** Comments from the external peer reviewers**

REFEREE COMMENTS

**Reviewer: 1**

Recommendation:

Comments:
**The authors have addressed almost all of my comments. This is a very thorough work; and in my view, will clearly inform the debate about the role of fructose in the most optimal pattern of human diets in relation to health outcomes.**

*Many thanks for your comment.*

There are only a couple of minor issues that they may care to consider in the final manuscript (and to set the record straight):

1. Introduction - reference 3 is only a commentary - I believe the original ecological analysis was first done by Gross et al. AJCN 2004 whee frutose and dietary fibre were first identiied as the two most significant predictors (one bad and one good) for obesity and diabetes in the US https://academic.oup.com/ajcn/article/79/5/774/4690186

*Many thanks for your observation. We have added this reference (reference #3).*

2. Discussion about mechanisms: This section is a bit weak; I would recommend a couple of references which they care to consider (Liu et al. GL and HDL and TG) as I view lipids/TG as the most consistent and significant biomarkers of insulin resistance.

Thank you for this suggestion. We agree that triglycerides and HDL-C are particularly reliable "clinical" markers of insulin resistance. We have added the suggested references with some supporting text to the discussion (P26, L578-580, references #161-162)

3. Conclusion: If the effects of fructose on cardiometabolic health outcomes really are energy and food sources dependent (as they conclude based on this 160 trials meta-analsyis), then it seems to me that the effect from those food sources must be beneficial to counter the adverse effects directly from fructose per se as preciously reported in sugars sweeten soft drinks. Further,

I think they should venture to provide further rationale to test different food sources in a large trial (how long?).

*We agree with the reviewer's interpretation that effect of some food sources (such as fruit in our synthesis) must be beneficial to counter-balance the harmful effects of others (such as SSBs providing excess energy in our synthesis). We have added a statement that there may be a rationale to test whether food sources with a signal for benefit, such as fruit, have "counter-balancing" advantages for glycemic control in a large high quality trial over the longer term (≥ 6 months). (P32, L720-722)*

Additional Questions:
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A fee for organising education?: No

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Reviewer: 2

Recommendation:

Comments:
BMJ.2017.038661.R1

General comments:
This a well conducted systematic literature review and meta-analysis, on an interesting and important topic. The amount of work involved in extracting data from such a large number of, probably quite messy and heterogeneous, studies is not to be under-estimated.

*Many thanks for your support.*

Major comments:
1. My main concern is the quality of evidence identified, to the extent that the conclusions might place more emphasis on the lack of high quality evidence. In particular, the was a paucity of properly conducted randomised controlled trials.

*We agree* that there is a paucity of properly conducted randomised controlled trials. *Our GRADE assessments for the certainty of the evidence were generally low across the outcomes. We have reinforced this point in the conclusions of the abstract (P5, L117-118) and main paper(P32, L718-722)* .

2. The authors have included reports containing both randomized and non-randomized controlled trials. It is not usual to combine different study designs like this, because we would anticipate this to be a source of heterogeneity.

*We agree that combining randomized and non-randomized controlled studies may be a source of heterogeneity. We did consider restricting our analyses to randomized controlled studies but felt that to exclude non-randomized controlled studies would be to discard valuable information, especially as the question was one of harm of different food sources. There was a large amount of valuable data from non-randomized studies that were otherwise well-controlled, and the randomization status of many of these studies was "unclear", owing to poor pre-CONSORT reporting requirements, and so an important proportion of these studies may have in fact been randomized or quasi-randomized, ensuring a balanced distribution of any prognostic confounders. We felt confident in prespecifying an approach that combined these designs, as we have combined randomized and non-randomized controlled studies in our previous systematic reviews and meta-*

*analyses related to sugars and cardiometabolic risk and have never found any evidence of effect modification. We did perform subgroup analyses by randomization in our present systematic review and meta-analysis and again found no evidence of effect modification with both designs giving very similar effect estimates.*

3. Similarly, more emphasis should be placed on the heterogeneity between the studies, which is >80% for some main results.

*We agree that heterogeneity is a very important consideration in our synthesis. Serious heterogeneity or "inconsistency" (based on evidence of substantial unexplained heterogeneity, I2≥50%) was one of the 5 criteria we used to downgrade the evidence as part of our GRADE assessments (P13, L277 and Table 2). Most of the evidence for HbA1c, fasting glucose, and fasting insulin based was accordingly downgraded for "inconsistency" based on this a priori criteria. We also dedicated a section to sources of heterogeneity (P22, L482-493) and emphasized heterogeneity as an important limitation (P30, L680-685) in our Discussion.*

4. The literature review is complete up to May 2017, which is nearly a year ago. It is more usual for systematic reviews to present results that are more up-to-date than this. However, I recognize the enormity of the task.

*Thank you. We agree and have updated the search to April 25 2018 (Abstract, P4, L79; Methods P9, L171-172; Figure 1).*

5. The forest plots and super plots should all have units on the horizontal axis. Otherwise the reader cannot tell how big or small any effect might be. This should be the whole point of the review. But just as important, all the key results lack units for the intervention. So we have a 0.18% reduction in HbA1c, but no way of knowing if this is for an impossibly large or realistically small intervention. This information should be more prominent in the results and abstract, otherwise the reader has no context for how easy it is to achieve that 0.18%.

*Many thanks again for this comment. We certainly agree with the importance of displaying the units. It may not have been readily noticeable but all of our figures (super plots and forest plots) display the outcome and units in the column headings at the top of each forest plot and super plot (as per Cochrane Collaboration formatting using RevMan software). These headings, however, were not carried over in the forest plots displayed over multiple pages in the supplementary material. We have now corrected this issue throughout. If the reviewer and editors would prefer this information below the horizontal axis, then we would be pleased to reformat our figures.*

*We also agree with the need to clarify the HbA1c units. These are absolute HbA1c units. That is, they represent an absolute reduction not a relative reduction in HbA1c. We have clarified this throughout.*

6. Results in the abstract and text focus on those that are statistically significant, rather than interventions and outcomes that were specified beforehand. For example "There was no significant effect in addition studies" is not supported with an estimate and confidence interval in the text. The result is that the results are not presented systematically, and the reader is steered towards the statistically significant results rather than the clinically important ones.

*We agree that the results are suboptimally presented in the abstract. We have struggled with presenting such a large amount of data in such a short format. One of the issues was our prespecified aim to look at the role of different food sources within 4 different levels of energy control. This approach led to a large number of comparisons to interpret and summarize. We have rewritten the abstract with a view to being more systematic (P4-5, L90-111).*

7. Whilst a large number of studies are included overall, the number for each separate analysis are still quite small, especially given the small size of many of the studies.

*We agree that number and size of the studies included for each separate analysis is quite small. We have presented this point an important limitation in the discussion (P27, L?). We have also called for more large, high quality randomized controlled trials to assess the effect of different food sources in the conclusion (P 32, L718-722).*

8. I'm afraid I didn't follow the argument for the conclusions that energy control and food source appear to mediate the effect of fructose-containing sugars on glycemic control. I felt the conclusions should place much more emphasis on the lack of good evidence. Having said that, the conclusion that "more studies are needed" is disappointing given the work involved, and means that this review is not a seminal work.

*Thank you for this important point. Although we agree that lack of good evidence gives us low certainty of the evidence, we feel that we still need to provide an answer to the question we set out to answer in the context of this context. That is, what is the effect of food form and energy control and how certain can we be in drawing any conclusions? We feel that the data does suggest that energy control and food form appear to be important mediators of the effect but acknowledge that the evidence on which this conclusion is based is of generally low certainty and, thus, more large, high quality randomized controlled trials are required. We have reworded the conclusions to make these points stronger in the abstract (P5, L117-118) and the main text (P32, L717-722).*

Minor comments:

9. The abstract and text are quite wordy. I suggest that some of the sensitivity analysis could be moved to supplementary material.

*Thank you for the excellent suggestion. We agree that the description of the sensitivity analyses and much of the subgroup analyses is quite dense and wordy. Rather than move some of the*

*description of these results to the supplementary material, we have revised the text for brevity in the Abstract (P5, L90-111) and the Results for HbA1c (P16, L336-348), fasting blood glucose (P17-18, L367-391), and fasting blood insulin (P20-21, L442-470).*

10. HbA1c values should be reported using the IFCC units (mmols/mol) instead of, or alongside, DCCT units (%).

*We agree that this added information may be useful to some readers but have added these units alongside the DCCT (%) units in the text of the abstract (P4, L92) main results (P14, L308). We used https://www.diabetes.co.uk/hba1c-units-converter.html to convert the units from % to mmols/mol.*

11. The manuscript needs the PRISMA checklist submitted alongside it. In such a long document, this is particularly helpful.

*We agree completely with the need for a PRISMA checklist. We did submit a PRISMA checklist and will resubmit it with the revised version of the manuscript and our responses (Appendix).*

12. I was uncomfortable with the assertion that DerSimonian and Laird random effects meta-analysis, yield conservative confidence intervals around effect estimates in the presence of heterogeneity. This implies that the resulting estimates therefore err on the side of caution. However, that's not necessarily the case. The random effects analysis tends to give greater weight to smaller studies. This may not yield the best pooled estimates. Furthermore, the wider confidence intervals simply reflect the greater uncertainty in the pooled estimate introduced by the inconsistency in results across included studies. The modelling process assumes that there is no one correct pooled estimate, but a distribution of correct estimates. The pooled estimate quoted is then the mean of that distribution of correct estimates. It does not pretend, therefore, that there is one right answer. The authors should therefore be more cautious in their interpretation of these estimates.

*The reviewer makes important points about the interpretation of DerSimonian and Laird random effects models. We agree that this model does imply a distribution of correct estimates with an estimated mean of this distribution that does not necessarily represent the "correct" answer. We prespecified this model, however, given the nature of the study units. It is unlikely that the studies are functionally equivalent being performed by different researchers under different trial conditions using food which can differ substantially even within categories based on their matrices, preparation, and pattern of consumption. The participants and other aspects of the interventions are also likely to have differed in ways that would have influenced the results of these studies, making random-effects more generalizable across populations and possible interventions. Although fixed effects models would have been much harder to justify in this context, we agree that it might be an overstatement to suggest random effects models yield more conservative estimates. We have removed this description of the models from our Methods (P12, L242-243) and*

*believe that we have been cautious in our interpretation by also considering fixed effects models when <5 studies were available (owing to the inability to calculate tau2 reliably with small numbers of studies) and by the application of GRADE in the interpretation of all pooled summary estimates.*

13. I-squared presents between-study heterogeneity as a proportion of total variation. It is good practice to present the absolute heterogeneity too. An easy way of doing this is to quote the range of observed estimates.

*We agree that a measure of the absolute heterogeneity would be useful. As suggested we have added the range of observed point estimates to the reporting of heterogeneity in the narrative of the results throughout.*

14. The order in which the studies are presented in the forest plots would be better either chronological or alphabetical. The current order is unclear.

*Many thanks for your comment. We agree that the forest plots are better presented in chronological or alphabetical order. They are already presented alphabetically within each fructose-containing food group. The fructose-containing food groups themselves, however, are not presented in alphabetical order.*

15. The forest plots and super plots should all have units on the horizontal axis. Otherwise the reader cannot tell how big or small any effect might be. This should be the whole point of the review.

*Many thanks again for this comment. We certainly agree with the importance of displaying the units. It may not have been readily noticeable but all of our figures (super plots and forest plots) display the outcome and units in the column headings at the top of each forest plot and super plot (as per Cochrane Collaboration formatting using RevMan software). These headings, however, were not carried over in the forest plots displayed over multiple pages in the supplementary material. We have now corrected this issue throughout. If the reviewer and editors would prefer this information below the horizontal axis, then we would be pleased to reformat our figures.*

Additional Questions:
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Reviewer: 3

Recommendation:

Comments:
As already mentioned in my first review, I think that Choo et al present here a very good analysis of the effects of fructose containing sugars on markers of glycemic control. This revised version has adequately addressed my initial questions, and has been altogether much improved through the input of all reviewers. It is most useful for medical practitioners since it very nicely addresses the issue of food sources as used in nutritional recommendations.

*Many thanks for your support.*

I have only a few minor comments
1) line 488-489: it should be specified here that recommendation of WHO and SACN regard added and free sugars, not total (which basically corresponds to total minus fruits for free, minus fruits and 100% fruit juices for added)

*Thank you for this important point. We have added these clarifications to the text of the Discussion (P24, L542-545) and defined "free" versus "added" sugars in the introduction (P8, L156-157).*

2) the paragraph on "catalytic effects" line 543-554 has been improved. I however still feel that it may be more confusing than informative to the reader first because the term catalytic may falsely suggest that it is operative only with small fructose doses; second because an increased glycogen synthesis may indeed lower postprandial blood glucose, but the fate of hepatic glycogen, and ist impact on blood glucose later during the day remains unknown. In my opinion, deleting it would do no harm to the article and remove a source of confusion to the reader, but leavs it to the authors and editors choice!

*We agree that the so called "catalytic effect" of fructose remains somewhat unclear. We have even just published two new randomized controlled trials that failed to demonstrate this mechanism acutely in people with and without diabetes. That being said, as it is often invoked as a mechanism to explain the ability of fructose to improve postprandial glycemia and glycemic control, we feel that it merits discussion with these caveats made clear. We have corrected the statement regarding the role of small doses, described the lack of data on the fate of the increase in hepatic glycogen and its ability to influence blood glucose later in the day, and highlighted recent contradictory findings (P27, L599-611).*

Additional Questions:
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Reviewer: 4

Recommendation:

Comments:
The authors have come back with a substantially revised manuscript - and generally responded satisfactorily to concerns.

*Many thanks for your support.*

One final point though. The authors have updated their search, but given the time the authors have taken to update/revise the paper, the search is still 11 months out of date (as of today), and thus will be >1 year out of date if and when published.

*Thank you for your comment. We agree completely with the need to update the search. We have updated the search through April 25 2018 (Abstract, P4, L79; Methods P9, L171-172; Figure 1).*

Additional Questions:
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