Author’s response to reviews

Title: Consumption of whole grains and cereal fiber and total and cause-specific mortality: prospective analysis of 367,442 individuals

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Version: 2 Date: 8 January 2015

Author’s response to reviews: see over
Dear Editor,

Re: MS: 1831869841478015: “Consumption of whole grains and cereal fiber and total and cause-specific mortality: prospective analysis of 367,442 individuals”

Tao Huang, Min Xu, Albert Lee, Susan Cho and Lu Qi

Thank you for your letter of December 2nd, 2014 in which you provided comments on the above manuscript, and provided an opportunity for us to further revise it. We have taken the reviewers’ comments and suggestions into consideration and revised the manuscript accordingly. On the following pages, please find our responses to the reviewers’ concerns, and details of the pages on which the changes have been made.

We had checked all style requirements for *BMC Medicine* one by one carefully. The manuscript has not been submitted nor is under consideration for publication by another journal. All authors have read the manuscript and are in agreement that the work is ready for submission to *BMC Medicine* and accept the responsibility for manuscript contents. None of the authors has any conflict of interest in the matter.

We believe that the quality of the manuscript has been considerably enhanced as a consequence of the review process. We hope that the revised paper now meets your approval for publication in *BMC Medicine*. Please do not hesitate to contact me if you need any further information.

Sincerely,

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**Reviewer 1's report**
Title: Consumption of whole grains and cereal fiber and total and cause-specific mortality: prospective analysis of 367,442 individuals
Version: 1 Date: 24 November 2014
Reviewer: Dagfinn Aune

**Reviewer's report:**
This is large study of whole grain intake and all-cause and cause-specific mortality including 46067 deaths among 367442 participants from the NIH-AARP Diet and Health Study. The study is well conducted and the results are important from a public health point of view. Some of the findings with regard to specific causes of death (respiratory disease, infections) are novel as well. I have some comments that should be addressed.

**Response:** We thank the reviewer for the encouraging comments!
Major compulsory revisions

Whole grain foods were defined as those containing at least 25% whole grains and/or bran. The amount of whole grain intakes provided in Table 2 – do they refer only to the whole grain part of each product or to the whole product (including also the non-whole grain parts)? Please clarify.

Response: Yes, the whole grains were defined as the whole grain part of each product. USDA’s Pyramid Servings Database was used to accurately estimate whole-grain intake from all foods in the FFQ. We have clarified this in PAGE 5.

It would have been interesting to know whether specific types of whole grain foods/products were associated with mortality and cause-specific mortality. Could the authors analyze and report results for the most important contributors to whole grain intake, e.g. whole grain cereals, whole grain breads/rolls, brown rice, cooked cereal similar to that provided in Table 2?

Response: Thanks for your thoughtful suggestions. However, this project was proposed to analyze the overall whole grain intake only; so we could not get access to individual contributors for in-depth analyses as suggested.

Could the authors also add results for whole grains and coronary heart disease and stroke (and stroke subtypes) mortality in addition to the overall result for cardiovascular disease in table 2?

Response: Such sub-grouping data (coronary heart disease and stroke) are not available in the NIH-AARP dataset.

The inverse association between whole grain intake and respiratory disease and infections are quite novel. In the EPIC study cereal fiber intake was also inversely associated with digestive disease (non-cancer) deaths as well, while Jacobs et al reported results for whole grains and a number of different specific causes of death (Am J Clin Nutr 2007;85:1606 -14, Table 2 and Table 6). Could the authors also add results for digestive disease deaths and perhaps others causes of death as reported by Jacobs et al? It would also be interesting if the authors could add results for whole grains and all other remaining causes of deaths than those reported in Table 2? As the study is quite large it may be one of the few with sufficient power to investigate less common causes of death which could be of interest from a hypothesis-generating viewpoint.

Response: Thanks for your thoughtful suggestions. Jacobs et al’s paper considered noncardiovascular, noncancer inflammatory diseases (e.g. infectious diseases, nervous system disorders, pneumonia, respiratory diseases, digestive system diseases, skin diseases, musculoskeletal and connective tissue disorders, genitourinary diseases). However, most of these diseases data (e.g. nervous system disorders, pneumonia, musculoskeletal and connective tissue disorders, genitourinary diseases) are not available in our dataset. Furthermore, we have already reported the results for Respiratory disease and Infections.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests

Reviewer 2's report
Title: Consumption of whole grains and cereal fiber and total and cause-specific mortality: prospective analysis of 367,442 individuals
Version: 1 Date: 28 November 2014
Reviewer: Michel de Lorgeril
Reviewer's report:
This is an interesting study evaluating whether consumption of whole grains and cereal fiber is associated with reduced total and cause-specific mortality. The study is huge (n=367,442), follow-up is long (14 years) and the number of death is considerable (>46,000).
Response: We thank the review for the encouraging comments!

Major aspect
They show several significant inverse associations confirming that whole grain consumption is safe and likely protective against several types of deaths. The authors however cannot (with such a study) answer to their apparent main question (end of the second paragraph in the Introduction): is protective effect of whole grain due to its cereal fiber components? Despite many statistical adjustments, a causal relation cannot be demonstrated with such a study and I suggest deleting this hypothesis. They can however prudently discuss the issue in their discussion section.
Response: We agree with reviewer, and have removed the sentence in PAGE 3 “Furthermore, whether protective effects of whole grains are due to its cereal fiber component remains unclear in the general population.”
Of note, in our analyses the associations of whole grains with total mortality were largely attenuated, though remained significant after adjustment for cereal fiber intakes. These observations suggest that cereal fiber, the main component of whole grains may at least partly account for the protective effects of whole grains on mortality. We have discussed this issue in discussion in PAGE 11, and revised the conclusion in PAGE 13

Minor aspects
In the Abstract, data about follow-up and number of death should in the result section not in the design section.
Response: We have revised it accordingly in abstract in PAGE 2.

Methods: it is not clear why extreme consumers (about 7,000) have been excluded, as they could provide some information. Was exclusion done before the first analyses? What were the exclusion criteria?
Response: Exclusion of individuals reporting extreme energy intake is widely used in nutritional epidemiology studies, because these participants are more likely to over- or under-report their intake. Yes, exclusion was done before the first analyses. We have added the related information in PAGE 4.

We need to know how alcohol intake and physical activity have been quantified.
Response: Information on alcohol intake and physical activity was self-reported using questionnaire. Alcohol intake was quantified in g/day; physical activity was quantified in hours per week as categories: never, rare, 1-2, 3-4, >=5 hrs/week.
We have added the related information in PAGE 5.

We would like to read in the article what are the main cereals consumed by that US population; proportions of wheat, whole wheat, rye, whole rye and so on.
We would like to read in the article what are the main fibers quantified in that study. Two simple Tables would be welcome.
Response: The main cereals consumed are ready-to-eat cereals, high-fiber cereals, cooked cereal, and other fiber cereals. We have added this information in PAGE 5. Main fibers are from fruit, grains, vegetables, and beans in the present study. We also added related information in the paper.
In the discussion section, it would be important the authors discuss a little bit more about what are the biological properties of the fibers they are supposed to have measured. If, as an epidemiological study, they report interesting data, they should mention that the issue is extremely complex. As an example, fibers are involved in the regulation of gut microbiota which is appearing as a major health issue. In addition, beside their own properties, certain fibers are intrinsically linked to grain polyphenols (arabinoxylans vs. ferulic acid) and their metabolism are ineluctably interconnected and also connected to the gut microbiota ...

**Response:** Thanks for thoughtful suggestions. We have revised the discussion accordingly in **PAGE 12** as “In addition, dietary fibers have specific and unique impacts on intestinal microbiota composition and metabolism; and recent studies have related gut microbiota with various chronic diseases such as obesity, CVD, diabetes and cancer. Further functional investigations are warranted to verify these potential mechanisms.”

**Quality of written English:** Needs some language corrections before being published
**Statistical review:** Yes, and I have assessed the statistics in my report.
**Declaration of competing interests:**
I declare that I have no competing interests