Author's response to reviews

Title: Exposure to the Chinese famine in early life and the risk of anaemia in adulthood

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Responses to reviewers

Reviewer: Tessa J Roseboom

Major compulsory revisions

Please provide more information on when and how the data were collected. It is unclear whether data were all collected in 2002 or later, and at what age of the participants?

Response: The data were collected in 2002. We have made it clear in the title of Table 1. Table 1 also shows the age of the participants by birth cohorts.

Please provide more data on when the famine started and ended and how this was assessed.

Response: Based on the literature (reference 9 and 10), the Chinese famine started in 1959 and ended in 1961. We followed the mainstream definition of Chinese famine studies and used Oct 1 1959-Sep 30 1961 as the famine exposure period. In our introduction we have provided references (reference 9 and 10).

Please provide information on how dietary intake was assessed

Response: Nutrients intakes (e.g. iron intake) were assessed using a 3-day weighed food diary which recorded all foods consumed by each individual, on three consecutive days. We provided the information on page 7.

Provide linear regression analyses on Hb levels as outcome rather than only on anemia

Response: Thank you for the suggestion. We conducted linear regression analyses and provided the regression coefficients in the revised manuscript (see page 9). The detailed information on regression analysis is shown below.

| Table Association of famine exposure during early life with risk of adulthood Hb in Chinese (n=2007) |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Exposed cohorts                                              | Nonexposed cohort                                             |                                                               |                                                               |                                                               |
|---------------------------------------------------------------|---------------------------------------------------------------|                                                               |                                                               |                                                               |
| Late childhood                                               | Mid childhood                                                 | Early childhood                                               | Fetal-exposed                                                 |                                                               |
| Both genders                                                 |                                                               |                                                               |                                                               |                                                               |
| -0.10 (-0.32 to 0.12)                                        | -0.07 (-0.29 to 0.15)                                         | 0.03 (-0.19 to 0.25)                                          | -0.24 (-0.49 to 0.00)                                         | 0.00                                                          |
| Men                                                          |                                                               |                                                               |                                                               |                                                               |
| -0.23 (-0.56 to 0.10)                                        | -0.07 (-0.40 to 0.27)                                         | 0.00 (-0.32 to 0.33)                                          | -0.32 (-0.71 to 0.06)                                         | 0.00                                                          |
| Women                                                        |                                                               |                                                               |                                                               |                                                               |
| 0.05 (-0.25 to 0.35)                                         | -0.04 (-0.34 to 0.26)                                         | 0.06 (-0.24 to 0.36)                                          | -0.14 (-0.46 to 0.18)                                         | 0.00                                                          |

Values are regression coefficients (95%CI) adjusted for income, education, residence (urban/rural), smoking, alcohol drinking, job (manual vs non manual), hypertension and BMI. In gender combined model, gender was also adjusted in the model.

Provide effect size in women also (on only separate effect in men)
Response: We have added RR for anemia in women in the text. See page 10. Detailed gender specific RRs were presented in Table 2. Regression coefficients were also provided in the text.

*The number of subgroups in the analyses is too large compared to the number of subjects. Famine exposure was measure of interest, then it was subdivided into men and women, low and high ses, obese and non obese and with or without hypertension, This is simply too much to make statements about with these numbers*

Response: We are aware of the relatively small number of participants in the fetal exposed cohort. We meant to examine, even among this relatively small sample of population, whether there is any evidence suggestive of effect modifications by major factors of interest. We were able to identify significant differences of anemia between the fetal exposed cohort and the non-exposed cohort. It seems that the sample has reasonable power. We agree with the reviewer that we may have limited power in sensitivity analysis when we subdivided the sample into subgroups. We have acknowledged this as a limitation. See page 13. “In sensitivity analysis, when we subdivided the sample into subgroups, the power of detecting a significant association in some subgroups may be limited given the relatively small number in certain subgroups”.

*The discussion needs to be worked on;*

*It is unclear which measurements were done and how on iron intake, also it is unclear how large the subsample was (and how this was distributed across exposure groups) and therefore the statement in the discussion that the effect on anaemia was not due to differences in intake is far too strong for the data currently provided. Please amend.*

Response: We have provided information on dietary measurements. It is based on 3-day weighted food records. The number of participants having dietary information was provided in the footnote of Table 1. In general the mean intake of iron was above the Chinese recommendation in each cohort.

*It is unclear how old people are but one would expect women >55 all to be postmenopausal - it does not fit their statement of lack of data on menstrual status in the women. Please provide more detail*

Response: In Table 1 we have provided the age of participants. There is no woman with age beyond 50. We feel that the confounding of menstruation is possible.

*Half the population was overweight so the authors statement that anemia coexisted with obesity in half the population exposed prenatally doesn't suggest that this has anything to do with famine exposure.*

Response: Although it is true that half of the population was overweight, the distribution of overweight differs by anemic status and famine exposure. Among
those who are anemic the prevalence of overweight differs between fetal exposure and non-exposed cohorts (48.2% vs 33.3%). We have modified our statement in page 9.

**Also I would like to see more discussion on the fact that those exposed prenatally will also have been exposed in early life since the famine lasted 3 years rather than 9 months. The effects of only exposure in pregnancy are thus difficult to assess.**

Response: We have adopted the reviewer’s excellent point in our discussion. See page 12. “Those exposed prenatally will also have been exposed in early life since the famine lasted for 3 years rather than 9 months. The effects of exposure in pregnancy only are thus difficult to assess.”

**The discussion about inflammation should be revised. If they want to know something about inflammation I would suggest measuring markers of inflammation rather than suggest (as the authors do) measuring ferritin and so on.**

Response: Thank you for the suggestion. We have revised the discussion. See page 9. “Future study should assess whether famine exposure affect biomarkers of inflammation such as C-reactive protein.”

**Please comment on selection bias due to selective mortality across famine exposure groups as well as selection bias due to reduced fertility - which will have been a problem in the prenatally exposed group.**

Response: Thank you for pointing out the possible selection bias. We have added in the discussion. See page 13. “Selection bias is possible due to selective mortality or reduced fertility across famine exposure groups especially in the fetal exposed group.”

**Also, I would like to see more in depth discussion of the biological mechanisms in para 2 of the discussion.**

Response: We concur with the reviewer that understanding the underlying biological mechanisms is important. The present study is an exploratory study; we do not have enough biomedical measurements to investigate the mechanisms. We discussed several hypotheses that may contribute to the mechanisms including inflammation, chronic diseases and stress in the manuscript (page 11-12).
Reviewer: Cheng Huang

This is a very interesting paper written in the spirit of previous research utilizing famines as a natural experiment to examine the effect of malnutrition in the critical period of life on adult chronic disease, a hypothesis originally raised by Barker and his team and later caught increasing attention in research community.

This paper is well written and easy to follow. The data are appropriate to test the hypothesis that prenatal exposure to the Chinese famine of 1959-61 may increase anemia in adulthood. That being said, several issues should be addressed before it could contribute to the literature with solid evidence.

Response: Thank you very much for the appraisal.

Major Compulsory Revisions

First, the interpretation of Barker’s hypothesis was overly simplified. A more careful review of previous work is also needed, which may better present the scientific significance of the present study in the context.

Response: As this is an exploratory study, we do not have enough biomedical measurements. Discussion on the biological mechanisms would be difficult. Several hypotheses have been suggested in our discussion including inflammation, chronic diseases and stress.

Second, this present study applied a simple comparison between cohorts. A more rigorous analytical approach is needed to disentangle the “famine” effect from age effect and other potential confounding factors. A difference in difference like model may work here (Chen and Zhou, 2007; Huang et al., 2010). The authors may either consider to measure and include regional differential in famine intensity at county level in the model (Huang et al., 2010) or to construct a difference in difference model with an interaction between rural/urban* cohorts. At minimum, results from analysis on rural sample only should be presented, since food supply to urban residents was guaranteed even in famine years.

Response: Because of the relatively small geographic region (one province) and sample size in the subgroups, we do not have enough power to subgroup analyses like a difference in difference model. However, we have added results from analysis on rural sample. We did find significant interaction between residence and famine exposure in relation to anemia. The manuscript was amended accordingly. See page 10.

Reference:


Response: We have cited this reference. See page 3.

The reference ‘Huang et al., 2010.’ Was cited as well.
Reviewer: Gerd Holmboe-Ottesen

This is an interesting paper suggesting a relation between early life exposure to famine and anaemia. The research question is well defined and the methods applied appropriate.

In my view, only minor revisions are necessary:

1. In Methods section it is mentioned that dietary assessment were done on one third of the households. However there is no mention of the methods used in estimating food/iron intake. This should be clarified.

Response: Thank you for the comments. Information on dietary intake measurement has been added in the method section. See page 7.

2. In results: First para, second to last sentence. Percentages (48.2 vs 33.3) in regard to coexistence of overweight and anaemia are different from the results given in Table 1 (below subtitle on ‘comorbidity’). Please give more details as how these figures have appeared and can be distinguished from the ones in the table.

Response: We have made it clear that the prevalence of coexistence of overweight and anemia is 16.2% in fetal exposed cohort. 48.2% is the prevalence of overweight among those who are anemic.

3. In Discussion, Page 8, 2nd para, last two sentences: Please give more information on how stress may affect anaemia.

Response: The exact mechanisms of how stress may affect anemia are not known. The two studies we cited showed that maternal stress affect iron levels. We have updated the reference of the human study (ref 30) and provided more information in the revised manuscript. See page 11.

4. Table 1: Units should be given to all figures that are means in the table.

Response: We thank the reviewer for the comment. Units have been added in the table.