BMJ - Decision on
Manuscript ID
BMJ.2017.038661

Body: 11-May-2017

Dear Dr. Sievenpiper

Manuscript ID BMJ.2017.038661 entitled "Food sources of fructose-containing sugars and glycemic control: A systematic review and meta-analysis of controlled trials"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Jose Merino (chair), Gary Collins (statistician), Elizabeth Loder, Wim Weber, John Fletcher, Rubin Minhas, Tiago Villlanueva, Georg Roggla, Daoxin Yin

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:
Title says 'controlled trials'; they included both randomized and non-randomized studies, so more information on the design of the non-randomized studies would be

useful. Table 1 has characteristics 'cross-over/parallel', but this won't necessarily describe the non-randomized studies.
There is a constant use of the term 'trials' throughout to cover all designs which should be avoided I think and replaced with 'studies'.
As such, should the Cochrane RoB tool be used on the non-randomized studies? Or something like the Newcastle-Ottawa scale?
Few studies had high RoB across all domains, but many had unclear RoB across the domains.
The search was done until Nov 2015, so 1.5 years out of date.
Ultimately, lots of heterogeneous small trials. Total n is only 5139 from 160 trials (median of 15 participants per trial).

- One editor felt the clinical relevance of this study was unclear. He was also not sure whether the paper added enough to these two previous papers:
Diabetes Care. 2012 Jul;35(7):1611-20. doi: 10.2337/dc12-0073.Sign in
Effect of fructose on glycemic control in diabetes: a systematic review and meta-analysis of controlled feeding trials.

Am J Clin Nutr. 2016 Dec;104(6):1562-1576. Epub 2016 Nov 9.Sign in
Effect of fructose consumption on insulin sensitivity in nondiabetic subjects: a systematic review and meta-analysis of diet-intervention trials.

- Another editor said there is quite a bit of discussion about whether fructose is bad or just another sugar and he expected the paper to be well received by the readership and was in favour.

-Another editor found it difficult to understand the four different trial designs. Would it be possible to clarify a bit further?

- Another editor was concerned about the evidence being "borderline" (predominantly proxy outcomes, short term data, etc) but he acknowledged the relevance of the topic.

- Another editor highlighted that you need to update the search but felt the paper seemed important from a public health and nutritional standpoint since so many foods are sweetened, and there is intense debate about whether some sweeteners are good or bad.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
1. It's a fair question to ask. Individual trials unlikely to have sufficient power to answer the question. Consistent answers across a range of different trials would be useful.
2. The actual review appears to have been conducted to a high standard.
3. My main concern is the inclusion of non-randomized trials. This may well reflect the nature of the studies in this area, but that does not avoid the inherent potential for bias in non-randomized studies. The authors note that results did not differ between randomized and non-randomized trials.

4. There is a lot of heterogeneity and this also limits the interpretation of the results. The authors have tried to explore different potential sources, but nothing really explains it.
5. I like the separation into different types of trials: substitution, addition, etc. This helps interpretation in a field where it's hard to tell if it is sugar, energy, whatever has replaced the sugar, etc.
6. The abstract feels slightly long, but the main finding from each of these types of trials should be presented regardless of statistical significance.
7. I felt slightly uncomfortable with the interpretation of some of the evidence, e.g. "There was no effect of total food sources of fructose-containing sugars in subtraction (low to high quality evidence) or ad libitum trials..." would be better phrased as being no *evidence of* an effect.
8. Similarly, the conclusion that "Pooled analyses showed that fructose-containing sugars from various food sources, especially fruit, are no worse in their effects on glycemic control ..." is phrased like an equivalence / non-superiority trial, but this does not reflect how the trials or the meta-analyses were set up. More care is needed to cautiously reflect the body of evidence, potentially with more nuanced phrasing.
9. Absolute heterogeneity (e.g. range of estimates across individual trials) should be presented alongside I-squared.
10. At times the estimates, confidence limits and p-values are presented to too many decimal places, giving a false sense of precision.

Additional Questions:
Please enter your name: Darren Greenwood

Job Title: Senior Lecturer in Biostatistics

Institution: University of Leeds

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
The authors conducted a very thorough systematic review and meta-analysis of different food sources of fructose-containing sugars and their effects on three markers of glycemic control (HbA1c, fasting blood glucose, fasting blood insulin). This manuscript looks to be an ambitious undertaking particularly taking into consideration the energy balance of all available trials that were identified to be suitable up until November 3 2015

Major comments:
1) The authors should consider including other important markers of glycemic control such as indices for insulin sensitivity or insulin resistance (e.g. Homeostatic Model Assessment of Insulin Resistance or HOMA-IR).
2) Figure 2 and Supplementary Figure 6 both presented results with respect to HbA1c in substitution trials for different food sources of fructose-containing sugars (fruits, SSB, LMR, etc.), but the results (MDs or the associated 95% CIs) were not consistent for any of the five food sources; only the estimate (95% CI) for total food sources was the same. The same inconsistency exists for substitution trials portion of Figure 3 and Supplementary Figure 13. The authors should explain why such inconsistency exists.
3) In Potential mechanisms under the Discussion section, the authors compared the glycemic indices of fructose and starch, citing the low GI of fructose itself as the potential source of benefit. In my opinion this is not a fair comparison, especially since the focus of this review is on food sources of fructose-containing sugars. The authors should at least consider the GI of the difference food sources, such as fruits, SSB, sweets, etc., which can be very different.
4) In Potential mechanisms under the Discussion section, the authors focused solely on the catalytic function of fructose in low GI fruits, but failed to discuss other potentially beneficial component of fruits, such as fiber content or micronutrients.
5) Overall more of the emphasis of the article was placed on the food sources of fructose-containing sugars, while less attention was given to the comparator foods (for example in the main finding figures 1 – 3). In my opinion it is very important to consider both sides of the substitution, especially when making recommendations to the general public. The majority of the comparators in this study were starch, and it seems like no trials included in this study used legumes or whole grain products as the comparator food, which are generally considered higher quality carbohydrates for glycemic control. The authors should acknowledge the lack of such trials.

Minor comments
1) Line 30 – 31: the statement that "public health advice to reduce free sugars does not distinguish between food sources of sugars" is not entirely true, since the US dietary guideline 2015-2020 specifically limits added sugars in the diet but not naturally occurring sugars such as those in fruits or milk.
2) Line 187: the authors should be consistent in using "to" or "-" when presenting range.
3) Line 211: the authors should be consistent in the number of digits used when presenting P-values. Similar comment for line 230.
4) Line 220: in Supplementary Figure 6, the line for the baseline HbA1c ≤ 6% group is missing the right half of the line. Also the legend is missing information regarding between subgroup analysis results for food source (same comment for Supplementary Figure 13 and 14.
5) Line 228 – 229: the authors stated that in addition trials, fructose-containing sugars from all food sources increased fasting blood glucose, but for mixed sources the effect estimate was negative in Figure 3.

6) Line 285: continuous dose-response for fasting insulin in addition trials was presented in Supplementary Figure 8E instead of 12C?
7) Line 287: continuous dose-response for fasting insulin in substitution trials was presented in Supplementary Figure 8D instead of 12B? The authors should also be consistent in whether to use hyphen or not throughout the text.
8) Line 338: the decreased risk of type 2 diabetes associated with higher fruit intake is not directly relevant to the adverse effects of SSB and should be cited elsewhere.
9) Line 361: NAFLD should be spelled out fully at first occurrence.
10) Line 369 – 370: I don't think it is appropriate to classify fruit as an alternative sweetener.
11) Line 422: without individual level data, the analysis cannot be called pooled analysis.
12) Line 426: the current dietary guidelines have shifted towards a dietary pattern-based approach instead of a food-based approach, as the authors stated in the Abstract Objective.
13) The quality of Figure 1, 2, and 3 appears to be substantially lower than the supplementary figures and the authors should consider improve the quality of these main finding figures.

Additional Questions:
Please enter your name: Simin Liu

Job Title: Professor

Institution: Brown University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 3

Recommendation:

Comments:

In this important meta-analysis, Choo et al assess the effects of fructose-containing caloric sweeteners on glycemic control in healthy subjects and in patients with diabetes mellitus. For this purpose, they made a comprehensive scan of the litterature and retrieved a large number of randomized clinical trials, which they assessed according to study design (ie substitution trials, addition trials, subtraction trials, and "ad libitum" trials. Furthermore, they obtain sufficient data to assess individually the effects of various sources of fructose-containing caloric sweeteners. Their results indicate that fructose-containing caloric sweeteners decreased HbA1c without significantly altering fasting plasma glucose and insulin in substitution trials (this effect was most marked with fruits as a source of fructose), and increased fasting plasma glucose and insulin concentration in addition trials without altering HbA1c (this effect was most marked with sugar sweetened beverages). Surprisingly, there was no significant effect in subtraction trials (possibly related to the lower number of trials in this category).
Altogether, these results corroborate earlier observations that fructose, compared to glucose or starch, induces lesser increases in blood glucose and insulin. The effect on Hba1c remains small, however (below the clinical significance level defined by major diabetes organizations), and hence this does not fully support that fructose has relevant beneficial effects on glycemic control. The major strength of this meta-analysis is to allow assessing separately the effects of fructose consumed with fruits, sweetened beverages, and other types of food. It supports the well accept concept that sugar-sweetened beverages but not whole fruits, exert deleterious metaboilic effects.
Altogether, this meta-analysis was well conducted, with adequate methodology, and results are clearly reported. I have only few comments
1) The potential confounding effects of non-nutritive sweeteners used in some subtraction trials may be taken into consideration (ie one may consider the possibility that beneficial effects of fructose subtraction were offset by deleterious effects of non-nutritive sweeteners.
2) the general discussion. while faithfully discussing the study results, is sometime a little bit confusing and/or makes some shot cuts from observations to recommendations. This is mainly due to failing to insert a brief paragraph stating what fasting insulin and glucose and HbA1c actually reflect (ie fasting parameters being a reflection of changes in insulin sensitivity, HbA1c being determined by 24-hour blood glucose.
3) along the same line, it would be cautious to clearly remind the reader that blood glucose control and glycemic index/glycemic loads represent only one side of the coin, and that effects on other cardiometabolic risk factors should be assessed before going to recommendations
minor
4) the part of the discussion related to "catalytic effects" of fructose is confusing and most likely not relevant to these studies. This whole concept is indeed relevant to document that fructose metabolites have regulatory actions on glucokinase and hepatic glucose uptake. However, fructose is present in our diet at doses substantially higher that these so-called "catalytic doses", and how dietary fructose interacts with glucose at the level of hepatic glucose homeostasis remains largely under-explored.

Additional Questions:
Please enter your name: Luc Tappy

Job Title: Professor, M.D.

Institution: Physiology Department, University of Lausanne Faculty of Biology and Medicine

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 4

Recommendation:

Comments:
Overall: This is a detailed analyses and balanced approach to the assimilation of the literature. The topic brings together a number of seemingly opposing arguments for the role of fructose intake in glycaemic control and is a timely piece given the current research and public interest in this area. More clarity is needed throughout the paper, particularly in the methods section. The authors are commended for their very detailed analysis however the sensitivity analyses and subgroup analyses results are largely not used to interpreted the main results and the discussion and conclusion need to be put in context more in light of the volume and quality of evidence and study heterogeneity. The abstract could also be a lot more representative of the main manuscript, in its current format it is somewhat oversimplified. The order of presentation of results could be paralleled better between the different sections and tables/figures. Following revisions, this is likely to make a good contribution to the field.

Abstract: overall the abstract needs more information on the identified food sources of fructose containing sugars. Also I find the results a little selective in terms of reporting the "stronger effects" for fruit and SSB, you should also report null food sources.
L30: this is a sweeping statement and is country specific, please revise to a more inclusive sentence given the potential international readership interest. There is also a mismatch between this sentence and the sentence that follows with the aim. The background provided is about free sugars but the aim is about fructose specifically. Can this be tied together better?
L35: this is already 18 months old. I think an update is warranted to identify any studies published particularly given the growing research interest in this area in very recent years.
L36: 7 days long?
L38: outcomes of interest? included outcomes?

L42: I think the results section would be more interpretable and relevant if they were presented by outcome rather than by trial design.
L42: "energy control" do you mean energy intake?
L42: When presenting the results, the volume of evidence should be made clear along with quality of evidence. it is important for the reader to understand that there are far fewer studies of subtraction and ad libitum than substitution and addition. It is therefore somewhat misleading to report 160 trials included without giving further detail.
L44: "excess energy from sugars displaced from diets", this suggests replaced by something else and isn't properly representative of what was actually included according to the description on line 119.
L45: "strict" this suggest that there was some element of energy intake control which I don't think is accurate from reading the methods section.
L46 and throughout the manuscript. It is important to say this is intake of fructose containing sugars. It doesn't have to be written on every occasion but unless it is specified you could well be referring to intravenous or other methods of exposure.
L47: It is not clear at this point in the manuscript what this p-value is for?
L48 "effect was stronger for fruit as a food source" this is not detailed enough. Also would larger effect be more accurate than stronger?
L50: please match decimal places.
L52: what about dairy and mixed sources as sources, these results are also significant.
L59: "Longer, larger, high quality trials are required", this requirement needs to be worked into the conclusion, not just appended to the end. How should the lack of longer, larger, high quality trails affect our interpretation of the reported results? As a reader I want to know how much confidence I should have in the results given the quality of the data and publication bias etc.
Introduction: very well balanced treatment of the literature.
L92: there is something not quite right about the position of the parentheses.
L96: The reference provided isn't about shift in focus of recommendations, it is just US recommendations, please find a more appropriate reference to support your point and think about your potential international audience when selecting this.
Methods: Needs some revision, at times they are not specific enough and require forward reading to fully understand what is being said.
L113: Honey and fruit and food sources rather than sub-groups of fructose containing sugars.
L124-125: Is this necessary information?
L127: "reports" it is not clear until the results section that you are using the words trials and reports to mean 2 different things.
L128 consensus of who?
L128: what is health status referring to? is it presence of diabetes or not, or does it go further?
L129: it is unclear at this point in the manuscript what "comparator form" means.
L131: using "included" in this manner suggests that this is not a comprehensive list.
L132: this paragraph is about data extraction and suddenly the authors jump to reporting data. I think this sentence would be better suited elsewhere in the manuscript.L135: it is not clear if the glycated blood protein data were extracted and then not reported or whether the change came at the point of data collection.
L137: your inability to contact or the authors failure to reply?
L138: assessed by who? all 4 data extractors?
L146: "were combined", this gives the impression that someone else has combined them. Would it be more appropriate to say available for combination?
L150-154: please provide some detail of the categories. Did you consider study size for subgroup analyses? There is likely some clinical heterogeneity between participants recruited to small versus large studies.
L156: do you mean marker of glycemic control?
L158: -159; this information would have been most useful at line 113.

L164: >10 studiers within trial design and/or outcomes and/or food sources?
L166: suspected from what? what were the criteria?
L169-171: this sentence is very difficult to read. It needs further punctuation.
L175: I don't see these factors listed in your data extraction.
L176: define wide
L177: publication bias here appears to be referring to small study effects, different to the publication described on line 166, therefore how was this publication bias determined?
L182: why were these excluded? was it based on the full review and not meeting the criteria? How it is written currently suggests that the decision was somewhat arbitrary.
L185: you need to specify in data extraction that these data were pulled.
L185: presented by trial design?
L194: "healthy and overweight" this is confusing; how the other similar surrounding sentences are constructed is more explicit.
L197: why "however"?
L199: please present an estimate of variance each time a mean/median is presented.
L202: please insert n after most trials.
L204: please insert n after very few trails.
L207: it would make the section titles more commensurate with each other if this and the following sections were renamed "outcomes:HbA1c"
L215: why are you selectively reporting this upper CI to three decimal places here. It is also not what is reported in figure 2 where it is actually reported as null.
L218: where are these analyses presented?
L220: higher baseline levels of what?
L221: but these were not significant.
L208-225: There are too many important results presented in supplementary materials only. While it is fine to give the extra detail in the supplementary material the results need to be better summarised in the main body of the paper otherwise you are treating supplementary material as main body tables/figures which makes it very difficult to navigate the manuscript.
L238: what does G2 stand for?
L238: what effect?
L238: it would be more informative to give information about the trial rather than the author of the paper e.g. how many of the 585 participants were part of this trail and thus excluded?
L245: outlier, defined how?
L251: is underlying disease status the same as health status described previously?
L278: include n of trial.
Discussion
L311: I think you need to include "4 trial designs" or something to that effect here.
L315: I am not convinced by the argument for a different effect for fructose from fruit given how the upper CI is essentially
L319 what about from dairy and mixed sources both have larger effect estimates according to your results.
L336: What about the dairy results?
L346: did you consider effects on de novo lipogenesis as a mechanism?
L351-354: but there are 32 trials for hba1c compared with 101 for glucose and 75 for insulin so this statement is unfounded.
L361: uric acid levels?
Line 361: are these references all trial data?
L362: I would prefer to see these results discussed with the main results as they affect the interpretation of the main results.
L382: national intakes of what country? Please remember the potential international readership when revising this.

L386: Can you put intakes of fructose in free living populations and in the included trials in this analysis in context of the dietary guidelines for sugars of 5-10% of energy intake?
L387: what about dental carriers? Do you mean, based on evidence for protection against dental carries?
L418: the information contained here is particularly important for interpreting the main results and understanding why the presentation of main results appears a little selective. This needs to be presented at the same time as the main results. See my previous comment RE line 362.
L429: here and throughout than manuscript I think you make more of the protective effect of fructose from fruit on HbA1c than the results warrant.
L436-441: this is just a description of the protocol, please expand and explain why these are strengths of the study.
L443-453: how did you attempt to overcome these limitations and how do they impact on the interpretation of the results?
L462: can you interpret this null in any way for the reader?
L464: What makes them important?
Figure 1: this could have a more informative title. What determined an endpoint as unsuitable? Do you mean outcomes other than those of interest? Do "acute/short term" refer to studies less than 7 days? Co-intervention trials as an exclusion should be made clear in the methods text. "irretrievable" was this before or after contacting authors?
Table 1: for trial size what are the numbers before parentheses? It is not clear from the footnotes if these are medians as well or something else.
Figure 2: I wonder as to the use of "total food sources", it isn't really total as this would suggest total fructose intake from all sources while this is intake of fructose from sources used in trials. Would combined sources be better? The result presented here for fruit in substitution trials contradicts the text. It is simply because of the number of decimal places presented but highlights how close to a null effect this result is. Please see my previous comment RE line 429. It would be useful to have a definition of what is included in these food groups at some point in the manuscript.
Supplementary table 1: Is there a legend missing.
Supplementary table 2: this would benefit from a more detailed title. The unit for body weight in Agebratt et al. is missing. There are two trials by Johnston et al included and they seem to have the same participants in both; did you make any considerations in your analyses for this? What does OP stand for? It doesn't appear to be in your footnotes.
Supplementary table 4: what do the notes in parentheses refer to? I see the definitions in the footnotes but I don't understand the relevance here and in other tables. Please include the n of each study and the total n in this table as it is crucial for interpretation of these analyses.
Supplementary figure 1: please include total n. Tables should be stand alone.
Supplementary figure 4: sugars-sweetened, do you mean sugar sweetened? This occurs more than one in the manuscript.
Supplementary figure 7: change in font.
Supplementary figure 14: unit for age is missing

Additional Questions:
Please enter your name: Laura O'Connor

Job Title: Lecturer

Institution: Manchester Metropolitan University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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