RESPONSE TO REVIEWERS

Additional comments by the committee:

1. **Title says 'controlled trials'; they included both randomized and non-randomized studies, so more information on the design of the non-randomized studies would be useful. Table 1 has characteristics 'cross-over/parallel', but this won't necessarily describe the non-randomized studies.**

   Response: We agree that more detail is required. We have elaborated on the design of the non-randomized controlled trials. We have indicated that nonrandomized studies differed only in whether the allocation to treatment was randomized in parallel designs or the sequence of treatments was randomized in crossover designs. A study was considered non-randomized if the authors explicitly stated that a method of randomization was not used or, randomization was not reported. We have added this description to the Methods section under "Study selection" (lines 169-195).

   There is a constant use of the term 'trials' throughout to cover all designs which should be avoided I think and replaced with 'studies'.

   Response: We agree that the use of the term "trials" may lead to confusion. We have replaced it with "studies" throughout.

2. **As such, should the Cochrane RoB tool be used on the non-randomized studies? Or something like the Newcastle-Ottawa scale?**

   Response: We agree that it is important to use the correct tool for assessing study quality. As these studies differ only in the use of randomization please see our responses to point # 1 above), "random sequence generation" is a domain in the ROB tool to assess the bias posed by this design issue and we are interpreting these studies together with the randomized controlled studies in our GRADE assessment, we felt that the RoB tool is still the most useful to the reader.

3. **Few studies had high RoB across all domains, but many had unclear RoB across the domains.**

   Response: Thank you for this observation. Most studies had unclear risk of bias across the 5 domains of RoB due to insufficient reporting to allow for a definitive judgment of risk of bias. Studies graded as high risk of bias provided explicit information documenting possible sources of bias. We have included the point that most studies had unclear risk of bias but did not interpret this poor reporting to necessarily mean that an overall serious risk of bias was present in the available studies (lines 301-

307). Our assessment is reinforced by the lack of any subgroup effect modification by the domains of the RoB (with the exception of fasting blood insulin in the addition studies).

4. **The search was done until Nov 2015, so 1.5 years out of date.**

   *Response: We agree that the search should be updated. We have included the updated search (through May 29, 2017) in the Abstract (line 79, line 90), Methods (lines 162-163), Results (lines 272-277) and in **Figure 1** and **Supplementary Table 1**.*

5. **Ultimately, lots of heterogeneous small trials. Total n is only 5139 from 160 trials (median of 15 participants per trial).**

   Response: Thank you for your observation. We did address the limitations of heterogeneity in the narrative description of our GRADE assessments (lines 431-447), GRADE table (Table 2), and in the strengths and limitations section of our discussion (lines 618-646).

6. **One editor felt the clinical relevance of this study was unclear. He was also not sure whether the paper added enough to these two previous papers:**
   a. **Diabetes Care. 2012 Jul;35(7):1611-20. doi: 10.2337/dc12-0073. Effect of fructose on glycemic control in diabetes: a systematic review and meta-analysis of controlled feeding trials.**
   b. **Am J Clin Nutr. 2016 Dec;104(6):1562-1576. Epub 2016 Nov 9. Effect of fructose consumption on insulin sensitivity in nondiabetic subjects: a systematic review and meta-analysis of diet-intervention trials.**

   Response: Thank you for your comment. We believe that our study has clinical relevance towards informing dietary guidelines due to the food based approach of our systematic review and meta-analyses. While the two cited papers have been conducted to a high quality, both studies have only looked at the effects of monomeric forms of fructose on glycemic control. As fructose is rarely found in the diet in isolation, but rather as fructose-containing sugars in the form of sucrose, HFCS, fruits or honey, this raises the important question of how dietary sources of fructose-containing sugars and the food sources that they are commonly consumed in might impact measures of glycemic control.

7. **Another editor said there is quite a bit of discussion about whether fructose is bad or just another sugar and he expected the paper to be well received by the readership and was in favour.**

   Response: Many thanks for your comment.

8. **Another editor found it difficult to understand the four different trial designs. Would it be possible to clarify a bit further?**

Response: We agree that further clarification of the four different study designs would be useful. We prespecified 4 study designs based on the control of energy: : 1) 'substitution' studies, in which food sources of fructose-containing sugars were compared with food sources of other non-fructose-containing macronutrients under energy matched conditions (isocaloric comparison); (2) 'addition' studies, in which excess energy from food sources of fructose-containing sugars was added to background diets compared to the same background diets alone without the excess energy from fructose-containing sugars with or without the use of low-calorie sweeteners to match sweetness (hypercaloric comparison); (3) 'subtraction' studies, in which energy from food sources of fructose-containing sugars was subtracted from background diets through displacement by water and/or low-calorie sweeteners, or by eliminating the food sources of fructose-containing sugars altogether compared with the original background diets (hypocaloric comparison); and (4) 'ad libitum' studies, in which food sources of fructose-containing sugars were compared with food sources of other non-fructose-containing macronutrients without any strict control of either the study foods or the background diets to allow for free replacement of the energy from fructose-containing sugars with the energy from other macronutrients (free-feeding comparison). We have revised the text both in the abstract (lines 82-86) and methods (lines 176-195) to capture these revised descriptions.

In reviewing our selection criteria for study design, we also noted that we included in error some studies that used ineligible interventions and comparators by our a priori criteria. We felt that interventions of liquid meal replacements should be excluded, as they are designed to be used in place of full meals or even full diets as opposed to "food sources" and the design did not allow for the isolation of the effect of the fructose-containing sugars. We also felt that substitution studies using the comparator isomaltoluse should be excluded. Our aim was to compare food sources of fructose-containing sugars to food sources of other ***non****-fructose-containing macronutrients under energy matched conditions in substation studies. As isomaltulose is itself a fructose-containing sugar, it is an unsuitable comparator. At the same time, we did not feel that isomaltuolse should be included as a an intervention as it is an alternative sweetener and not one of the main fructose-containing sugars (*fructose, sucrose, HFCS, honey, or fruit*) that we intended to study. To clarify these eligibility criteria, we have added a statement in the Methods section under the heading "Study Selection" (lines 173-176) that indicates that we excluded studies of meal replacements or interventions or comparators of rare sugars that contained fructose (e.g. isomaltulose or melzitose) or were low-calorie epimers of fructose (e.g. allulose, tagatose, sorbose).*

9. Another editor was concerned about the evidence being "borderline" (predominantly proxy outcomes, short term data, etc) but he acknowledged the relevance of the topic.

Response: Thank you for pointing out this important matter. While we agree that some of the outcomes were only proxy measures for the development of diabetes (fasting glucose and fasting insulin), the measurement of HbA1c as a reflection of longer term glycemic control has been highly correlated with disease outcome. We also agree that the short duration of several studies presents a limitation to the interpretation of our results, however, subgroup analyses looking at study duration

greater than or less than 8 weeks did not show any differences across outcomes for all of our analyses.

10. **Another editor highlighted that you need to update the search but felt the paper seemed important from a public health and nutritional standpoint since so many foods are sweetened, and there is intense debate about whether some sweeteners are good or bad.**

    *Response: Thank you for your support. We agree that an update of our search is warranted. We have updated our search (through May 29, 2017) in the Abstract (line 79, line 90), Methods (lines 162-163), Results (lines 272-277) and in **Figure 1** and **Supplementary Table 1**.*

Reviewer: 1

Comments:

1. **It's a fair question to ask. Individual trials unlikely to have sufficient power to answer the question. Consistent answers across a range of different trials would be useful.**

   Response: Many thanks for your support.

2. **The actual review appears to have been conducted to a high standard.**

   Response: Many thanks for your support.

3. **My main concern is the inclusion of non-randomized trials. This may well reflect the nature of the studies in this area, but that does not avoid the inherent potential for bias in non-randomized studies. The authors note that results did not differ between randomized and non-randomized trials.**

   Response: Thank you for raising this important matter. We agree that the inherent possibility for bias in non-randomized trials is an important consideration, however, we have included non-randomized studies as they can provide additional information when we are looking at harm. Furthermore, we did observe that randomized and non-randomized studies did not differ in our subgroup analyses as you have mentioned. We have therefore added this as strength and not as limitation of our study, please see "Strengths and Limitations" section (lines 610-616).

4. **There is a lot of heterogeneity and this also limits the interpretation of the results. The authors have tried to explore different potential sources, but nothing really explains it.**

Response: Thank you for your comment. We agree that the substantial heterogeneity present in several of our analyses may limit confidence in our results as noted under the "strengths and limitations" section, (lines 627-632).

5. **I like the separation into different types of trials: substitution, addition, etc. This helps interpretation in a field where it's hard to tell if it is sugar, energy, whatever has replaced the sugar, etc.**

   Response: Many thanks for your comment.

6. **The abstract feels slightly long, but the main finding from each of these types of trials should be presented regardless of statistical significance.**

   Response: Thank you for your comment. We agree of the importance of presenting results from all of our analyses, however we were limited to presenting only significant findings due to the limitations on our abstract word count.

7. **I felt slightly uncomfortable with the interpretation of some of the evidence, e.g. "There was no effect of total food sources of fructose-containing sugars in subtraction (low to high quality evidence) or ad libitum trials..." would be better phrased as being no *evidence of* an effect.**

   Response: Thank you for your comment. We have revised our abstract according to your suggestion (line 102).

8. **Similarly, the conclusion that "Pooled analyses showed that fructose-containing sugars from various food sources, especially fruit, are no worse in their effects on glycemic control ..." is phrased like an equivalence / non-superiority trial, but this does not reflect how the trials or the meta-analyses were set up. More care is needed to cautiously reflect the body of evidence, potentially with more nuanced phrasing.**

   Response: We agree that the wording in this case is misleading. We have completely reworded the conclusions section to be more reflective of the data (lines 104-109).

9. **Absolute heterogeneity (e.g. range of estimates across individual trials) should be presented alongside I-squared.**

   Response: We agree that it is important to show the individual study estimates from which the I2-statistic is derived. The forest plots showing individual study estimates are in the supplementary material for HbA1c (Supplementary Figures 2-5), fasting blood glucose (Supplementary Figures 10-13), and fasting blood insulin (Supplementary Figures 18-21).

10. **At times the estimates, confidence limits and p-values are presented to too many decimal places, giving a false sense of precision.**
Response: Thank you for pointing out this issue. We have made the change throughout the manuscript and supplementary material, reporting all p-values to two decimal places or as <0.001 when we have more than three decimal places of significance.

Reviewer: 2

Comments:

1. **The authors conducted a very thorough systematic review and meta-analysis of different food sources of fructose-containing sugars and their effects on three markers of glycemic control (HbA1c, fasting blood glucose, fasting blood insulin). This manuscript looks to be an ambitious undertaking particularly taking into consideration the energy balance of all available trials that were identified to be suitable up until November 3 2015**

*Response: Many thanks for your comment. We agree that an update of our search is warranted. We have updated our search (through May 29, 2017) in the Abstract (line 79, line 90), Methods (lines 162-163), Results (lines 272-277) and in **Figure 1** and **Supplementary Table 1**.*

Major comments:

1. **The authors should consider including other important markers of glycemic control such as indices for insulin sensitivity or insulin resistance (e.g. Homeostatic Model Assessment of Insulin Resistance or HOMA-IR).**

Response: Thank you for your suggestion. We agree that other markers of glycemic control including indices for insulin sensitivity and resistance are important, and will consider conducting further analyses looking at these outcomes in a future project.

2. **Figure 2 and Supplementary Figure 6 both presented results with respect to HbA1c in substitution trials for different food sources of fructose-containing sugars (fruits, SSB, LMR, etc.), but the results (MDs or the associated 95% CIs) were not consistent for any of the five food sources; only the estimate (95% CI) for total food sources was the same. The same inconsistency exists for substitution trials portion of Figure 3 and Supplementary Figure 13. The authors should explain why such inconsistency exists.**

Response: Thank you for pointing out this very important discrepancy. We have noted this error in the creation of our figures and recreated them with the correct values according to our updated analyses (Figures 2-4, Supplementary Figures 2-5, 10-13, 18-21).

3. **In Potential mechanisms under the Discussion section, the authors compared the glycemic indices of fructose and starch, citing the low GI of fructose itself as the potential source of benefit. In my**

opinion this is not a fair comparison, especially since the focus of this review is on food sources of fructose-containing sugars. The authors should at least consider the GI of the difference food sources, such as fruits, SSB, sweets, etc., which can be very different.

Response: Thank you for pointing out this very important matter. We agree that the GI of different food sources of fructose-containing sugars are an important consideration and have incorporated it into our Discussion (lines 524-546).

4. **In Potential mechanisms under the Discussion section, the authors focused solely on the catalytic function of fructose in low GI fruits, but failed to discuss other potentially beneficial component of fruits, such as fiber content or micronutrients.**

   Response: Many thanks for your comment. We have revised our manuscript to incorporate your suggestion (lines 532-534).

5. **Overall more of the emphasis of the article was placed on the food sources of fructose-containing sugars, while less attention was given to the comparator foods (for example in the main finding figures 1 – 3). In my opinion it is very important to consider both sides of the substitution, especially when making recommendations to the general public. The majority of the comparators in this study were starch, and it seems like no trials included in this study used legumes or whole grain products as the comparator food, which are generally considered higher quality carbohydrates for glycemic control. The authors should acknowledge the lack of such trials.**

   Response: Thank you for your comment. We agree that this is a very valid observation and have incorporated it into our Discussion under potential mechanisms (lines 526-529).

Minor comments:

1. **Line 30 – 31: the statement that "public health advice to reduce free sugars does not distinguish between food sources of sugars" is not entirely true, since the US dietary guideline 2015-2020 specifically limits added sugars in the diet but not naturally occurring sugars such as those in fruits or milk.**

   Response: You raise an important point. You are correct that current guidelines do focus on free or added sugars as a proxy for food sources. With the exception of SSBs, this approach, however, does not look at specific food sources and may miss important interactions with the food matrix (e.g. fruit juice, whole grain cereals, or sweetened yogurt). Whether the evidence for SSBs can be generalized to other important food sources of fructose-containing sugars in their effects on surrogate markers of type 2 diabetes has not yet been determined. We have reworded the sentence to capture this expanded rationale in the Abstract (lines 72-77) and Introduction (lines 144-150).

2. **Line 187: the authors should be consistent in using "to" or "-" when presenting range.**

   Response: Thank you for pointing out this issue. We have made changes in our manuscript, all the ranges read with "-" in order to be consistent, as you have suggested.

3. **Line 211: the authors should be consistent in the number of digits used when presenting P-values. Similar comment for line 230.**

   Response: Thank you for pointing out this issue. We have made the change throughout the manuscript and supplementary material, reporting all p-values to two decimal places or as <0.001 when we have more than three decimal places of significance.

4. **Line 220: in Supplementary Figure 6, the line for the baseline HbA1c ≤ 6% group is missing the right half of the line. Also the legend is missing information regarding between subgroup analysis results for food source (same comment for Supplementary Figure 13 and 14.**

   Response: Thank you for your comment. We have corrected the figures with our updated analyses.

5. **Line 228 – 229: the authors stated that in addition trials, fructose-containing sugars from all food sources increased fasting blood glucose, but for mixed sources the effect estimate was negative in Figure 3.**

   Response: Thank you for your comment. By "all food sources" we were referring to the summary effect from total food sources of fructose-containing sugars, which showed an overall increase in fasting blood glucose. However, our updated analyses no longer shows a significant increase in fasting blood glucose under addition conditions, so we have removed this from our results. We have been more careful in our wording to distinguish between total fructose-containing sugars independent of food sources from the specific food sources throughout the results section.

6. **Line 285: continuous dose-response for fasting insulin in addition trials was presented in Supplementary Figure 8E instead of 12C?**

   Response: Thank you for noticing this inconsistency. We have corrected the supplementary figure references.

7. **Line 287: continuous dose-response for fasting insulin in substitution trials was presented in Supplementary Figure 8D instead of 12B? The authors should also be consistent in whether to use hyphen or not throughout the text.**

   Response: Many thanks for noticing these typos and inconsistencies. We have corrected the supplementary figure reference and we any hyphens throughout the manuscript.

8. **Line 338: the decreased risk of type 2 diabetes associated with higher fruit intake is not directly relevant to the adverse effects of SSB and should be cited elsewhere.**

   Response: Many thanks for your comment. We agree that the decreased risk of type 2 diabetes associated with higher fruit intake is not directly relevant to the adverse effects of SSB, however, they are both food sources of fructose-containing sugars with different effect on the risk of developing type 2 diabetes. We have modified our discussion accordingly in the Discussion (lines 514-521)

9. **Line 361: NAFLD should be spelled out fully at first occurrence.**

   Response: Thank you for your comment. As requested, we have revised our manuscript according to your suggestion in the Discussion (line 574).

10. **Line 369 – 370: I don't think it is appropriate to classify fruit as an alternative sweetener.**

    Response: Thank you for your comment. We agree. This mention has mention of fruit as an alternative sweetener has been removed (lines 599-600).

11. **Line 422: without individual level data, the analysis cannot be called pooled analysis.**

    Response: Thank you for your comment. We agree that the term "pooled analysis" may lead to some confusion with individual patient level pooled analyses. We have removed this term from the Abstract (lines 104-109) and Conclusions (lines 653-685).

12. **Line 426: the current dietary guidelines have shifted towards a dietary pattern-based approach instead of a food-based approach, as the authors stated in the Abstract Objective.**

    Response: Thank you for your comment. We agree that dietary guidelines are shifting from a focus on single nutrients to a focus dietary patterns. We have revised our manuscript to reflect this wording in the Discussion (lines 596-597).

13. **The quality of Figure 1, 2, and 3 appears to be substantially lower than the supplementary figures and the authors should consider improve the quality of these main finding figures.**

    *Response: Thank you for this observation. As requested, we have attempted to improve the quality of our main figures (**Figures 1-4**).*

Reviewer: 3

Comments:

In this important meta-analysis, Choo et al assess the effects of fructose-containing caloric sweeteners on glycemic control in healthy subjects and in patients with diabetes mellitus. For this purpose, they made a comprehensive scan of the litterature and retrieved a large number of randomized clinical trials, which they assessed according to study design (ie substitution trials, addition trials, subtraction trials, and "ad libitum" trials. Furthermore, they obtain sufficient data to assess individually the effects of various sources of fructose-containing caloric sweeteners.

Their results indicate that fructose-containing caloric sweeteners decreased HbA1c without significantly altering fasting plasma glucose and insulin in substitution trials (this effect was most marked with fruits as a source of fructose), and increased fasting plasma glucose and insulin concentration in addition trials without altering HbA1c (this effect was most marked with sugar sweetened beverages). Surprisingly, there was no significant effect in subtraction trials (possibly related to the lower number of trials in this category).

Altogether, these results corroborate earlier observations that fructose, compared to glucose or starch, induces lesser increases in blood glucose and insulin. The effect on Hba1c remains small, however (below the clinical significance level defined by major diabetes organizations), and hence this does not fully support that fructose has relevant beneficial effects on glycemic control. The major strength of this meta-analysis is to allow assessing separately the effects of fructose consumed with fruits, sweetened beverages, and other types of food. It supports the well accept concept that sugar-sweetened beverages but not whole fruits, exert deleterious metaboilic effects.

Altogether, this meta-analysis was well conducted, with adequate methodology, and results are clearly reported. I have only few comments

1. **The potential confounding effects of non-nutritive sweeteners used in some subtraction trials may be taken into consideration (ie one may consider the possibility that beneficial effects of fructose subtraction were offset by deleterious effects of non-nutritive sweeteners.**

   Response: Thank you for your comment. The issue of confounding from non-nutritive sweeteners is an important one. We did address this issue through our subgroup analyses. We did not find evidence of confounding. There was no significant effect modification by comparator in the addition studies. That is, the effect did not differ between non-nutritive sweeteners, water, and diet alone (Supplementary Figures 15 and 23).

2. **The general discussion. while faithfully discussing the study results, is sometime a little bit confusing and/or makes some shot cuts from observations to recommendations. This is mainly due to failing to insert a brief paragraph stating what fasting insulin and glucose and HbA1c actually reflect (ie fasting parameters being a reflection of changes in insulin sensitivity, HbA1c being determined by 24-hour blood glucose.**

   Response: We agree that it is important to indicate what the different measures of glycemic control reflect to understand the effect of fructose-containing sugars on these measures. We have rewritten

the Discussion under potential mechanisms to capture the differences between these measures as way of explaining our results (lines 542-546).

3. **Along the same line, it would be cautious to clearly remind the reader that blood glucose control and glycemic index/glycemic loads represent only one side of the coin, and that effects on other cardiometabolic risk factors should be assessed before going to recommendations**

   Response: Thank you for this excellent point. We agree and have incorporated the evidence for the effect on other cardiometbolic risk factors to the Discussion (lines 571-574).

Minor

4. **The part of the discussion related to "catalytic effects" of fructose is confusing and most likely not relevant to these studies. This whole concept is indeed relevant to document that fructose metabolites have regulatory actions on glucokinase and hepatic glucose uptake. However, fructose is present in our diet at doses substantially higher that these so-called "catalytic doses", and how dietary fructose interacts with glucose at the level of hepatic glucose homeostasis remains largely under-explored.**

   Response: Thank you for raising this important matter. We agree that a "catalytic" effect of fructose may not be that relevant to the available studies for the reasons you have provided. We have added these points to our Discussion under potential mechanisms (lines 554-559).

Reviewer: 4

Comments:

1. **Overall: This is a detailed analyses and balanced approach to the assimilation of the literature. The topic brings together a number of seemingly opposing arguments for the role of fructose intake in glycaemic control and is a timely piece given the current research and public interest in this area. More clarity is needed throughout the paper, particularly in the methods section. The authors are commended for their very detailed analysis however the sensitivity analyses and subgroup analyses results are largely not used to interpreted the main results and the discussion and conclusion need to be put in context more in light of the volume and quality of evidence and study heterogeneity. The abstract could also be a lot more representative of the main manuscript, in its current format it is somewhat oversimplified. The order of presentation of results could be paralleled better between the different sections and tables/figures. Following revisions, this is likely to make a good contribution to the field.**

Abstract:

2. **overall the abstract needs more information on the identified food sources of fructose containing sugars. Also I find the results a little selective in terms of reporting the "stronger effects" for fruit and SSB, you should also report null food sources.**

   Response: Thank you for your suggestion. We have better incorporated the effect of food sources in the Abstract (lines 90-103).

3. **L30: this is a sweeping statement and is country specific, please revise to a more inclusive sentence given the potential international readership interest. There is also a mismatch between this sentence and the sentence that follows with the aim. The background provided is about free sugars but the aim is about fructose specifically. Can this be tied together better?**

   Response: Thank you for your comment. We have reworded the sentence to be more inclusive and better connected the sentences (lines 72-77).

4. **L35: this is already 18 months old. I think an update is warranted to identify any studies published particularly given the growing research interest in this area in very recent years.**

   *Response: Thank you for pointing out this important matter. We agree that an update of our search is warranted. We have updated our search (through May 29, 2017) in the Abstract (line 79, line 90), Methods (lines 162-163), Results (lines 272-277) and in **Figure 1** and **Supplementary Table 1**.*

5. **L36: 7 days long?**

   Response: Thank you for your *comment. As requested, we have clarified that the studies were of ≥7 days duration (line 80).*

6. **L38: outcomes of interest? included outcomes?**

   Response: Thank you for your comment. We have revised the wording for clarity (lines 85-86).

7. **L42: I think the results section would be more interpretable and relevant if they were presented by outcome rather than by trial design.**

   Response: Thank you for your suggestion. As pointed out by another reviewer, one of the strengths of our analysis is the organization by level of energy control. We feel that it is best to maintain the organization of our results by level of energy control.

8. **L42: "energy control" do you mean energy intake?**

Response: Thank you for your comment. By energy control we are referring to the nature of the comparison as opposed to the nature of the intake on each arm. We have clarified what is meant by level of energy control in the eligibility criteria (lines 82-86).

9. **L42: When presenting the results, the volume of evidence should be made clear along with quality of evidence. it is important for the reader to understand that there are far fewer studies of subtraction and ad libitum than substitution and addition. It is therefore somewhat misleading to report 160 trials included without giving further detail.**

   Response: Thank you for your comment. We agree that this distinction is useful for the main paper, but we do not have the room in the abstract word count (up to 400 word) to include this extra information.

10. **L44: "excess energy from sugars displaced from diets", this suggests replaced by something else and isn't properly representative of what was actually included according to the description on line 119.**

    Response: Thank you for your comment. We have clarified our description of subtraction trials (line 84).

11. **L45: "strict" this suggest that there was some element of energy intake control which I don't think is accurate from reading the methods section.**

    Response: Thank you for your comment. We have clarified our description of ad libitum design in (line 85).

12. **L46 and throughout the manuscript. It is important to say this is intake of fructose containing sugars. It doesn't have to be written on every occasion but unless it is specified you could well be referring to intravenous or other methods of exposure.**

    Response: Thank you for your suggestion. As our manuscript refers only to "food sources" of fructose-containing sugars, we feel that it is implicit that that administration was by oral intake in all cases.

13. **L47: It is not clear at this point in the manuscript what this p-value is for?**

    Response: Thank you for your comment. The p-values represent the significance of the mean differences. To avoid confusion, we have removed all p-values and will allow readers to interpret significance based on the 95% CI in each case (lines 90-103).

14. **L48 "effect was stronger for fruit as a food source" this is not detailed enough. Also would larger effect be more accurate than stronger?**

Response: Thank you for your comment. We agree that the statement as written was not clear. Fruit is no longer significant and so have removed it from the results (lines 90-103).

15. **L50: please match decimal places.**

Response: Thank you for your suggestion. Our updated analysis did not show a significant effect of fructose-containing sugars on fasting blood glucose under substitution conditions so we have removed this result from our abstract, but we have matched other decimal places throughout the manuscript.

16. **L52: what about dairy and mixed sources as sources, these results are also significant.**

Response: Thank you for this important observation. We have updated the abstract to reflect the contribution of the other food sources based on the updated meta-analyses (lines 90-103).

17. **L59: "Longer, larger, high quality trials are required", this requirement needs to be worked into the conclusion, not just appended to the end. How should the lack of longer, larger, high quality trails affect our interpretation of the reported results? As a reader I want to know how much confidence I should have in the results given the quality of the data and publication bias etc.**

Response: Thank you for this important suggestion. We agree that it is important to consider how our assessment of the evidence affects our confidence in the results. We have included all of our GRADE assessments (lines 90-103) and provided a statement that "more studies are required to improve our confidence in the estimates" (lines 108-109). The specific reasons for downgrades are too many to discuss in the abstract and are included in the main paper.

Introduction:

18. **Very well balanced treatment of the literature.**

Response: Thank you for your support.

19. **L92: there is something not quite right about the position of the parentheses.**

Response: Thank you for your comment. We have corrected the position of the parentheses (lines 141-142).

20. **L96: The reference provided isn't about shift in focus of recommendations, it is just US recommendations, please find a more appropriate reference to support your point and think about your potential international audience when selecting this.**

Response: We agree that other relevant examples are needed to illustrate this paradigm shift. We have provided a new citation to a review paper that discusses this transition in international guidelines (reference 21, line 145).

21. **Methods: Needs some revision, at times they are not specific enough and require forward reading to fully understand what is being said.**

Response: Thank you for your suggestion. We have attempted to clarify our methods section according to your comments below.

22. **L113: Honey and fruit and food sources rather than sub-groups of fructose containing sugars.**

Response: We agree that fruit is not a fructose-containing sugar and have removed its mention here. We consider honey and syrups (including HFCS) as "sugars" as they are used as sweeteners added directly to food and are not consumed as foods per se. (line 171)

23. **L124-125: Is this necessary information?**

Response: Thank you for your comment. We have modified these lines but have kept the patient involvement statement as required by The BMJ (http://www.bmj.com/about-bmj/resources-authors/article-types/research#patients). (lines 197-198)

24. **L127: "reports" it is not clear until the results section that you are using the words trials and reports to mean 2 different things.**

Response: Thank you for your comment. We apologize for the confusion. We have used more careful language to clarify that a report of a study or studies is the unit of the search strategy, while a study comparison contained in a report is the unit of the analyses. (lines 190-195)

25. **L128 consensus of who?**

Response: Thank you for your comment. We have revised our manuscript to reflect consensus between reviewers (lines 212-213, 216-217).

26. **L128: what is health status referring to? is it presence of diabetes or not, or does it go further?**

Response: Thank you for your comment. The term "health status" refers to any documented health condition of the study participants (otherwise healthy, overweight/obese, metabolic syndrome, diabetes, hypertension, CHD, stroke, etc.). To improve clarity, we have changed the term "health status" to "disease status" throughout.

27. **L129: it is unclear at this point in the manuscript what "comparator form" means.**

Response: Thank you for your comment. We apologize for the confusion. Comparator form refers to the control that is free of or lower in fructose containing sugars with which the intervention (the food source of fructose containing sugars) is compared. To improve clarity, we have changed the term "comparator form" to just "comparator" throughout.

28. **L131: using "included" in this manner suggests that this is not a comprehensive list.**

    Response: Thank you for your comment. To improve clarity and denote that the list is comprehensive, we have changed the word "included" to "were". (lines??)

29. **L132: this paragraph is about data extraction and suddenly the authors jump to reporting data. I think this sentence would be better suited elsewhere in the manuscript.L135: it is not clear if the glycated blood protein data were extracted and then not reported or whether the change came at the point of data collection.**

    Response: Thank you for your comment. We have included our decision to report HbA1c rather than glycated blood proteins under this section to clarify why HbA1c values were reported and reflect that this decision came at the point of our data collection. (lines??)

30. **L137: your inability to contact or the authors failure to reply?**

    Response: Thank you for your comment. Our apologies for the confusion. We were referring the authors' failure to reply. We have revised the sentence for clarity. (lines??)

31. **L138: assessed by who? all 4 data extractors?**

    Response: Thank you for your comment. Risk of bias was assessed during the data extraction process, in which all reports were individually extracted at least twice by four separate reviewers (lines 133-134).

32. **L146: "were combined", this gives the impression that someone else has combined them. Would it be more appropriate to say available for combination?**

    Response: Thank you for your suggestion. To improve the clarity, we have used your suggested wording (lines 133-134).

33. **L150-154: please provide some detail of the categories. Did you consider study size for subgroup analyses? There is likely some clinical heterogeneity between participants recruited to small versus large studies.**

Response: Thank you for your suggestion. We have provided details regarding all of our subgroup categories as suggested (lines 159-69). We agree that study size is also an important consideration, however, we did not specify it as one of our a priori subgroups as the effect of sample size is assessed through publication bias analyses for small study effects. We did not detect any evidence of significant small study effects (lines??).

34. **L156: do you mean marker of glycemic control?**

Response: Thank you for your comment. We no longer mention this point here. To avoid confusion, we prefer the term "outcome measures of glycemic control" and have applied it throughout the manuscript.

35. **L158: -159; this information would have been most useful at line 113. L164: >10 studiers within trial design and/or outcomes and/or food sources?**

Response: Thank you for your suggestion. We apologize for the confusion. We have rewritten the entire statistical analysis section for greater clarity and flow. We have also clarified that ≥10 studies refers to number of studies per outcome. (lines??).

36. **L166: suspected from what? what were the criteria?**

Response: Thank you for your comment. We agree that this wording is confusing. By suspected, we were referring to evidence of publication bias based on the criteria in the sentence prior. We have dropped the word "suspected" and rewritten the sentence for greater clarity (lines??).

37. **L169-171: this sentence is very difficult to read. It needs further punctuation.**

Response: Thank you for your suggestion. We have revised this sentence for clarity *(lines??).*

38. **L175: I don't see these factors listed in your data extraction.**

Response: Thank you for pointing this out. Risk of bias was assessed using the Cochrane Collaboration risk of bias tool. To clarify our presentation of the methods, we have now described this in a separate section under, "study quality" (lines??). The other factors inconsistency, indirectness, imprecision and publication bias were not directly extracted from the studies, but were rather derived from an assessment of our primary analyses (e.g. inconsistency from the assessment and quantification of heterogeneity, imprecision from the 95% CIs of the pooled effect estimates, and publication bias from the publication bias analyses) or an assessment of the extracted study characteristics for the assessment of indirectness.

39. **L176: define wide**

Response: Thank you for your comment. We defined a 95% CI as "wide" based on whether it crossed the prespecified threshold for a minimally important harm and/or benefit (that is, whether it crossed the pre-specified minimally important difference [MID]). We have clarified this statement (line ??).

40. **L177: publication bias here appears to be referring to small study effects, different to the publication described on line 166, therefore how was this publication bias determined?**

    Response: Thank you for your comment. We agree that this statement is confusing. To be consistent with our description of the assessment of publication bias in the statistical analysis section above, we have clarified that the publication bias was determined based on evidence of significant publication bias (line ??).

41. **L182: why were these excluded? was it based on the full review and not meeting the criteria? How it is written currently suggests that the decision was somewhat arbitrary.**

    Response: Thank you for your comment. We have revised our manuscript to clarify that reports were exclude for failure to meet the eligibility criteria (line ??).

42. **L185: you need to specify in data extraction that these data were pulled.**

    Response: Thank you for your comment. We have included in our description of the methods for data extraction that these data were extracted. (line ??).

43. **L185: presented by trial design?**

    Response: Thank you for your comment. We have revised this sentence for greater clarity (line ??).

44. **L194: "healthy and overweight" this is confusing; how the other similar surrounding sentences are constructed is more explicit.**

    Response: Thank you for pointing this out. We have revised this sentence for greater clarity (line ??).

45. **L197: why "however"?**

    Response: Thank you for your comment. We agree that the word "however" was misplaced. We have removed it and revised the sentence (line ??).

46. **L199: please present an estimate of variance each time a mean/median is presented.**
    Response: Thank you for your suggestion. As requested, we have included the range for each median as an estimate of variance (line ??).

47. **L202: please insert n after most trials.**

Response: Thank you for your comment. We agree that including the number of studies included in each analysis would be useful, especially for analyses with few trials. We have added his information throughout the results section.

48. **L204: please insert n after very few trails.**

Response: Thank you for your comment. We agree that including the number of studies included in each analysis would be useful, especially for analyses with few trials. We have added his information throughout the results section.

49. **L207: it would make the section titles more commensurate with each other if this and the following sections were renamed "outcomes:HbA1c"**

Response: Thank you for your suggestion. We have renamed these headings according to your suggestion throughout the results section.

50. **L215: why are you selectively reporting this upper CI to three decimal places here. It is also not what is reported in figure 2 where it is actually reported as null.**

*Response: Thank you for your comment. As requested, we have corrected the decimals to match our values reported in **Figure 2** and **Supplementary Figure 2**. All 95% CIs and p-values have been updated and checked for accuracy based on our updated analyses.*

51. **L218: where are these analyses presented?**

*Response: Thank you for your comment. These results are presented in **Supplementary Table 3**. To improve clarity, we have clarified the link to the supplementary table in the text and also renamed the table, "Select sensitivity analyses in which the systematic removal of an individual study altered the significance of the effect estimate or the evidence for heterogeneity" **(Supplementary Table 3)***

52. **L220: higher baseline levels of what?**

Response: Thank you for your comment. We have removed this finding from our results as our updated analysis no longer showed a significant effect of baseline Hba1c levels.

53. **L221: but these were not significant.**

Response: Thank you for your comment. We have removed this finding from our results as per the comment above.

54. **L208-225: There are too many important results presented in supplementary materials only. While it is fine to give the extra detail in the supplementary material the results need to be better summarised in the main body of the paper otherwise you are treating supplementary material as main body tables/figures which makes it very difficult to navigate the manuscript.**

    Response: Thank you for your suggestion. We agree that there are many important results presented in the supplementary materials. We have attempted to work within word count constraints to include a greater description of the supplementary results throughout the results section.

55. **L238: what does G2 stand for?**

    Response: Thank you for your comment. G2 stands "group 2" as the report by Campos et al. included the results for 2 distinct groups, which were counted as 2 separate studies in our analyses. This is detailed in the legend of our table of characteristics on supplementary table 1. We have also defined "group 2" as "G2" at its first mention in the text (line ??).

56. **L238: what effect?**

    Response: Thank you for your comment. The statement in question no longer exists, but we have revised the text for clarity through the results section.

57. **L238: it would be more informative to give information about the trial rather than the author of the paper e.g. how many of the 585 participants were part of this trail and thus excluded?**

    Response: Thank you for your suggestion. We have incorporated a greater description of relevant study information (line ??).

58. **L245: outlier, defined how?**

    Response: Thank you for your comment. This section was removed from our manuscript as a continuous fructose dose was no longer observed in our updated analyses.

59. **L251: is underlying disease status the same as health status described previously?**

    Response: Thank you for pointing this out. To ensure continuity, we have changed this term to "underlying disease status" throughout the manuscript.

60. **L278: include n of trial.**

    Response: Thank you for your comment. As requested, we have added the number of participants from the description of the studies removed during sensitivity analyses (line ??).

Discussion

61. **L311: I think you need to include "4 trial designs" or something to that effect here.**

    Response: Thank you for your suggestion. We agree and have included this information. (line ??).

62. **L315: I am not convinced by the argument for a different effect for fructose from fruit given how the upper CI is essentially**

    Response: Thank you for your comment. Fruit is no longer significant and so this finding has been removed throughout the manuscript.

63. **L319 what about from dairy and mixed sources both have larger effect estimates according to your results.**

    Response: Thank you for bringing up this important point. These results have changed with the inclusion of the new studies and reclassification of the dairy studies as substitution studies in our updated analyses. Both findings, however, remain significant, and we have included a discussion of the results from dairy and mixed food sources. (line ??)

64. **L336: What about the dairy results?**

    Response: Thank you for your suggestion. We agree that a discussion of our dairy results would be useful. We have incorporated an interpretation of dairy results in our discussion of potential mechanisms. (line ??)

65. **L346: did you consider effects on de novo lipogenesis as a mechanism?**

    Response: Thank you for your comment. We have included a discussion of de novo lipogenesis (DNL) as a possible mechanism for the fasting blood glucose and insulin increasing effects in the addition studies (line ??).

66. **L351-354: but there are 32 trials for hba1c compared with 101 for glucose and 75 for insulin so this statement is unfounded.**

    Response: Thank you for comment. We agree have removed this statement. (line ??).

67. **L361: uric acid levels?**

Response: Thank you for your suggestion. We have revised our manuscript to include this improved wording (line ??).

68. **Line 361: are these references all trial data?**

Response: Thank you for your comment. These references refer to a series of systematic review and meta-analyses of controlled intervention studies of the effect of fructose on related cardiometabolic endpoints. We have revised the sentence to clarify the level of evidence from which these data are drawn (line ??).

69. **L362: I would prefer to see these results discussed with the main results as they affect the interpretation of the main results.**

Response: Thank you for your suggestion. We have renamed this section, "Sources of heterogeneity", and moved it up under the discussion of the main results. *(line ??).*

L382: national intakes of what country? Please remember the potential international readership when revising this.

Response: Thank you for your comment. We have revised our manuscript to clarify our reference to levels of American dietary intake. (line ??).

70. **L386: Can you put intakes of fructose in free living populations and in the included trials in this analysis in context of the dietary guidelines for sugars of 5-10% of energy intake?**

Response: Thank you for your comment. As suggested, we have put our results in the context of the public health targets for the sugars of 5%, 10%, and 25% *(line ??).*

71. **L387: what about dental carriers? Do you mean, based on evidence for protection against dental carries?**

Response: Thank you for your comment. We were referring to the evidence for protection against the development of dental carries but this discussion has since been removed to accommodate the many other requested changes.

72. **L418: the information contained here is particularly important for interpreting the main results and understanding why the presentation of main results appears a little selective. This needs to be presented at the same time as the main results. See my previous comment RE line 362.**

Response: Thank you for your comment. As requested, we have moved all of the relevant discussion items regarding subgroup analyses and sensitivity analyses up with the discussion of the main

results. The specific results referred to in your comment are no longer relevant with the updated meta-analyses and have been removed. (lines??)

73. **L429: here and throughout than manuscript I think you make more of the protective effect of fructose from fruit on HbA1c than the results warrant.**

    Response: Thank you for this point, which is well taken and applies even more now with the updated meta-analyses, as fruit is no longer significant. We have removed the mention of fruit here from the main conclusion. (lines??)

74. **L436-441: this is just a description of the protocol, please expand and explain why these are strengths of the study.**

    Response: Thank you for your comment. We have revised the text to make it clearer why each of the protocol elements described are strengths. (lines??)

75. **L443-453: how did you attempt to overcome these limitations and how do they impact on the interpretation of the results?**

    Response: Thank you for your comment. Our apologies for the confusion. We addressed the limitations by using them to downgrade the evidence by the GRADE approach. As such, the limitations combined with the strengths informed the overall quality (certainty) of the evidence for each outcome and our conclusions. To reflect these points better, we have revised our limitations section. *(line ??).*

76. **L462: can you interpret this null in any way for the reader?**

    Response: Thank you for your comment. The ad libitum result is no longer null. We have included an interpretation of the null subtraction trial result under the section potential mechanisms *(line ??) and here in the conclusion (line ??)*

77. **L464: What makes them important?**

    Response: Thank you for your comment. For clarity, we have changed the word "important" to "common" (line ??).

78. **Figure 1: this could have a more informative title. What determined an endpoint as unsuitable? Do you mean outcomes other than those of interest? Do "acute/short term" refer to studies less than 7 days? Co-intervention trials as an exclusion should be made clear in the methods text. "irretrievable" was this before or after contacting authors?**

Response: Thank you for your comments. Unsuitable endpoints referred to studies that did not report outcomes of interest as you have mentioned. We have clarified our breakdown to indicate that acute/ short term studies referred to those lasting <7 days. Co-intervention studies were studies that included multiple interventions in a single treatment arm (one of which may have included fructose-containing sugars), making it difficult to disentangle the effect of fructose-containing sugars from that of the other interventions. Studies were categorized as irretrievable after contacting authors. (Figure 1)

79. **Table 1: for trial size what are the numbers before parentheses? It is not clear from the footnotes if these are medians as well or something else.**

Response: Thank you for your comment. The values represent medians and ranges as reported in our legend: "[1,2,3]Values are reported as Medians and Interquartile Ranges (IQR)[1], ranges[2] or percent ratios[3]." (Table 1)

80. **Figure 2: I wonder as to the use of "total food sources", it isn't really total as this would suggest total fructose intake from all sources while this is intake of fructose from sources used in trials. Would combined sources be better? The result presented here for fruit in substitution trials contradicts the text. It is simply because of the number of decimal places presented but highlights how close to a null effect this result is. Please see my previous comment RE line 429. It would be useful to have a definition of what is included in these food groups at some point in the manuscript.**

Response: Thank you for your comment. We apologize for the confusion. We use the term "total food sources" to denote the total food source from the available studies. To make this clearer, we have used the term "individual food sources" when discussing specific foods. We feel that the use of these terms together makes their respective definitions clearer. These terms are now used consistently throughout the manuscript.

81. **Supplementary table 1: Is there a legend missing.**

Response: Many thanks for the observation. We have included a legend in the supplementary Table 1.

82. **Supplementary table 2: this would benefit from a more detailed title. The unit for body weight in Agebratt et al. is missing. There are two trials by Johnston et al included and they seem to have the same participants in both; did you make any considerations in your analyses for this? What does OP stand for? It doesn't appear to be in your footnotes.**

Response: Thank you for your comments. To improve clarity, the title of Table 2 has been changed to "Characteristics of included intervention studies of the effect of food sources of fructose-containing sugars on glycemic control". As requested, we have added the unit for body weight in Agebratt et al.

The two studies by Johnston did include the same participants in both substitution studies. One was done under matched condition of neutral energy balance and the other under conditions of matched positive energy balance, each with its own intervention and control. We did not account for participants being the same, as each study was a separate study event with its own separate intervention and control and so there was no double counting. OP means outpatient, and it has been added to the footnote. (Supplementary Table 2).

83. **Supplementary table 4: what do the notes in parentheses refer to? I see the definitions in the footnotes but I don't understand the relevance here and in other tables. Please include the n of each study and the total n in this table as it is crucial for interpretation of these analyses.**

Response: Many thanks for your comments. Please note that Supplementary Table 4 is now Supplementary Table 3. The notes in parentheses are used to differentiate the study from the other study taken from the same report. We included more than one study comparison in the case of some reports and so have used codes in parentheses as unique identifiers. We have added the number of participants in the intervention and the control arms for each study that was removed during sensitivity analyses. We have also added the total number of remaining studies in the analysis. (Supplementary Table 3)

84. **Supplementary figure 1: please include total n. Tables should be stand alone.**

Response: We agree that it is Important to add the total n to this figure and that all tables and figures should be able to stand alone. As requested, we have added the total n to the legend of Supplementary Figure 1.

85. **Supplementary figure 4: sugars-sweetened, do you mean sugar sweetened? This occurs more than one in the manuscript.**

Response: Thank you for your comment. We used the term "sugars-sweetened" instead of "sugar sweetened" to capture all fructose-containing sugars, as the term "sugar" from a labelling and regulatory perspective refers to "sucrose". This same terminology was adopted by the UK SACN committee in their report on carbohydrates and health (for Scientific Advisory Committee on Nutrition. Carbohydrates and Health. Public Health England. London 2015. Accessed at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf). That being said, if the editors prefer, then we are happy to use the term "sugar sweetened".

86. **Supplementary figure 7: change in font.**

Response: Thank you for your observation. As requested, the font in supplementary figure 7 has been changed.

87. Supplementary figure 14: unit for age is missing

Response: Thank you for your observation. We have added the units for age to Supplementary Figure 14.