Author’s response to reviews

Title: Whole grain food diet slightly reduces cardiovascular risks in obese/overweight adults: a systematic review and meta-analysis

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Author’s response to reviews:

Thanks for all the editors’ and reviewers’ comments about this manuscript. All the answers are as follows:

1. Q: Technical Comments- No List of Abbreviations

R: We have added the list of the abbreviations.

2. Q: Editor Comments: Please include also CRP in your objectives!

R: We have added the CRP in objectives.

3. Answer to Stefano Omboni (Reviewer 1): Thanks for the comments.

Q: Methods. The authors must specify whether they used a fixed or random effect (I guess they used the second).

R: We used the random effect and we revised it in the manuscript at statistical analysis.
Q: Results. Looking at Table 1 I realize that there are several missing data among the primary outcomes of the study. These data may be the general clinical data and not the real outcome data presented in the tables. Since results are presented for these studies without mentioning in the methods whether there was missing information and whether this was treated in some way, this must be specified.

R: Table 1 showed the baseline information of included articles instead of the outcome information. Not all the included articles contain all relevant information and we represent it as not available. Other meta-analysis studies also represent like this.

Q: Results. Figures 2, 3 and 4 are split in two sections. What is the meaning of these subgroups?

R: In order to investigate the source of heterogeneity, subgroup analysis was conducted in three outcomes with positive results.

Q: The authors claim that a whole grain diet significantly reduces LDL-cholesterol, though the p value is =0.05, which is not significant. The study is able to show only a negligible effect on body weight and PCR. Thus, the conclusion that whole grain had a moderate effect on these variables may be excessive. Conclusions should be smoothed.

R: We have changed the “moderate” to “slight” in conclusion.

Q: Discussion. Given the modest results of the meta-analysis, there is too much speculation about the possible origin of the outcomes. The discussion should focus on the results.

R: We have added the overall results in the first sentence of the discussion. We also talked about the origin of the outcomes in different RCTs and focused on the results. We think it’s essential to talk about the possible origin of the outcomes.

Q: Discussion. Limitations of the study should be discussed. Why authors did not plan a sensitivity analysis, for instance according to study duration and type of diet?

R: We have discussed the limitations of this study in the manuscript. We have done the subgroup analysis and it didn’t work according to type of diet so we didn’t plan a sensitivity analysis.
Q: Discussion. The authors discuss results of subgroup analysis. However, these data are never shown in the results.

R: We have added the relevant details in the manuscript.

4. Answer to Christopher Wong (Reviewer 2): Thanks for the comments.

Q: The authors need to first clarify the rationale for the present analysis. The mention a systematic review and meta-analysis in the introduction but it is not clear whether this is re-addressed in the discussion. There should be an adequate discussion of these prior studies and how the present analysis extends previous observations.

R: We have rewritten the discussion. We have added the overall results in the first sentence of the discussion. We also talked about the origin of the outcomes in different RCTs.

Q: Further information on the methodology needs to be provided. For example, the authors talk about their objective being "to evaluate the impact of whole grain foods on body weight in patients with overweight or obesity" - however, the methodology does not mention any inclusion criteria specifically focussing on these patients. No subgroups are mentioned in the methods yet are reported on later. Was the protocol registered?

R: We have added the obese/overweight standard in “Eligibility criteria and data extraction”. Subgroups were added in “Statistical analysis” of the methods. This manuscript was registering in PROSPERO and the record ID was 157399.

Q: The results of subgroup analyses are mentioned in the discussion section - these should be included and expanded on in the results (as well as the methods section). It is not clear how these subgroups were exactly defined. One presumes the Figures are divided into these subgroups, but this is not mentioned in the labels.

R: We have added the subgroup analysis in the part of methods and results. We have revised the label in Figure 2-4 (subgroup name: positive results and negative results).

Q: The discussion needs revision to better present the findings of the analysis in the context of prior literature. The manuscript would benefit from review by English language review

R: We have added the main findings in the first paragraph of the discussion. We also have the English language reviewed by the professional company and we have provided the certification.
5. Answer to Thomas Agbaedeng, B.Sc. (Hons.), Ph.D. (Reviewer 3): Thanks for the comments.

Q: Major Comments to the Author

The present manuscript should be sent for language proofreading - it was very difficult to follow.

R: We have the English language reviewed by the professional company and we will provide the certification.

Q: Abstract

1. The authors have not commented on what the problem the investigated was. They also have not stated the aim(s) of the current study in the Background. Here, the authors need to indicate that the study is a "systematic review and meta-analysis."

R: We agree with your comments and revised the related contents in the Background.

Q: 2. The Methods is in a very poor state. The primary and secondary outcomes should be separated - at present, this is very ambiguous. Was quality appraisal performed? This should be summarised.

R: We accepted your suggestion and modified the apart of Methods.

Q: 3. In the Results, the authors should briefly summarise the search results. The presentation of the results has not been correctly done. The mean difference (MD) and 95% CI should be reported first before p-value. Also, the mean difference can be abbreviated after first use.

R: We corrected corresponding contents in the Results according to your recommendations.

Q: 4. The Conclusion should be revised for improvement.

R: We agree with your suggestion and revised the Conclusion apart.
Q: Introduction

The background is not very coherent. There are bits of information added everywhere, thus making the whole section difficult to follow.

R: We rewrote the corresponding contents according to your comments.

Q: Methods 1. The "Data sources" subsection is inadequate. There is no registration number provided - it is a requirement that all systematic reviews and meta-analysis be prospectively registered on PROSPERO. The authors should provide the dates the searches were performed and date range for the searches. What is also missing is how the authors went from online database search to study inclusion. What software did they use for reference sorting?

R: Our protocol has are registering in PROSPERO(ID:157399). We started searching the relevant articles at June, 2019. It lasts about 2-3 months. We searched the articles in three databases including Pubmed, Embase and Cochrane library. We screened the articles by using Endnote.

Q: 2. The authors should provide the initials of the investigators that performed data extraction and assessment of study bias.

R: We have revised it according to your comments.

Q: 3. The authors indicate that they extracted data on "cardiovascular outcomes;" however, they have not described which outcomes, in particular, they extracted. These should clarified.

R: We have added it in the part of “Eligibility criteria and data extraction”.

Q: 4. The "Data analysis" is missing the statistical methods used for the analysis.

R: We have described the method of data analysis in the part of Statistical analysis including software.
Q: Results 1. In the flowchart, the authors state that 995 abstract (not abstracts) was retrieved. Does this mean that articles without abstracts, e.g., case reports, were excluded before retrieval of abstracts for sorting? This not a correct format of reporting search strategies. The combined database references retrieved should be indicated, followed by the numbers excluded at title stage, abstract stage, and fulltext. Additionally, the authors state "950 abstract excluded." They need to provide the reasons for the exclusion.

R: We have revised the flow chart according to your suggestion. We did not exclude the case reports e.g. before retrieval of abstracts for sorting. The selection process was carried out through Endnote software.

Q: 2. The Results sections is very limited in terms of the reporting. The authors have not reported the baseline characteristics in detail, other than referring readers to the Table 1. The Outcome of the "Assessment of bias" has not been reported. Reading the results from the pooled analyses, it is difficult to appreciate the level of statistical heterogeneity. Strongly suggest the authors revise the entire Results. It should divided into subsections, with subheadings.

R: We have added the baseline information in part of “Study characteristics”. We also added the part of “Assessment of bias”. We have divided the results into three subsections (Study characteristics, Cardiovascular outcomes, Assessment of bias). Most of the statistical heterogeneity were less than 50%, we thought it was acceptable.

Q: 3. For figures 2-5, the subgroups have not been well defined. The authors should correct this by providing the subgroup names on the forest plots.

R: We have added the subgroup names (positive results and negative results) in Figure 2-4. Figure 5 did not have the subgroup.

Q: Discussions 1. The first paragraph should be used for summarising the major findings of the meta-analysis. Currently, this has not been done. Stating the hypothesis of the study for the first in the Discussions sections is bad practice - this should be corrected.

R: We have added the main findings in the first paragraph of the discussion.
Q: 2. On line 59, the authors state that subgroup analysis was done; however, this was not indicated in the Results nor in the Data analysis. The authors should elaborate on this in the Results.

R: We have added the subgroup analysis in the Methods and Results.

Q: 3. The lack of acknowledgement of limitations of the study is very concerning.

R: We have added the limitation part in the manuscript.

Q: Minor Comments to the Author 1. Suggest the authors create a continuous line numbering, rather than the present one that restarts in each page. The pages must also be numbered.

R: We have added the continuous line numbers and page numbers.

Q: 2. In academic writing, the last item in list is always preceded by the conjunction "and." Unfortunately, this has not be obeyed throughout this manuscript. For example, instead of "weight, blood pressure, body mass index, waist circumference, cholesterol." lines 16-19 (2nd Methods page), have "weight, blood pressure, body mass index, waist circumference, and cholesterol."

R: We have revised it.

Q: 3. All abbreviations should be written in full at first use, followed by the abbreviation in parenthesis. Please define CVD on line 11 (1st Introductory paragraph).

R: We have defined the CVD in part of abstract. And we also check the abbreviations in the whole manuscript.

Q: 4. The phrase "...the most effective cardiovascular risk factors." (lines 16-20, 1st Introductory paragraph) does not make any sense.

R: We have deleted this phrase.
Q: 5. Change "…heart protection compounds…" on line 30 to "…cardioprotective compounds…”

R: We have revised it.

Q: 6."Whole grains" are associated with increased satiety, not lower, as hinted in between lines 56, 1st Introductory page, and 1 in the 2nd Introductory page.

R: What we described was that high intake of whole grains was associated with lower BMI, not lower satiety.

Q:7. Under eligibility criteria and data extraction,

a. The phrase "Studies would be included when satisfying the following criteria…” should be revised as "Studies were included if they satisfied the following criteria…”

b.In the 3rd point, delete the definite article "the".

R: We have revised it.

6. Answer to Harshal Waghulde (Reviewer 4): Thanks for the comments.

Q: 1.Table 1 formatting makes it little difficult to read the content. Please reformat the table.

R: We have revised the format of Table 1.

Q: 2. The abbreviations in the manuscript need to be defined at its first use. Please ensure that all the non-standard abbreviations are properly defined at its first use.

R: We have defined all the abbreviations at its first use and we added the list of abbreviations in the manuscript.

3. Please provide the list of abbreviations used in the manuscript.

R: We have defined all the abbreviations at its first use and we added the list of abbreviations in the manuscript.
Q: 4. Figure quality need to be improved, most of the text is blurry to read properly.
R: We will submit all figures again with high quality.

Q: 5. In figure 9B, different colored symbols need to be explained in the figure legend.
R: We have added the figure legends (Red color: high risk of bias; Yellow color: unclear risk of bias; Green color: low risk of bias).

Q: 6. Do you need to provide the contact information of the authors other than corresponding author on the title page as per journal guidelines? Please verify.
R: We have provided all the authors’ email addresses in the submitting system.

7. Answer to Kristina Selthofer-Relatic, Assist.prof, PhD, cardiologist (Reviewer 5):
R: Thank you very much for the support of our article.

8. Answer to Adina Binti Abdullah (Reviewer 6): Thanks for the comment.
Q: a) the analysis did not identify which whole grain diet exert the effect
R: All included articles did not have same components of whole grain. So we can only compare whole grain as a whole with other diet.

Q: b) the inclusion of studies with high risk of bias
R: We have performed the assessment of bias showed in Figure 9 by using Cochrane Collaboration’s tool. As the randomized controlled trials involved dietary intervention, some researches failed to implement blind intervention on subjects which leading to high performance bias. And we found that no other significant biases were observed.

Q: c) the sub-group analysis was not presented in the result section but discuss in the discussion section
R: We have added the subgroup analysis in part of methods and results.
Questions in the attached PDF: how do you select study according to 'data extraction'?

R: The selection process was performed by using the Endnote software to filter the abstracts.

Q: “In order to investigate the source of heterogenity, subgroup analysis was conducted in three outcomes with positive results.” Do not discuss results not presented in result section.

R: We have added the subgroup analysis in results.

Q: “In our review, the interventions covered barley, oat, wheat, rye and quinoa, and few studies only gave ambiguous definition”. I feel this may be the issue with the analysis as the researchers could not conclusively recommend which whole grain diet is beneficial.

R: All included articles did not have same components of whole grain. So we can only compare whole grain as a whole with other diet.

We also revised format according to the reviewer’s comments.