BMJ - Decision on
Manuscript ID
BMJ.2018.046063

Body: 21-Aug-2018

Dear Mrs. Toews,

I write regarding Manuscript ID BMJ.2018.046063 entitled "Health Effects of Non-sugar Sweeteners: Systematic Review and Meta-analysis"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We are interested in proceeding with it and hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, after which we will make a final decision about the paper.

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.

Please let me know if I can be of any assistance during the revisions process.

Very truly yours,

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.

Decision: Put points

Present: Jose Merino (chair); Angela Wade (statistician); Wim Weber; Tiago Villanueva; Sophie Cook; Elizabeth Loder
Decision: Cautious put points with Sievenpiper to see the revision

* We thought this was a timely review since this topic is widely debated and it is probably useful to summarize the state of the evidence and identify what sort of research needs to be done.

* Is it possible to put some additional numerical results in the abstract? We find that citations and usefulness of the abstract are increased if top-line citable numbers are included there. The abstract should contain some effect estimates.

* We think you are somewhat overly critical of the importance of your findings. Despite the low level of certainty in the evidence presented, the findings are important and there do seem to be some clinical implications. This is the most

rigorous review to date of a very important matter, so it seems reasonable to conclude that on the basis of existing information there is no compelling evidence of health benefit and a suggestion of possible harm from these substances.

* Can you be more specific about the exact research question(s) this review attempts to answer. One of the editors felt is was somewhat unclear.

* It would be helpful if Table 2 included the outcomes studied

* We agreed with reviewer Cornelius re the emphasis on effect when the majority of trials are observational, you should be careful to attribute such terminology to the RCT results only.

* We were concerned about the comment regarding the inclusion criteria and comparisons made.

* Is there a reason that publication bias was not assessed, or did we miss it?

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where (page number) you have dealt with them in the paper. Please return both a track changes and clean version of the manuscript.

Comments from Reviewers

Reviewer: 1

Comments:
"Health Effects of Non-sugar Sweeteners: Systematic Review and Meta-analysis" aims to assess the effects of non-sugar sweeteners on different health outcomes in subgroups of the population. My major concern is that it's premature to re-assess the literature as very little new data has become available which has not already been assessed by others.

1. Few outcomes of interest were amendable to meta-analysis and several of these have been reported in prior systematic reviews and meta-analysis. Azad et al 2017, 'Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies' (CMAJ), for example, included reports <= January 2016, just 4 months short of the current submission. Their conclusions concerning observational studies were also different than those reported in the current submission. The submitting authors discuss other systematic reviews/meta-analysis but not this recent and more applicable report by Azad et al. The current submission only reiterates limitations of previous systematic reviews and this is the lack of quality data to inform robust conclusions.
2. An important critic of the Azad et al report by Sievenpiper et al, 'The importance of study design in the assessment of nonnutritive sweeteners and cardiometabolic health' (CMAJ 2017) is also applicable to the current submission and the authors should discuss this limitation if not address it in the analysis.
3. Because few studies were amendable to meta-analysis much of the paper is simply reciting results from individual studies and thus does not constitute an effective systematic review.
4. Observational studies report 'associations' and not 'effects'. The title and full-text needs to be revised to consider appropriate terminology. This is important since 35 of the 57 studies examined were non-RCTs. The latter should also be stated in the abstract, which together with the title incorrectly suggests the report is largely weighted by RCTs.
5. Authors switch between NNS and NSS throughout. This is confusing.

6. Duration of trial would of course impact difference in total energy intake (Figure 1). Is there another approach to the meta-analysis that directly accounts for duration? Perhaps, energy intake/day.

Additional Questions:
Please enter your name: Marilyn Cornelis

Job Title: Assistant Professor

Institution: Northwestern 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

Fees for consulting?: No

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Reviewer: 2

Comments:
This meta-analysis aims at assessing the health-related effects of non-nutritive sweeteners in adults and children. It is both timely and relevent in the present context of very high obesity prevalences in many countries, and also in the present controversies regarding potential adverse effects of these compounds.
The meta-analysis (litterature search, identification of questions, data extraction, etc.) appears to be state of the art, and is very well presented. The major conclusion is that there are presently few studies addressing these effects, and that levels of evidence for beneficial/adverse effects are low. It has the great merit of underlying the need for structured research in this field.
I have only two minor comments:
1) the use of non-sugar sweeteners throughout the paper is somewhat confusing, since sugar alcohols for exemples are non-sugar sweeteners. The classification used in fig p 28 (nutritive- vs non nutritive sweeteners is more appropriate. It would be useful also to briefly describe this class in the text.page 13, line 31 et seq: one may consider mentioning together with the weigth loss associated with intervention, the duration of intervention and the total excess weight of participants (ie is a 1.99 kg weight loss clinically significant)

minor comment: Table 2, study three (blackburn): control mentions avaidance of NNS (non-nutritive or non-sugar sweeteners)

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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Speaker fees from Nestlé SA, Switzerland
Research funds from Soremartec Italy srl
Consulting fees from Millenium pharmaceuticals Inc, USA

Reviewer: 3

Comments:
This manuscript by Toews and colleagues presents the results of a systematic review and meta-analysis of studies evaluating the effects of of the health effects of non-sugar sweeteners. Overall, this is a very comprehensive summary of the literature that should be useful to clinicians, regulators and health agencies. The breadth of scope of this review, all health outcomes, is ambitious and results in limited discussion of the findings given space restrictions but this is not necessarily a major concern given the scarcity of data for most health outcomes. The paper does suffer from other important limitations, however, which fall into two categories as detailed below.

1. The authors have compared the effects of NSS against any alternative, including comparisons against caloric sweeteners, other non-caloric sweeteners, any type of sugar, no interventions, placebos or water. While this strategy will allow the inclusion of a larger number of studies it has the problem that it will does not allow for the separation of caloric effects (i.e. effects due to decreased caloric intake when replacing caloric sweeteners including plain sugar) from non-caloric effects (i.e

effects due to specific NSS attributable to its inherent molecular structure/biological activity). Given the scarcity of the data for most health outcomes examined this is, for the most part, more a theoretical issue deserving of comment in the discussion section than a practical one. However, for some outcomes, there appears to be enough studies to provide estimates that can separate caloric from non-caloric effects. For example, for the estimates for the effect on body weight (summarized in Figure 3), which are described in the text as estimates from RCTs comparing NSS against sugars or placebo, there appears to be enough studies to provide separate estimates for comparison against other sugars (caloric effect) and against placebo (non-caloric effect). At minimum, there will be enough data to provide estimates for one of the two strata. A similar situation may be at play in the report of effects on blood pressure.

2. The authors state that only studies were the type of NSS was "sufficiently specified" were included in the review. While this choice seems logical at first sight it is likely to leave out of the review the majority of large population-based prospective cohort studies that are sufficiently large and have enough statistical power to actually be able to address questions of the relation between NSS and common health outcomes (e.g. CVD, diabetes, common cancers). This is because the overwhelming majority of these studies would describe the main exposure to NSS as intake of "diet sodas," "diet beverages," or related terms rather than describe the specifc NSS since, in practical terms, most beverages within a specific market will use a very limited number of NSS for sodas (arguably the most important source of between-person variation in NSS intake) and therefore describing the exposure as "diet soda" is almost as good as mentioning the predominant NSS used in that country's market during the study period. While this major limitation (potentially ignoring the majority of the data by this one choice) could be forgiven if the goal were to try to identify the difference in non-caloric effects of different NSS (e.g. does aspartame have different health effects than saccharin or sucralose) the authors not only make no effort to present such contrasts but also the available data does not appear to be sufficient to make them. Thus, all the comparisons presented are, de facto, providing an estimate of the effect of NSS as a class rather than as individual molecules. Given this, why then make a decision that can lead to ignoring the majority of the data? The authors themselves suggest that this choice could have directly led to a major limitation of their study. Specifically, in the last paragraph of the discussion they correctly point out the studies identified in this review may not reflect exposure to NSS in real life. Including studies of how NSS are used in real life might help. Doing so may also address some of the issues articulated by the authors in the next to last paragraph of the discussion. In my opinion, this specific decision is a very clear example of how some meta-analyses can actually hinder, rather than advance, knowledge.

Additional Questions:
Please enter your name: Jorge 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

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Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 4

Comments:
Review of BMJ.2018.046063
TITLE: Health Effects of Non-sugar Sweeteners: Systematic Review and Meta-analysis.

General remarks.

This manuscript concerns a systematic review of the effects of non-nutritive sweetener (NNS) consumption on various health outcomes in healthy adults and children as well as overweight populations in weight loss studies. Standard Cochrane review methodology was adopted. The authors stated that they prepared this review in order to inform a WHO guideline on the use of NNS, and to provide information on implications for actions by health experts and policy makers. The main outcome variables examined included body weight, Diabetes/ glycemic control, eating behavior, cancer, and blood pressure. The essential outcomes of the systematic review is that out of the 56 studies that were included in the analysis, there was no statistically significant difference in the key output variables obtained between groups consuming NNS versus those not receiving NNS, or consuming lower doses (page 18). The strengths and weaknesses of the present analysis were discussed in relation to similar publications; and unanswered questions, together with future research challenges were briefly outlined. In particular the authors pointed out the difficulty in reliably estimating individual sweetener intake/dosage since manufacturers routinely use several different sweeteners in any given product, although the present analysis included mostly single-sweetener data which may not accurately reflect true NNS exposure.
The manuscript is a continuation of preliminary research published last year, and of importance to policymakers. The research question was clearly defined, overall study design appropriate and methodology adequately described. References are up to date, Abstract is clearly written.

Specific comments.

1. In the Discussion the authors cite their preparatory mapping review containing 372 datasets for analysis, which was published the previous year. The authors discuss the reasons why the present systematic study selection contains fewer datasets in the final analysis. This involved excluding studies which did not provide sufficient information on the experimental design, or lacked other reporting

details (page 18). Another issue under discussion was an inability to compare the effect of different doses of NNS in children, therefore the authors could not assess the effect of dosage on any particular health outcome variable. Comparisons of the health effects of high dose NNS intake versus low dose intake in adults and in children were numbers 2 and 5 out of the 6 stated research questions the authors sought to answer (page 5). Given the fact that the authors had previously carried out the preparatory review and must have known that the majority of data sets available for analysis did not contain dosage and frequency information, how realistic were these two questions? Secondly, the relevance of these 2 questions in the present manuscript can be questioned on the grounds that ascertaining dose-related health outcomes may likely not have been part of the stated aims of the original studies from which the present analysis is derived. It is a moot point as to whether these 2 questions should have been part of the Introductory 6, or placed in the Discussion of unanswered questions for future studies.

2. The preparatory mapping review on health outcomes of NNS (ref 93) included data from diabetic populations. However in the present study, diseased populations (including diabetics) and pregnant women were excluded. Could the authors expand on the justification for these exclusions, particularly since the 2nd health outcome variable present in the Results section (after body weight) is labeled 'Diabetes/glycemic control'. Diabetic patients are often advised by healthcare professionals to reduce sugar intake where possible, and indeed the American Diabetes Association released a statement recommending the use of NNS. Therefore for this vulnerable population, data on health outcomes relating to NNS consumption is arguably particularly relevant.

3. Including the term 'pregnant women' in the same sentence as 'diseased populations' may be construed as a little insensitive. Although there have only been 2 studies which demonstrated an association between infant overweight and prenatal NNS exposure (whilst 3 others showed no association), the data indicating that a significant percentage of pregnant women consume NNS-sweetened products (Archibald AJ et al, 2018), suggests that it would have been informative to include these studies in an analysis, or at least point to the necessity for future well-constructed research in this area.

4. For the 'unanswered questions and future research' section, the first recommendation was that future studies assessing the health effect of NNS should have an intervention period of at least 7 days (page 19 line 38). At first I thought this was a typo, but then it also appears in the Abstract. It is hard to see how any measurable changes in the health output variables used in this study (Body Weight, Glucocentric/Diabetes control, Energy intake, Cancer, Blood pressure) could occur after just 7 days, or even weeks of exposure. Is the 7 days a subjective or objective recommendation?

5. The second recommendation is for transparency and precision in reporting type and dosage of NNS in future studies (I'm assuming authors were not referring to animal research). This is rather superficial and not at all easy to achieve, since the manufacturers themselves do not give dose/quantity data on their products, and as pointed out already many products contain a mixture of NNS to contribute to overall consumer taste satisfaction. Many of the NNS consumption/health outcome studies were excluded from the present analysis for failing to report the type & dose of NNS. This should not be viewed entirely as a criticism of study designers, since so-called 'diet' soda and 'sports' beverages from which a significant portion of NNS exposure is derived contain a heterogeneous mixture of different NNS, with one product containing mixture A in ratio B, while another brand/flavor has a different mixture/ratio. Table-top NNS do not all contain the same type of NNS either, making retrospective studies very difficult to accurately establish type/dose of NNS exposure. Equally, designing human intervention studies mimicking today's NNS usage would be a challenge for the aforementioned reasons. Perhaps the authors could expound on this a bit more. Should the authors be recommending more transparency from product manufacturers?

6. Lastly, future recommendations should include targeting the research towards the populations who are most at risk of NNS exposure: Diabetics (since they are often advised to reduce sugar consumption and encouraged to consider NNS as a substitute); children (always enthusiastic consumers of diet beverages and sugar-free candies/gum); and pregnant women, since the health outcome for offspring exposed to NNS in utero is far from clear.

Additional Questions:
Please enter your name: Kate S. Collison

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Institution: King Faisal Specialist Hospital & Research Centre

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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