

BMJ - Decision on
Manuscript ID
BMJ.2017.038661.R
1

Body:

16-Apr-2018

Dear Dr. Sievenpiper:

Manuscript ID BMJ.2017.038661.R1 entitled "Food sources of fructose-containing sugars and glycemic control: A systematic review and meta-analysis of controlled intervention studies in people with and without diabetes" which you submitted to BMJ,

Thank you for sending us your paper. We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise your paper as explained below in the reviewers comments. We are provisionally offering acceptance but will make the final decision when we see the revised version. The comments from the reviewers and general requirements for submission are available at the end of this letter.

We are looking forward to reading the revised manuscript and, we hope, making a final acceptance decision.

Please note that the BMJ might choose to shorten content or replace or re-size images for the print issue.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Yours sincerely

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com,

** 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.

. 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 fructose and dietary fibre were first identified 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>

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.

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-analysis), 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 previously 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?).

Additional Questions:

Please enter your name: Simin Liu

Job Title: Professor and Director

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: 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.

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, there was a paucity of properly conducted randomised controlled trials.

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.

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

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.

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%.

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.

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.

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 glycemc 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.

Minor comments:

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

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

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

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.

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.

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.

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.

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: 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.

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)

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 its 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 leaves it to the authors and editors choice!

Additional Questions:

Please enter your name: Luc TAPPY

Job Title: Professor of Physiology

Institution: University of Lausanne

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

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Reviewer: 4

Recommendation:

Comments:

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

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.

Additional Questions:

Please enter your name: Gary Collins

Job Title: Professor of Medical Statistics

Institution: University of Oxford

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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