Author's response to reviews

Title: Is dietary zinc protective for Type 2 diabetes? Results from the Australian Longitudinal Study on Women's Health

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Author's response to reviews: see over
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Revised submission
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Title: Is dietary zinc protective for Type 2 diabetes? Results from the Australian Longitudinal Study on Women’s Health.
Authors: Khanrin P Vashum, Mark McEvoy, Zumin Shi, Abul M Hasnat, Md R Islam, David Sibbritt, Amanda Patterson, Julie Byles, Deborah Loxton and John Attia

Dear Dr. Liatis

Please find enclosed the revised manuscript ‘Is dietary zinc protective for Type 2 diabetes? Results from the Australian Longitudinal Study on Women’s Health’ in response to the reviewers comments.

Thank you for your comments and suggestions and for the chance to resubmit the manuscript. The manuscript has been revised according to the reviewer’s suggestions and each of their comments has been addressed individually in the attached response letter. We sincerely thank the reviewers for these suggestions.

The revised manuscript has been read and approved for resubmission to BMC Endocrine Disorders by all authors. We believe the manuscript has been revised to your approval and hope that it will be now suitable for publication in BMC Endocrine Disorders.

I look forward to hearing from you.

Regards,

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Is dietary zinc protective for Type 2 diabetes? Results from the Australian Longitudinal Study on Women's Health

Thank you for the comments and suggestions for our manuscript. The manuscript has been revised as per the reviewer’s suggestions. (Response in italic/bold and changes is highlighted in red in the manuscript.)

Reviewer's report

**Reviewer #1 (Remarks to the Author):**
Reviewer: Meropi Kontogianni

This is an interesting work, revealing data regarding zinc intake and zinc/iron ratio and type 2 diabetes risk in a population based prospective study.

- **Major Compulsory Revisions**
  1. Background: this section is rather too long (~4 pages) and gives much information regarding the associations between zinc intake and type 2 diabetes. I would suggest shortening this introduction and incorporating part of this information in the discussion section. The animal/supplementation studies for example could be omitted.

   **As suggested the introduction section has been shortened (<2 pages) and the animal/supplementation studies has be omitted.**

2. Methods, Dietary assessment: “The validation of the FFQ against a 7-day weighted food record showed fair correlation for dietary zinc intake (Pearson correlation coefficient = 0.4)” this is not a good correlation and should be acknowledged in the limitations section, as well as the difficulty of estimating macro and micronutrient intakes through FFQs.

   **The correlation coefficient along with the limitations of FFQs in estimating macronutrients and micronutrients has been acknowledged in the limitations section of the discussion.**

3. Results, Page 13: “Of particular interest in this investigation, those in the highest quintile of zinc intake also had the highest intake of dietary iron”. Authors could mention which were the most commonly recorded dietary sources of zinc in the study sample.

   **The information has been added as suggested and the sentence now reads as:**
Of particular interest in this investigation, those in the highest quintile of zinc intake also had the highest intake of dietary iron. The most commonly recorded dietary source of zinc was meat, fish and poultry as the major contributors, though cereals and dairy products were also a substantial source.

4. Results, Table 2: “Energy-adjusted zinc [median(min, max)]” – I am not sure whether the reader understands what is reading. An explanation about what -1.25, -0.48, 0.01, 0.50 and 1.24 reflect would be helpful

Explanation regarding these numbers has been added in the result section.
- Minor Essential Revisions
  1. Results, Page 13, line 9: the word depression appears two times
    Thank you for pointing this out. The typo has been corrected.

- Discretionary Revisions
  1. Tables: too many decimals in the P-values
    Thank you for the suggestion. We have decreased the number of decimal point for the p-values.

Level of interest:
An article of importance in its field
Quality of written English:
Acceptable
Statistical review:
Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
'I declare that I have no competing interests'
Thank you for your comments.

Reviewer #2 (Remarks to the Author):
Reviewer: Stephen Myers
The manuscript
“Is dietary zinc protective for Type 2 Diabetes? Results from the Australian Longitudinal Study on Women’s Health” by Vashum et al. describe findings that suggest that a higher total dietary zinc intake and a high zinc/iron ratio is associated with a lower risk of type 2 diabetes in women.
Major compulsory revisions

The manuscript was well written and addresses an important issue, type 2 diabetes. Both the title and the abstract accurately convey the work presented and summarize effectively the research findings. The reference material is appropriate however, in addition to many studies implicating dietary zinc in glycaemic control in both animal models and humans, there is also equally many studies that have found the converse. I feel that these studies were not captured in the discussion and should be discussed in light of the current findings here.

In addition to studies implicating dietary zinc in glycaemic control, current studies with the findings that zinc supplementation has no effect on glycaemic parameters have been added into the discussion section.

We have now added the following text in the discussion:

A more recent systematic review and meta-analysis of 25 articles, which included 22 studies on T2D, concluded that zinc supplementation has beneficial effects on glycaemic control [29]. The review however had several limitations including differences in zinc doses, sample size, study duration, limited availability of data on zinc intake and variation in baseline parameters and so the conclusions remain in doubt. Despite all this study supporting the effect of zinc in glycaemic control in T2D, there are equally many studies that have found that zinc supplementation have no effect on glycaemic parameters such as Hb1Ac and glucose levels[30-32]. Another study also did not find differences in glycaemic control among patients with T2D treated with oral zinc compared to placebo despite improving zinc status[33]. Hence, despite the positive effects of supplemental zinc observed in animals and cellular studies the connection between dietary zinc supplementation and its role in cellular signalling in humans remains unclear and requires further investigation.

Although I think this study has benefit, it is difficult to conclude definitively that a higher dietary zinc/iron ratio was associated with a lower risk of type 2 diabetes in women. For example, confounding factors may include; where the food was grown and the different zinc levels in soils, zinc in cosmetics, zinc in drinking water (approximately < 3 mg/L but can be much higher as a result of corrosion from zinc-coated pipes and galvanized rain water tanks). In its current form, the manuscript should identify these limitations in the study design and address other confounding factors that may contribute to the results presented here. For example, other minerals, vitamins etc. could also be responsible for the observed outcomes. I think the manuscript has merit but needs to address these issues.
We acknowledge the existence of additional environment sources of zinc that may have contributed to the overall intake of zinc. However given the random sample of subjects selected for this investigation this additional exposure is unlikely to have affected some quintiles of zinc intake more than others. Hence, the amount of zinc consumed by all study participants is likely to be an underestimate and this will bias the observed association between dietary zinc and type 2 diabetes towards the null. This means that the true association will be larger than that observed in this study. We also agree that other confounding variables not controlled for in the analysis suggests that our estimate of the effect of zinc on type 2 diabetes risk may be subject to some residual confounding; however given that the most important dietary (including multivitamin use) and non-dietary confounders have been controlled for we believe that this residual confounding is small. We have provided a more detailed description of this in the discussion.

We have now added the following text to the limitations section of the discussion:

“Another concern is that the existence of additional environment sources of zinc that may have contributed to the overall intake of zinc. However given the random sample of subjects selected for this investigation this additional exposure is unlikely to have affected some quintiles of zinc intake more than others. Hence, the amount of zinc consumed by all study participants is likely to be an underestimate and this will bias the observed association between dietary zinc and type 2 diabetes towards the null. Given that an FFQ was used to estimate dietary zinc intake and that there may by some environmental sources of zinc consumption the true estimate of the association will actually be larger than that observed in this study”.

“There is also the possibility that other confounding variables may not have been controlled for in the analysis and this suggests that our estimate of the effect of zinc on type 2 diabetes risk may be subject to some residual confounding; however given that the most important dietary (including multivitamin use) and non-dietary confounders have been controlled for this residual confounding is likely to be small”.

The discussion was a little disconnected when mentioning dietary zinc supplementation and the role of zinc in insulin signalling. It is clear that zinc has insulin mimetic properties and is implicated in cell signalling and glucose homeostasis however I don’t think the use of this literature in this current context is justified given that the very small pool of “free” zinc that is available for signalling has only been studied in cell culture models and is mobilized from intracellular stores by an external stimulus. The connection between dietary zinc supplementation and its role in cellular signalling is not clear. Perhaps the discussion should make comment on this.
We agree that the connection between dietary supplemental zinc and type 2 diabetes risk in humans remains unclear and have amended the discussion to reflect this.

Minor essential revisions
How was it determined that “Those who were lost to follow-up were not significantly different but were more likely to be born outside Australia, less educated or a current smoker” in Research Design and Methods, The Australian Longitudinal Study on Women’s Health, line 34-36?

We compared our study sample characteristics to that of the baseline characteristics and found that those lost to follow-up were more likely to be born outside Australia, less educated or a current smoker.

What does “fair” mean in “The validation of the FFQ against a 7-day weighted food record showed fair correlation...” in Dietary Assessment, line 12?

The word fair has been omitted and further explanation of the correlation has been made in the method section and also mentioned its’ limitation in the discussion section.

We thank you for your comments and suggestion.