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OPEN PEER REVIEW

Association Between Maternal Copper/Zinc Intake and the Risk of Preterm Birth

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1 Original submission

1 comment · 7 Feb 2024

Vahideh Aghamohammadi Reviewer

MAJOR REVISION 7 Feb 2024

Thank you very much for the opportunity to review this manuscript. There are a few points that can be included in this article for its improvement:
- Please include a table regarding the dietary intake of participants.
- Please specify the number of FFQ items.
- Please describe the methods of anthropometric measurements in the methods section.
- Please specify whether 24 hrs. or the FFQ was used to investigate dietary intake.
- It is better to adjust for macronutrient intake in addition to energy intake.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

April 10, 2024

Dear Editor,

We would like to thank you and all reviewers for your insightful comments concerning the revisions of our manuscript entitled "*Association between maternal copper/zinc intake and risk of preterm birth*". We have carefully reviewed the reviewers' comments, and we have addressed all their questions/critiques/concerns point-by-point as below. All changes made to the text were tracked so that they may be easily identified. We believe that our manuscript has been significantly improved, and we hope it is now suitable for publication.

If you have any problems with our manuscript, please do not hesitate to contact us.

Reviewers' Comments:

Reviewer 1:

1- Please mention the references used for sentences in lines 25, 27, 35, 37, 39, 42, 43, 51, 54, 57, 65, 322, 327,330, 333, 368, 378, 388, 405, 407.

Response: Thanks for the suggestions. We have cited the relevant references to support these sentences.

2- To use the abbreviation “Zn” in line 52, please place it in the sentence before it inside parentheses.

Response: Thanks for the reminding. We have revised the word as suggested.

3- What do you mean by “physical fertility” in line 86?

Response: We apologize for the confusion. "Physical fertility” was replaced with “obstetric history” in the revised manuscript.

4- "In line 94, do you mean the second trimester (>27 weeks) as the third trimester period?"

Response: Yes. We are sorry for this typographical error and correct.

5- In line 100, the abbreviation 'RNI' is sufficient. The previous sentence refers to the abbreviation and its full form {Recommended nutrient intake (RNI)}.

Response: Thanks for the reminding. We have revised the sentence as suggested.

6- In the “Statistical analysis” section of the Materials and methods, line 129, the BMI has been abbreviated for the first time. It is better to initially write out its full form ('body mass index') before using the abbreviated form.

Response: Thanks for the reminding. We have revised the sentence as suggested.

7- No information is provided about the sampling method or sample size determination. Please explain the method by mentioning the reference about choosing selection of the sample size and its methodology

Response: Thanks for suggestions. We have included all subjects who meet the inclusion criteria of our study without conducting sample size calculations. With our sample size approaching nearly ten thousand individuals, we have arrived at a size that we consider adequate for this research.

8- In the results section of the abstract, the results should be reported with numbers and P values.

Response: Thanks for the reminding. We have revised the results section of the abstract as suggested.

9- The discussion needs to be edited, some explanations are unnecessary and extra.

Response: Thanks for the reminding. We have revised the discussion section as suggested.

Reviewer 2:
Thank you very much for the opportunity to review this manuscript. There are a few points that can be included in this article for its improvement.:

- Please include a table regarding the dietary intake of participants.

Response: Thanks for suggestions. We have uploaded a table regarding the dietary intake of participants as supplemental materials in the revised manuscript.

- Please specify the number of FFQ items.

Response: Thanks for the reminding. The number of FFQ items is 40. We have added this information in the revised manuscript as suggested.

- Please the methods of anthropometric measurements in the methods section.

Response: Thanks for the reminding. We have added the methods of anthropometric measurements in the methods section in the revised manuscript as suggested.

- Please specify that for investigation of dietary intake, 24 hrs. have been used or FFQ?

Response: We apologize for the confusion. FFQ was used for investigation of dietary intake. We have deleted the wrong sentence in the new manuscript.

- It is better in addition to energy intake, intake of macronutrients is adjusted.

Response: We appreciate the suggestion. We agree that adjusting for intake of macronutrients in addition to energy intake could provide valuable insights. However, we regret that we do not possess relevant data to perform such adjustments in our study. We have included it as a limitation for discussion in our manuscript. Thank you for your insightful feedback

Reviewer 3:
The study design of a prospective birth cohort is appropriate to investigate the association between maternal nutrient intake and preterm birth risk. The recruitment of 8897 pregnant women from a major hospital provides a reasonably large sample size.

- One potential weakness in the results section is the lack of data on actual biomarkers of copper and zinc status in the study participants.
- The study relied solely on estimated dietary intakes of copper and zinc from food frequency questionnaires. While this can provide a reasonable approximation, it does not directly measure the absorbed and utilized amounts of these minerals in the body.
- Measuring biomarkers such as serum/plasma levels or concentrations in red blood cells could have strengthened the findings by:
1) Validating if the reported dietary intakes accurately reflected the women's copper and zinc nutritional status during pregnancy.
2) Accounting for potential differences in absorption and metabolism of these minerals that dietary intake estimates may not capture.
3) Allowing the analyses to relate preterm birth risk directly to objectively measured copper and zinc levels rather than just estimated intakes.
4) Enabling the identification of specific threshold concentrations of these biomarkers associated with increased preterm birth risk.
- While logistically more complicated, incorporating biomarker data could have provided more definitive evidence about the roles of copper and zinc nutritional status, rather than just dietary intake levels, in influencing preterm birth risk. The lack of such data is a limitation acknowledged by the authors.

Response: We appreciate the insightful feedback provided by the reviewer regarding the potential weakness in our results section concerning the absence of data on actual biomarkers of copper and zinc status in our study participants. We acknowledge that relying solely on estimated dietary intakes from food frequency questionnaires may not fully capture the absorbed and utilized amounts of these minerals in the body. Unfortunately, we do not have access to such biomarker data in our study. However, we have acknowledged this limitation and emphasized the need for future research endeavors to include biomarker measurements to strengthen the findings. We thank the reviewer for highlighting this important aspect, and we are committed to addressing it in future studies.

Here are some suggestions for how the authors could improve the discussion section:
1. Expand on the potential biological mechanisms:
- Provide more details on how copper and zinc specifically contribute to reducing oxidative stress and their roles in relevant pathways/processes during pregnancy.

- Discuss how deficiencies in these minerals may disrupt maternal-fetal transfer, placental function, or other pregnancy-related physiological processes that could increase preterm birth risk.

Response: We thank the reviewer for the reviewer's insightful suggestions, which has strengthened the depth and clarity of our discussion section. The discussion section has been revised as suggested.

2. Address the temporality issue:
- Since nutrient intakes were assessed across trimesters, discuss if the timing of deficiencies (e.g. preconception, early vs late pregnancy) may have differential impacts on preterm birth pathways.
- Relate their findings to hypothesized biological windows where copper/zinc might be most critical.

Response: We thank the reviewer for the reviewer's insightful suggestions, which has strengthened the depth and clarity of our discussion section. The discussion section has been revised as suggested.

3. Compare dietary intake vs supplement effects:
- Acknowledge the inability to tease apart effects of copper/zinc from food sources vs supplements as a study limitation.
- Discuss how the bioavailability and metabolic fates may differ between dietary and supplemental sources of these minerals.

Response: We thank the reviewer for the reviewer's insightful suggestions, which has strengthened the depth and clarity of our discussion section. The discussion section has been revised as suggested.

4. Explore effect measure modification:
- Examine if the observed copper-zinc interaction and adverse effects differed by maternal characteristics like age, pre-pregnancy BMI, comorbidities etc.

Response: We appreciate the reviewer's suggestion to examine potential interactions between copper and zinc and adverse effects based on maternal characteristics such as age, pre-pregnancy BMI, and comorbidities. However, after careful consideration, we have decided not to conduct this specific statistical analysis in our current study. Our primary focus was to investigate the overall relationship between copper and zinc status and the risk of adverse pregnancy outcomes, including preterm birth. While exploring interactions by maternal characteristics could provide additional insights

into subgroup differences, our study's sample size and design may not be adequately powered to detect meaningful interactions. Nevertheless, we acknowledge the importance of considering maternal characteristics as potential effect modifiers and recognize that future research with larger sample sizes and more comprehensive data may be better suited to explore these interactions in depth.

- Discuss potential vulnerability factors that could modify how nutrient deficiencies impact preterm birth risk.

Response: We thank the reviewer for the reviewer's insightful suggestions, which has strengthened the depth and clarity of our discussion section. The discussion section has been revised as suggested.

5. Public health implications:
- Expand on the prevalence of inadequate copper/zinc intakes among pregnant women globally, especially in low-resource settings.
- Discuss pragmatic interventions like dietary counseling, fortification, or supplementation strategies to optimize nutritional status.

Response: We thank the reviewer for the reviewer's insightful suggestions, which has strengthened the depth and clarity of our discussion section. The discussion section has been revised as suggested.

2 Revision 1

1 comment · 16 May 2024

Vahideh Aghamohammadi Reviewer

ACCEPT 16 May 2024

The authors have addressed all the points well.