Title: Early-life Exposure to the Chinese Famine of 1959-61 and Risk of Hyperuricemia: Results from the China Health and Retirement Longitudinal Study

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Author’s response to reviews:

Dear Editors and Reviewers,

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled "Early-life Exposure to the Chinese Famine of 1959-61 and Risk of Hyperuricemia: Results from the China Health and Retirement Longitudinal Study" (PUBH-D-19-04032). Those comments are all valuable and helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made substantial efforts to revise the manuscript which we hope meet with approval. All changes to the manuscript are marked in red in the paper. Below are our responses to specific comments.

Response to the Reviewer 1’s comments:

1. More than half of participants was overweight and obesity in this study, which seems to higher than general population. I suggestion to state in the discussion.

Author’s response

We added a new paragraph to address this comment in the Discussion section. Additionally, we observed 52.5% of all participants aged 50-59 years in 2015 and 46.9% of men were overweight and obesity, which was higher than men aged 15-49 years (36.4%) in 2014[40]. Thus, we might speculate whether age or famine effects could increase the prevalence of overweight and obesity. Although a previous study indicated the association between the risk of overweight, obesity and exposure to famine in early life in women aged 54-56 years but not in men[39], more detailed evidence and prospective cohorts are needed to confirm the risk of health caused by famine exposure in early life.

2. Although adjusting for the effect of age using the age-balanced group, the effect of age still exists, that should be mentioned in the Discussion section.
Author’s response

We added a sentence in Page 5.
In addition, although the age-balanced control was used to avoid the age-related biases, the difference of age between the age-balanced control and fetal-exposed group still exists.

3. The family history of Hyperuricemia could be a confounder without controlled in this study.

Author’s response

We used public data from CHARLS to analyze, but the family history of hyperuricemia was not included in the questionnaire. Due to the limitation of data availability, this study lacks an adjustment for the family history of hyperuricemia in the model. This problem is stated in Page 5 and will be included in the future research agenda.

4. The CHARLS survey conducted several waves, could you provide the results of other wave in this study?

Author’s response

The venous blood-based biomarkers could be found only in the 2011 and 2015 Wave of CHARLS. Thus, we repeated our analysis in the 2011 Wave of CHARLS. Although we did not find the association between the exposure to famine in early life and the risk of hyperuricemia in the 2011 Wave of CHARLS, it’s likely why this is the case. There were only 85 cases of all included participants (n = 1963) diagnosed as hyperuricemia in the 2011 Wave of CHARLS, while there were at least 81 cases in the fetal-exposed group in the 2015 Wave of CHARLS. So we had much more statistical power to find the association between the exposure to famine in early life and the risk of hyperuricemia in the 2015 Wave of CHARLS.

Responses to Reviewer 2’s Comments:

1. Page 3, Lines 23-28: Why adjust hypertension and diabetes in the model when used unconditional logistic regression to calculate OR and 95% CI for risk of hyperuricemia? I think this adjustment may introduce other potential confounding factors and reduce the accuracy of the estimation.

Author’s response

We calculated the odds ratios (ORs, Unexposed versus Fetal-exposed) when unadjusted or adjusted for hypertension and diabetes in the model. After adjusted hypertension and diabetes, the percent change of OR was only 1.9%. And after adjusted hypertension and diabetes, the model was better (P=0.037) by the likelihood ratio test. So, we chose to add hypertension and diabetes to the model.
2. Page 3, Line 32: The full name of SPSS should be Statistical Product and Service Solutions, which was modified in 2000.

Author’s response

We changed and marked the full name of SPSS in Page 3.

3. Pages 3, Lines 38-39: Statistical statistic and P-value should be provided and be used to determine whether the differences between the groups are similar. In addition, in table 1, the comparison between groups should have a total statistic and P-value such as F or Chi-square value, rather than only giving a Bonferroni correction P-value marks.

Author’s response

We added a sentence in Page 3.
The differences of smoking and hypertension between three famine exposure subgroups were statistically significant ($\chi^2 = 6.345$, $P = 0.042$; $\chi^2 = 13.536$, $P < 0.001$).
And we have provided the Chi-square value and P-value between the groups in Table 1.

4. Page 3, line 55: 95%CI has the same effect as P value, so P value can be removed directly as well as in the Table 2 and Table S2.

Author’s response

We removed P-value in Page 3, Table 2 and Table S2.

5. Page 4, Lines 7-8: What other covariates have been adjusted to include? Please state this in the text or label it at the bottom of the table.

Author’s response

We labeled the covariates at the bottom of Table 3 and Table S3.

6. Page 4, Lines 58-60: The discussion about interaction is unconvincing and does not seem to have much to do with the results of the study. I suggest further interaction analysis between early-life exposure to famine and famine severity be performed to add the reliability.

Author’s response

We assessed the interaction between early-life exposure to famine and famine severity, and reorganized the paragraph in Page 4.
Consistent with some studies[20, 23, 39], we did not find any larger famine effects among adults born in severely affected versus less severely affected areas. This result may be explained by a great variation of famine severity in the county-level mortality[19], which caused the misclassification of famine severity. Further studies should be conducted that collect historical demographic records at the local level and find a more reliable indicator to better distinguish famine severity.

We appreciated for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.
Once again, thank you very much for your constructive comments and suggestions.

All the best,
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