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Abstract—Concerns have been raised about the adverse effect of fructose on blood pressure. International dietary guidelines, however, have not addressed fructose intake directly. A systematic review and meta-analysis was conducted to assess the effect of fructose in isocaloric exchange for other carbohydrates on systolic, diastolic, and mean arterial blood pressures. Studies were identified using Medline, Embase, and Cochrane databases (through January 9, 2012). Human clinical trials of isocaloric oral fructose exchange for other carbohydrate sources for ≥7 days were included in the analysis. Data were pooled by the generic inverse variance method using random-effects models and expressed as mean differences with 95% CI. Heterogeneity was assessed by the Q-statistic and quantified by I^2. Study quality was assessed using the Heyland Methodological Quality Score. Thirteen isocaloric (n=352) and 2 hypercaloric (n=24) trials met the eligibility criteria. Overall, fructose intake in isocaloric exchange for other carbohydrates significantly decreased diastolic (mean difference: −1.54 [95% CI: −2.77 to −0.32]) and mean arterial pressure (mean difference: −1.16 [95% CI: −2.15 to −0.18]). There was no significant effect of fructose on systolic blood pressure (mean difference: −1.10 [95% CI: −2.46 to 0.44]). The hypercaloric fructose feeding trials found no significant overall mean arterial blood pressure effect of fructose in comparison with other carbohydrates. To confirm these results, longer and larger trials are needed. Contrary to previous concerns, we found that isocaloric substitution of fructose for other carbohydrates did not adversely affect blood pressure in humans. (***Hypertension*. 2012;59:00-00.) • Online Data Supplement**

Key Words: blood pressure ■ fructose ■ meta-analysis ■ diabetes mellitus ■ guidelines

Hypertension remains a major risk factor for stroke, cardiovascular disease, renal disease, and death. It accounts for 10% of the total annual health budget in developed countries.[1] By 2025, the number of people living with hypertension is expected to reach 1.56 billion people.[2] Despite the complications associated with hypertension, two thirds of patients remain untreated or treated ineffectively.[3]

Dietary factors that increase blood pressure (BP) are of interest to public health authorities, and recent attention has focused on fructose.[4,5] The introduction of refined sugars into the food supply and the subsequent rise in sugar consumption has mirrored the increase in the prevalence of hypertension over the last century.[5] Furthermore, animal data regarding fructose and BP are inconsistent and exhibit considerable interspecies variability. Dogs fed fructose show no effect on BP,[6] whereas rat studies have consistently shown that chronic high fructose intake raises systolic BP (SBP).[7–10] These observations led to the development of a highly reproducible fructose-induced hypertensive rat model.[9,11] Human studies, however, are inconsistent. Recent reports from the Harvard Health Professionals and Nurses cohorts have shown no association between fructose and hypertension risk.[12] Clinical

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This trial has been registered at www.clinicaltrials.gov (identifier NCT01363791).

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intervention studies, however, have shown conflicting results: fructose has been shown to increase and decrease BP.[13–18]

Few nutrition guidelines address fructose directly. BP guidelines have not addressed the effect of fructose or any other sugars on BP in their guidelines.[19,20] Only the American Heart Association, Canadian Diabetes Association, and American Diabetes Association have addressed fructose directly but only based on proposed lipid effects.[21–24] To assess whether fructose has an adverse effect on BP and build an evidence base for dietary guidelines, we conducted a systematic review and meta-analysis of controlled feeding trials investigating the effects of fructose on BP.

Methods

The Cochrane Handbook for Systematic Reviews of Interventions was used as a guideline for this meta-analysis.[25] Reporting of results followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[26]

Study Strategy

Relevant controlled feeding trials were identified using Medline, Embase, and the Cochrane Central Register of Controlled Trials through January 9, 2012, using the search terms and Boolean operators: "fructose AND (blood pressure OR BP OR SBP OR DBP OR mean arterial pressure OR MAP)." Manual searches of references cited by published studies also supplemented the database search.

Inclusion Criteria

Human trials that investigated the effect of isocaloric or hypercaloric fructose compared with other carbohydrate sources (CH_2O) on SBP, diastolic BP (DBP), or mean arterial BP (MAP) were included. Investigators must have administered fructose and control CH_2O orally for a minimum of 7 days. We excluded trials in which fructose was administered exclusively as sucrose or high-fructose corn syrup, because this did not permit us to isolate the effect of fructose. Studies were considered to be "isocaloric" when the fructose intervention was compared with its CH_2O comparator under iso-energetic conditions (ie, even if both arms were hypocaloric relative to weight maintenance requirements) and "hypercaloric" when the oral fructose was provided as a supplement to the control diet, providing excess energy relative to the control diet alone. No restriction was placed on language.

Data Extraction

Studies that met the inclusion criteria had their study characteristics and results extracted by 3 independent reviewers (V.H., L.C., and D.D.W.). These data included study design, randomization, blinding, sample characteristics, comparator, dose, follow-up, fructose form, compliance measures, and macronutrient profile of the background diet. Disagreements were resolved by consensus and when necessary with J.L.S. All of the disagreements were concerning the Heyland Score.[17,27,28]

Start and end mean±SD for SBP, DBP, and MAP were recorded when provided, as well as any reported *P* values for differences between start and end values and between treatments. MAP was calculated for studies that reported SBP and DBP end points but not MAP using the following formula: MAP = ⅔ DBP + ⅓ SBP. The SDs for these calculated MAPs were calculated using the following formula:

$$\frac{1}{\sqrt{N}} \cdot \sqrt{\left(\frac{1}{3}\right)^2 s_{SBP}^2 + \left(\frac{2}{3}\right)^2 s_{DBP}^2}$$

where N is the sample size, and s is the SD. All of the data were entered in triplicate into a spreadsheet template (Microsoft Excel, Microsoft Corp). Trials that did not report either change-from-start differences within or between treatments or end differences between treatments had these imputed from the available data using standard formulas.[25] Authors were contacted, when possible, to request additional information. Missing SD values were imputed from the pooled SD from other published reports.[29]

The quality of each study was assessed using the Heyland Methodological Quality Score (MQS).[30] Studies could receive a maximum score of 13 points. Studies with a score of ≥8 were considered high quality. Points were awarded based on the quality of the study methods, sample selection and follow-up, and intervention.

Statistical Analyses

Data were analyzed using Review Manager (RevMan) version 5.0.25 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Pooled analyses for isocaloric and hypercaloric fructose feeding trials were conducted using the Generic Inverse Variance method using random-effects models. Analyses were stratified by diabetes mellitus status. Our overall analysis combined the nondiabetic with the prediabetic/diabetic participants. Mean end points of SBP, DBP, and MAP were compared between fructose and its respective CH_2O comparator. Data were expressed as mean differences (MD) with 95% CIs. To mitigate the unit-of-analysis error from including trials with multiple intervention arms, we combined arms to create single pairwise comparisons. Because correlation coefficients could not be derived for paired analyses of crossover trials,[31] we made assumptions about the degree of correlation between treatment and control end values. We assumed a conservative degree of correlation of 0.50, with sensitivity analyses done at 2 additional levels, 0.25 and 0.75. A 2-sided *P* value <0.05 was set as the level of significance for an effect. The Q-statistic assessed and I^2 quantified the interstudy heterogeneity with significance set at $P<0.10$. An I^2 ≥50% indicated "substantial" heterogeneity, and ≥75% indicated "considerable" heterogeneity. Sources of heterogeneity were explored using a priori subgroup analyses of CH_2O comparator (starch, glucose, sucrose, and high-fructose corn syrup), dose (Canadian Diabetes Association threshold of ≤60 g/d or >60 g/d),[22] follow-up (≤4 weeks or >4 weeks), fructose form (fluid, mixed, or solid), study quality (MQS <8 or ≥8), randomization (yes or no), and study design (crossover or parallel). Systematic removal of studies was conducted during sensitivity analyses to determine whether any single study exerted an undue influence on the overall results. Subgroup analyses were conducted only for nondiabetic participants, because only 2 trials,[14,17] with conflicting results, had been undertaken in prediabetic/diabetic participants.

Metaregressions were performed to assess the significance of subgroup effects (Stata 11.2, StataCorp, College Station, TX). Publication bias was investigated by visual inspection of funnel plots and formally tested using Egger and Begg tests.

Results

Search Results

Figure 1 shows the flow of literature. The search identified 319 reports, 303 of which were determined to be irrelevant on review of the titles and abstracts. The remaining 16 reports were reviewed in full. A total of 11 reports were selected for analysis, providing data for 15 trials: 13 isocaloric[14,15,17,27,28,32–36] and 2 hypercaloric feeding trials,[27,37] with a median follow-up of 4.0 weeks (range: 15.5 days to 10 weeks).

Study Characteristics

The Table shows the characteristics of the 13 isocaloric (n=352) and 2 hypercaloric feeding trials (n=24). Eleven of the isocaloric trials were in nondiabetic participants, and 1 each in prediabetic and diabetic participants. Five isocaloric trials were randomly assigned and 4 have a parallel design. Six of the isocaloric trials used starch as a CH_2O comparator, 7 in glucose, 1 in high-fructose corn syrup, and 1 in sucrose. Fructose was administered in solid (2 trials), mixed (4 trials),

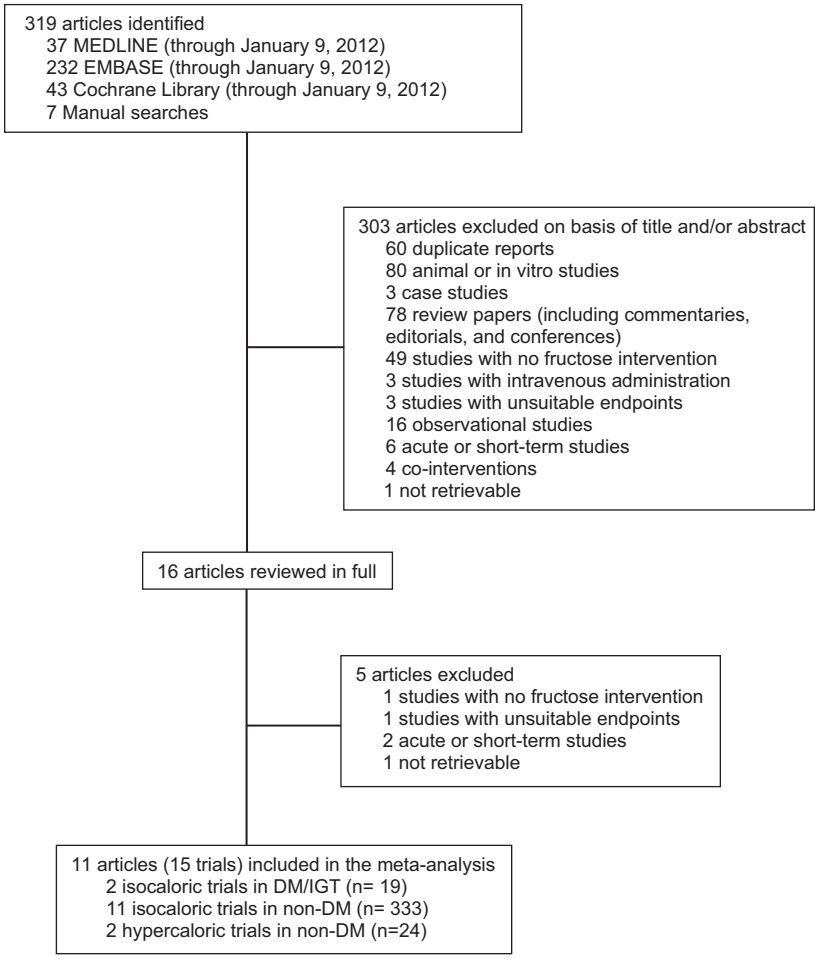

Figure 1. Flow of the literature search.

and fluid (7 trials) forms at a median dose of 78.5 g/d (range: 53–182 g/d). The background diet in the isocaloric trials consisted of 43% to 55% energy (E) CH_2O, 13% to 20% E protein, and 30% to 42% E fat. Four of the isocaloric trials were metabolically controlled, 3 were partially metabolically controlled, and 6 were not controlled. Seven trials took BP measurements using an automated technique, 2 used manual, 1 used continuous ambulatory measurements, and 3 did not specify. Three trials considered BP as a primary end point, 1 as secondary, and 9 did not specify. Median follow-up was 4.0 weeks (range: 15.5 days to 10.0 weeks). Eight of the 13 isocaloric trials were scored as high quality with an MQS $\geq$8.

There were 2 reported hypercaloric trials. Both hypercaloric trials used a nonrandomized, crossover design. Both administered fructose in a fluid format at a median dose of $\approx$143 g/d (+18% to 25% E). The background diet consisted of 55% E CH_2O, 15% E protein, and 30% E fat in both trials. One of the trials used an automated technique to measure BP and the other did not specify. Both trials did not specify the type of end point for BP. Median follow-up was 7 weeks (range: 4–10 weeks). Both hypercaloric trials scored as low quality with an MQS $<$8.

Isocaloric Feeding Trials

Systolic BP

Isocaloric exchange of fructose for other CH_2O had no effect on SBP in the overall analysis or in analyses stratified by diabetes status (Figure 2). There was significant evidence of interstudy heterogeneity in the prediabetes/diabetes mellitus stratum. The use of broader correlation coefficients (0.25 and 0.75) did not alter these main findings; however, using correlation coefficient of 0.75, interstudy heterogeneity became significant in the overall analysis (data not shown). Sensitivity analyses in which each individual study was systematically removed, and the effect estimate recalculated without it, showed that the removal of Madero et al[34] resulted in a significant SBP-lowering effect in the nondiabetic stratum and the overall analysis.

To conserve power, a priori subgroup analyses were carried out using data only from isocaloric trials in nondiabetes to test for possible fructose effect modifiers on SBP by study design characteristics (Figure S1, please see the online-only Data Supplement). We found no significant effect modifiers of SBP by metaregression analysis. There was significant evidence of interstudy heterogeneity, however, if the study had a parallel study design or an MQS score $<$8 ($I^2 \geq 61\%$; $P<0.10$).

Diastolic BP

Isocaloric exchange of fructose for other CH_2O had a significant DBP-reducing effect in the overall analysis and in the nondiabetes stratum but no significant effect in the prediabetes/diabetes mellitus stratum (Figure 3). Only the prediabetes/diabetes mellitus stratum showed no significant evidence of interstudy heterogeneity. The use of broader correlation

Table. Characteristics of the 13 Isocaloric (n=352) and 2 Hypercaloric Feeding Trials (n=24)

Study Identification	Subjects, n (M:F)†	Age, y	Design‡	Method of Blood Pressure Measurement	Blood Pressure End Point	Setting
Isocaloric trials						
No diabetes mellitus						
Aeberli et al[32]	29 N (29:0)	26.3±6.6	C	Automated sphygmomanometer after 15-min rest in supine position, measurements were made at baseline and end of intervention	Neither	Outpatient, Zurich, Switzerland
Aeberli et al[32]	29 N (29:0)	26.3±6.6	C	Automated sphygmomanometer after 15-min rest in supine position, measurements were made at baseline and end of intervention	Neither	Outpatient, Zurich, Switzerland
Brymora et al[33]	28 CKD (17:11)	59±15	C	24-H ambulatory blood pressure monitoring measurements were made at baseline, wk 6, and wk 12	Primary	Outpatient, Toruń, Poland
Hallfrisch et al[15]	12 N (12:0)	39.8±8.3	C	Automatated sphygmomanometer after 5-min rest in sitting position, measurements were made weekly	Neither	Metabolic ward/outpatient, Maryland
Hallfrisch et al[15]	12 HI (12:0)	39.5±7.3	C	Automatated sphygmomanometer after 5-min rest in sitting position, measurements were made weekly	Neither	Outpatient, Oklahoma
Koh et al[17]	9 N (3: 6)	50±15	C	Automatated sphygmomanometer after 5-min rest in sitting position 2 measurements were made 5 mins apart, measurements were made at beginning and end of intervention	Primary	Outpatient, Oklahoma
Madero et al[34]	107 OW/OB	38.8±8.8	P	Manual sphygmomanometer after 10-min rest in sitting position, 3 measurements were made at 5-min intervals, measurements were made weekly	Secondary	Outpatient, Mexico City, Mexico
Sibernegal et al[35]	20 N (12:8)	~30.5±8.9	P	N/A	Neither	Outpatient, Tübingen, Germany
Stanhope et al[27]*	32 OW (16: 16)	53.75±7.8	P	Automated sphygmomanometer measurements were made twice daily during inpatient periods	Neither	Outpatient (8 wk), clinical research center inpatient (2 wk), California
Stanhope et al[36]	48 N (27:21)	27.6±7.1	P	N/A	Neither	Outpatient (12 d), clinical research centre inpatient (3.5 d), California
Swarbrick et al[28]	7 OW/OB (0:7F, PM)	50–72	C	N/A	Neither	Residential facility inpatient, California
Prediabetes						
Koh et al[17]	9 IGT (3: 6)	54±18	C	Automatated sphygmomanometer after 5-min rest in sitting position 2 measurements were made 5 mins apart, measurements were made at beginning and end of intervention	Primary	Outpatient, Oklahoma
Type 2 diabetes mellitus						
Koivisto et al[14]	10 DM2 (4:6)	61±9.5	C	Manual sphygmomanometer after 5-min rest in sitting position	Neither	Inpatient, hospital, Helsinki, Finland
Hypercaloric trials						
No diabetes mellitus						
Lê et al[37]	7 N (7:0)	24.7±3.5	C	Measurement taken 3 times over 20-min period	Neither	Outpatient Lausanne, Switzerland
Stanhope et al[27]*	17 OW/OB (9:8)	52.5±13.2	C	Automated sphygmomanometer measurements were made twice daily during inpatient periods	Neither	Clinical research center inpatient (2 wk), outpatient (8 wk), California

*Stanhope et al[27] included a 2-wk baseline isocaloric period followed by 8 wk of hypercaloric feeding and finally followed by 2 wk of isocaloric feeding, for a total study duration of 10 wk. Thus, we considered the comparison between glucose and fructose arms at week 10 as the isocaloric trial and the comparison of fructose at week 8 with the control diet at week 0 as the hypercaloric trial.

†N indicates normal; CKD, chronic kidney disease; HI, hyperinsulinemic; OW, overweight; OB, obese; IGT, impaired glucose-tolerant; DM2, type 2 diabetes mellitus; PM, postmenopausal.

‡C indicates crossover and P indicates parallel.

§Yes indicates that all food was prepared and provided by a metabolic kichen at the research institution; partial indicates that some food was prepared and provided by investigators; no indicates supplements of fructose and other carbohydrate on top of an ad libitum diet.

‖Doses preceded by "≈"represent average doses; % E indicates percentage of total daily caloric intake.

¶Fructose was provided one of 3 forms: (1) liquid, where all or most of the fructose was provided as a beverage or crystalline fructose to be added to liquid for consumption; (2) solid, where all or most of the fructose was provided in prepared food; or (3) mixed, a combinaton of liquid and solid forms of fructose.

#Comparator refers to the reference carbohydrate (starch, glucose, sucrose, or high-fructose corn syrup).

**Study quality was assessed by the Heyland Methodological Quality Score (MQS).

coefficients (0.25 and 0.75) did not alter these main findings; however, using correlation coefficient of 0.25, the interstudy heterogeneity in the overall analysis became nonsignificant, and using a correlation coefficient of 0.75, interstudy heterogeneity became significant in the prediabetic/diabetic stratum (data not shown). Sensitivity analyses in which each individual study was systematically removed showed that the removal of Stanhope et al[27] or Brymora et al[33] resulted in a loss of significance in the overall analysis and in the nondiabetic stratum.

A priori subgroup analyses were carried out using data only from isocaloric trials in nondiabetes to test for possible fructose effect modifiers on DBP by study design character-

Table. Continued

Metabolic§	Randomization	Fructose Dose, g/d‖	Fructose Form	Carbohydrate Comparator	Macronutrient Profile, Carbohydrate:Protein:Fat % E	Energy Balance	Follow-Up	MQS**	Funding
No	Yes	85.0 (≈14% E)	Fluid	Glucose	52:14:33	Neutral	3 wk	9	Swiss National Science Foundation, Vontobel Foundation
No	Yes	115.9 (≈19% E)	Fluid	Glucose, sucrose	55:13:31	Neutral	3 wk	9	Swiss National Science Foundation, Vontobel Foundation
No	No	53 (≈9% E)	Mixed	Starch	55:15:30	Neutral	6 wk	8	Nicolaus Copernicus University, National Institutes of Health
Yes	No	≈74.2 (7–15% E)	Solid	Starch	43:15:42	Neutral	5 wk	8	N/A
Yes	No	≈74.2 (7–15% E)	Solid	Starch	43:15:42	Neutral	5 wk	8	N/A
Partial	No	≈78.5 (15% E)	Mixed	Glucose	50–55:15–20:30–35	Neutral	4 wk	8	N/A
No	Yes	≈60 g/d (≈13% E)	Mixed	Starch	55:15:30	Negative	6 wk	7	Consejo Nacional de Ciencia y Tecnologia grant, National Institutes of Health
No	Yes	150 (≈21% E)	Fluid	Glucose	50:15:35	Positive	4 wk	7	German Research Foundation, Zentrum Ernährungsmedizin Tübingen-Hohenheim
No	No	≈182 (25% E)	Fluid	Glucose	55:15:30	Positive	10 wk	6	National Institutes of Health, National Center for Research Resources, National Institutes of Health Roadmap for Medical Research, American Diabetes Association
Partial	No	168 (25% E)	Fluid	Glucose, High Fructose Corn Syrup	55:15:30	Positive	15.5 d	6	National Institutes of Health/National Heart, Lung, and Blood Institute, National Center for Research Resources
Yes	No	≈125 (25% E)	Fluid	Starch	55:15:30	Neutral	10 wk	7	National Research Initiative Competitive Grant, Co-operative Agreement with Western Human Nutrition Research Center, Clinical and Translational Science Center's Clinical Reearch Center, University of California, National Institutes of Health, American Diabetes Association
Partial	No	≈64 (15% E)	Mixed	Glucose	50–55:15–20:30–35	Neutral	4 wk	8	N/A
Yes	Yes	≈55 (20% E)	Fluid	Starch	50:20:30	Neutral	4 wk	9	Finnish Academy of Science, Nordisk Insulinfod, Else and Wilhelm Stockmann's Foundation
No	No	≈103.5 (+18% E)	Fluid	Starch	55:15:30	Positive	4 wk	7	Swiss National Science Foudnation, Novartis Consumer Health Foundation
No	No	≈182 (+25% E)	Fluid	Starch	55:15:30	Positive	10 wk	6	National Institutes of Health, National Center for Research Resources, National Institutes of Health Roadmap for Medical Research, American Diabetes Association

istics (Figure S2). We found no significant effect modifiers of DBP by metaregression analysis. Unexplained interstudy heterogeneity was seen in studies that used glucose as a CH_2O comparator, have a follow-up period >4 weeks, administered fructose in either a fluid or mixed format, have either a crossover or a parallel study design, or have an MQS score ≥8 ($I^2 \geq 50\%$; $P \leq 0.10$).

Mean Arterial Pressure

Isocaloric exchange of fructose for other CH_2O had a significant MAP-reducing effect in the overall analysis and in the nondiabetes stratum but no significant effect in the prediabetes/diabetes mellitus stratum (Figure 4). Significant evidence of interstudy heterogeneity was seen across all 3 of the strata ($I^2 \geq 97\%$; $P \leq 0.10$). The use of broader correlation coefficients (0.25 and 0.75) did not alter these findings. Sensitivity analysis in which each individual study was systematically removed showed that the removal of Madero et al,[34] Silbernagel et al,[35] or Koh et al[17] resulted in the loss of significance in the overall analysis.

A priori subgroup analyses were carried out using data from only isocaloric trials in nondiabetes to explore effect modifiers of fructose on MAP (Figure S3). We found no significant effect modifiers of MAP by metaregression analysis. Unexplained interstudy heterogeneity remained in these analyses ($I^2 \geq 53\%$; $P \leq 0.01$).

Hypercaloric Feeding Trials

The 2 trials that reported hypercaloric fructose feeding showed conflicting MAP results, with no significant overall effect and evidence of interstudy heterogeneity. Sensitivity analysis using a correlation coefficient of 0.25 showed the summary effect to be significant ($P = 0.03$).

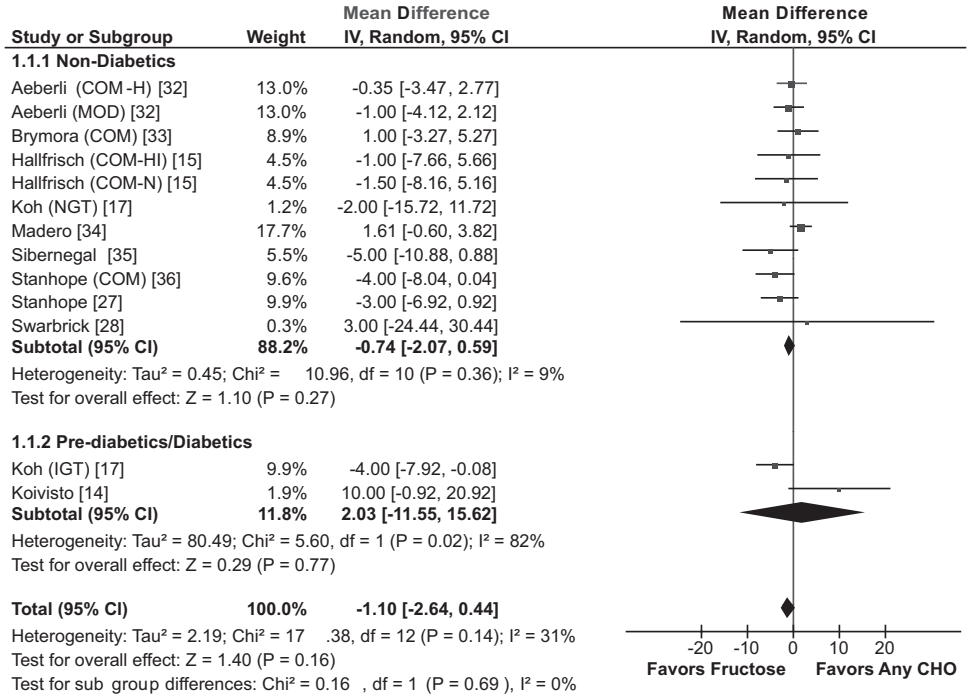

Figure 2. Forest plots of feeding trials investigating the effect of isocaloric exchange of fructose for carbohydrates on systolic blood pressure (SBP) in diabetic, prediabetic, and nondiabetic participants. Three pooled effect estimates (**diamonds**) are shown: 1 each for trials in diabetes mellitus/prediabetes, nondiabetes, and their combination. Paired analyses were applied to all of the crossover trials. Data are mean differences (MD) with 95% CIs, where MD is interpreted as follows. *P* values are for generic inverse variance random-effects models. Interstudy heterogeneity was tested by Cochrane's Q (I^2) at a significance level of $P<0.10$ and quantified by I^2, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and $\geq 75\%$ considerable heterogeneity.

Publication Bias

Neither visual inspection of funnel plots nor Egger or Begg tests provided sufficient evidence of publication bias for SBP (Egger test $P=0.683$; Begg test $P=0.854$), DBP (Egger test: $P=0.943$; Begg test $P=1.000$), or MAP (Egger test: $P=0.260$; Begg test: $P=0.807$; Figures S4 through S6).

Discussion

This meta-analysis of 13 isocaloric controlled feeding trials (n=352) with a median follow-up of 4 weeks found a significant DBP- and MAP-lowering effect when fructose was substituted for other carbohydrates but no effect on SBP. Hypercaloric fructose feeding did not significantly affect MAP.

The present study is in agreement with prospective cohort studies[12] in failing to demonstrate an adverse effect of fructose on BP but at odds with acute clinical studies and animal models. Acute clinical studies have reported an increase in BP after fructose intake,[13,16,18] and rat studies have consistently shown that chronic high fructose intake raises SBP.[7–10] This discrepancy between the results of our study and those of observational and intervention studies may be explained by heterogeneous conditions of BP measurement. Studies included in our systematic review did not specifically measure postprandial BP,[16,18] at which time the adverse effects of fructose on BP have been most consistently shown in humans[16,18] and laboratory rats.[7–10] Furthermore, although our analysis suggests that casual BP is not elevated in response to longer-term fructose consumption, most of these studies investigated BP after an overnight fast when fructose may have been completely metabolized. Because intermittent elevations of BP are a risk factor for permanent hypertension, it may be beneficial for future studies to collect ambulatory BP measurements to better elucidate the effect of fructose on BP.

Fructose is proposed to raise BP via increasing uric acid production, which exerts hemodynamic effects, such as increased oxidative stress, endothelial dysfunction, and activation of the renin-angiotensin-aldosterone system.[4,5] As a proof of concept, this mechanism was investigated directly in humans. Perez-Pozo et al[38] reported a randomized, 2-week crossover trial in which participants were fed 200 g/d of fructose and then randomized to either allopurinol, a xanthine oxidase inhibitor that inhibits the production of uric acid, or placebo for 2 weeks. Allopurinol was shown to prevent the fructose-induced phenotype of raised uric acid and BP. The authors concluded that the excessive fructose intake induced hypertension via elevated uric acid. However, 200 g of fructose is more than twice the 95th percentile of intake in the United States,[39] and the treatment effect of fructose was not compared with another source of carbohydrate under isocaloric conditions. We did not see such an effect in the present analysis. Five of the isocaloric trials that are included in our analysis that measured uric acid showed no significant change[15,17,33–35]; however, the fructose dose in these studies was <200 g and when compared with other sources of carbohydrates. Whether these mechanisms are sufficient to exert chronic and clinically significant effects on BP in humans is uncertain.

Dose remains an important consideration in the interpretation of our analyses. The discrepancy between our results and those of Perez-Pozo et al[38] and animal models[7–10] may be explained by differences in fructose dose. Whereas the median fructose dose in the available isocaloric trials included in our meta-analysis was ≈78.5 g/d (range: 53–182

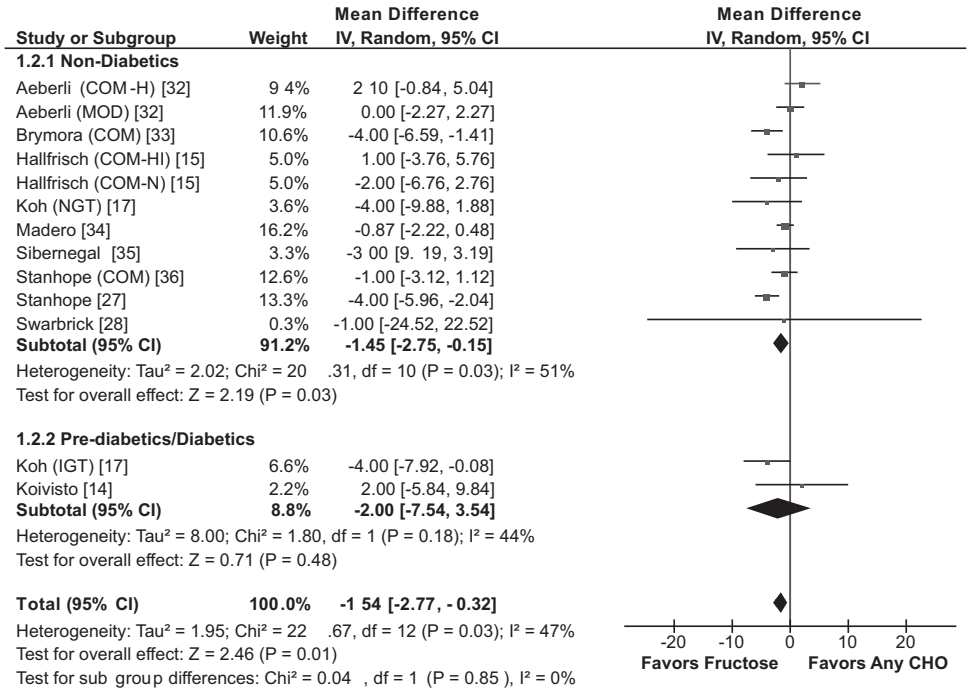

Figure 3. Forest plots of feeding trials investigating the effect of isocaloric exchange of fructose for carbohydrates on diastolic blood pressure (DBP) in diabetic, prediabetic, and nondiabetic participants. Three pooled effect estimates (**diamonds**) are shown: 1 each for trials in diabetes mellitus/prediabetes, nondiabetes, and their combination. Paired analyses were applied to all of the crossover trials. Data are mean differences (MD) with 95% CIs, where MD is interpreted as follows. *P* values are for generic inverse variance random-effects models. Interstudy heterogeneity was tested by Cochrane's Q (I^2) at a significance level of $P<0.10$ and quantified by I^2, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and $\geq 75\%$ considerable heterogeneity.

g/d), or ≈20.5% of energy (range: ≈9% to 25%), it was well below that used to induce BP increases in the Perez-Pozo et al[38] study (200 g) and animal models (≈60% E).[7–10] This evidence for a BP-raising effect is derived from trials of fructose doses that are well above the >95th percentile of intake (87 g/d) in the United States, according to the National and Health and Nutrition Examination Survey III.[39] Even for the group with the highest level of exposure, males and females aged 19 to 22 years, of whom ≤10% consume ≥100 g/d,[39] it is difficult to make generalizations. There is a clear need for larger and longer trials of fructose feeding at generalizable doses (<87 g/d) to confirm whether "real-world" fructose exposure contributes to the burden of hypertension and by association vascular and renal disease.

We found no significant effect modifiers of fructose on SBP, DBP, or MAP. In a previous meta-analysis on the effect of fructose on triglycerides in type 2 diabetes mellitus, we reported significant effect modification by dose (>60 g/d), follow-up (>4 weeks), and comparator (starch).[40] Livesey and Taylor,[41] in their meta-analysis on the effect of fructose on triglycerides, glycated hemoglobin, and body weight, also reported significant effect modification by dose (>50 g/d and >100 g/d for postprandial and fasting triglycerides, respectively). We did not see similar sources of effect modification in our meta-analysis. Substantial interstudy heterogeneity remained unexplained in our analysis. Other unmeasured sources of heterogeneity across the available trials need to be considered, including differences in techniques of BP measurement, whether BP was obtained as a primary or secondary end point, and different efficiencies of fructose absorption across different age groups.[42,43] Because of insufficient variability, we could not formally test for heterogeneity in these domains.

There are several limitations to our work. First, the external validity of the BP effects remains a concern given that the participant pool was small and, of the total 352 participants, only 19 were classified as having diabetes mellitus or prediabetes; therefore, our conclusions may not be generalizable to the population of those living with these conditions. Second, only 2 hypercaloric studies assessed MAP, and only 1 of the hypercaloric studies reported SBP and DBP. Third, the data provided by Madero et al[34] must be interpreted carefully. Although this study met all of our specified inclusion criteria, they used fruits as a vehicle for fructose administration. Fruits contain compounds such as vitamin C, quercetin, and resveratrol that may alter the metabolic effects of fructose. Fourth, the lack of reporting of baseline values and test statistics in some of the included trials necessitated imputation of several data points. We overcame this problem by selecting a conservative correlation ($r=0.5$) between treatment and control end values, according to the methods proposed by Elbourne et al,[31] and then performed sensitivity analyses at 2 other levels (0.25 and 0.75). Lastly, subgroup analysis at 0.25 and 0.75 changed some subgroups from non-significant to significant. This finding may suggest a lack of robustness in the data.

Perspectives

Most concerns regarding the adverse effects of fructose on BP are based on results of studies using rat models[7–10] and acute human studies.[13,16,18] The present meta-analysis, however, shows a significant DBP- and MAP-lowering effect and a trend

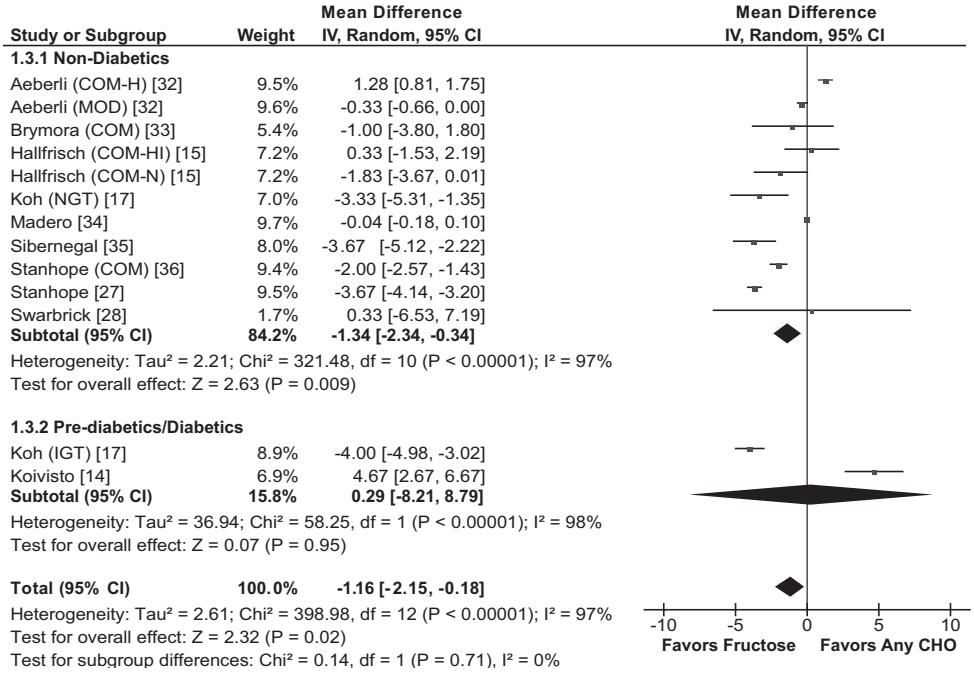

Figure 4. Forest plots of feeding trials investigating the effect of isocaloric exchange of fructose for carbohydrates on mean arterial pressure (MAP) in diabetic, prediabetic, and nondiabetic participants. Three pooled effect estimates (**diamonds**) are shown: 1 each for trials in diabetes mellitus/prediabetes, nondiabetes, and their combination. Paired analyses were applied to all of the crossover trials. Data are mean differences (MD) with 95% CIs, where MD is interpreted as follows. *P* values are for generic inverse variance random-effects models. Interstudy heterogeneity was tested by Cochrane's Q (I^2) at a significance level of $P<0.10$ and quantified by I^2, where $I^2 \geq 50\%$ is considered to be evidence of substantial heterogeneity and $\geq 75\%$ considerable heterogeneity.

favoring SBP in the overall analysis and in the nondiabetic stratum when fructose was exchanged isocalorically for other carbohydrates. Given the small participant pool in our analyses, larger and longer human trials are needed to gain a better assessment of the effect of fructose on BP. Because elevated uric acid has been proposed as a mediator of the effects of fructose on BP, future meta-analyses of human trials should also consider this end point. These trials will help resolve whether the potential role of fructose in the development of the hypertension epidemic should be reconsidered.

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ONLINE SUPPLEMENT

FOR

EFFECT OF FRUCTOSE ON BLOOD PRESSURE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CONTROLLED FEEDING TRIALS

S1

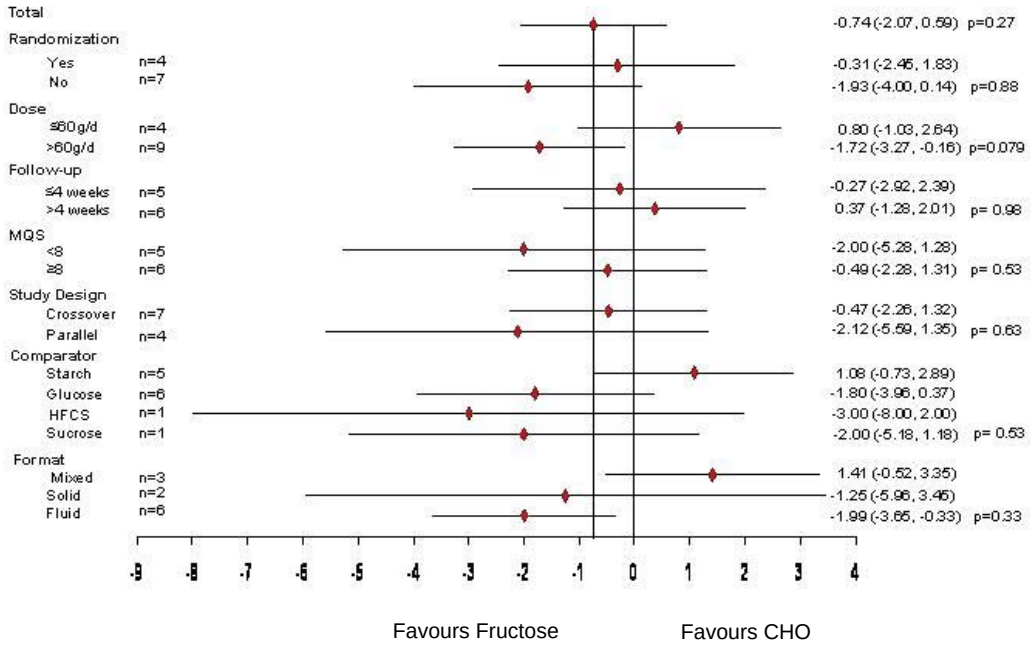

Figure S1- Forest plots of subgroup analyses investigating the effect of isocaloric exchange of fructose for carbohydrate on SBP in non-diabetic participants. Subgroups include choice of carbohydrate comparator (glucose or starch), dose (≤ or >60g/d), length of follow-up (≤ or > 4 weeks), randomization (yes or no), fructose format (solid, mixed, fluid), study design (crossover or parallel), and MQS (< or ≥8). Data are mean differences (MD) with 95% CI. The number of trials in each subgroup are reported as "n." Differences between subgroups were tested using meta-regression and the significance level was reported as p-value, where p>0.05 is considered to be significant.

S2

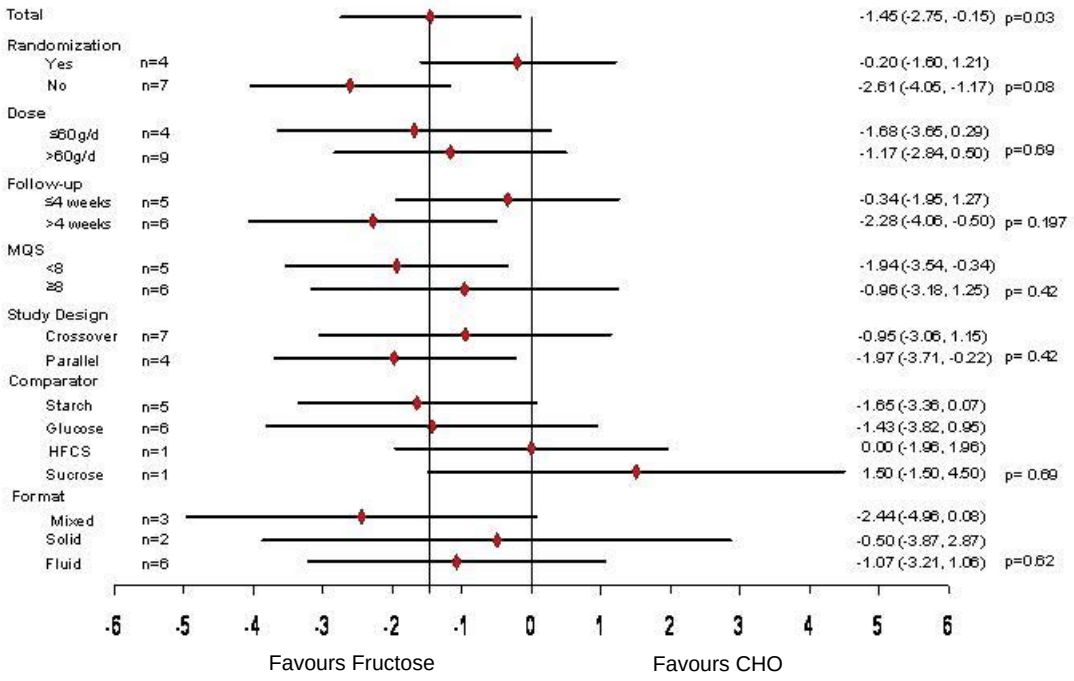

Figure S2- Forest plots of subgroup analyses investigating the effect of isocaloric exchange of fructose for carbohydrate on DBP in non-diabetic participants. Subgroups include choice of carbohydrate comparator (glucose or starch), dose (≤ or >60g/d), length of follow-up (≤ or > 4 weeks), randomization (yes or no), fructose format (solid, mixed, fluid), study design (crossover or parallel), and MQS (< or ≥8). Data are mean differences (MD) with 95% CI. The number of trials in each subgroup are reported as "n." Differences between subgroups were tested using meta-regression and the significance level was reported as p-value, where p>0.05 is considered to be significant.

S3

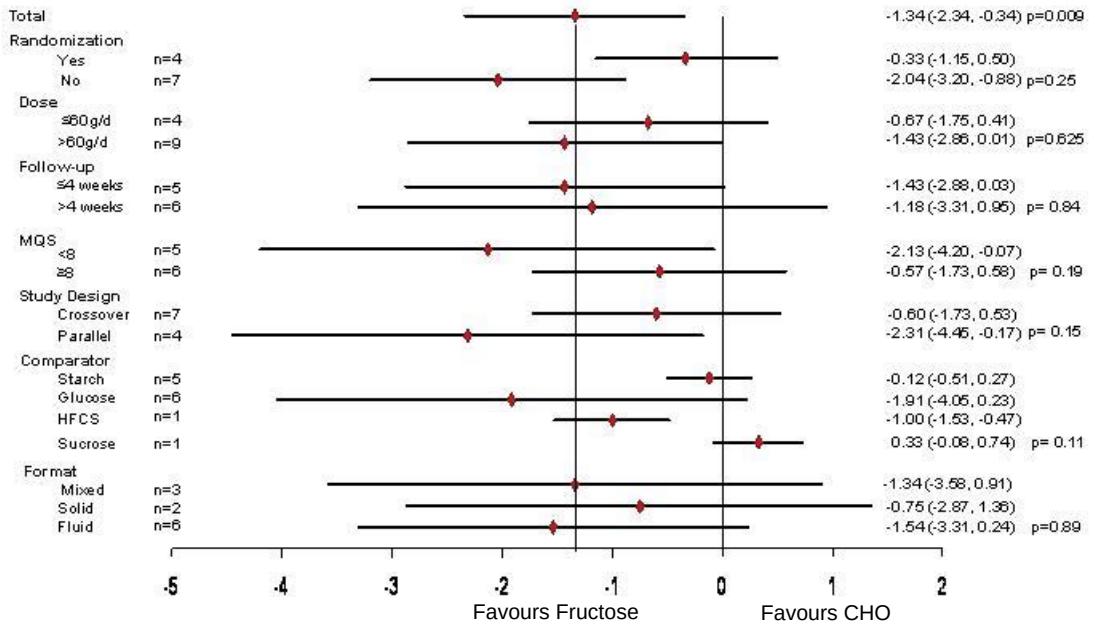

Figure S3- Forest plots of subgroup analyses investigating the effect of isocaloric exchange of fructose for carbohydrate on MAP in non-diabetic participants. Subgroups include choice of carbohydrate comparator (glucose or starch), dose (≤ or >60g/d), length of follow-up (≤ or > 4 weeks), randomization (yes or no), fructose format (solid, mixed, fluid), study design (crossover or parallel), and MQS (< or ≥8). Data are mean differences (MD) with 95% CI. The number of trials in each subgroup are reported as "n." Differences between subgroups were tested using meta-regression and the significance level was reported as p-value, where p>0.05 is considered to be significant.

S4

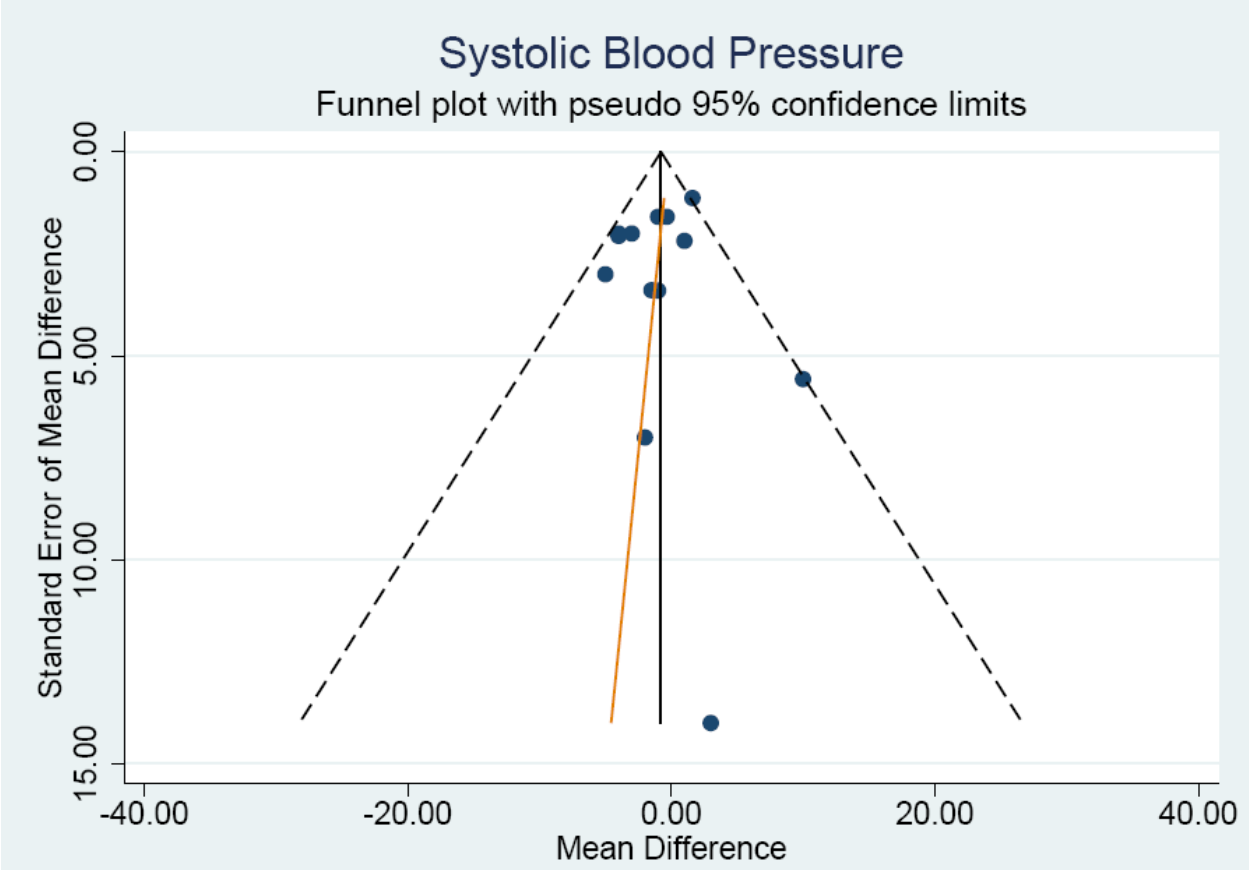

Figure S4- Funnel plots for the effect of fructose in isocaloric exchange for other carbohydrate on SBP. The dashed lines represent the pooled effect estimate expressed as a mean difference (MD). The solid fitted lines represent Egger's regression test for funnel-plot asymmetry.

S5

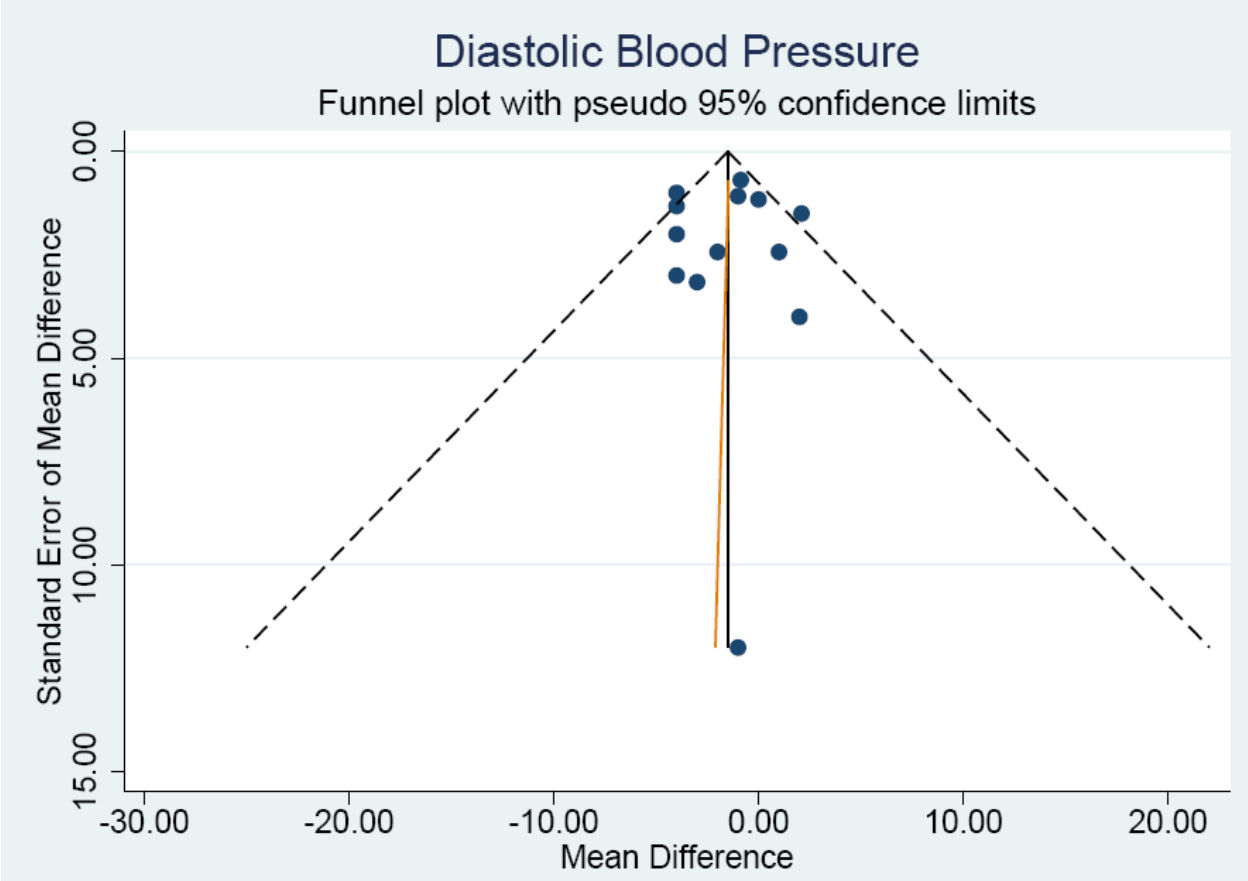

Figure S5- Funnel plots for the effect of fructose in isocaloric exchange for other carbohydrate on DBP. The dashed lines represent the pooled effect estimate expressed as a mean difference (MD). The solid fitted lines represent Egger[1]s regression test for funnel-plot asymmetry.

S6

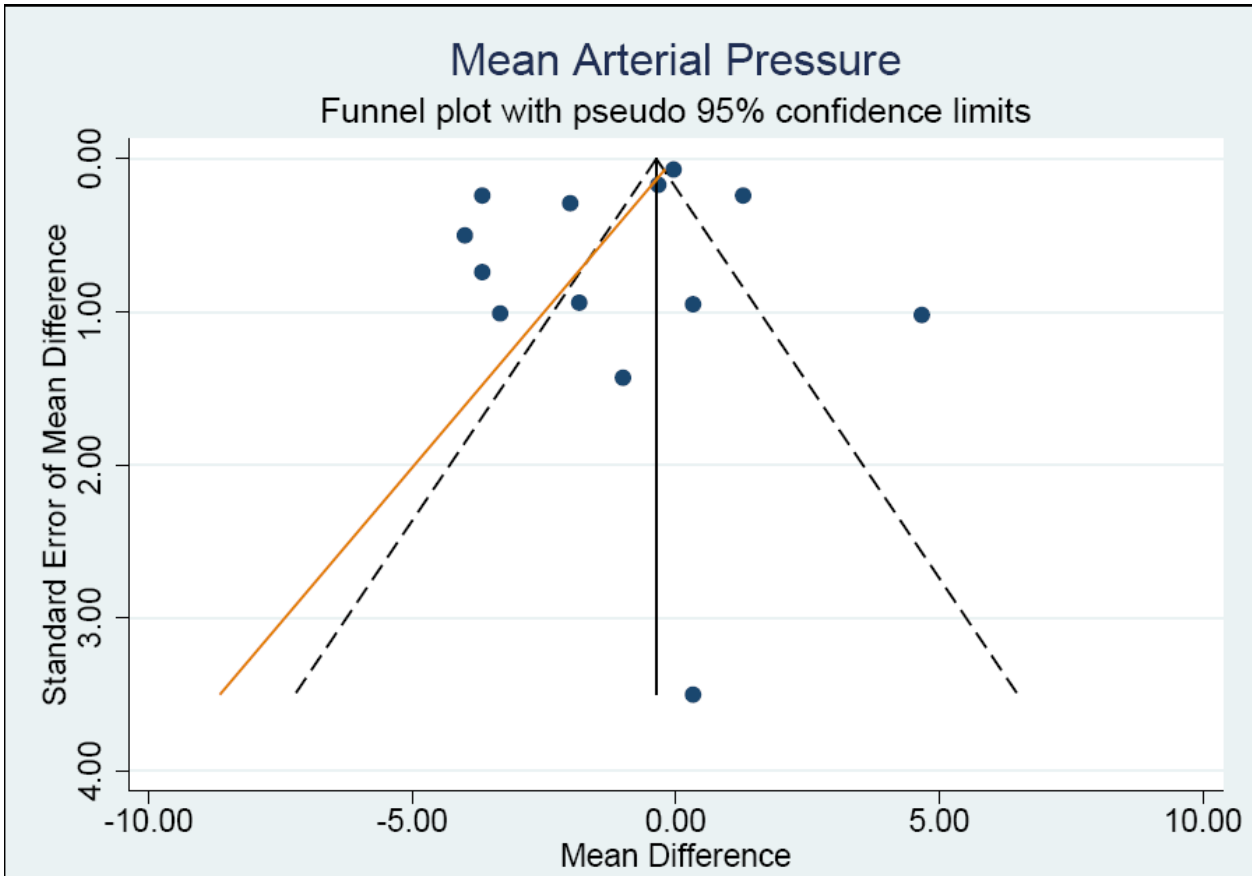

Figure S6- Funnel plots for the effect of fructose in isocaloric exchange for other carbohydrate on MAP. The dashed lines represent the pooled effect estimate expressed as a mean difference (MD). The solid fitted lines represent Egger's regression test for funnel-plot asymmetry.

S7

Author	Contribution to Manuscript
Vanessa Ha HBSc	-final year undergraduate student -developed search strategy -conducted the search and identified relevant articles -conducted data analysis and interpretation -prepared first draft of manuscript -revised and finalized manuscript
John L. Sievenpiper MD, PhD	-research co-supervisor -developed concept of project -developed protocol of project -supervised the conduct of project -supervised data analysis and interpretation -revised intellectual content of manuscript
Russell J de Souza RD, ScD	-epidemiologist and biostatician -developed protocol of project -supervised the conduct of project -supervised data analysis and interpretation -revised intellectual content of manuscript
Laura Chiavaroli MSc	-research co-ordinator -extracted relevant study characteristics and data from each included study -assisted in the data and statistical analysis -revised intellectual content of manuscript
D. David Wang	-3rd year undergraduate student -extracted relevant study characteristics and data from each included study -assisted in data management and interpretation -revised intellectual content of manuscript
Adrian I Cozma HBSc	-final year undergraduate student -assisted in search -assisted in extraction of study characteristics and data from each included study -assisted in data management and interpretation -revised intellectual content of manuscript
Arash Mir-Rahimi HBSc	-MSc student -developed protocol of project -assisted in search -assisted in extraction of study characteristics and data from each included study -assisted in data management and interpretation -revised intellectual content of manuscript
Matthew E Yu HBSc	-final year undergraduate student -assisted in search -assisted in extraction of study characteristics and data from each

	included study -assisted in data management and interpretation -revised intellectual content of manuscript
Amanda J Carleton MSc	-MSc student -developed protocol of project -assisted in search -assisted in extraction of study characteristics and data from each included study -revised intellectual content of manuscript
Marco DiBuono PhD	-Director of Research at the Heart and Stroke Foundation -developed protocol of project -Designated knowledge user -revised intellectual content of manuscript
Alexandra L Jenkins RD, PhD	-Research Scientist -developed protocol of project -Designated knowledge user -revised intellectual content of manuscript
Lawrence A Leiter MD	-Endocrinologist/Research Scientist -developed protocol of project -Designated knowledge user -revised intellectual content of manuscript
Thomas MS Wolever DM, PhD	-Physician/Research Scientist -developed protocol of project -Designated knowledge user -revised intellectual content of manuscript
Joseph Beyene PhD	-Epidemiologist and Biostatician -developed protocol of project -revised intellectual content of manuscript
Cyril WC Kendall PhD	-Research Scientist -developed protocol of project -revised intellectual content of manuscript
David JA Jenkins MD, PhD, DSc	-University Professor/Physician/Research Scientist -overall supervision - guarantor -developed protocol of project -assisted in data analysis and interpretation -revised intellectual content of manuscript

Figure S7- List of contributions to the present study by each author