Effect of Fructose on Blood Pressure

A Systematic Review and Meta-Analysis of Controlled Feeding Trials


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 I². 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;59:787-795.) • 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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From the Clinical Nutrition and Risk Factor Modification Centre (V.H., J.L.S., L.C., R.J.d.S., D.D.W., A.I.C., A.M., M.E.Y., A.J.C., A.L.J., L.A.L., T.M.S.W., C.W.C.K., D.J.A.J.) and Keenan Research Center of the Li Ka Shing Knowledge Institute and Division of Endocrinology and Metabolism (L.A.L., T.M.S.W., D.J.A.J.), St Michael’s Hospital, Toronto, Ontario, Canada; Departments of Nutritional Sciences (V.H., R.J.d.S., L.C., D.D.W., A.I.C., A.M., M.E.Y., L.A.L., T.M.S.W., C.W.C.K., D.J.A.J.) and Medicine (L.A.L., D.J.A.J.), Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; Departments of Pathology and Molecular Medicine (J.L.S.) and Clinical Epidemiology and Biostatistics (R.J.d.S., J.B.), Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada; Dalla Lana School of Public Health (J.B.), University of Toronto, Toronto, Ontario, Canada; Population Health Sciences Research Institute (J.B.), Hospital for Sick Children, Toronto, Ontario, Canada; Heart and Stroke Foundation of Ontario (M.D.), Toronto, Ontario, Canada; College of Pharmacy and Nutrition (C.W.C.K.), University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

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Correspondence to John L. Sievenpiper, Risk Factor Modification Centre, St Michael’s Hospital, #6137-61 Queen St East, Toronto, Ontario M5C 2T2, Canada. E-mail john.sievenpiper@medportal.ca

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intervention studies, however, have shown conflicting results: fructose has been shown to increase and decrease BP.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{25} Reporting of results followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.\textsuperscript{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\textsubscript{2}O) on SBP, diastolic BP (DBP), or mean arterial BP (MAP) were included. Investigators must have administered fructose and control CH\textsubscript{2}O 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\textsubscript{2}O 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.\textsuperscript{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: \(\text{MAP} = \frac{2}{3} \text{DBP} + \frac{1}{3} \text{SBP}\). The SDs for these calculated MAPs were calculated using the following formula:

\[
\frac{1}{N} \sqrt{\left(\frac{1}{3}\right)^2 s_{\text{SBP}}^2 + \left(\frac{2}{3}\right)^2 s_{\text{DBP}}^2}
\]

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.\textsuperscript{25} Authors were contacted, when possible, to request additional information. Missing SD values were imputed from the pooled SD from other published reports.\textsuperscript{29}

The quality of each study was assessed using the Heyland Methodological Quality Score (MQS).\textsuperscript{30} Studies could receive a maximum score of 13 points. Studies with a score of \(\geq 8\) 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\textsubscript{2}O 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,\textsuperscript{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\textsuperscript{2} quantified the interstudy heterogeneity with significance set at \(P<0.10\). An I\textsuperscript{2} \(\geq 50\%\) indicated “substantial” heterogeneity, and \(\geq 75\%\) indicated “considerable” heterogeneity. Sources of heterogeneity were explored using a priori subgroup analyses of CH\textsubscript{2}O comparator (starch, glucose, sucrose, and high-fructose corn syrup), dose (Canadian Diabetes Association threshold of \(\leq60\) g/d or >60 g/d),\textsuperscript{27} follow-up (<4 weeks or \(\geq 4\) weeks), fructose form (fluid, mixed, or solid), study quality (MQS \(<8\) or \(\geq 8\)), 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,\textsuperscript{14,17} with conflicting results, had been undertaken in prediabetic/diabetic participants.

Meta-regressions 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,\textsuperscript{14,15,17,27,28,32–36} and 2 hypercaloric feeding trials,\textsuperscript{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\textsubscript{2}O comparator, 7 in glucose, 1 in high-fructose corn syrup, and 1 in sucrose. Fructose was administered in solid (2 trials), mixed (4 trials),
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) CH2O, 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 ≥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 143 g/d (+18% to 25% E). The background diet consisted of 55% E CH2O, 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 CH2O 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 al34 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 (I2=61%; P<0.10).

**Diastolic BP**

Isocaloric exchange of fructose for other CH2O 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

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**Table:**

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Number of Trials</th>
<th>Median Dose (g/d)</th>
<th>Range of Dose (g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocaloric</td>
<td>11</td>
<td>78.5</td>
<td>53–182</td>
</tr>
<tr>
<td>Hypercaloric</td>
<td>2</td>
<td>143</td>
<td>118–250</td>
</tr>
</tbody>
</table>

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**Figure 1:** Flow of the literature search.
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. or Brymora et al. 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>
<thead>
<tr>
<th>Study Identification</th>
<th>Subjects, n (M:F)†</th>
<th>Age, y</th>
<th>Design‡</th>
<th>Method of Blood Pressure Measurement</th>
<th>Blood Pressure End Point</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocaloric trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aeberli et al.22</td>
<td>29 N (29:0)</td>
<td>26.3±6.6</td>
<td>C</td>
<td>Automated sphygmomanometer after 15-min rest in supine position, measurements were made at baseline and end of intervention</td>
<td>Neither</td>
<td>Outpatient, Zurich, Switzerland</td>
</tr>
<tr>
<td>Aeberli et al.22</td>
<td>29 N (29:0)</td>
<td>26.3±6.6</td>
<td>C</td>
<td>Automated sphygmomanometer after 15-min rest in supine position, measurements were made at baseline and end of intervention</td>
<td>Neither</td>
<td>Outpatient, Zurich, Switzerland</td>
</tr>
<tr>
<td>Brymora et al.23</td>
<td>28 CKD (17:11)</td>
<td>59±15</td>
<td>C</td>
<td>Automated sphygmomanometer after 15-min rest in supine position, measurements were made at baseline and end of intervention</td>
<td>Primary</td>
<td>Outpatient, Torun, Poland</td>
</tr>
<tr>
<td>Haltfrisch et al.25</td>
<td>12 N (12:0)</td>
<td>39.8±8.3</td>
<td>C</td>
<td>Automated sphygmomanometer after 5-min rest in sitting position, measurements were made at baseline and end of intervention</td>
<td>Neither</td>
<td>Metabolic ward/outpatient, Maryland</td>
</tr>
<tr>
<td>Haltfrisch et al.25</td>
<td>12 HI (12:0)</td>
<td>39.5±7.3</td>
<td>C</td>
<td>Automated sphygmomanometer after 5-min rest in sitting position, measurements were made weekly</td>
<td>Neither</td>
<td>Outpatient, Oklahoma</td>
</tr>
<tr>
<td>Koh et al.17</td>
<td>9 N (3:6)</td>
<td>50±15</td>
<td>C</td>
<td>Automated sphygmomanometer after 5-min rest in sitting position 2 measurements were made at baseline and end of intervention</td>
<td>Primary</td>
<td>Outpatient, Oklahoma</td>
</tr>
<tr>
<td>Madero et al.26</td>
<td>107 OW/OB</td>
<td>38.8±8.8</td>
<td>P</td>
<td>Manual sphygmomanometer after 10-min rest in sitting position, 3 measurements were made at 5-min intervals, measurements were made weekly</td>
<td>Secondary</td>
<td>Outpatient, Mexico City, Mexico</td>
</tr>
<tr>
<td>Sibernegal et al.25</td>
<td>20 N (12:8)</td>
<td>−30.5±8.9</td>
<td>P</td>
<td>N/A</td>
<td>Neither</td>
<td>Outpatient, Tübingen, Germany</td>
</tr>
<tr>
<td>Stanhope et al.27*</td>
<td>32 OW (16:16)</td>
<td>53.75±7.8</td>
<td>P</td>
<td>Automated sphygmomanometer measurements were made twice daily during inpatient periods</td>
<td>Neither</td>
<td>Outpatient (8 wk), clinical research center inpatient (2 wk), California</td>
</tr>
<tr>
<td>Stanhope et al.28</td>
<td>48 N (27:21)</td>
<td>27.6±7.1</td>
<td>P</td>
<td>N/A</td>
<td>Neither</td>
<td>Outpatient (12 dt), clinical research centre inpatient (3.5 dt), California</td>
</tr>
<tr>
<td>Swarbrick et al.29</td>
<td>7 OW/GB (0:7F, PM)</td>
<td>50–72</td>
<td>C</td>
<td>N/A</td>
<td>Neither</td>
<td>Residential facility inpatient, California</td>
</tr>
<tr>
<td>Prediabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koh et al.27</td>
<td>9 IGT (3:6)</td>
<td>54±18</td>
<td>C</td>
<td>Automated sphygmomanometer after 5-min rest in sitting position 2 measurements were made at baseline and end of intervention</td>
<td>Primary</td>
<td>Outpatient, Oklahoma</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koivisto et al.14</td>
<td>10 DM2 (4:6)</td>
<td>61±9.5</td>
<td>C</td>
<td>Manual sphygmomanometer after 5-min rest in sitting position</td>
<td>Neither</td>
<td>Inpatient, hospital, Helsinki, Finland</td>
</tr>
<tr>
<td>Hypercaloric trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al.27</td>
<td>7 N (7:0)</td>
<td>24.7±3.5</td>
<td>C</td>
<td>Measurement taken 3 times over 20-min period</td>
<td>Neither</td>
<td>Outpatient Lausanne, Switzerland</td>
</tr>
<tr>
<td>Stanhope et al.27*</td>
<td>17 OW/GB (9:8)</td>
<td>52.5±13.2</td>
<td>C</td>
<td>Automated sphygmomanometer measurements were made twice daily during inpatient periods</td>
<td>Neither</td>
<td>Clinical research center inpatient (2 wk), outpatient (8 wk), California</td>
</tr>
</tbody>
</table>

*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 kitchen 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 "%E" represent average doses; % E indicates percentage of total daily caloric intake.
#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).
\textbf{Table. Continued}

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

\textbf{Mean Arterial Pressure}

Isocarbohydrate exchange of fructose for other \(\text{CH}_2\text{O}\) 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.\textsuperscript{34} Silbernagel et al.\textsuperscript{35} or Koh et al.\textsuperscript{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 \(I^2 \geq 53\%; P \leq 0.01\).

\textbf{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 \((P=0.03)\).
Effects models. Interstudy heterogeneity was tested by Cochrane’s Q (I_2) at a significance level of 0.05. This discrepancy 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.

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 with a median follow-up of 4 weeks found a significant increase in BP 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 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 consumption, 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,15,18 at which time the adverse effects of fructose on BP have been most consistently shown in humans16,18 and laboratory rats.7–10 Furthermore, although our analysis suggests that casual BP is not clinically significant effects on BP in humans is uncertain. 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 al38 and animal models7–10 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

<table>
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<th>Study or Subgroup</th>
<th>Weight</th>
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<th>Mean Difference</th>
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<td></td>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>1.1.1 Non-Diabetics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aeberli (COM-H) [32]</td>
<td>13.0%</td>
<td>-0.35 [-3.47, 2.77]</td>
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<tr>
<td>Aeberli (MOD) [32]</td>
<td>13.0%</td>
<td>-1.00 [-4.12, 2.12]</td>
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<tr>
<td>Brynora (COM) [33]</td>
<td>8.9%</td>
<td>1.00 [3.27, 5.27]</td>
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<tr>
<td>Hallfrisch (COM-H) [15]</td>
<td>4.5%</td>
<td>-1.00 [-7.66, 5.66]</td>
<td></td>
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<tr>
<td>Hallfrisch (COM-N) [15]</td>
<td>4.5%</td>
<td>-1.50 [-8.16, 5.16]</td>
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<tr>
<td>Koh (NGT) [17]</td>
<td>1.2%</td>
<td>-2.00 [-15.72, 11.72]</td>
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<tr>
<td>Madero [34]</td>
<td>17.7%</td>
<td>1.61 [0.60, 3.82]</td>
<td></td>
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<tr>
<td>Silbernagel [35]</td>
<td>5.5%</td>
<td>-5.00 [-10.88, 0.88]</td>
<td></td>
</tr>
<tr>
<td>Starhoepe (COM) [36]</td>
<td>9.6%</td>
<td>-4.00 [-8.04, 0.04]</td>
<td></td>
</tr>
<tr>
<td>Starhoepe [27]</td>
<td>9.9%</td>
<td>-3.00 [-6.92, 0.92]</td>
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<tr>
<td>Swarbrick [28]</td>
<td>0.3%</td>
<td>3.00 [-24.44, 30.44]</td>
<td></td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>88.2%</td>
<td>-0.74 [-2.07, 0.59]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.45; Chi² = 10.96, df = 10 (P = 0.36); I² = 9%
Test for overall effect: Z = 1.10 (P = 0.27)

1.1.2 Pre-diabetics/Diabetics

Koh (IGT) [17] 9.9% -4.00 [-7.92, -0.08]
Koivistö [14] 1.9% 10.00 [-9.20, 20.92]
Subtotal (95% CI) 11.8% 2.03 [-11.55, 15.62]
Heterogeneity: Tau² = 80.49; Chi² = 5.60, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.29 (P = 0.77)

Total (95% CI) 100.0% -1.10 [-2.64, 0.44]
Heterogeneity: Tau² = 2.19; Chi² = 38, df = 12 (P = 0.14); I² = 31%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for sub group differences: Chi² = 0.16 , df = 1 (P = 0.69 ), I² = 0%

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. 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 (I²) at a significance level of P<0.10 and quantified by I², where I²=50% is considered to be evidence of substantial heterogeneity and ≥75% considerable heterogeneity.
effects models. Interstudy heterogeneity was tested by Cochrane’s Q ($I^2$) at a significance level of 0.25. There were 20 end points, most of which were based on a single study. The number of studies included in each end point, therefore, is small and the power to detect heterogeneity is low. Because of this, we consider the conclusions in the sections below to be tentative and based on a low level of evidence of heterogeneity. We did not observe any significant effect modifiers of fructose on BP, other than age group (60 g/d), or ~20.5% of energy (range: ~9% to 25%).

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). 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 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, 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). 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 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, 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.

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 al34 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 and acute human studies. The present meta-analysis, however, shows a significant DBP- and MAP-lowering effect and a trend
facing SBP in the overall analysis and in the non-diabetic 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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### Disclosures

J.L.S. has received several unrestricted travel grants from the Coca-Cola Company to present research at meetings and is a coinvestigator on an unrestricted research grant from the Coca-Cola Company. J.L.S. has also received travel funding and honoraria from Abbott Laboratories, Archer Daniels Midland, and the International Life Sciences Institute North America, as well as research support, consultant fees, and travel funding from Pulse Canada. R.J.D.S., J.B., and C.W.C.K. are coinvestigators on an unrestricted grant from the Coca-Cola Company. C.W.C.K. has served on the scientific advisory board and received research support, travel funding, consultant fees, or honoraria from Pulse Canada, Barilla, Solae, Unilever, Hain Celestial, Loblaws Supermarkets, Oldways Preservation Trust, the Almond Board of California, the International Nut Council, Paramount Farms, the California Strawberry Commission, the Canola and Flax Councils of Canada, and Saskatchewan Pulse Growers. C.W.C.K. also receives partial salary funding from research grants provided by Unilever, Loblaws Supermarkets, and the Almond Board of California. D.J.A.J. holds an unrestricted grant from the Coca-Cola Company and has served on the scientific advisory board for or received research support, consultant fees, or honoraria from Barilla, Solae, Unilever, Hain Celestial, Loblaws Supermarkets, Sanitarium Company, Herbalife International, Pacific Health Laboratories Inc, Metagenics/MetaProteomics, Bayer Consumer Care, Oldways Preservation Trust, The International Tree Nut Council Nutrition Research & Education, The Peanut Institute, Procter and Gamble Technical Centre Limited, Griffin Hospital for the development of the NuVal System, Pepsi Company, Soy Advisory Board of Dean Foods, Alpro Soy Foundation, Nutritional Fundamentals for Health, Pacific Health Laboratories, Kellogg’s, Quaker Oats, The Coca-Cola Sugar Advisory Board, Agrifoods and Agriculture Canada (AAFC), Canadian Agriculture Policy Institute (CAPI), Abbott Laboratories, the Almond Board of California, the California Strawberry Commission, Orafti, the Canola and Flax Councils of Canada, Pulse Canada, and the Saskatchewan Pulse Growers. D.J.A.J. also holds additional grant support from the Canadian Institutes of Health Research, Canadian Foundation for Innovation, Ontario Research Fund, and Advanced Foods and Material Network. T.M.S.W. is the president, A.L.J. a vice president and director of research, and L.C., a clinical research coordinator at GI Laboratories (Toronto, Ontario, Canada). V.H., A.I.C., D.D.W., M.E.Y., A.M., A.J.C., M.D., and L.A.L. have no declared conflicts of interest related to this article.

### References


Effect of Fructose on Blood Pressure: A Systematic Review and Meta-Analysis of Controlled Feeding Trials


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FOR

EFFECT OF FRUCTOSE ON BLOOD PRESSURE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CONTROLLED FEEDING TRIALS
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.
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.
**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.
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.
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's regression test for funnel-plot asymmetry.
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.
<table>
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<tr>
<th>Author</th>
<th>Contribution to Manuscript</th>
</tr>
</thead>
</table>
| 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 biostatistician  
- developed protocol of project  
- supervised the conduct of project  
- supervised data analysis and interpretation  
- revised intellectual content of manuscript |
| Laura Chiavaroli MSc                        | - 3rd year undergraduate student  
- 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                               | - 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 |
| Adrian I Cozma 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 |
| 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 |
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<tr>
<td>Amanda J Carleton MSc</td>
<td>included study&lt;br&gt;-assisted in data management and interpretation&lt;br&gt;-revised intellectual content of manuscript</td>
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<tr>
<td>Marco DiBuono PhD</td>
<td>-Director of Research at the Heart and Stroke Foundation&lt;br&gt;-developed protocol of project&lt;br&gt;-Designated knowledge user&lt;br&gt;-revised intellectual content of manuscript</td>
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<tr>
<td>Alexandra L Jenkins RD, PhD</td>
<td>-Research Scientist&lt;br&gt;-developed protocol of project&lt;br&gt;-Designated knowledge user&lt;br&gt;-revised intellectual content of manuscript</td>
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<td>Lawrence A Leiter MD</td>
<td>-Endocrinologist/Research Scientist&lt;br&gt;-developed protocol of project&lt;br&gt;-Designated knowledge user&lt;br&gt;-revised intellectual content of manuscript</td>
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<td>Thomas MS Wolever DM, PhD</td>
<td>-Physician/Research Scientist&lt;br&gt;-developed protocol of project&lt;br&gt;-Designated knowledge user&lt;br&gt;-revised intellectual content of manuscript</td>
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<td>Cyril WC Kendall PhD</td>
<td>-Research Scientist&lt;br&gt;-developed protocol of project&lt;br&gt;-revised intellectual content of manuscript</td>
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<tr>
<td>David JA Jenkins MD, PhD, DSc</td>
<td>-University Professor/Physician/Research Scientist&lt;br&gt;-overall supervision&lt;br&gt;-guarantor&lt;br&gt;-developed protocol of project&lt;br&gt;-assisted in data analysis and interpretation&lt;br&gt;-revised intellectual content of manuscript</td>
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**Figure S7**- List of contributions to the present study by each author