Subject: BMJ - Decision on Manuscript ID BMJ.2015.029745

Body: 26-Nov-2015

Dear Dr. Aune

Manuscript ID BMJ.2015.029745 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 and discussed it at our manuscript committee meeting. 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 report from the manuscript meeting, 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.

Tiago Villanueva
Assistant Editor
tvillanueva@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_Mask=0ddfce1d06b34ded91aac13fb7f75ea8

**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Jose Merino (chair), Doug Altman (statistician), Alison Tonks, Georg Roggla, Anita Jain, Helen Macdonald, Tiago Villanueva

Decision: Put points

Detailed comments from the meeting:

First, 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 committee:

- Our statistician made the following comments:
  p13/7: Why was 7 servings per day optimal? Isn’t this rather a lot??
  p14/37 – 18/41: a very long and largely unreadable run through the various analyses shown in figs 2-7 plus supplementary figures. This is tough stuff to wade through – much of it simply repeats what’s shown in the figures. Not a good use of space – unreadable! Would be better in my view to have one or more tables summarising the results of all the analyses. Then I found that this is in Table 1!!
  “Study quality was assessed using the Newcastle-Ottawa scale (NOS) which awards 0-9 stars based on the selection, comparability, and outcome assessment.[36] We considered studies with 0-3, 4-6, and 7-9 stars to represent low, medium and high quality studies.” Summary ratings show median of 8/9 which is surprisingly high.
  All studies were included in the meta-analysis regardless of methodological quality – but few of low quality it seems
  p18/50: There are few studies in each analysis thus low power to detect small study effects. Suppl figs 85-89 do show some suggestion of larger effects being in small studies only.
  19/50: popn attrib risk calcs give very precise estimates with no CIs. I’m very sceptical about all of these calcs. No comment here about very strong (and unreasonable) assumptions – see p21 where they say “Under the assumption that the observed associations are causal”. Also unclear what is being compared to what here. They did adjust for lots of things and say it made no difference: “the associations observed persisted” but results not shown. (22/41). But these adjustments would be at the study level I assume as don’t have IPD. So are very dependent on what was adjusted for in primary studies. The NOS requires reviewers to indicate what they seek adjustment for but this isn’t specified here. NOS doesn’t address several issues e.g. missing data.
  - One editor felt that you do not make a good case for novelty in the introduction or the discussion. She was also concerned that you barely seem to mention confounding, and she could not find a clear statement about covariates (and adjustment for them) in these studies. She also did not see sensitivity analyses according to study quality, and not much discussion of study quality in general. She considered that even though this may be a useful update, she was not convinced that this was a priority for The BMJ.
  - Another editor felt that it was not clear what the study adds. She also felt that the messaging needs to reflect that effect sizes may differ in other populations. She added that, considering that the variety of whole grains and food preparations is immense, it might be helpful if the introduction talks about the variety of grains or food preparations that fall under refined and whole grain categories.
  - Another editor felt that the paper lacks relation to a real world setting. He considered that very few people
probably eat 3 portions of whole grain, which is what was assessed in the study. He considered that these whole grain eaters may be rather different in many ways than the general population. He was also not fully convinced of the relevance of this paper for general readers.

- Another editor felt that the paper needs to more clearly focus on the research question and what is new. She highlighted that you should also make the clinical/how this feeds into dietary advice content easier to understand.

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 Reviewers**

**Reviewer: 1**

**Recommendation:**

**Comments:**

Manuscript ID BMJ.2015.029745 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 the opportunity to review this very relevant meta-analysis on whole grains and risk/mortality of several chronic diseases. I believe that the overall aim of the study is highly relevant, and that BMJ is a very suitable journal for publishing such a paper on a topic which could have a very broad public health impact.

I have the following major and minor comments for the authors to consider.

**Major:**

Overall, the methodological quality of the study is very high, and the PRISMA checklist is followed in a systematic way. However, the presentation of the results is a bit unstructured and the inclusion criteria (which diseases under study, incidence or mortality) and overall aim is not completely clear.

1. **Endpoints**
   - Abstract: In the “study selection” part it is stated that prospective studies of whole grains in relation to cardiovascular disease, total cancer and all-cause mortality are included. In the “results” part, there is reported on cardiovascular disease, total cancer, all-cause mortality AND respiratory diseases, infectious diseases and diabetes. Why this discrepancy?

   - It is, thought out the manuscript, not clear when RISK (incidence) and MORTALITY is investigated. This needs to be very clearly stated, also in the presented Figures.

   - In the flow chart, it would be very helpful if an extra level in the bottom could be added with information about how many studies (and publications) are available for each disease endpoint, and whether the endpoint is incidence or mortality.

2. **Whole-grain assessment**
   - Whole-grain intake is given as whole-grain products rather than as g/day. It is recommended to use g/day because this eases comparability between studies. It might be that it is not possible to calculate the intake in g/day in this meta-analysis since many of the study simply state the intake in whole-grain products/day. It is, however, important that this is mentioned and discussed. See this reference for more information: Ross, A. B., et al. (2015). “Recommendations for reporting whole-grain intake in observational and intervention studies.” Am J Clin Nutr. 2015 May;101(5):903-7.

   - 7-7.5 servings is set to the recommended level. It is not clear how and why this cut-off is chosen?

   - In Scandinavia, the recommended level is 75 g/dag, which roughly is equal up to 250 g whole-grain products. In the Scandinavian EPIC cohorts, where the whole-grain intake is among the highest in observational studies, only participants in the highest quartile comply with this recommendation. (ref. Kyro, C., et al. (2012). “Intake of whole grain in Scandinavia: intake, sources and compliance with new national recommendations.” Scand.J.Public Health 40(1): 76-84.) In other cohort studies, very few comply with the recommendation. Thus, it can be relevant to discuss whether it is from both a statistical and a public health viewpoint relevant to calculate the “population attributable risk (PAR)” based on this recommendation. It may be relevant to calculate what impact it will have if people just consumed half of the recommended level. PAR could be shown for both 7 servings per day and for 3,5 servings per day.

   - It is assumed that the proportion of brown rice is 25% of total rice consumed. Even though a reference is added on this, it is not completely clear how the authors came to the conclusion that 25% of the rice consumption must be brown rice?

**Minor:**

- In the results section, it is mentioned that the strongest reduction is observed in at lower whole-grain intakes. Is this due to statistical power, since the majority of the participants in observational studies are in this range? Or do you believe that it has a biological plausible explanation? If the latter is this case, this can be mentioned more in the discussion. From a public health point of view it would then have a great impact, if especially people with a very low whole-grain intake increased their intake. This group might especially be a difficult group to reach with...
nutritional campaigns etc.
- Page 10, bottom, “and checked by (DCG) for accuracy”. Who is DCG? Is it the co-author Darren Greenwood? It is not completely clear from the abbreviation.

I would be happy to review the revised manuscript.

Additional Questions:
Please enter your name: Anne Tjønneland
Job Title: Research Leader
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?: No
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: None

Reviewer: 2
Recommendation:
Comments:
This is an excellent and comprehensive meta-analysis of whole grain intake and risk of CVD, cancer, and all-cause mortality. I have the following minor comments.

1. How comparable of the serving sizes across studies? The authors used 3 servings per day of whole grain intake (about median across studies) as the basis for their main results. As a reader, it is hard to link 3 servings/d to actual amounts of, for example, bread or bowl of breakfast cereal. Please make this serving size more understandable in the abstract.

2. The premature death estimates were based on if whole grain intake was increased to 7 servings per day. Would the authors please provide more information on this? I basically would like to know whether this amount is realistic.

3. What is the rationale for choosing 3 knots for the splines analyses? Often times based on my personal experience, the shape might have changed dramatically if using different number of knots. How robust were the results presented in this paper?

4. Why excluding one study at a time for the influence analyses. This seems too exploratory to me, and better to have a priori hypothesis for such sensitivity analyses. For example, which dietary assessment tools used to measure grain intake and associated validation studies are important for many studies conducted worldwide.

Additional Questions:
Please enter your name: Xuehong Zhang
Job Title: Instructor
Institution: Harvard Medical School and Brigham and Women's hospital
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
Reviewer: 3

Recommendation:

Comments:
I find this review about whole grains in relation to risk/mortality of several major diseases of high relevance. I further think that this paper is highly suitable for BMJ, because it is important that e.g. general practitioners and other health professionals are aware of the role of whole grains in prevention of especially non-communicable diseases.

The study is of very high analytical quality in relation to the applied methods. I, however, have concerns regarding the identification of included studies, and I also think that difficulties in whole-grain assessment needs to be addressed further. Below please find detailed comments:

Major comments:
- It is unclear to me when incidence or mortality is investigated? And in all studies of both incidence and mortality are included, or is it a priori is decided to focus on specially mortality. If so, why are incidence studies also included. I think that it would be fair to include both, but it is of outmost importance that it clearly is described in the text and tables/figures, whether the study is on incidence or mortality.
- It is not clear which diseases that it a priori was decided to include. In the abstract for instance, T2D is not mentioned in the study selection, but T2D is investigated. This needs to be more clear.
- Whole-grain assessment: It is important that difficulties in assessing the whole-grain intake is discussed including the reason for not reporting the whole-grain intake in g/day.
- It needs to be addressed why seven servings were set as optimal reference. Please add a reference and argue for choosing this cut-off. For instance, in Norway, Sweden and Denmark the recommendation is 75 g/day. These Scandinavian recommendations could be mentioned.

If the above mentioned comments are addressed, I definitely think that the study would be suitable for publication in BMJ.

Additional Questions:
Please enter your name: Cecilie Kyø

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?: No
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:
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Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)
2. Name of the ethics committee or IRB, ID # of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)
3. Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).
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10. Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).

11. Please ensure the paper complies with The BMJ's style, as detailed below:

a. Title: this should include the study design eg "systematic review and meta-analysis."

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript uris to openly accessible websites where these materials can be found.

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.)
iii. For a case control study: OR (odds ratio) for strength of association between exposure and outcome.
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.

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g. Footnotes and statements

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Date Sent: 26-Nov-2015