Dear Dr. Aune

Manuscript ID BMJ.2015.029745.R1 entitled “Whole grain consumption and the risk of cardiovascular disease, cancer, and all-cause mortality – a systematic review and dose-response meta-analysis of prospective studies”

Thank you for sending us your paper. We sent it for external peer review again. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the reviewer’s comments, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Tiago Villanueva
Assistant Editor
tvillanueva@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=b834e178b45e4b249067bd81901f995

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).

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.

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.
- First line of the discussion: please avoid priority statements.

Additional Questions:
Please enter your name: Cecilie Kyrø
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
Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No
If you have any competing interests (please see BMJ policy) 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

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.
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).
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.

Other comments relating to reading the revised version:
4. PRISMA is not a guide for conducting a systematic review (p176).
5. Table 1 should explain what the RRs are and also be explicit that 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.
7. How were CIs for splines calculated?
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.
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.

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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Deadline: Your revised manuscript should be returned within one month.

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When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://resources.bmj.com/bmj/authors/types-of-article/research).

Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

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4. Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

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e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)

ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)

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iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)

v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

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