# Food sources of fructose-containing sugars and glycemic control: A systematic review and meta-analysis of controlled intervention studies in people with and without diabetes

Vivian L Choo1,2, Effie Viguiliouk1,2, Sonia Blanco Mejia1,2, Adrian I Cozma1,2, Tauseef A Khan1,2, Vanessa Ha1,3, Thomas MS Wolever1,2,4,5, Lawrence A Leiter1,4,5, Vladimir Vuksan,1,2,4, Cyril WC Kendall1,2,6, Russell J de Souza1,3, David JA Jenkins1,2,4,5 and John L Sievenpiper1,2,4

1Toronto 3D (Diet, Digestive Tract and Disease) Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, ON, Canada; 2 Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada; 3Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada and 4Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; 5Division of Endocrinology, St. Michael’s Hospital, Toronto, ON, Canada; 6College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada

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Corresponding Author:
John L Sievenpiper MD, PhD, FRCPC
Toronto 3D Knowledge Synthesis and Clinical Trials Unit
Clinical Nutrition and Risk Factor Modification Centre,
St. Michael's Hospital
61 Queen Street East, Toronto, ON, M5C 2T2, CANADA
Tel: 416 867 7475
Fax: 416 867 7495
Email: john.sievenpiper@medportal.ca

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WHAT THIS PAPER ADDS

What is already known on this topic

Current dietary guidelines recommend a reduction to <5-10% energy in free sugars, especially fructose-containing sugars from sugars-sweetened beverages (SSBs).

Fructose-containing sugars from SSBs have shown an adverse association with diabetes incidence in systematic reviews and meta-analyses of prospective cohort studies and free fructose adding excess energy to diets has shown a harmful effect on glycemic control in systematic reviews and meta-analyses of controlled intervention studies.

As dietary guidelines shift from a focus on single nutrients to a focus on dietary patterns, it is unclear whether the evidence for SSBs and excess energy from fructose holds for other important food sources of fructose-containing sugars at different levels of energy control.

What this study adds

Our systematic review and meta-analysis of 155 controlled intervention studies suggests that most food sources of fructose-containing sugars do not have a harmful effect on glycemic control in energy-matched substitutions for other macronutrients but several food sources do have harmful effects when adding excess energy to the diet, especially SSBs.

While awaiting further research, public health professionals should be aware that harmful effects of fructose-containing sugars on glycemic control appear to be mediated by energy and food source.

ABSTRACT

Objective: As dietary guidelines move to dietary pattern-based recommendations, it is unclear whether the evidence supporting current recommendations to reduce free sugars, especially those from sugar-sweetened beverages (SSBs), holds for all food sources. Our objective was to assess the effect of different food sources of fructose-containing sugars on glycemic control at different levels of energy control.

Design: Systematic review and meta-analysis of controlled intervention studies

Data Sources: MEDLINE, EMBASE, and The Cochrane library through April 25, 2018.

Eligibility criteria for selecting studies: We included controlled intervention studies of ≥ 7-days assessing the effect of different food sources of fructose-containing sugars on glycemic control in people with and without diabetes. We prespecified 4 study designs based on energy control: substitution studies (sugars in energy matched comparisons with other macronutrients); addition studies (excess energy from sugars added to diets); subtraction studies (energy from sugars subtracted from diets); and ad libitum studies (sugars freely replaced by other macronutrients without control for energy). Outcomes were HbA1c, fasting blood glucose, and fasting blood glucose insulin.

Data extraction and synthesis: Four independent reviewers extracted relevant data and assessed risk of bias. Data were pooled using random effects models and expressed as mean differences with 95% confidence intervals (95% CIs). The overall certainty of the evidence was assessed using GRADE.

Results: We included 155 study comparisons (N=5,086). Whereas total fructose containing sugars had no harmful effect on any outcome in substitution or subtraction studies with a decrease seen in HbA1c (mean difference, -0.22% [95% CI to -0.35, -0.08%], -25.9mmol/mol [-27.3 to -24.4mmol/mol]) in substitution studies, there was a harmful effect on fasting insulin in addition (4.68pmol/L [1.40 to 7.96]) and ad libitum (7.24pmol/L [0.47 to 14.00]) studies. There was interaction by food source with specific food sources showing beneficial-effects (fruit and fruit juice) or harmful-effects (sweetened-milk and mixed sources) in substitution studies and harmful-effects (SSBs and fruit juice) in addition studies on at least one outcome. The majority of the evidence was low quality.
Conclusions: Energy control and food source appear to mediate the effect of fructose-containing sugars on glycemic control. Whereas most food sources of fructose-containing sugars (especially fruit) do not have a harmful effect in energy-matched substitutions with other macronutrients, several food sources of fructose-containing sugars (especially SSBs) adding excess energy to diets do have harmful effects. Our certainty in these estimates is low. More high-quality randomized controlled trials are needed.
Registration: ClinicalStudies.gov identifier, NCT02716870.

## INTRODUCTION

The role of sugars in the development of cardiometabolic disease is actively debated (1, 2). In particular, fructose has recently emerged as a serious public health concern, as ecological parallels have been drawn between the introduction of high fructose corn syrup (HFCS) as a popular sweetener during the 1970s and global rises in obesity and diabetes prevalence (3, 4).

Despite early considerations for the use of fructose as an alternative sweetener in people with diabetes due to its observed potential to lower postprandial glycemic excursions when compared to isocaloric amounts of starch (5), a mounting body of evidence has suggested that fructose may be particularly detrimental to metabolic health, even more so than other sugars (6). This view has received support from ecological evidence(4) as well as animal (7-9) and select human intervention studies(10-12). However, higher levels of evidence from systematic reviews and meta-analyses of controlled human intervention studies have failed to demonstrate adverse glycemic effects unique to fructose, and have even shown a beneficial effect on glycated blood proteins of fructose in isocaloric substitution for other carbohydrates in the diet in people with diabetes (13).

Whether there exists a causal link between fructose and the development of diabetes and related cardiometabolic co-morbidities continues to be contested, though much less appreciated in this debate are the consumption patterns and levels at which fructose is normally consumed in the diet. Fructose is rarely consumed in isolation under real world conditions (14). It is present in a variety of food sources containing comparable amounts of glucose, and the proportion of fructose co-ingested with glucose has been suggested to influence fructose metabolism (15). In its most commonly consumed form, sucrose (table sugar), fructose is part of a disaccharide with glucose in a 50:50 ratio. HFCS is also a glucose-fructose mix, with varying fructose content (42-55% molecular weight) in a free, unbound monosaccharide form. Similarly, less refined sources of fructose-containing sugars, including honey, agave and maple syrup, are composed of varying proportions of fructose and glucose, while natural sources of fructose present in various fruit and

vegetables also co-exist with glucose. These fructose-containing sugars are found in the diet in a variety of food sources, ranging from “nutrient poor” sources of added sugars such as sugars-sweetened beverages (SSBs), to “nutrient dense” sources of bound sugars such as fruit. Evidence from prospective cohorts on diabetes risk have shown differential associations depending on the food source of the sugars (positive associations with SSBs (16, 17) and inverse association with fruit (18, 19)).

As dietary guidelines shift from nutrient-based recommendations to more food and dietary pattern-based recommendations (20, 21) , it is important to understand the role of the food matrix in modifying the effect of fructose-containing sugars. Current recommendations from the WHO, U.S., and England have focussed on the reduction of added or free sugars (added sugars plus sugars contained in fruit juices) to <5-10% energy (20, 22, 23), especially free fructose-containing sugars from sugars-sweetened beverages (SSBs) (20). Whether the evidence for added or free sugars and SSBs can be generalized to all food sources of fructose-containing sugars in relation to their effects on surrogate markers of type 2 diabetes has not yet been determined. We conducted a systematic review and meta-analysis of controlled intervention studies to determine the effect of food sources of fructose-containing sugars at different levels of energy control on glycemic control in people with and without diabetes.

## METHODS

This systematic review and meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews and interventions(24), with all results reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (25). The study protocol was registered at ClinicalStudies.gov, (identification number, NCT02716870).

### Data Sources

Medline, EMBASE and the Cochrane Central Register of Controlled Studies were searched through April 25, 2018 using the following search terms: fructose OR dietary sucrose, OR HFCS OR sugar OR sugar* sweetened beverage* OR honey AND glyc?em* OR insulin OR HbA1c OR fructosamine OR blood glucose OR gly* albumin (Supplementary Table 1). Validated filters from McMaster University Health Information Research Unit were applied to limit the database search to controlled studies only (26), and electronic searches were supplemented with manual searches of references from included studies.

### Study Selection

We included reports of controlled intervention studies lasting ≥7 days investigating the effect of diets of fructose-containing sugars (fructose, sucrose, HFCS, honey, syrups) from various food sources compared with control diets free of or lower in fructose-containing sugars on outcome measures of glycemic control (fasting glucose, fasting insulin, and HbA1c) in people with and without diabetes. We excluded reports of studies of meal replacements and studies of interventions of rare sugars that contained fructose (e.g. isomaltulose or melzitose) or were low-calorie epimers of fructose (e.g. allulose, tagatose, sorbose) or studies that used these sugars as the comparator. Four study designs based on the control of energy were prespecified: 1) 'substitution' studies, in which food sources of

fructose-containing sugars were compared with food sources of other non-fructose-containing macronutrients under energy matched conditions (isocaloric comparison); (2) 'addition' studies, in which excess energy from food sources of fructose-containing sugars was added to background diets compared to the same background diets alone without the excess energy from fructose-containing sugars with or without the use of low-calorie sweeteners to match sweetness (hypercaloric comparison); (3) 'subtraction' studies, in which energy from food sources of fructose-containing sugars was subtracted from background diets through displacement by water and/or low-calorie sweeteners, or by eliminating the food sources of fructose-containing sugars altogether compared with the original background diets (hypocaloric comparison); and (4) 'ad libitum' studies, in which food sources of fructose-containing sugars were compared with food sources of other non-fructose-containing macronutrients without any strict control of either the study foods or the background diets to allow for free replacement of the energy from fructose-containing sugars with the energy from other macronutrients (free-feeding comparison). Reports containing both randomized and non-randomized controlled intervention studies were included. An intervention study was considered non-randomized if the authors explicitly stated that a method of randomization was not used or randomization was not reported in the allocation of participants to the intervention or control treatments in parallel designs or the sequence of the treatments in crossover designs. In reports containing more than one study comparison, we included all available study comparisons.

Patient and Public Involvement

No patient/public was involved in the design, writing or editing of this study.

Data Extraction

Data from included reports were individually extracted at least twice by four separate reviewers. Relevant information included number of participants, setting, underlying disease status of participants, study design, level of feeding control, randomization, comparator, fructose-containing sugars type, food sources of fructose-containing sugars, macronutrient profile of the diets, follow-up duration, energy balance, and funding sources. The three outcome variables were HbA1c, fasting blood glucose, and fasting blood insulin. HbA1c was reported instead of total glycated blood proteins as originally indicated in our protocol (identification number, NCT02716870), as mean differences for these values were considered more clinically relevant and did not require the use of standardized mean differences needed to the different glycated blood proteins. Authors were contacted for missing outcome data when it was indicated that an outcome was measured but not reported. In the absence of numerical values for outcome measurements and inability to obtain the original data from authors, values were extracted from figures using Plot Digitizer where available(1). All discrepancies between reviewers were resolved through consensus or, where necessary, arbitration by the senior author.

Study quality

Included studies were assessed for risk of bias by at least 2 of the reviewers using the Cochrane Collaboration Risk of bias Tool(27). Final assessments were based on consensus between reviewers.

Data Synthesis and Analysis

We used Review Manager (RevMan) version 5.2 (Copenhagen, Denmark) for primary analyses and Stata (version 12, College Station, TX, USA) for subgroup, dose response, and publication bias analyses. We performed separate analyses for the 4 prespecified study designs based on the control of energy (substitution, addition, subtraction, and ad libitum studies) and stratified analyses by food sources of sugars for each of three outcome variables (HbA1c, fasting blood glucose, and fasting blood insulin). The principal effect measure was the mean pair-wise difference (MD) in change from baseline (or, when not available, the post-treatment value) between the food sources of fructose-containing sugars arm and the comparator arm with results reported as mean differences (MD) with 95% confidence intervals (CI). We extracted the estimates of the MD and corresponding 95% confidence intervals for each outcome. Change-from-baseline differences were preferred over end differences and paired analyses were applied to all crossover trials with the use of a within-individual correlation coefficient between treatments of 0.5 as described by Elbourne et al.(28). When at least two studies provided data, we performed a DerSimonian and Laird random effects meta-analysis. When less than 5 studies were available for analysis, we also considered fixed effect estimates. Heterogeneity was assessed by the Cochran Q test (significant at $P<0.10$) and quantified by the I2 statistic (range 0%-100%)(29). The interaction of fructose-containing sugars x food source was assessed using the Chi-square statistic. Other sources of heterogeneity were explored using sensitivity and subgroup analyses. We carried out sensitivity analyses by systematically removing each study from the meta-analyses and recalculating the summary association. A study whose removal explained the heterogeneity, changed the significance of the effect, or altered the effect size by 10% or more, was considered an influential study. If ≥10 studies per outcome were available (30, 31), then we conducted a priori subgroup and analyses using meta-regression. Categorical subgroup analyses were done for energy balance (positive, neutral, negative), comparator (starch, glucose, fat, lactose, maltrodextrin, diet alone, water, non-nutritive sweeteners, protein, mixed sources), fructose-containing sugars type (fruit, sucrose, fructose, HFCS, honey), fructose-containing sugars dose (≤10%, >10% energy (22, 32)), baseline values for HbA1c (≤7%, >7%), fasting glucose (≤5.5, >5.5 mmol/L based on median values) and insulin (≤96.6, >96.6 pmol/L based on median values), age (≤18, >18), study design (crossover, parallel), follow-up duration (< 8weeks, ≥ 8 weeks) , randomization (yes, no), level of feeding control (supplemented, dietary advice and metabolically controlled), underlying disease status (diabetes, overweight/ obese, metabolic syndrome criteria, otherwise healthy), and individual domains of risk of bias (sequence generation, allocation concealment, blinding of participants/ personnel and outcome assessors, incomplete outcome data, selective outcome reporting). Continuous dose response analyses were performed using meta-regression to assess linear dose-response gradients and non-linear meta-regression (MKSPLINE procedure) with knots at the public health thresholds of 5% (22, 23), 10% (22, 33), and 25% (34) energy to assess non-linear dose-threshold effects. If ≥10 studies per outcome were available(35), then we assessed publication bias by inspection of funnel plots and formal testing with the Egger and Begg tests. If there was evidence of publication bias, then we used the Duval and Tweedie trim and fill method to adjust for funnel plot asymmetry by imputing missing study data (36).

Grading of the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty in our estimates and produce evidence profiles (37) using GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University, Canada, 2015). Evidence was graded as high, moderate, low or very low quality. Included controlled intervention studies were graded as high quality evidence by default and downgraded based on pre-specified criteria. Criteria to downgrade evidence included risk of bias (assessed through the Cochrane Risk of Bias tool), inconsistency (substantial unexplained heterogeneity, $I2>50\%$, $P<0.10$), indirectness (presence of factors that limited the generalizability of the results), imprecision (the 95% CI for pooled effect estimates crossed a minimally important difference [MID] for benefit or harm for HbA1c [±0.3%], fasting blood glucose [±0.5 mmo/L], and fasting blood insulin [±10 pmol/L]), and publication bias (significant evidence of publication bias).

## RESULTS

### Search Results

The systematic search and selection of literature is shown in Figure 1. 4,442 reports were identified from database and manual searches, of which 4,157 were excluded based on title and abstract. 285 reports were reviewed in full, of which an additional 164 reports were excluded for failure to meet the eligibility criteria. 118 reports of controlled intervention studies (5, 11, 12, 38-152) including a total of 155 study comparisons in 5,086 participants were included in the final analysis.

### Study Characteristics

A summary of the mean study characteristics is presented by the 4 prespecified study designs (substitution, addition, subtraction, and ad libitum studies) in Table 1, with a breakdown of individual study characteristics in Supplementary Table 2. Study sizes were relatively small, ranging from a median of 15 participants (range 6-318) in subtraction studies to 39 (range 8-236) participants in ad libitum studies. The majority of studies were performed in an outpatient setting, with almost half of all substitution (43/108), addition (12/35) and subtraction (1/5) studies conducted in the USA, and all ad libitum studies conducted in European countries. Participants tended to be middle aged, with approximately equal ratios of males to females in substitution, addition and ad libitum studies, but proportionately more females in subtraction studies. Most studies were conducted in those with diabetes (34%, 37/108) or otherwise healthy participants (26%, 28/108) in substitution studies; otherwise healthy (34%, 12/35) or overweight/obese (29%, 10/35) in addition studies; overweight or obese (80%, 4/5) in subtractions studies; and otherwise healthy (43%, 3/7) in ad libitum studies. Most studies were randomized (72% [78/108] of substitution studies, 66% [23/35] of addition studies, 80% [4/5] of subtraction studies and 100% [7/7] of ad libitum studies). Follow up duration was relatively short, ranging from a median of 4.5 weeks (range 1- 52 weeks) in substitution studies to 12 weeks (range 1-36 weeks) in subtraction studies. Fructose-containing sugars doses ranged from a median of 12.2% (range 7.7-25.0%) of total energy intake in addition studies to 23% (range 13.0-26.0%) of total energy intake in ad libitum studies, and were mostly in the form of mixed food sources in substitution (45/108) and ad libitum (6/7) studies while most addition (12/35) and subtraction (4/5) studies used sugars-sweetened beverages. Most studies were funded by agency sources (government, not-for-profit health agency or university sources), except for ad libitum trails which were primarily funded by agency-industry funding.

Study quality

A summary of the risk of bias assessments by the Cochrane Risk of Bias Tool is shown in Supplementary Figure 1. Owing to poor reporting standards, most studies were assessed as having unclear risk of bias across the 5 domains of bias. Few studies were assessed as having high risk of bias with only 20.3% (24/118), 23.7% (28/118), 1.7% (2/118), 8.5% (10/118) of studies assessed as high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and incomplete outcome data, respectively. Overall, no serious risk of bias was detected.

Outcomes: HbA1c

The effect of different food sources of fructose-containing sugars on HbA1c are shown in Figure 2 and Supplementary Figures 2-5. Total fructose-containing sugars independent of food sources showed a significant beneficial effect on HbA1c in substitution studies (30 study comparisons, MD=-0.22% [95% CI, -0.35 to -0.08], -25.9mmol/mol [95% CI, -27.3 to -24.4mmol/mol], p<0.01, substantial heterogeneity [I2=82%, p <0.001]). There was no significant effect in addition (6 study comparisons, substantial heterogeneity [I2=83%, p<0.001]), subtraction (1 study comparison) or ad libitum (1 study comparison) studies. Although formal tests of interaction by food source were not significant in the substitution or addition studies, an interaction appeared to be present in the substitution studies, as fruit was the major driver of the effect accounting for 30% of the weighted benefit as the only food source that showed a significant decrease in HbA1c (6 study comparisons, MD=-0.19% [95% CI, -0.35 to -0.03], -25.6mmol/mol [95% CI, -27.3 to -23.8mmol/mol], p=0.02, substantial heterogeneity [I2=78%, p <0.001]). An interaction by food source could not be assessed at the other levels of energy control, as only one food source category was assessed in the subtraction (SSBs) and ad libitum (baked goods, sweets and desserts) studies.

Sensitivity analyses for HbA1c are presented in Supplementary table 3. The removal of each study did not explain the heterogeneity or change the significance of the effect.

A priori subgroup analyses for HbA1c are presented in supplementary figures 6 and 7 and dose-response analyses for HbA1c are presented in Supplementary Figure 8 and 9. A priori subgroup analyses did not reveal any effect modification in substitution studies. There was evidence of a dose threshold seen at 10% energy by MKSPLINE procedure with the largest decreases seen only at doses ≤10% energy (P=0.04). No subgroup or dose-response analyses were conducted for addition, subtraction or ad libitum studies, as less than 10 studies were available for analyses.

Outcomes: Fasting Blood Glucose

The effect of different food sources of fructose-containing sugars on fasting blood glucose are shown in Figure 3 and Supplementary Figures 10-13. Total fructose-containing sugars independent of food sources had no effect on fasting blood glucose in substitution studies (99 study comparisons, substantial heterogeneity [I2=65, p<0.001]), addition studies (28 study comparisons, substantial heterogeneity [I2=71, p<0.001]), subtraction studies (4 study comparisons, substantial heterogeneity [I2=59, p=0.06]) or ad libitum studies (6 study

comparisons, no evidence of heterogeneity). There was a significant interaction by food source in addition studies (P<0.001): SSBs (11 study comparisons, MD= 0.12 mmol/L [95% CI, 0.03 to 0.22], substantial heterogeneity [I2=74], p<0.001) and fruit juice (2 study comparisons, MD= 0.29 mmol/L [95% CI, 0.09 to 0.49], no evidence of heterogeneity) showed a significant harmful effect, while fruit (7 study comparisons), fruit drinks (3 study comparisons), sweetened chocolate (1 study comparison), added sweeteners (3 study comparisons), and mixed sources (1 study comparison) showed no significant effect on fasting blood glucose. No significant interaction by food source was seen in the substitution, subtraction or ad libitum studies, although only one food source category was assessed in the subtraction studies (SSBs) and ad libitum studies (mixed sources).

Sensitivity analyses for fasting blood glucose are presented in Supplementary Table 3. Removal of anyone of 6 addition studies (38, 46, 72, 105, 114, 123) changed the significance from non-significant to significant but did not change the magnitude or direction of the effect or the evidence of substantial heterogeneity. Removal of the subtraction study by Campos et al. 2015 (group 2 [G2]) (60) explained all of the heterogeneity, changing the direction but not the lack of significance of the effect on fasting blood glucose. Finally, removal of the subtraction study by Tate et al. 2012 (148) explained most of the heterogeneity (I2=32%, P=0.23) but did not change the direction or lack of significance of the effect on fasting blood glucose.

A priori subgroup analyses for fasting blood glucose are presented in Supplementary Figures 14-17 and dose-response analyses for fasting blood glucose are presented in Supplementary Figure 8 and 9. There was significant effect modification by fructose-containing sugars dose (≤10% energy or >10mmol/L) with a further threshold effect (25% energy) identified by the MKSPLINE procedure, comparator (starch, glucose, fat, mixed, lactose, dairy), baseline fasting blood glucose (≤5.5mmol/L or >5.5mmol/L), feeding control (dietary advice, supplementation, or metabolic), or underlying disease status (otherwise healthy, overweight/obese, diabetes, Metabolic syndrome, or NAFLD) in the substitution studies (P<0.05). A significant subgroup effect was also observed by baseline fasting blood glucose (≤5.5mmol/L or >5.5mmol/L) in addition studies (P=0.01). None of the subgroup or dose-response analyses explained the substantial heterogeneity in the substitution and addition studies. No subgroup or dose-response analyses were conducted for subtraction or ad libitum comparisons as less than 10 studies were available for analyses.

Outcomes: Fasting Blood Insulin

The effect of different food sources of fructose-containing sugars on fasting blood insulin are shown in Figure 4 and Supplementary Figures 18-21. Total fructose-containing sugars independent of food sources had a harmful effect on fasting blood insulin in addition studies (23 study comparisons, MD=4.68 pmol/L [95% CI, 1.40 to 7.96], p< 0.01, substantial heterogeneity [I2=58%, p<0.001]) and ad libitum studies (4 study comparisons, MD=7.24 pmol/L [95% CI, 0.47 to 14.00], p=0.04, no evidence of heterogeneity [I2=0%, p=0.46). There was no effect in substitution (70 studies, substantial heterogeneity [I2=62%, p<0.001]) or subtraction (3 studies, substantial heterogeneity [I2=79%, p<0.01]) studies. There was a significant interaction by food source in substitution studies (P<0.001): fruit juice (1 study

comparison, MD=-13.89 pmol/L [95%CI, -27.50 to -0.28], P=0.05) showed a beneficial effect; sweetened low-fat milk (2 study comparisons, MD=18.95 pmol/L [95%CI, 9.09 to 28.80], P<0.001, no evidence of heterogeneity) and mixed sources (25 study comparisons, MD=7.74 pmol/L [95%CI, 2.94 to 12.53], P<0.01, no substantial heterogeneity) showed a harmful effect; and fruit (6 study comparisons, no evidence of heterogeneity), dried fruit (1 study comparison), SSBs (17 study comparisons), baked goods, sweets, and desserts (10 study comparisons, no evidence of heterogeneity), and added sweeteners (8 study comparisons, substantial heterogeneity [I2=83, p<0.001]) showed no significant effect on fasting blood insulin. No significant interaction by food source was seen in the addition, ad libitum , or subtraction studies, although SSBs accounted for >50% of the weighted harm in addition studies and mixed sources was the exclusive food source of fructose-containing sugars in the ad libitum studies.

Sensitivity analyses for fasting blood insulin are presented in Supplementary table 3. Removal of the addition study by Hollis et al. 2009 (83)explained some of the heterogeneity (I2=42%, P=0.02), without changing the significance, magnitude, or direction of the effect. Removal of either one of two substitution studies (92, 104) changed the evidence of significance from non-significant to significant without changing the magnitude or direction of the effect or the evidence of substantial heterogeneity. Removal of the subtraction study by Campos et al. (G2) (60) explained nearly all of the heterogeneity (I2=1%, P=0.31) changing the significance and magnitude but not the direction of the effect. Removal of the ad libitum study by Raben et al. 2000 (C) (124) eliminated the evidence for the significance but not the direction of the effect or evidence of no substantial heterogeneity.

A priori subgroup analyses for fasting blood insulin are presented in supplementary figures 22-25 and dose-response analyses for fasting blood insulin are presented in Supplementary Figure 8 and 9. There was significant effect modification in substitution studies by level of feeding control (dietary advice, supplementation, or metabolic) or risk of bias for blinding of participants, personnel and outcome assessors (low, high, or unclear) in the substitution studies (P<0.05). None of the subgroup or dose-response analyses explained the substantial heterogeneity in the substitution studies. No subgroup or dose-response analyses were significant in the addition studies. No subgroup analyses were conducted for the subtraction or ad libitum studies, as less than 10 studies were available for analyses.

Publication Bias

The publication bias assessment is shown in Supplementary Figures 26 and 27 for all analyses where ≥10 studies were available. There was no evidence of publication bias for the effect of food sources of fructose containing sugars on HbA1c, fasting blood glucose, or fasting blood insulin. Although the Begg test was significant (P=0.04), visual inspection of funnel plots and the Egger test did not show evidence of publication bias for the effect of food sources of fructose containing sugars on fasting blood glucose in substitution studies. Adjustment for funnel plot asymmetry by the Duval and Tweedie method also did not alter the results.

GRADE Assessment

A summary of the overall quality of evidence assessment for the effect of total fructose-containing sugars independent of food source on the outcome measures of glycemic control is shown in Table 2. The certainty in the evidence was variable for HbA1c (low, low, low, and low), fasting blood glucose (low, low, moderate, and moderate) and fasting blood insulin (low, low, low, and moderate) across substitution, addition, subtraction, and ad libitum studies, respectively. Evidence for HbA1c was downgraded for inconsistency in substitution and addition studies, indirectness in subtraction and ad libitum studies, and for imprecision in substitution, addition, subtraction and ad libitum studies. Evidence for fasting blood glucose was downgraded for inconsistency in substitution and addition studies, and for imprecision in substitution, addition, subtraction and ad libitum studies. Similarly, evidence for fasting blood insulin was downgraded for inconsistency in the substitution, addition, and subtraction studies, and for imprecision in substitution, addition, subtraction and ad libitum studies.

## DISCUSSION

Our systematic review and meta-analysis of 155 studies involving 5,086 participants with and without diabetes showed variable effects of food sources of fructose-containing sugars on three outcome measures of glycemic control at median doses ranging from 12.2-23% energy over median follow-up durations of 4.5-12 weeks. Four types of study designs were identified based on energy control. In substitution studies, total food sources of fructose-containing sugars in energy matched comparisons with other macronutrients (mainly refined starches) showed a beneficial effect on HbA1c with no effects on fasting blood glucose or insulin, while individual food sources showed decreasing (fruit juice), null (fruit, SSBs, baked goods, added sweeteners) or increasing (sweetened-milk, mixed sources) effects on fasting blood insulin. In addition studies, total food sources of fructose-containing sugars supplementing diets with excess energy compared to the same diet alone without the excess energy showed a harmful effect on fasting blood insulin without affecting HbA1c or fasting blood glucose, while individual food sources showed harmful effects on both fasting blood glucose (SSBs and fruit juice) and insulin (SSBs, mixed sources). In the ad libitum studies, total food sources of fructose-containing sugars freely replacing other macronutrients showed a harmful effect on fasting blood insulin (for which the effect was derived exclusively from mixed food sources inclusive of SSBs) without affecting HbA1c or fasting blood glucose. No effect of food sources of fructose-containing sugars was observed in subtraction studies.

### Sources of heterogeneity

Methodological and clinical sources of heterogeneity had an influence on our results. Sensitivity analyses revealed evidence of instability in the significance of our pooled estimates. Removal of anyone of 6 studies (38, 46, 72, 105, 114, 123) changed the significance from non-significant to significant for fasting blood glucose in the addition studies, while the removal of a study by Raben et al. 2000 (C) (124) changed the significance from significant to non-significant for fasting blood insulin in the ad libitum studies. None of the studies explained any of the heterogeneity. Removal of the study by Campos et al. (G2) (60), however, did both explaining the heterogeneity and changing the significance of the effect. This sensitivity analysis revealed a consistent beneficial effect of reducing excess calories from fructose-containing sugars on fasting blood insulin in

subtraction studies. The reason for the strong influence of this study is unclear. As Campos et al. (G2) (60) was a small study (n=15) that received most of the weight in the analysis (>50%), it is possible that its true within-study variances were seriously underestimated, leading to an important outlier effect on the pooled estimate for fasting blood insulin (153).

Subgroup analyses also revealed evidence of effect modification under certain conditions. Greater improvements in fasting blood glucose were observed in participants with higher baseline fasting glucose in substitution and addition studies, suggesting a regression-to-the-mean phenomenon. These effects were concordant with the observed subgroup modification by underlying disease status in addition studies, demonstrating a greater beneficial effect on fasting blood glucose in patients with diabetes. Although a significant subgroup effect by level of feeding control and age were also observed in addition studies where fasting blood glucose was significantly reduced when dietary advice was the method of feeding control or the age of participants was ≤ 18 years, only one study was available for each of these analyses and neither analysis explained the substantial heterogeneity. The relevance of the subgroup analysis for feeding control is also brought into question by the finding of an opposite result for fasting blood insulin in substitution studies. The categorical subgroup analyses revealed a significant effect modification by dose, whereby fasting blood glucose was lower at doses of ≤10% energy, suggesting that intakes that meet current recommendations to consume no more than 10% of energy from free or added sugars (22, 33) may have advantages. These results, however, are difficult to interpret in the absence of a linear dose response gradient or dose threshold effect in continuous analyses at this threshold or the other public health thresholds of 5% free sugars (22, 23) and 25% added sugars (34).

Results in the context of other studies

Our findings agree with two other previously conducted systematic reviews and meta-analyses of controlled intervention studies which demonstrated a beneficial effect of the isocaloric substitution of fructose for other carbohydrates on glycated blood proteins in participants with (equivalent to ~0.53% reduction in HbA1c)(13) and without (fructose intake <90 g/d significantly improved HbA1c dependent on dose, study duration and severity of dysglycemia) diabetes (154). Although the modest decrease of -0.14% in HbA1c from our analysis did not exceed the clinically meaningful threshold of 0.3% proposed by the U.S Food and Drug administration for the development of new drugs for diabetes as observed in the previous meta-analysis (32), our findings suggest that food sources of fructose-containing sugars may have modest benefits for long term glycemic control when they replace other macronutrients on a calorie-for-calorie basis. On the other hand, our results suggest that food sources of fructose-containing sugars providing excess energy to the diet may raise fasting blood insulin agreeing with the findings from our previous systematic reviews and meta-analyses that fructose providing excess energy increases insulin resistance (155).

Our data also agree with evidence from prospective cohort studies of the relation of fructose-containing sugars with diabetes risk. While we failed to observe an adverse association of total fructose-containing sugars independent of food source with incident diabetes in an earlier systematic review and meta-analysis of the available prospective

cohort studies (156), differential associations have been shown for different food sources of sugars. Systematic reviews and meta-analyses of prospective cohort studies have shown an adverse association with SSBs (16, 17) but a protective association with fruit (18, 19), associations which are consistent with our findings of an harmful effect of SSBs on fasting blood glucose and insulin in addition studies and beneficial effect of fruit on HbA1c in substitution studies.

Potential mechanisms

Several proposed mechanisms may explain the observed beneficial effect of food sources of fructose-containing sugars on HbA1c when substituted for other calories in the diet. Fructose has a relatively low glycemic index (GI) of 16 compared to reference carbohydrates such as starch with a GI of 100 (157). As a majority of the comparators used in substitution studies were in the form of starch, replacement of these high-GI carbohydrates with fructose may have reduced the overall GI of the diet, leading to long term glycemic improvement (158) through alleviation of beta-cell stress (159, 160). There is also evidence that high-GI diets are associated with reliable clinical markers of insulin resistance such as higher triglycerides and lower HDL-C (161, 162) . The low GI of fruit may explain why it was the main food source driving a significant improvement in HbA1c in substitution studies, especially when compared to intermediate GI food sources such as SSBs or sweets, which provide calories from sugars in the absence of any nutritional value. The higher fiber content of fruit may contribute to lower postprandial glycemic excursions. Particularly, viscous gels formed by the pectin in fruit may delay gastric emptying and slow down the release of sugars (163). A secondary analysis of a randomized controlled trial of the effect of a 6-month low-GI intervention showed that low-GI fruit intake was the strongest predictor of the reduction in HbA1c in people with type 2 diabetes (164). Whether or not low-GI food sources of fructose-containing sugars would show similar effects when compared to other low-GI carbohydrate foods, including legumes or some whole grains, remains to be determined as there is a lack of studies using high quality carbohydrate comparators. While a low-GI mechanism may have contributed to the observed decrease in HbA1c in the substitution studies), especially as it relates to fruit, it did not extend to improvements in fasting blood glucose and insulin. Although the summary effect estimates for both outcomes tended to be in the direction of benefit (with the possibility of additional studies providing sufficient power to confirm any beneficial effects), a mechanism that targets postprandial excursions in glucose and insulin would not necessarily be expected to lead to meaningful improvements in these fasting measurements which are more determined by changes in insulin sensitivity (158).

An alternative mechanism accounting for the observed beneficial effects of food sources of fructose-containing sugars on HbA1c in substitution studies relates to a so called “catalytic“ effect of fructose whereby fructose metabolites have regulatory actions on glucokinase and hepatic glucose uptake. There is evidence that fructose, especially at small doses of ≤10g/meal (a level obtainable from fruit), may improve glycaemia by the ability of fructose-1-P to up regulate glucokinase activity through the glucokinase regulatory protein, resulting in decreased hepatic glucose production (165) and increased glycogen synthesis(166). The relevance of this mechanism is unclear. It has not been reliably shown (167, 168) under different experimental conditions and would be expected to have

disproportionally greater effect on fasting blood glucose and insulin than HbA1c, the opposite of what we found. How dietary fructose interacts with glucose at the level of hepatic glucose homeostasis remains largely under-explored.

The increase in insulin in the absence of a harmful effect on HBA1c or fasting blood glucose with sweetened low-fat milk in the substitution studies may relate to an isolated insulinotropic effect of dairy proteins. The ability of protein, especially dairy proteins, co-ingested with carbohydrate to stimulate glucose stimulated insulin secretion has been well described (169-171). This isolated finding does not necessarily imply harm, as fasting glucose was not increased and sweetened and unsweetened low-fat dairy, especially in the form of yogurt, is associated with decreased risk of weight gain and diabetes incidence (172).

In contrast, the observed harmful effects of food sources of fructose-containing sugars on glycemic control in addition studies appear to be largely driven by the energy contribution of the sugars. Fructose-containing sugars supplementing diets with excess calories may promote ectopic weight gain, contributing to downstream insulin resistance and impaired glycemic control. Related effects have been reported in systematic reviews and meta-analyses of controlled intervention studies of fructose overfeeding for body weight (173), blood pressure (174), uric acid levels (175), markers of Non-Alcoholic Fatty Liver Disease (NAFLD) (176) and postprandial triglycerides (177). Although fructose more than other carbohydrates (because of its ability to enter glycolysis as an unregulated substrate) has been proposed to increase de novo lipogenesis (DNL) leading to weight gain and its downstream cardiometabolic disturbances, this mechanism has been shown to be a minor pathway for fructose disposal (178). It is also not unique to fructose-containing sugars per se and weight gain with metabolic disturbances would be expected for the overconsumption of food sources of other dietary macronutrients (179).

The lack of a protective effect of interventions to reduce excess energy from food sources of fructose-containing sugars in subtraction studies is unclear. It may represent compensation, in which the decrease in energy from food sources of fructose-containing sugars are compensated by replacement with energy from other food sources or spontaneous changes in physical activity that decrease energy expenditure preventing weight loss and its downstream metabolic benefits. Compensation may have been more apparent in these studies as they had the longest median follow-up (12-weeks). It may explain why longer term (median follow-up,~ 1 year) subtraction studies designed to displace excess energy from SSBs have only shown a weight-loss benefit in specific subgroups of overweight or obese individuals (180). The instability in the significance of the pooled effect estimates may have also played a role. Removal of the studies Campos et al. (G2) (60) explained the heterogeneity revealing significant beneficial effects on fasting insulin, suggesting that this study may have masked a true benefit of interventions to reduce fructose-containing sugars.

Implications

As dietary guidelines shift from a focus on individual nutrients towards a focus on foods and dietary patterns, our findings may have implications for guiding recommendations on important food sources of fructose-containing sugars in the prevention and management of diabetes. As various food sources of fructose-containing sugars tended to demonstrate

improvements in HbA1c, encouraging the consumption food sources of sugars such as fruit, yogurt, and whole grain cereals to replace foods high in refined starches within the recommendation to consume no more than 10% of energy from free sugars (22, 32) may be an effective strategy for improving glycemic control, especially in people with diabetes. As SSBs tended to impair fasting blood glucose and insulin when adding excess energy to the diet, public health strategies to reduce consumption of this food source of fructose-containing sugars may be useful, especially as SSBs provide empty calories in absence of any nutritional "value". While these findings highlight the role of food sources of fructose-containing sugars on glycemic control, other important cardiometabolic parameters should also be taken into consideration in future syntheses.

Strengths and Limitations

Our systematic review and meta-analysis has several strengths, including: 1) a comprehensive and reproducible search and selection process of the literature examining the effect of food sources of fructose-containing sugars on glycemic control, 2) collation and synthesis of the totality of the available evidence from a large body (155 studies, n=5,086) of controlled intervention studies which give the greatest protection against bias (noting that results did not differ between randomized and non-randomized studies), and 3) an assessment of overall quality of evidence using the GRADE assessment approach.

Several of our analyses presented limitations. First, despite the inclusion of a large number of studies, there was a limited number of studies using particular food sources. For example, there were no study comparisons available for sweetened breakfast cereals or yogurt and only one study comparison was available for sweetened chocolate and two study comparisons for sweetened low-fat milk for any of the analyses. Many analyses also had only one or two study comparisons available for inclusion: baked goods, sweets and desserts for HbA1c in substitution and addition studies (1 study); fruit juice for fasting blood glucose and insulin in substitution studies (1 study); mixed sources for fasting blood glucose and insulin in addition studies (1 study); SSBs for HbA1c in substitution studies (2 studies); and fruit juice for fasting blood glucose in additions studies (2 studies). As a result, we elected only to do GRADE assessments for total food sources. Second, substantial unexplained heterogeneity was present in all analyses for the substitution studies, as well as the addition studies for HbA1c, fasting blood glucose, and fasting blood insulin. Although there was also substantial heterogeneity present in the subtraction studies for HbA1c, fasting blood glucose and insulin, and ad libitum studies for HbA1c, the removal of individual studies during sensitivity analyses explained this heterogeneity, and so we did not downgrade for inconsistency. Third, serious indirectness was present in some analyses as only one trial in 240 overweight and obese women was available in the HbA1c subtraction analysis, and similarly, one trial in 10 patients with diabetes was available in the HbA1c ad libitum analysis. Although the small sample sizes of the included studies (median sample sizes ranged from 15 participants in subtraction studies to 39 participants in ad libitum studies) are another potential source of indirectness, we did not downgrade the evidence for indirectness owing to the very large number of included studies (155 study comparisons) representing a diverse range of study conditions and metabolic phenotypes across a large total number of participants (n=5,086). We also did not downgrade for indirectness based on the relatively short duration of follow-up (median follow-up, 4.5-12 weeks), as we felt that it was sufficient

to assess the question of harm (a decision shared with an earlier WHO commissioned review of the evidence for sugars and body weight (181). Finally, there was evidence of serious imprecision in all of the analyses. As the 95% CIs crossed the MIDs for HbA1c, fasting blood glucose and fasting blood insulin, these analyses were downgraded for serious imprecision.

Weighing the strengths and limitations, we graded the certainty in the evidence using GRADE from low quality for HbA1c, low to moderate quality for fasting blood glucose and low to moderate quality for fasting blood insulin across the four study designs based on energy control.

## CONCLUSION

In conclusion, the effects of food sources of fructose-containing sugars on glycemic control appear to be both energy and food source dependent. Food sources of fructose-containing sugars, especially fruit, substituted for equal amounts of calories from other macronutrient sources (mainly refined starches) led to improvements in HbA1c without adversely affecting fasting blood glucose or insulin. However, when several food sources of fructose-containing sugars added excess energy to the diet, especially SSBs, significant increases in fasting blood glucose and insulin were observed. The same was also seen for the effect of mixed food sources (inclusive of SSBs) of fructose-containing sugars freely replacing other macronutrients on fasting blood insulin without a harmful effect on HbA1c or fasting blood glucose. The anticipated benefit of interventions to reduce the excess energy from sugars, however, was not seen reliably, suggesting that compensatory behaviours may be an important consideration. The lack of any harm and even advantages were most pronounced in those with higher HbA1c and fasting blood glucose baseline levels or who had diabetes. While our findings may suggest that common food sources of fructose-containing sugars do not have harmful effects on glycemic control in energy matched replacement of other less sugary foods, our GRADE assessment suggests that more research is likely to have an important influence on many of our estimates. More large, high quality studies using a greater variety of food sources of fructose-containing sugars are required to assess the durability of these effects and understand whether certain food sources with an apparent signal for benefit, such as fruit, may even have advantages for glycemic control under free living conditions over the longer term (≥ 6 months). While awaiting these data, policy and guidelines makers should consider the influence of energy control and food source in the development recommendations to reduce sugars for the prevention and management of diabetes.

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## CONTRIBUTIONS

VLC, SBM and JLS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: VLC, JLS and DJAJ. Acquisition, analysis and interpretation of data: VLC, EV, SBM, AIC, VH, LAL, TMSW, TAK, DJAJ and JLS. Drafting of the manuscript: VLC. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: VLC and SBM. Study supervision: JLS and DJAJ. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; Thomas M S Wolever is a part owner and the President of Glycemic Index Laboratories, Inc, Toronto, Canada, and has authored several popular diet books on the glycemic index for which he has received royalties from Phillipa Sandall Publishing Services and CABI Publishers. He has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for CIHR, CDA, Dairy Farmers of Canada, McCain Foods, Temasek Polytechnic, Northwestern University, Royal Society of London, Glycemic Index Symbol program, CreaNutrition AG, McMaster University, Canadian Society for Nutritional Sciences, National Sports and Conditioning Association, Faculty of Public Health and Nutrition—Autonomous University of Nuevo Leon, Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD). Vladimir Vuksan has a Canadian (2,410,556) and American (7,326.404) patent on the medical use of viscous fiber blend for reducing blood glucose for treatment of diabetes, increasing insulin sensitivity, reduction in systolic blood pressure and blood lipids issued. Cyril WC Kendall has received research support from the Advanced Foods and Material Network, Agrifoods and Agriculture Canada, the Almond Board of California, the American Pistachio Growers, Barilla, the California Strawberry Commission, the Calorie Control Council, CIHR, the Canola Council of Canada, the Coca-Cola Company (investigator initiated, unrestricted grant), Hain Celestial, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Kraft, Loblaw Companies Ltd., Orafti, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. He has received travel funding, consultant fees and/or honoraria from Abbott Laboratories, the Almond Board of California, the American Peanut Council, the American Pistachio Growers, Barilla, Bayer, the Canola

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TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ETHICS APPROVAL

Not required.

DATA SHARING STATEMENT

No additional data are available.

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Figures and Tables
Figure 1. Flow of literature for the effect of food sources of fructose-containing sugars on glycemic control.
Figure 2. Summary super-plot for the effect of food sources of fructose-containing sugars on HbA1c. N= Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for summary effects of individual food sources and total on HbA1c. Analyses were conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using the Cochran's Q statistic (chi-square) at a significance level of $P<0.10$.
Figure 3. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood glucose. N= Number of participants. Data are expressed as weighted mean

differences (MD) with 95% CIs for summary effects of individual food sources and total on fasting blood glucose. Analyses were conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using the Cochran's Q statistic (chi-square) at a significance level of P<0.10.

Figure 4. Summary super-plot for the effect of food sources of fructose-containing sugars on fasting blood insulin. N= Number of participants. Data are expressed as weighted mean differences (MD) with 95% CIs for summary effects of individual food sources and total on fasting blood insulin. Analyses were conducted using generic inverse variance random-effects models (≥ 5 trials available) or fixed effects models (<5 trials available). Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of P<0.10.