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.

We thank you very much for your interest in our manuscript. We appreciate your consideration of its strengths and its potential for improvement. The comments made by the editorial conference and the peer reviewers are very valuable to us and we gladly considered them in the revision of our review. Please find our responses below in italics. All page numbers refer to the marked copy of the manuscript.

* 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 gladly added numerical data to the abstract as follows:

"Our search resulted in 13941 unique records. 67 references, reporting on 56 individual studies provided data for this review of which 35 were observational studies. In adults, there was evidence of very low and low certainty from a limited number of small studies for a small beneficial effect of NSSs on BMI (MD -0.6, 95% CI –1.19 to -0.01, 2 studies, n=174), fasting blood glucose (MD -0.16 mmol/l, 95% CI -0.26 to -0.06, 2 studies, n=52), energy intake (MD -1064.73 kJ, 95% CI -1867.03 to -262.44, 4 studies, n=278), sugar intake (MD -89.71 g, 95% CI -127.63 to 51.80, 3 studies, n=135), and blood pressure (systolic: MD -4.90 mmHg, 95% CI -9.78 to -0.03; diastolic: -3.27 mmHg, 95% CI -7.21 to 0.67, 3 studies, n=202). Lower doses of NSSs were associated with lower weight gain (MD -0.09 kg, 95% CI -0.13 to -0.05, 1 study, n=17934) compared to higher doses (very low certainty of evidence). For all other outcomes no differences were detected when comparing no NSSs usage to NSSs usage, or comparing different doses of NSSs. There was no evidence of any effect of NSSs on overweight and/or obese adults actively trying to lose weight (very low to moderate certainty). In children, a smaller increase in BMI z-score was observed with NSSs intake compared to no intake (MD -0.15, 95% CI -0.17 to -0.12, n=528, moderate certainty of evidence), but no significant differences were observed in body weight (MD -0.60 kg, 95% CI -1.33 to 0.14, 2 studies, n=467, low certainty of evidence), or when comparing different doses of NSSs (very low to moderate certainty). There was no evidence of any effect of NSSs on overweight and/or obese children actively trying to lose weight (very low to low certainty of evidence)."

* 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.

Thank you for highlighting your understanding of the review findings and their importance. We agree and added the following in the beginning of the discussion (p. 19): "This review constitutes the most comprehensive systematic review of a broad range of benefits and harms of NSSs in a generally healthy population of adults and children. It follows rigorous systematic review methods. Overall, we included 56 studies in adults and children, which assessed the associations and effects of NSSs with/ on different health outcomes. For most outcomes there seemed to be no statistically or clinically relevant difference between those being exposed to NSSs and those not being exposed to NSSs or being exposed to lower doses of NSSs. There was no compelling evidence for health benefit from NSSs and potential harms could not be excluded. The certainty of the included evidence ranged from very low to moderate and our confidence in the reported effect estimates is accordingly limited."

* 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.

We appreciate your concern and would like to amend the respective section to be more precise. However, the review is very broad in scope, so are the review questions. We used the PICO format to phrase the questions. The questions contain information on all four aspects, i.e. general/healthy population (Population), consumption of NSSs (Intervention), no NSSs consumption(Comparator), relevant health outcomes (Outcome). What is meant with relevant health outcomes is described in the methods section (p. 6) in order to keep the introductory section brief. We are open to suggestions on how to improve the reporting of our research questions more precisely.

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

We added information on the outcomes from primary studies, relevant to this systematic review to table 2 (starting p. 19).

* 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 appreciate the detailed comment and have revised the wording in the entire manuscript and the title. The new title reads: "Non-sugar sweeteners and health: systematic review and meta-analyses of randomised, and non-randomised controlled trials and observational studies"

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

We understand the reviewers' and editors' comment about the in- and exclusion criteria as well as the issues regarding reporting of the review's research questions in the introductory section. Both aspects are dependent on the guideline process this review is a part of; the review will inform a global WHO guideline on use of non-sugar sweeteners (NSSs) in a general, healthy population of adults and children. The guideline process follows the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach where research questions are drafted prospectively by an expert panel (here WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on diet and health). Furthermore, the panel also provided input on relevant in- and exclusion criteria for primary studies. This process has led to the review conceptualization as reported in the manuscript (systematic review protocol registered at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017047668*). In order to clarify this, we have added the following to the introductory section (p. 4f): "The World Health Organization (WHO) is developing guidance on the use of NSSs by adults and children based on the evidence generated by this systematic review. Following the guidance of the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health this review seeks to comprehensively assess the relationship between commonly consumed NSSs and health by addressing the following research questions:"*

*And the methods section (p. 5): "*The inclusion and exclusion criteria for this review were established prospectively and were based on their relevance for a WHO global guideline for use of NSSs by a generally healthy population.*"*

Kindly, also see our responses to the individual reviewers' comments on these issues below.

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

During the review process we considered dissemination bias and tried to decrease its effects on the review by e.g. searching for relevant studies in study registries and considering the effect of the funding sources of the primary studies. Further, we had planned to statistically assess our results for publication bias, but the low number of studies did not allow for a proper assessment of this bias. In the manuscript we address this issue as follows on page 7: "We planned to create funnel plots when data of ten or more studies were available to assess the likelihood of dissemination bias. Since none of the meta-analyses included ten studies or more, a thorough assessment of dissemination bias was not feasible." An assessment of dissemination bias is also part of the GRADE assessment that was conducted for all outcomes of this review.

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.

Thank you very much for your insightful comments and your suggestions to improve our manuscript. We agree that the systematic review by Azad et al. is relevant to the broad field of research and we added a brief description of their results to our discussion section. On page 20 it reads as follows: "A recent systematic review by Azad et al. found no statistically significant effect of non-nutritive sweeteners on BMI, body weight, fat mass, waist circumferences and HOMA-IR."
However, we were cautious in comparing our results to results of other systematic reviews in the field, because the research questions and clinical inclusion criteria differ among the reviews and do not allow for a straight comparison of the different pieces of research. The review by Azad et al. for example only partly overlapped with our review with respect to the relevant outcomes. Furthermore, in the particular review the authors included only children older than twelve years of age and studies with a minimum duration of six months and unspecified non-nutritive sweetener. These criteria have inevitably led to a different pool of included studies and thus explain the different findings.

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.

We agree with Sievenpieper's critique of the review by Azad et al. and research conducted in the field of NSSs in general. The letter matches well with the description of methodological challenges described in a research paper by Sylvetsky et al.[1].
*We expanded our discussion to stress the points made by the authors starting on page 21: "*Results of observational studies in the field should be interpreted with caution and attention should be payed to plausible residual confounding as well as reverse causality issues such as a higher consumption of NSSs by overweight or obese populations aiming at weight management [2]. Lastly, appropriate, long-term studies that consider baseline consumption of sugar and NSSs [1] and use an appropriate comparator to answer their research questions [2] should investigate whether NSSs might be a safe

and effective alternative to sugar. All study results need to be interpreted in light of these study design characteristics [1, 2]."

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.

We appreciate your concern about the effectiveness of this review. There are relatively few studies that could be combined in a clinically and methodologically sensible manner indeed. The reasons for this are diverse, starting with differences in study design and differences in outcomes looked at and outcome measures used and reported by primary study authors. We addressed the usefulness of harmonised outcome measures in our discussion section as follows (page 21) in order to improve primary and secondary research in this area: "Consistent use of core outcome measures and consensus on timing and mode of assessment would further facilitate pooling of data across studies."

Despite including relatively few meta-analyses, we hold the view that our research is an important piece of research because it addresses a clear question by summarising studies, uses systematic and explicit methods to identify, select, and critically appraise relevant studies, and collects and analyses data from them as defined in the Cochrane Handbook Chapter 1.2.2 (https://handbook-5-1.cochrane.org/).

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.

Thank you. We corrected the wording throughout the manuscript and the title and added the information suggested by you to the abstract.

5. Authors switch between NNS and NSS throughout. This is confusing.

The terminology was harmonized throughout the paper; we now consistently use NSSs. Thank you for pointing us to this issue.

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.

Thanks for pointing out this unclear element of the review. We corrected the terminology to "daily" energy intake as reported in the studies which should also clarify the issue regarding energy intake and duration of trial.

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.

This is an important comment. Prior to submitting the manuscript we extensively discussed which term was most appropriate. We decided to use the term "non-sugar sweeteners" because it is also used by the CODEX Alimentarius (part of the Joint Food and Agriculture Organization of the United Nations [FAO]/ World Health Organization [WHO] Food Standards Programme), and this review was conducted in support of guidelines being developed by the World Health Organization. This explanation was also added to the manuscript (p. 4) and the Figure 1 was revised accordingly.

It would be useful also to briefly describe this class in the text.page 13, line 31 et seq:

*We gladly added a description of the class in the introduction of the paper. The whole section on page 4 reads: "*To date most NSSs have been synthesized, but through research and development in food chemistry and processing the number of natural NSSs is increasing [3]. NSSs differ from sugars not only in their taste properties, but also in how the body metabolizes them [4] and how they in turn impact physiological processes [5]. NSSs are generally sweeter than sucrose, but contain far fewer or no calories. Each sweetener is unique in its sweetness intensity, persistence of the sweet taste, coating of the teeth and aftertaste effect [6]."

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)

We agree that information on study duration and baseline weight are relevant in order to interpret the review findings. We have made the respective additions to the text that now reads as follows (p. 14): "Subgroup analysis by body weight status, suggested that NSSs use by overweight and/or obese individuals (not trying to lose weight, mean body weight 86.87 kg) resulted in reduced body weight of 1.99 kg (95% CI -2.84 to -1.14, 3 studies, n=146, duration of studies: 4 weeks to six months) but no change in body weight in normal weight individuals (0.03 kg, 95% CI -0.03 to 0.09, 2 studies n=110) (Figure 3)."

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

Thanks for pointing this out. We amended the table by adding the literal description of the control intervention as described in the study publication. It now reads (p. 8): "Avoidance of low energy 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

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

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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.

Thanks for your detailed comment on this relevant issue. We agree that this information is crucial in the interpretation of findings. Splitting the studies in meta-analyses by comparator would, however, result in even poorer statistical power of analyses. This is why we rarely separated the analyses by comparator; however, type of comparator was considered in subgroup analyses were sensible (see also response to next comment). We added this point to our discussion of unanswered questions. The respective section now reads as follows (p. 21): "To date several studies on the effects of NSSs on different health outcomes have been conducted. However, their methodological and/or reporting quality is mostly limited and often not sufficiently detailed to include their results in meta-analyses. Moreover, included studies differ substantially in their design, i.e. choice of population, intervention, comparator and outcome measures. Given these relevant differences between studies we were unable to reliably review the effects of single sweeteners or caloric versus non-caloric effects. Both factors might play a role in how NSSs affect health and should be considered in future research."

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.

*True, there are instances where a differentiation between caloric and non-caloric comparators is feasible and sensible. Accordingly, we have added information to the results section and the figures in the supplement, see for example page 12: "*Only one study used placebo as comparator [7] while the other studies used caloric sweeteners as comparator [8-11]*."*
This might, to some degree, allow for a fairer interpretation of the review findings. However, we hold the view that the heterogeneity among primary studies, i.e. study duration, study population, baseline consumption of caloric and non-caloric sweeteners etc. influence the strength and direction of effect. Hence, information on the comparator might only add limited information to the overall interpretation of the effectiveness of the review results which, thus, have to be interpreted with caution.

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.

Thank you for this comprehensive comment. We agree with your critique and addressed the issues as follows.
Regarding in and exclusion criteria which lead to excluding a number of cohort studies, we followed the guidance of the WHO NUGAG group. WHO develops its guidelines according to the GRADE approach which foresees the definition of research questions as well as in- and exclusion criteria prospectively, based on perceived clinical relevance of the expert group. This is now reflected more clearly in the introductory section and methods section (see also response to comments by the BMJ editorial conference).
This review serves as a basis for a global WHO recommendation on NNSs use by healthy adults and children. The WHO expert committee (NUGAG) desired for this systematic review to be specific/explicit in relation to NSSs being studied Therefore, it was decided that studies that did not specify the type of sweetener in the intervention/ exposure should be excluded. While this led to exclusion of some studies, perception was that it is not a very large number of studies; further, some of the studies not specifying type of NNS were excluded for other reasons as well, such as a very short study duration or the inclusion of diseased participants.
Hence, regarding the inclusion of cohort studies, we decided to briefly discuss their findings as follows (p. 20): "There are a few large prospective cohort studies [12-15] that investigated the association of NSSs with different health outcomes. NSSs under investigation were not sufficiently specified in order to be included in our review. However, their results indicate an increased risk of higher BMI, higher risk of type-2 diabetes with higher NSSs consumption. These results conflict with the ones in this review. However, their findings need to be interpreted with caution as outlined below. It is desirable that the results of such cohort studies are verified by studies which specify the type of sweeter used.*"*

*The associations of different types of sweeteners with health outcomes were the focus of this review. So we fully share your opinion that such comparisons would have been the more informative. However, given the scarcity of available study data that would allow for such comparisons and poor statistical power we pooled the available data across different sweeteners. In order to provide information on differences by type of sweetener, we added information on type of sweetener and comparator where applicable throughout the results section. For example as follows (p. 14): "*There

seemed to be no consistent difference in effect between studies using aspartame [8, 9, 11], stevia [7] or a combination of sweeteners [10] as intervention."
Having added this information, we have to emphasize what you also point out above: data are insufficient to make comparisons between sweeteners. The studies differ by additional factors, i.e. study population, study duration, comparator etc. Therefore, we need to be very cautious in drawing any firm conclusions from this.

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

Funds for research?: No

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?

The review was part of a WHO guideline development process for a global guideline for sweetener use in healthy adults and children. The WHO NUGAG Subgroup on diet and health formulated the research questions based on their relevance for the guideline. The guideline process followed the GRADE approach where research questions as well as in- and exclusion criteria are defined based on their clinical relevance regardless of the available evidence. Therefore, we report all initially defined research questions in the introductory section. Moreover, there is -in our opinion- also value in clearly pointing out research gaps. So, while we agree that it was foreseeable that only little data is available to address some of these questions, we hope that this work will encourage and facility future research on these important health 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.

We understand that the presentation of the research questions might be perceived as unclear. The review was conducted to serve as basis for a WHO recommendation on sweetener use in an overall healthy population. An expert committee discussed and drafted relevant research questions prospectively. In order to transparently document this process we listed research questions that were initially formulated in the introductory section of the manuscript. As you point out correctly, our results show that there is no evidence available to answer these research questions. So we transparently reported this finding in the results chapter.
In order to highlight that studies comparing the effects of different dosages of NSSs are needed, we added the following to the discussion section (p. 21): "Future research might consider exploring the effects of different combinations of sweeteners administered in doses similar to different real life use patterns and compare the effects of higher versus lower doses of NSSs."

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.

*This review serves as basis for a global WHO guideline on sweetener use in healthy adults and children. Hence, the scope of this particular review was limited to populations who were healthy at baseline and diseased populations were excluded. We have clarified the background for the review in the introductory section as follows (p. 4): "*The World Health Organization (WHO) is developing guidance on the use of NSSs by adults and children based on the evidence generated by this systematic review. Following the guidance of the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health this review seeks to comprehensively assess the relationship between commonly consumed NSSs and health by addressing the following research questions:*"*

*And added the following to the methods section in order to clarify the in- and exclusion criteria (p. 5): "*The inclusion and exclusion criteria for this review were established prospectively and were based on their relevance for a WHO global guideline for use of NSSs by a generally healthy population.*"*

3. Including the term 'pregnant women' in the same sentence as 'diseased populations' may be construed as a little insensitive.

Thank you for pointing this out; we fully agree with you. We changed the wording as follows (p. 5): "Studies including diseased populations were excluded as were in vitro and animal studies. Studies with pregnant women were also excluded."

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.

We also deem information on effects of sweeteners on different population groups highly relevant. However, as outlined above this reviews' scope was to assess the effects of sweeteners on health in order to inform a global WHO guideline on sweetener use in a generally healthy population. Therefore, during the guideline process, the WHO expert panel decided not to include pregnant women. Still, research in pregnant women and their offspring is very relevant. So we added the following to the section "Unanswered questions and future research " (p. 21): "Besides studying the effects on NSSs in a general healthy population of adults and children, research should be conducted on diseased populations and other subpopulations, including pregnant women and their offspring and populations who use NSSs in amounts higher than average, such as diabetic patients[16]."

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?

We could not agree more regarding the comment on study duration and regret proposing the cut-off of seven days. We revised the discussion section as follows: "We also recommend that future studies assess the effects of NSSs on health outcomes with an appropriate study duration. Study planning should consider the duration necessary for plausible, relevant effects to occur in the different outcomes of interest."
In the abstract we now wrote: "Future studies should assess the effects of NSSs on health with an appropriate intervention duration"

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?

*This is a very good point, indeed, and we agree that it might foster thorough research if type and amount of sweetener were specified in more detail by product manufacturers. We hope that the following addition reflects your comment satisfactorily (p. 21): "*Precise reporting of sweetener content, i.e. type and amount of sweeteners, in ready-to-consume foods and beverages is highly desirable and could be facilitated by more detailed information on ingredients provided by 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.

*Thank you for sharing this information. We gladly added this to our discussion of future research as follows (p. 21): "*Besides studying the effects on NSSs in a general healthy population of adults and children, research should be conducted on diseased populations and other subpopulations, including pregnant women and their offspring and populations who use NSSs in amounts higher than average, such as diabetic patients[16]*."*
Based on information from a study by Sylvestky et al. conducted in the United States NSSs consumption is lower among children than among adults [17]. Hence, we are cautious about proposing that children are a group explicitly prone to using NSSs. We hope that the comment above reflects the research need in children to an appropriate degree.

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