To the editor:
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.

The section on “Patient and public involvement” has been revised as per the journal’s specifications. Thus, the following text has been added on Page 14 (lines 10-15):

“None of the participants or patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. None of the participants or patients were asked to advise on interpretation or writing up of results. The results will be disseminated through press releases issued from each of the participating institutions in each of the 21 countries and through use of social media.”

Response to Statistical Review

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).

We thank the reviewer for the suggestion. We realize that we should have performed random effects model as the sites represented different regions and the intakes vary by region. We have now performed a meta-analysis with random effects and the figure (Supplementary figure 4) is added as supplementary material. The following line has been removed from the results section. “the results were consistent with the Cox-frailty full model”. We have now added these results to state the following text (Page 17)

“When meta-analysis was performed for region specific analyses, the overall associations between refined grain intake and clinical outcomes were not significant (HR composite event=1.03 (95% CI:0.96 to 1.09); P for heterogeneity=0.001, HR total mortality=1.04 (95% CI:0.98, 1.10); P for heterogeneity=0.13 and HR major CVD= 1.01 (95% CI:0.89 to 1.12); P
for heterogeneity <0.001)), but a significant positive association was observed for all the three outcomes for China (Supplementary Figure 4A). Even when the association was examined for 50 g increase in intake of refined grain there was a positive effect in China for all the three outcomes but not overall for all regions (Supplementary Figure 4B). Whole grain and rice were not associated with any of the outcomes (Supplementary Figure 4C, 4D).” The regional differences observed in the association of refined grain with outcome has been added to the discussion (Page 19-20).

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.

Thank you for pointing out this error in reporting. The sentence has now been changed to the text on Page 15 (lines 19-22):

“Significant positive associations were observed in high intake regions, but not in low intake regions for composite events, total mortality and major CVD (Figure 1, Supplementary Table S8a and 8b, all p for interaction>0.05).”

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.

We have now included the meta-analysis figures in the Supplementary material as Supplementary figure 4 (Legend in Supplementary Appendix on page 65). The figure now reports the random effects model and not the fixed effects model.

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).

The sentence has been removed and replaced page 17 with:

“When meta-analysis was performed for region specific analyses, the overall associations between refined grain intake and clinical outcomes were not significant (HR composite event=1.03 (95% CI:0.96 to 1.09); P for heterogeneity=0.001, HR total mortality=1.04 (95% CI:0.98, 1.10); P for heterogeneity=0.13 and HR major CVD= 1.01 (95% CI:0.89 to 1.12); P for heterogeneity <0.001)), but a significant positive association was observed for all the three outcomes for China (Supplementary Figure 4A). Even when the association was examined for 50 g increase in intake of refined grain there was a positive effect in China for all the three outcomes but not overall for all regions (Supplementary Figure 4B). Whole grain and rice were not associated with any of the outcomes (Supplementary Figure 4C, 4D).”

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.
The meta-analysis, as explained as a response to the first question, has now been done using the random effects model and the findings are reported in the results, while a figure has been included in the Supplement (Supplementary figure 4A, 4B and 4C,4D).

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).

All errors in the forest plots have been corrected. Africa was excluded from all regional analysis as the sample sizes were not sufficient. South East Asia is not analysed for the association between refined grain intake and total mortality as the model did not converge and robust estimates could not be obtained. So, these regions were excluded as appropriate in the meta-analysis.

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).

The discussion now includes a section on refined grain intake in China (Pages 19-20) with the text below added:

“When we conducted meta-analysis by regions of the PURE data, the association of refined grains with clinical outcomes was seen in China and not in other regions. This difference might have been due to the highest refined grain intakes in China compared to other regions along with a wide range of intakes reported. Longitudinal trends have indicated an increase in consumption of refined grains in China\textsuperscript{33,34}. There has been a change from traditional rice-based pattern to a modern dietary pattern which included increasing wheat intakes. Wheat intake in China has been steadily increasing over two decades (1991-2011) and has been positively associated with risk of cardiovascular disease\textsuperscript{35}. The level of refinement of wheat and intake of refined wheat, however, has not been reported in previous studies.”