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 (I² 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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Fructose and Lipids

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Fructose and 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 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], apo lipoprotein 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 (MOS).\(^27\) 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. To generate SE for included crossover trials, we assumed paired analyses as described by Elbourne, 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.

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. 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; <100 g/day or ≥100 g/day), 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 and Begg 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.
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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**Figure 1.** Flow of the literature.
### 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 | MOSk | 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 |
| Grigorescu 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) | 8 T1DM, 2 T2DM | 43 (11) | OP, France | P | Supp | Yes | ≈25 (~5% E) | Mixed | Starch | 55:30:15 | Neutral | 52 weeks | 7 | Agency, industry |
| **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) | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| **Fructose** |
| 5 T1DM, 1 T2DM | 48 (17) | | | | | | | | | | | | |
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 | MGS¶ | 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 |
| 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 |
| Nestel et al 1970—Study 1 (50) | 3 HTG (2M:1F) | 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 |
| Nikkilä 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 |
| 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 |
| Cybulskia 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 |

Hypertiglyceridemia & insulin resistance

| 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 | MGS¶ | Funding Source§ |
|-------------------------|--------------|---------------------------|---------|--------|----------------|---------------|--------------|---------------|-------------|--------|----------------|-----------|-------|-----------------|
| 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 |
| Nestel et al 1970—Study 1 (50) | 3 HTG (2M:1F) | 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 |
| Nikkilä 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 |
| 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 |

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 | MGS¶ | 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 |
| Forster and Heller 1973 (65) | 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 |
| 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 | IP, USA | C | Met | Yes | ~85 (17% E) | Mixed | Glucose | 55:30:15 | Neutral | 6-weeks | 9 | Agency |
| Sunehag et al 2002 (47) | 12 N (8M: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 |
| 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 |

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/DB      | 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/DB     | 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         | 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       | 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       | 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     | 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         | 28.0 (27.2)              | IP/OP, USA | P       | Met/Supp      | No           | 168 (25% E) | Liquid       | Glucose     | 55:30:15 | Positive       | 2-weeks   | 6     | Agency           |
| 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       |
| Johnston et al 2013—A (15)| 32 OW      | 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      | 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         | 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        | 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 (11) 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

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| 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 | MQSk | 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)      | 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.

k 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 al32 age was based on 10 participants.

** Four trials9,10,13,16 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.

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### Fructose and Lipids

#### Study or Subgroup Year N (any CHO) N (Fructose) Mean difference (95% CI) LDL-C (mmol/L)

**Diabetes**
- Crapo et al. 1986 7 7 -0.53 [-2.31, 1.25]
- Osei et al. 1987 9 9 -0.41 [-0.96, 0.14]
- Mcateer et al. 1987 10 10 -0.20 [-0.87, 0.47]
- Grigoresco et al. 1988 8 8 -0.07 [-0.31, 0.17]
- Osei et al. 1989 13 13 -0.34 [-1.03, -0.35]
- Anderson, et al. 1989 14 28 0.18 [-0.43, 0.79]
- Blayo et al. 1990 12 14 0.37 [-0.86, 1.60]
- Bantle et al. 1992 18 18 0.30 [-0.06, 0.66]
- Koivisto et al. 1993 10 10 0.43 [-0.19, 1.05]
- Malerbi et al. 1996 16 16 -0.10 [-0.34, 0.14]

**Subtotal** -0.02 [-0.17, 0.12]

Heterogeneity: \( \tau^2 = 0.00; \ Chi^2 = 9.77 \ df = 9 \ (P = 0.37); \ I^2 = 8\% \)
Test for overall effect: \( Z = 0.32 \ (P = 0.75) \)

**HTG/Insulin Resistant**
- Cybulskia et al. 1982 22 16 -0.28 [-0.75, -0.18]
- Koh et al. 1988 9 9 -0.06 [-0.55, 0.43]
- Reiser et al. 1989 10 10 0.21 [0.32, 0.74]

**Subtotal** -0.07 [-0.35, 0.22]

Heterogeneity: \( \tau^2 = 0.00; \ Chi^2 = 1.92 \ df = 2 \ (P = 0.38); \ I^2 = 0\% \)
Test for overall effect: \( Z = 0.46 \ (P = 0.64) \)

**Normal**
- Hallfrisch et al. 1983 24 24 0.21 [-0.27, 0.69]
- Bossetti et al. 1984 8 8 0.13 [-0.42, 0.67]
- Koh et al. 1988 9 9 -0.11 [-0.39, -0.17]
- Reiser et al. 1989 11 11 0.33 [0.04, 0.62]
- Swanson et al. 1992 14 14 0.27 [0.03, 0.51]
- Bantle et al. 2000 24 24 0.00 [-0.56, 0.56]
- Swarbrick et al. 2008 7 7 -0.18 [-2.09, 1.73]
- Ngo Sock et al. 2009 11 11 0.00 [-0.20, 0.20]
- Stanhope et al. 2009 15 17 -0.09 [-0.72, 0.55]
- Stanhope et al. 2011 32 32 -0.25 [-0.53, 0.03]
- Madero et al. 2011 56 51 0.20 [0.47, 0.87]
- Silbernagel et al. 2011 10 10 0.21 [-0.13, 0.54]
- Aberli et al. 2013 9 9 0.06 [-0.33, 0.44]

**Subtotal** 0.07 [-0.04, 0.18]

Heterogeneity: \( \tau^2 = 0.01; \ Chi^2 = 14.52 \ df = 12 \ (P = 0.27); \ I^2 = 17\% \)
Test for overall effect: \( Z = 1.26 \ (P = 0.21) \)

**Total** 0.03 [-0.05, 0.11]

Heterogeneity: \( \tau^2 = 0.00; \ Chi^2 = 28.00 \ df = 25 \ (P = 0.31); \ I^2 = 11\% \)
Test for overall effect: \( Z = 0.71 \ (P = 0.48) \)
Test for subgroup differences: \( \Chi^2 = 1.49 \ df = 2 \ (P = 0.47); \ I^2 = 0\% \)

**Favors fructose** **Favors any CHO**

*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.
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
| Study or Subgroup          | Year | N (any CHO) | N (Fructose) | Mean difference (95% CI) | Non-HDL-C (mmol/L) |
|---------------------------|------|-------------|--------------|--------------------------|-------------------|
| Diabetes                  |      |             |              |                          |                   |
| Crapo et al.              | 1986 | 7           | 7            | -0.39 [-0.95, 0.17]      |                   |
| Osei et al.               | 1987 | 9           | 9            | -0.80 [-0.99, -0.61]     |                   |
| Mcateer et al.            | 1987 | 10          | 10           | -0.20 [-0.33, -0.07]     |                   |
| Grigoresco et al.         | 1988 | 8           | 8            | -0.02 [-0.18, 0.14]      |                   |
| Thorburn et al.           | 1989 | 3           | 5            | 0.08 [-0.46, 0.62]       |                   |
| Anderson et al.           | 1989 | 28          | 14           | 0.09 [-0.04, -0.22]      |                   |
| Osei et al.               | 1989 | 13          | 13           | -0.58 [-0.82, 0.34]      |                   |
| Blayo et al.              | 1990 | 14          | 12           | 0.22 [0.02, 0.42]        |                   |
| Bantle et al. T2DM        | 1992 | 12          | 12           | 0.08 [-0.08, 0.24]       |                   |
| Bantle et al. T1DM        | 1992 | 6           | 6            | 0.52 [0.29, 0.75]        |                   |
| Koivisto et al.           | 1993 | 10          | 10           | 0.26 [-0.02, 0.54]       |                   |
| Maleri et al.             | 1996 | 32          | 32           | -0.10 [-0.21, 0.01]      |                   |
| Subtotal                  |      |             |              |                          | -0.07 [-0.25, 0.12]|

Heterogeneity: Tau² = 0.09; Chi² = 127.25 df = 11 (P < 0.0001); I² = 91%
Test for overall effect: Z = 0.71 (P = 0.48)

| HTG/Insulin Resistant     |      |             |              |                          |                   |
| Cybulska et al.           | 1982 | 16          | 22           | -0.21 [-0.33, -0.09]     |                   |
| Koh et al.                | 1988 | 9           | 9            | -0.07 [-0.28, 0.14]      |                   |
| Reiser et al.             | 1989 | 10          | 10           | 0.58 [0.37, 0.79]        |                   |
| Subtotal                  |      |             |              |                          | 0.09 [-0.36, 0.55] |

Heterogeneity: Tau² = 0.16; Chi² = 40.17, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.40 (P = 0.69)

| Normal                    |      |             |              |                          |                   |
| Hallfrisch et al.         | 1983 | 24          | 24           | 0.23 [0.14, 0.32]        |                   |
| Bossetti et al.           | 1984 | 8           | 8            | 0.08 [-0.08, 0.24]       |                   |
| Koh et al.                | 1988 | 9           | 9            | -0.10 [-0.21, 0.01]      |                   |
| Reiser et al.             | 1989 | 11          | 11           | 0.34 [0.15, 0.53]        |                   |
| Swanson et al.            | 1992 | 14          | 14           | 0.29 [0.19, 0.39]        |                   |
| Bantle et al.             | 2000 | 24          | 24           | 0.08 [0.06, 0.10]        |                   |
| Swarbrick et al.          | 2008 | 7           | 7            | -0.20 [-1.08, 0.68]      |                   |
| Stanhope et al.           | 2009 | 15          | 17           | 0.18 [0.05, 0.31]        |                   |
| Ngo Sock et al.           | 2009 | 11          | 11           | 0.20 [0.05, 0.35]        |                   |
| Stanhope et al.           | 2011 | 32          | 32           | -0.35 [-0.45, -0.25]     |                   |
| Aberli et al.             | 2013 | 9           | 9            | 0.08 [-0.09, 0.25]       |                   |
| Heden et al.              | 2014 | 40          | 40           | 0.00 [-0.03, 0.03]       |                   |
| Subtotal                  |      |             |              |                          | 0.09 [-0.02, 0.20] |

Heterogeneity: Tau² = 0.02; Chi² = 144.72, df = 11 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.00 (P = 0.05)

| Total                     |      |             |              |                          |                   |
|                          |      |             |              |                          | 0.02 [-0.05, 0.09] |

Heterogeneity: Tau² = 0.03; Chi² = 336.68, df = 26 (P < 0.00001); I² = 92%
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Chi² = 2.14, df = 2 (P = 0.34), I² = 6.5%

Favors fructose  Favors any CHO

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 I² statistic, where I²≥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.
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 (I²=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).
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 (I² = 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]**  |                |
| **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]** |                |
| **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]** |                |
| **Total**         |      |             |              | **0.00 [-0.04, 0.04]**  |                |

**Favors any CHO**
**Favors Fructose**

**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 $\geq 75\%$ considerable heterogeneity. Any CHO denotes any carbohydrate comparator. HDL-C indicates high density lipoprotein; HTG, hypertriglyceridemic; 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 (I²=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 (I²=77%, P<0.01). Sensitivity analyses revealed that removal of Ngo Sock et al10 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 (I²=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

| Study or Subgroup | Year | N (any CHO) | N (Fructose) | Mean difference (95% CI) in apoB (mmol/L) |
|-------------------|------|------------|-------------|------------------------------------------|
| Stanhope et al.   | 2009 | 15         | 17          | 0.20 [0.00, 0.40]                         |
| Stanhope et al.   | 2011 | 16         | 16          | 0.16 [0.00, 0.32]                         |
| Total             |      |            |             | 0.18 [0.05, 0.30]                         |

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.80 (P = 0.005) Favors Fructose Favors any CHO

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 I² statistic, where I²≥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.

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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 (I² = 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. Categorical subgroup analyses and continuous multivariate metaregression analyses were not undertaken owing to the small number of trials.

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 (I² = 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. 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 misclassified the doses for 2 trials. Earlier meta-analyses of the effect of fructose on lipids found a fasting triglyceride-increasing effect of fructose only at >60 g/day in people with diabetes and of ≥100 g/day across individuals with different metabolic phenotypes. 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, metabolic phenotype for postprandial triglycerides, and comparator, duration of follow-up, and design for triglycerides in those with diabetes. 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. 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 (MOS<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 A, 8.2% of trials for triglycerides, and 14.8% of trials 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. Seventh, the subgroup analyses were underpowered. Although we did attempt to explore the relative contribution of the subgroups with metaregression 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, dietary pulses, nuts, garlic, or combination of these in some dietary patterns, such as the dietary portfolio, 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 and Canadian Diabetes Association 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 from 2008 (100 g/day) and Sievenpiper 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). 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 post-prandial triglycerides, as we have recently published. 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 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.

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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