lipids and blood pressure are relatively modest, a reduction of intake is likely to have public health relevance, especially in the context of the modification of several risk factors that have synergistic effects in terms of cardiovascular risk (76). Risk of cardiovascular disease was increased by 6% in men and 12% in women for each 0.2-mmol/L increase in triglyceride concentrations in a meta-analysis of prospective studies by Hokanson and Austin (77), whereas risk of stroke was shown to be reduced by 4.5% for each 0.1-mmol/L reduction in LDL cholesterol in a meta-analysis by Labreuche et al (78). The difference we observed in HDL cholesterol was very small and of questionable significance. A meta-analysis by Neal et al (79) suggested that modest reductions in blood pressure (range: 3–6 mm Hg SBP and 1–4 mm Hg DBP) over the long term were associated with reductions in risk of stroke, coronary heart disease, cardiovascular events, and mortality in the order of 20–30%. Although an understanding of the extent to which changes in energy intake and body weight influence the effect of sugars on cardiometabolic risk is of inherent interest, individual and public health benefits that might be expected to accrue from the reduction in intake of added sugars does not depend on an understanding of the mechanism.

A strength of this review was that it involved a comprehensive approach to identifying relevant English-language studies, and included data from all relevant studies regardless of the experimental design. The observed heterogeneity appears to be insufficient to detract from the overall conclusion that free sugars have the potential to adversely influence lipid concentrations and blood pressure. Crossover trials, which are generally considered to have a more-robust design than that of parallel trials because of reduced intraparticipant variability (80) constituted a significant body of data to the overall analysis. In some studies, effects of sugar intakes on blood pressure or lipid outcomes were reported as nonsignificant with insufficient data reported to accurately calculate the SEM difference. We felt it was important to include these studies because they represented a large body of evidence for our analysis. For these studies, we approximated the SEM difference rather than omitting data. The effect of doing so was to give a more-conservative estimate of effects of sugars on blood pressure and lipids, which enhanced our confidence in the findings (81). The inclusion of both controlled trials and studies that primarily involved the modification of free sugars without strict control of total food intake enabled the additional understanding of mechanisms as well as the strengthening of nutritional recommendations regarding free-sugar intakes. Our previous review (3) suggested that advice to reduce sugars without specifying a replacement energy resulted in a decrease in body weight. This study has shown benefit in terms of lipids and blood pressure regardless of whether an energy balance was achieved.

Limitations of these findings were those inherent to the primary research on which they were based, notably the inadequacy of dietary intake data, variation in the nature and quality of the dietary intervention, small numbers of participants, and relatively short study duration (<8 wk) of many trials. The limited number of ad libitum studies that involved a reduction in sugar intakes in the intervention arm relative to usual intakes in the control arm (*see* online supplementary Figures 5–8, 13, and 14 under “Supplemental data” in the online issue) precluded definitive conclusions regarding this subgroup.

In conclusion, this systematic review and meta-analyses provide evidence that dietary free sugars influence blood pressure and serum lipids independently of the effect of sugars on body weight. Although effects of sugars on blood pressure and lipids are relatively modest, our findings support the idea that reducing free-sugar intakes might be expected to reduce blood pressure and serum lipids.

The authors’ responsibilities were as follows—LATM and JM: jointly conceived the study; LATM: led the research and supervised the work of AJH and RMJ; LATM, AJH, and RMJ: developed the study protocol, conducted searches, assessed inclusion, extracted data, assessed validity, and did meta-analyses; and all authors: contributed to interpreting data and writing the manuscript and read and approved the final draft of the manuscript. All authors declare support from the University of Otago and Riddet Institute but no other financial relations with any organizations that might have an interest in the submitted work in the previous 3 y and no other relations or activities that could appear to have influenced the submitted work.

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