

02-Oct-2018

Dear Mrs. Toews,

Manuscript ID BMJ.2018.046063.R1 entitled "NON-SUGAR SWEETENERS AND HEALTH: SYSTEMATIC REVIEW AND META-ANALYSES OF RANDOMISED, AND NON-RANDOMISED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES"

Thank you for sending us your revised paper.

I sent your paper back to one of the previous reviewers, who has some remaining concerns. I am not certain the different viewpoints can be reconciled, but perhaps you can give some thought to more fully acknowledging the point of the reviewer in your discussion.

Thanks!

Elizabeth Loder, MD, MPH
eloder@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: xxx (chair), yyy (statistician), [and list other eds who took part]

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:

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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.

Thank you very much for processing our manuscript so quickly. We appreciate the opportunity to revise the manuscript once more and address the peer reviewer's concern. Kindly find our response below in italics.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:

The authors have made strong and convincing arguments in regards to my first concern. The authors' main argument regarding my second concern regarding inclusion and exclusion criteria, and related concerns from other reviewers, is that the search process was specified a priori by a WHO expert panel and that this review is closely following their instructions.

While I understand that the authors are working within the constraints of a very specific mandate from WHO, I remain very concerned about the decisions regarding inclusion and exclusion criteria, in particular the decision to include only studies where the NSS was "sufficiently specified." As I argued in my initial review, this decision will likely leave out of the review most of the literature evaluating the association between artificially sweetened beverages and major chronic diseases. For example, with the criteria used the authors are able to identify two RCTs evaluating the effect of NSS on glycemic control described under the heading "Diabetes/glycemic control" and three RCTs evaluating the effect on blood pressure but no studies evaluating CHD as an outcome. Collectively these five trials included fewer than 300 individuals. This specific search criteria, however, left out of the review at least one prospective cohort study of 40,000+ individuals followed for over 20 years evaluating the association of diet sodas with incidence of CHD (de Koning et al. Circulation 2012). There are likely to be many more papers like this, especially since BMJ published in 2015 a systematic review summarizing data from 10 prospective cohort studies on the relation between artificially sweetened beverages and incidence of type 2 diabetes (Imamura et al BMJ 2015). The impact of that seemingly innocuous decision can be major and is likely much larger than as described by the authors in their revised discussion of the findings.

Thank you very much for your effort to review our manuscript and drawing our attention to the issue of inclusion and exclusion criteria for the review. In establishing the inclusion and exclusion criteria, concern was noted regarding studies in which exposures or interventions were described simply as diet beverages, diet soda, non-sugar-sweetened foods or drinks, etc. Such descriptions left too much uncertainty in terms of what was actually being consumed in studies employing these terms, e.g. did such foods and/or beverages contain no sugars or just reduced sugars; did they contain sugar alcohols (studies assessing sugar alcohols were not included in this review); or, in the case of beverages, were they simply water, or other unsweetened beverages. Therefore, the inclusion of studies employing vague terms to describe exposures or interventions might result in the inclusion of studies that were not entirely relevant to specific questions being asked about non-sugar sweeteners as defined in the inclusion and exclusion criteria.

Still, we take your concern very seriously and fully agree that long term data are crucial to draw conclusions on several outcomes of our review. We have revised our discussion section to reflect more clearly that there are additional studies that hold important data on the relation between health and non-nutritive sweeteners and that the included studies on the outcomes in question have limitations. The section now reads as follows (p. 20): "There are a few large prospective cohort studies⁹⁸⁻¹⁰² with long term follow-up that investigated the association of NSSs with different health outcomes. However, NSSs under investigation were not sufficiently specified to match the inclusion criteria of this review. Still, their results indicate an increased risk of higher BMI, higher risk of type-2 diabetes with higher NSSs

consumption or lower risk of cardiovascular disease with intake of artificially sweetened sodas compared to sugar sweetened sodas, respectively. Partly, these results conflict with the ones from the findings of this systematic review. Included studies investigated long term health outcomes for a relatively short duration, e.g., cardiovascular health^{29 33 37-39 44 47 48 71 72 85 86} outcomes or diabetes^{35 37 39 44 72 83} investigated for six months or less. Long term studies with sufficient statistical power are key to investigating long term health outcomes such as incidence of diabetes or cardiovascular health. Hence, it is desirable that the results of large, long term cohort studies are verified by studies which specify the type of sweetener used."

Additional Questions:

Please enter your name: Jorge E Chavarro

Job Title: Associate Professor of Nutrition and Epidemiology

Institution: Harvard School of Public Health

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

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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If you have any competing interests (please see BMJ policy) please declare them here:

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c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

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v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

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g. Footnotes and statements

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