Author’s response to reviews

Title: Health outcomes of non-nutritive sweeteners: analysis of the research landscape

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Author’s response to reviews:

Answer to the comments and suggestions of Reviewer 1

We thank the reviewer for the insightful comments and suggestions that helped us to improve the
quality of our paper. We respond to the specific points raised as follows:

I. TITLE: The inclusion of observational studies in the scoping review means that the word
"effects" in the first part of the title does not accurately reflect the content of the manuscript.
I suggest rephrasing the title to better reflect the aim of the scoping review, and use of the
term health outcomes rather than health effects.

We thank the reviewer for drawing our attention to this misleading expression. We corrected it to
“health outcomes” as advised.

II. ABSTRACT: The abstract should be rewritten using the sections: Background, Methods,
Results and Conclusions as per the Author Instructions. These sections in the abstract should
closely reflect the key content of the corresponding sections of the manuscript. The results
presented in the abstract should align with the main aim and key objectives of the study. The
abstract is very important and should provide an informative and easy-to-follow summary of
what was done and what was found.

Very important: All the comments and edits made for each section below are also relevant to the
abstract, and must be included when the abstract is rewritten.

We structured the Abstract into separate Background-Methods-Results-Conclusions sections as
advised. We also made changes to its content, so that the Methods part better reflects how the
review was performed and the Results describe both the results of the search and the assessment of evidence.

III. /1. INTRODUCTION: The term "objective" is used in the abstract and the term "aim" is used in the manuscript - be consistent. Also the aim presented at the end of the introduction is incomplete when compared to the objective presented in the abstract. A different aim is then presented in the Methods (line 48, page 5).

We rephrased the term „objective” to „main aim” in the abstract.

We expanded the sentence “The aim of this scoping review was to map the available evidence about the health outcomes possibly associated with regular NNS consumption“ at the end of the Introduction by adding “by examining the extent, range, and nature of research activity in this area” to express exactly the same as the sentence “The main aim of this scoping review was to map the evidence about health outcomes possibly associated with regular NNS consumption by examining the extent, range, and nature of research activity in this area” presented in the Abstract.

In the Methods section the first sentence (“We used the approach of a scoping review (including a process known as evidence mapping) [13, 14] to compile all relevant evidence about the health effects of NNSs consumption from the scientific literature”) expresses the main aim of this manuscript, which is in line with the aim presented in the Abstract and the Introduction. Lines 43-55 on page 5 try to give a short explanation about the essence of the method called evidence mapping. To avoid misunderstanding, we deleted the expression “The aim is…” from this explanation.

III/2. Please rephrase the main aim and objectives of the study. The main aim (overall purpose) should be comprehensively stated at the end of the Introduction, followed by the objectives, formulated as the detailed, feasible steps to accomplish the main aim.

The main aim was "to map the evidence about health outcomes possibly associated with regular NNS consumption by examining the extent, range, and nature of research activity in this area"

The specific objectives for this overall aim should be clearly stated - elaborate on the concepts of health outcomes, extent, range and nature of research activity.

The gap described in the Introduction systematically flows into the motivation for the scoping review on page 5. The main aim and objectives should logically follow from this motivation. The purpose of the study is clear, but the steps that were taken to accomplish this aim (objectives) are not clearly presented.
We included a paragraph after the main aim, at the end of the Introduction section, describing the specific objectives of the study, as advised by the Reviewer.

III/3. A slightly more detailed description of the approach to a scoping review, including the process of evidence mapping, should also be included in the Introduction.

This description of the approach to a scoping review is presented in the Methods section.

III/4. The Introduction only mentions non-discretionary intake of NNSs, but the scoping review includes both non-discretionary intake and discretionary use of NNSs by consumers (in tea or coffee for example). Therefore, a brief discussion of current literature on the discretionary use of NNSs should also be included in the Introduction.

In the Introduction we write about “food and beverages sweetened with NNS”. In our understanding this means all types of food sweetened with NNS, covering, discretionary food and also core/ non-discretionary food intake.

III/5. Please add references to the first paragraph on page 5.

References were added, as advised.

III/6. For ease of reading and to supplement the current information, I suggest capturing details about the different types of NNSs in a table, and also including the information related to where their use is approved in the table - without repeating information in the text and table.

We added a new Table with the available NNSs and their Acceptable Daily Intake (ADI) levels.

IV. METHODS: The methods should correspond with the stated objectives ensuring that methods used for each objective are included and documented in way that they are replicable. Certain sections of the Methods are currently vague and require more detail.

IV/1 Inclusion criteria - include no restriction based on language here;

We included “no language restriction” to inclusion criteria, as advised.
IV/2. were only the listed Ass, NNCSs and NNSs included? If yes, make this clear; were any forms or dosages of NNSs eligible for inclusion?

To make this clear, we included „any type and any dosage of ASs or NNCSs or NNSs” among inclusion criteria.

IV/3. Search strategy - why were there different search dates for AS and NNCS and NNS?

On the 25th May 2017 we updated both searches, as advised by Reviewer 2 in order to update the included evidence and harmonize the date of the last search.

IV/4. Data extraction and management - line 12 page 7: should no. 6) be the size of the study sample and not the size of the study population?

We thank the reviewer for this helpful remark. We corrected the misleading expression „study population” to „study sample”, not only in the text, but also in Tables.

IV/5. More detail is needed to explain what is meant by the sentence on the use of Bubble charts on page 7. What are bubble charts? How are they used to highlight correlations? Perhaps providing an example of this will be helpful.

To explain how bubble charts highlight relations we added the following sentence: „Bubble charts are multi-variable graphs, which plot points along a grid where the X and Y axis are separate variables (in our case they represent sweetener types and health outcomes), and additionally, the different colours of the plotted points represent a third variable (in our case they show study type).“

IV/6. Line 8 page 6: write out the abbreviation DC the first time it is used

We wrote out this abbreviation as advised, the first time we used it.

IV/7. Line 36 page 7: the word 'analyzed' should be replaced with the word 'summarized'

We corrected the misleading expression.
V. RESULTS: The reporting of the results should be improved and should be in accordance with the objectives once they are formulated. There are currently inconsistencies, namely: directions of effects are provided in Table 2 and 3 for primary studies, but are not included in Table 1 for systematic reviews; also health outcomes reported on by systematic reviews are not included in Figure 2; the terms used for the various outcomes and groupings in the text (from line 48 page 8 to end of Results section) are inconsistent with the terms used in Figure 2 - please edit to use consistent terms and groupings in the text and figures.

The primary objective of this scoping review was to systematically summarize primary studies, therefore in Table 2 and Table 3, which summarize available studies for a special health outcome, detailed information on primary studies is provided (including also direction of effect for each included primary study). Summarizing systematic reviews was a secondary objective of this review, in this case – as we now formulated at the end of the Introduction – we aimed to compare the main characteristics (inclusion criteria, limitations, searched databases) of the available systematic reviews. Since most of these systematic reviews describe several outcomes it would be very difficult (and since primary studies for each outcome are summarized and described in detail in the manuscript, also somewhat redundant) to visualise direction of effect for each outcome in case of the systematic reviews.

The same explanation applies also to Figure 2. We do not think that systematic reviews should be visualised here.

We harmonized the wording as advised.

V/2. Please include the headings that are described in lines 33 to 41, page 8 (short-term outcomes, long-terms outcomes in healthy populations and health outcomes in diseased populations) above the relevant categories of outcomes - this makes it easier for the reader to follow. Also include these categories in Figure 2.

We included subheadings for the categories “I. Short-term outcomes”, “II. Long-term outcomes in healthy populations” and “III. Health outcomes in non-healthy populations” as advised.

V/3. Currently, the references to all 372 included studies are not reported. The references for all the included studies should be added when they are reported on in the Results section, as has been done in line 54 on page 8 for eating behaviour and metabolic effects.

We thank the Reviewer for this comment, we added relevant references for all health outcomes.
We further added the following explanation to the Results section: “In this manuscripts we report on relevant systematic reviews, clinical trials, cohort studies, case-control and cross-sectional studies.”

V/4. It would also be very useful to extract and report on the form and dose (or dose range) of the NNSs intervention or exposure in the included studies, when reported. This is very important for comparisons between studies and would add to the interpretation of the included research. I would suggest extracting and including this data, where possible.

Thank you for this comment. We agree, that dose (or dose range) of the NNSs intervention or exposure will be an important part of a systematic review and meta-analysis, which might be planned based on the results of this scoping review. However, we also think, that presenting doses is beyond the scope of this scoping review: describing doses for each included study would make it more difficult for the reader to follow, and the main message of the manuscript might be lost among the amount of information presented.

V/5. It would also be useful to report the eligible NNSs not addressed by any included studies, if applicable.

These gaps are visualized in Figures 2 and 3, where the reader can see in the bubble chart which of the NNS - health outcome relations were investigated in none of the included studies. We added the following sentence to the Discussion: “Eligible NNS not addressed by any of the included primary studies were: neotame, alitame, neohesperidin DC, thaumatin and brazzein.”

V/6. Line 51 page 7: delete the word PRISMA please, this is not a systematic review

We modified the word to: “PRISMA Flow Diagram adapted for the scoping review process”.

V/7. Line 56 page 7: the following phrase does not make sense: Of those full texts of fifteen papers could not be retrieved

We deleted the misleading part of this sentence as advised: “Fifteen papers could not be retrieved; all others were available for detailed full-text assessment.”

V/8. Line 33 page 8: the word discuss should be replaced by the word report
We replaced the word „discuss” by „report”, as advised.

V/9. First sentence under Cancer on page 9: what is meant by dedicated systematic review versus broad systematic review? Please clarify - is reference 19 a systematic or narrative review?

We revised the misleading sentence. Yes, the reference in question is a systematic review.

V/10. Table 3 should be completely revised to reflect each of the 16 studies on dental caries, much like Table 2. In its current form it is confusing and does not add any value in better understanding the nature and extent of the studies reporting on NNSs and dental caries. It is currently not possible to sensibly link the population, interventions, outcomes, study design and effects and thus the information cannot be interpreted in a meaningful way.

We revised the table as advised.

V/11. Line 12 page 13: should be Obstetric not Obstetrical

We corrected this term as advised.

VI. /1. DISCUSSION: The summary of the findings should be about the main aim and objectives of the study, and should not be centred on the directions of effects/associations reported by the 372 studies for selected outcomes. This is particularly important since the strengths of effects/associations (and variation around these effects) are not reported, and these studies have not been critically appraised, which could lead to invalid interpretations of this evidence. The study sought to scope the health outcomes and nature and extent of the research evidence in this area, and not to report generally on some findings of studies on selected outcomes.

We completely revised the “Summary of findings” section, as advised.

VI/2. Line 19 page 17: should be Strengths and limitations of study

We modified this subheading to “Strengths and limitations of this scoping review”.

VI/3. Line 56 page 17: the 'strength of effect' has not been extracted or reported, only the direction of effect - please correct

Thank you for the comment; we made the correction as advised.

VI/4. Line 15 to 20 on page 18: please substantiate or reference this general statement about methodological limitations of existing systematic reviews

This sentence refers to Table 1, which contains all the methodological limitations seen in the included reviews.

VI/5. Line 38 to 46 on page 18: this eligibility criteria described as 'our primary focus' conflicts with what is reported in the methods section under Inclusion criteria where no mention is made of clear definition of intervention/exposure. The exclusion of studies that defined interventions as diet drink/beverage/soda (line 23 to 46 on page 18) should rather be included in the limitations section as a limitation; remove the etc. in the final sentence.

We deleted the misleading part of this sentence.

We did not exclude studies with a diet drink/beverage/soda intervention from our scoping review.

VI/6. Line 53 page 18: The Implications of findings section is currently too vague and should be much more specific - I suggest using the EPICOTplus framework to assist with improving this section. Statements should be substantiated and explained in detail.

Thank you for this comment. We completely revised the “Implications of findings for practice, policy and future research” section based on Brown 2006 (BMJ 2006;333:804-6), as recommended by the Reviewer:

“Current evidence demonstrates that there is a need for both, further primary research and high quality comprehensive systematic reviews including meta-analyses, to inform future recommendations about the health benefits and risks of NNS to inform and support health care practice and public health decision-making

This scoping review highlights the need for studies, which investigate the long-term effects of individual sweeteners on some of the less well-researched health outcomes (e.g. headaches, depression or other mood disorders, Alzheimer's disease, risk of preterm delivery). Future studies need to be rigorous in design and conduct, with well-defined interventions (providing
information on type and dosage of the non-nutritive sweetener) and controls. Study reports should include detailed descriptions of all methodological aspects to enable proper interpretation of results.

Systematic reviews are required for health outcomes with large number of primary studies, but without conclusive evidence (e.g. appetite and short term food intake, risk of cancer, dental caries, risk of diabetes, glycaemic control in subjects with diabetes and blood pressure control in hypertensive patients) to support the formulation of recommendations and to be able to decide whether further, well-designed primary studies are required.”

VII.1. CONCLUSIONS: This section is currently focused on generalizations of selected effects reported by the 372 studies, and should be rewritten to report on findings pertaining to the main aim of the study. This is particularly important since the strengths of effects/associations (and variation around these effects) in the studies are not reported in this paper, and these studies have not been critically appraised, which could lead to invalid interpretations of this evidence.

To report on findings pertaining to the main aim of the scoping review we completely revised the Conclusion section:

“There are numerous evidence gaps related to the health effects of NNSs in both healthy and diseased populations. In healthy subjects appetite and short term food intake, risk of cancer, risk of diabetes, risk of dental caries are the most investigated health outcomes, all of them without any conclusive evidence. There is a need for well-conducted systematic reviews to quantitatively summarize results and assess their validity. Besides, there are numerous health outcomes, like incidence of headaches in association with NNS consumption, depression, Alzheimer’s disease, risk of preterm delivery, behavioural effects, cardiovascular effects or risk of chronic kidney disease, which were investigated in only few number of studies and further research activity is needed. A systematic review is also required to make formulating recommendation for subjects with diabetes and hypertension on using NNS possible.”

VII/2. Figure 1: Please clarify what is meant by "wrong publication format" since there were no limitations on study design.

We added: *All manuscripts which described neither a primary study nor were systematic reviews (e.g. narrative summaries, commentaries, and letters) were excluded as “Wrong publication format”
VII/3. I suggest including the dates for each of the search yields and the names of the databases searched.

Detailed information on the searches (including search dates and databases searched) is provided in the text (see Methods part, „Search strategy”).

VII/4. I suggest including a comprehensive list (or sensible groupings) of the health outcomes possibly associated with regular NNS consumption covered by the 372 studies, since this is the main aim of the scoping review (perhaps as a textbox under the last textbox)

The health outcomes investigated for association with regular NNS consumption are delineated in the Discussion under the subheading ‘Summary of findings’ and visualized in the bubble charts.

VII/5. Figure 2: Please add explanations for all abbreviations used in the figure;
Correct spelling errors in the words obstetric and caries;
Add more detail on what is meant by Blood profile (is this lipids?), Tolerance and Other;
It is unclear what is meant by non-As in the figure?

Both, Figure 2 and Figure 3 were completely revised and updated.

We added explanations for all abbreviations in Figure 2.
We corrected the erroneously typed words.
We changed the misleading outcome names. New categories are: ‘Laboratory parameter’ (instead of ‘Blood profile’), ‘Appetite, food intake’ (instead of ‘Eating behavior’), ‘Chon. kidney disease’ (instead of “Kidney disease”). We added an explanation for the categories ‘Laboratory parameter’ (“haematological parameters, blood chemistries and hormone levels”) and ‘Other’ (“any other health outcome, which couldn't be classified to any of the above listed categories”).

Please, see ‘e’ for the explanation of ‘non-AS’: “the investigated intervention/exposure is a combination of NNS and other non-sugar sweeteners (e.g. sugar alcohols)”
Answer to the comments of Reviewer 2

The only major concern is that the review was completed in January 2016 - around 15 months ago - and new research has been published in the interim that arguably should be included.

Would it be possible to update the review incorporating evidence published up until December 2016?

We thank the reviewer for his efforts to improve the quality of our manuscript.

We updated the search on 25th May 2017 and included all relevant studies published until this date (in total 48 new studies were included).