Author's response to reviews

Title: A Prospective Study of Dietary Selenium Intake and Risk of Type 2 Diabetes

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Author's response to reviews: see over
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Dr Kylie Hesketh
Associate Editor
BMC Public Health

RE: MS # 2059743726396100 - A Prospective Study of Dietary Selenium Intake and Risk of Type 2 Diabetes

Dear Dr Hesketh:

Please find enclosed our further revised manuscript which addresses the reviewers’ comments. What follows is a point-by-point response to the comments provided as part of the review process. Please be aware that in the revised manuscript we have used the yellow "highlighting" feature in Word to mark the areas that have been modified compared to the original submission.

Reviewer: Simin Liu

Minor Essential Revisions

1. It may be useful to elaborate a bit more how high selenium intake could increase the risk of diabetes.

   Re: Indeed, in the original version of our manuscript we attempted to discuss in greater detail potential mechanisms to explain adverse effects of high selenium intake on glucose metabolism and diabetes risk. However, we were asked by one of the reviewers to shorten that section. Following this reviewer’s suggestion, we have provided a more detailed discussion of this issue in the revised manuscript and added a few references.

2. The discussion of misclassification is quite vague and would benefit from a more specific description of how biases might be operating in this study setting.

   Re: We have attempted to address in depth all the potential limitations and biases of this study (pages 10-12). However, following this reviewer’s suggestion, we have further discussed this issue in the revised manuscript.

3. Table 1: Suggest that you remove reference to “cases” for the “Non-diabetics cases” and instead refer to them as “Non-diabetics.”

   Re: done.
**Discretionary Revisions**

4. **Statistical Analysis: It may be interesting to examine interactions with smoking and alcohol intake.**

   *Re:* Indeed, we tested the interaction of selenium intake with both smoking and alcohol intake. Neither interaction was statistically significant. We have added a sentence on this issue in the revised manuscript.

5. **Statistical Analysis/Discussion: red meat, selenium intake and diabetes risk.**

   *Re:* We have calculated odds ratios of type 2 diabetes across quintiles of red meat intake. Compared to the bottom quintile (reference category), risk estimates are as follows: 1.14(0.74-1.75); 1.13(0.74-1.74); 0.94(0.59-1.48); 1.31(0.84-2.03). Unfortunately, we do not have data on compounds such as preservatives, additives, and nitrates, which are found in red meat and might confound the observed associations of selenium intake with diabetes risk as pointed by this reviewer. However, we have mentioned this point in the context of unmeasured confounding in the discussion section.

6. **Statistical Analysis: Given the likely high correlation between dietary components, did you check for multicollinearity issues in your models?**

   *Re:* The correlations between selenium and dietary components were as follows: selenium – animal proteins: 0.53; selenium - saturated/polyunsaturated fat ratio: 0.08; selenium – energy intake: 0.72; selenium – alcohol intake: 0.12. Based on these coefficients, we can exclude multicollinearity issues in our analyses.

7. **Statistical Analysis: Do you have data on fruit and vegetable intake to include in the model?**

   *Re:* We do have data on fruit and vegetable intake. Indeed, when we include these macronutrients in the models, there is no evidence of major confounding effect by these factors. Compared to the bottom quintile (reference category), risk estimates of diabetes risk across selenium quintiles are as follows: 1.46(0.89-2.40); 1.48(0.89-2.47); 1.74(1.03-2.94); 2.62(1.45-4.72); P trend 0.001. The odds ratio for diabetes associated with a 10 µg/d increase in selenium intake is 1.29(1.09-1.53).

8. **Statistical Analysis: Suggest fitting a quadratic spline model to explore the shape of the trend across the range of selenium intake.**

   *Re:* Following this reviewer’s suggestion, to further explore the shape of the relationship between dietary selenium intake and diabetes, we used restricted quadratic splines with knots at the 10th, 50th and 90th percentiles of the selenium intake distribution. The spline plot was performed with the R statistical software. This analysis further reiterates the linearity of the relationship between selenium intake and risk of diabetes. We have mentioned these results in the revised manuscript, and enclosed a figure for review purposes only. In fact, we believe that this figure would not substantially add to the results displayed in table 4.
Reviewer: Mario Siervo

1. I would only recommend to add a reference to support the choice of the method the authors have used to adjust nutritional intake for energy intake

Re: done.

We would like to thank you and the reviewers for thoughtful comments and suggestions. We truly appreciate your interest in our work. We believe that as a result of the review process our paper has further improved and hope that it is now acceptable for publication in BMC Public Health.

Please send all correspondence to my attention.

Look forward to hearing from you.

Sincerely,

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