08-Sep-2020
BMJ-2020-055688.R1
Associations of cereal grains intake with cardiovascular disease and mortality across 21 countries in the Prospective Urban and Rural Epidemiological Study: A prospective cohort study

Dear Dr. Swaminathan

Thank you for sending us your revised paper. Our statistician for this paper, Prof Perera, has requested some minor revisions before I am able issue a formal acceptance. Please see his report below.

Please also provide a sentence or two describing "Patient and public involvement" in your research. A description of the research subjects is not what this section is about. We want to know how patients and the public were involved in the design, conduct, reporting and dissemination of your research. Please see the guidance on our website to see what this covers.
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Yours sincerely,

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** Comments from the external peer reviewers**

Statistical report.

Comments:
BMJ. 055688.R1 Associations of cereal grains intake with cardiovascular disease and mortality across 21 countries in the Prospective Urban and Rural Epidemiological Study: A prospective cohort study
Stats Report
Many thanks to the authors for the response to the reviewers’ comments. I found them comprehensive and generally adequate. I have however one major concern regarding their interpretation of their results from their sensitivity analysis which I think: a) needs more complete reporting and b) requires them to be more nuanced in their Discussion/Conclusion (including their bottom line).
In their response to my initial - Major issue: Substantial heterogeneity of exposure and possibly of outcomes across the different countries/regions – the authors carried out a "meta-analysis of region-wise estimates of hazard ratios adjusting for all covariates in the full model, for each grain type", which I think is a very good approach to evaluate these regional differences. They present these results
by region as well as the pooled fixed effect estimate and say that "the results were consistent with the Cox-frailty full model”. Although, the overall pooled estimate is consistent with their primary analysis, the independent estimates by region are not. The final pooled estimate is particularly dominated by the results from China which show a significant detrimental association for refined grains. This direction of effect is consistent for South East Asia and possibly the Middle East but all other regions show the opposite effect, that is a protective/no effect (point estimate/confidence interval) of the use of refined grains.

This is an important finding and needs to be reported and included as part of the Discussion. This is actually consistent with their subgroup analysis between high and low intake regions (Figure 1). By the way, the phrase: "The associations were not different between high intake and low intake regions", is not really consistent with their analysis. For example, there is no evidence of a linear association in the low intake regions while there appears to be a threshold effect at the highest intake level >=350g/d but even then, this is still not statistically significant.

Given this, I believe that inclusion of the meta-analysis figures for ALL analyses (as given in the response to reviewers’ comments but not currently included in their manuscript) need to be provided as supplementary material. Also that they need to make allowances to explain the potential differences by region observed. The association for refined grains is mainly driven by a couple of regions. I also found the phrase: "The meta-analysis of region specific effects were consistent with the findings of the overall Cox frailty model described above” to be misleading (based on the above). Related to this last point, a sensitivity analysis using random effects for pooling instead of fixed would have given results leading to different conclusions (no effect of refined grains on composite outcome). Would be useful to hear the authors’ views as to why they chose a fixed effect approach as based on the data, a random effects model would appear to be the more appropriate choice. By the way, the forest plot given in their response has a few mistakes (e.g. inclusion of Africa and exclusion of North America in one of their analyses).

Besides the inclusion of the forest plots by regions and the meta-analytical estimates as supplementary material, I believe, there needs to be more nuanced presentation of the results as there are significant regional differences in total intake AND in associations. What is already provided in the Discussion regarding the possible lack of effect in whole grains is also needed for refined grains and to a lesser extent to white rice too. By the way, these regional differences might also help them explain some of the differences observed between their and other studies (which mainly focus on European and North American populations).

Additional Questions:

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Job Title: Professor of Medical Statistics

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