Dear editor and dear reviewers

Thank you very much for the additional comments and suggestions. We have modified the manuscript according to the comments below. We have also updated the literature search and the statistical analyses as there have been published five additional publications (Shi et al, 2015, Xu et al, 2015, Wang et al, 2016, Bongard et al, 2016, and Helnæs et al, 2016), two of which reported on whole grains and the remaining reporting on total grains, bread, refined grains and breakfast cereals. We hope this is sufficient for the manuscript to be accepted for publication in BMJ.

On behalf of all the co-authors

Yours sincerely

DagfinnAune

Please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the Editors:

* Please remove calculations about premature deaths avoided if grain intake was increased to 120 g/d (see reviewer 2's comments).

RESPONSE: We have removed all calculations of attributable risks.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
I read this revised manuscript about whole grains and all-cause and cause-specific risk and mortality with great interest. I think that the authors did a great job addressing review comments.

RESPONSE: Thank you very much!

Besides the few extra comments below, I have no further comments to add.

I think that this meta-analysis addresses a important topic, and that it could have a large and broad public health impact, as many countries are still to focus more on increasing the whole-grain intake of the general population, due to the many health benefits elegantly illustrated in this meta-analysis.

Few extra comments:
- Supplementary tables 3, add a column indicating the actual outcomes under study (e.g. for CVD, indicating that the outcome is incidence of ischemic heart disease). I know that it is mentioned in the table, but it would be more clear, if it had a separate column.
RESPONSE: We have added a separate column to Supplementary Tables 3-6 which indicates whether the outcome is incidence or mortality from the specific outcome. For the remaining outcomes in Supplementary Tables 7-12 all are from mortality.

- First line of the discussion: please avoid priority statements.
RESPONSE: We have modified the sentence so it reads: “This dose-response meta-analysis found an inverse association between whole grain intake and several major chronic disease outcomes, including coronary heart disease, stroke, cardiovascular disease overall, total cancer, all-cause mortality as well as less common causes of death such as mortality from respiratory disease, diabetes, infectious disease, and all non-cardiovascular, non-cancer causes of death.”

Additional Questions:
Please enter your name: CecilieKyrø

Job Title: Postdoc
Institution: Danish Cancer Society Research Center
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No
Funds for research?: Yes
Funds for a member of staff?: No
Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No
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If you have any competing interests <A HREF="http://www.bmj.com/sites/default/files/attachments/resources/2011/07/bmjpolicyondeclarationofinterestsmarch2014.pdf" target="_new">(please see BMJ policy)</a> please declare them here: No, I have no competing interest.

My research is funded by Innovation Fund Denmark (ELIN-B0603-00580B)
Reviewer: 2

Recommendation:

Comments:

I thank the authors for their very detailed replies to comments on the submitted version. While I find such studies very interesting, as I’m sure most of us do, I’m quite sceptical about whether we can draw reliable inferences. In all such studies the risk of residual confounding is considerable. I’m in favour of transparency but I do question whether we need 22 supplementary tables and 95 supplementary figures.

RESPONSE: We agree with the referee that there is a large number of supplementary tables and figures, but think these add important details for particularly interested readers and also better enable readers to assess limitations and strengths. A lot of the material contained in the supplementary appendix is required by the PRISMA guidelines (search strategy, list of excluded studies and exclusion reason, study characteristics, subgroup analyses, study quality assessment, funnel plots, results of sensitivity analyses). Lastly, for consistency with several other meta-analyses on other plant foods and antioxidants and mortality which we have conducted (under review) and for which we used the same format we would prefer to keep this information in the supplement.

Specific comments in response to the authors’ responses:
1. I queries the use of 7 servings a day as optimal. The authors have not changed this. While it is fine to use 7 as the reference the term “optimal” is surely inappropriate. In the context of diet in particular I think this term is unwise.

RESPONSE: The text where the term “optimal” was referred to was deleted together with the calculations of attributable risks.

2. I'd prefer that the authors note that tests for “publication bias” do have low power when there are few studies, not that they may have low power. And note that it is recommended that funnel plots not be used with fewer than 10 studies (Sterne et al BMJ 2011;343:d4002).

RESPONSE: We modified the sentence so it reads: “There was no evidence of publication bias for the remaining outcomes, although the number of studies was moderate and power to detect such bias is low when there are few studies.” We have deleted the funnel plots for analyses with less than 10 studies.

3. The authors present calculations of numbers of deaths saved if grain intake was increased to 120 g/d. Such calculations make very strong assumptions. Apart from the relevance of the actual studies to the general population, no account is taken of other changes to the diet that would occur if someone increased grain intake.

RESPONSE: We have deleted all calculations of attributable risks and the text describing it.

Other comments relating to reading the revised version:
4. PRISMA is not a guide for conducting a systematic review (p176).

RESPONSE: We agree with the reviewer and have amended our sentence referring to the PRISMA criteria so that it now reads: We followed standard criteria (PRISMA criteria) for reporting meta-analyses.(37)

5. Table 1 should explain what the RR’s are and also be explicit that RR<1 favours those with higher intake.

RESPONSE: We added to both table 1 and 2 the following: “RR (95% CI) = relative risk and 95% confidence intervals. RR<1 favours those with higher intake”
6. Figures. It would be good to reduce the size of the black squares in forest plots so that the CIs can be seen.
RESPONSE: We have reduced the size of the black squares so the CIs are visible for most of the studies. However, for a couple of studies the CIs are so narrow that it was not possible to make the CIs visible.

7. How were CIs for splines calculated?
RESPONSE: We added to the statistical methods section: "The 95% CIs were derived from the standard errors of the differences in linear predictors between each given point on the dose-response curve and a stated reference value, computed from the covariate values and the covariance matrix of the estimated coefficients."

8. I don’t really get a good idea from the figures of the range of intakes – I’d find it useful to know what was the range of intakes of each food of most people in the studies. But I’m not sure how easily that can be summarised across studies.
RESPONSE: We have added scatter plots for the nonlinear analyses to the supplement to give an indication of the range of whole grain intake across studies (Supplementary Figures 2, 4, 6, 8, 10, 12, 14, 16, 18, 20).

9. The existence or not of an association is defined by P value. P>0.05 shows lack of evidence of an association – it doesn’t demonstrate lack of association. This is especially so as there are fewer than 10 studies for most analyses and thus low power. So it's not good to say that there was no association. Of course nor does P<0.05 demonstrate that there is an association. I think that the words used to summarise the results should not be based solely on P values.
RESPONSE: We agree with the reviewer and have modified the sentence in the first paragraph of the discussion so it reads: “There was also a 19%, 36%, 20%, and 21% reduction in the relative risk of mortality from respiratory disease, diabetes, infectious disease, and all non-cardiovascular, non-cancer causes of death, respectively, with a high vs. low intake of whole grains, but no evidence of an association was observed for mortality from nervous system disorders in the high vs. low or linear dose-response analysis.”

Additional Questions:
Please enter your name: Doug Altman
Job Title: Statistician
Institution: Univ of Oxford
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No
Funds for research?: No
Funds for a member of staff?: No
Fees for consulting?: No
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