Author’s response to reviews

Title: Association between anemia and frailty in 13,175 community-dwelling adults aged 50 years and older in China

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Author’s response to reviews:

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Editor, Aisling M. O'Halloran
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RE: BGTC-D-19-00496
Association between anemia and frailty in 13,175 community-dwelling older adults in China

Dear Editor, Aisling M. O'Halloran
Thank you very much for your letter, and to the reviewers for their thoughtful critique of our manuscript. Reviewer comments in italics and our specific responses in plain text follow. Changes to the manuscript are indicated in the text by using track changes.

Reviewer 1 Comment 1: Age - the authors include non-geriatric population in the study (Younger than 65). This population comprised large part of the general population of the study (44%). There is no clear reason for that decision. The prevalence of frailty in this population is low and including it in the study adds irrelevant dependencies (e.g it might be that this younger cohort is more educated than the oldest cohort - this may cause educated population in the study to be less frail due to the age factor and not due to other relevant inherent factor of education). I suggest to exclude these non geriatric population from the study or to address the decision to include it in the discussion.
Response: Thank you for the suggestion. While the older population is often defined as people aged 60 and older or 65 and older, these age cut-offs may not be as relevant of less developed countries than in more developed countries. People 50 years and older in China represented 25 percent of the total population in 2010 and projected to reach almost 50 percent in 2050 (U.S. Census Bureau, 2012). Furthermore, 50 years old signifies qualification for old-age social insurance programs, unlike in many developed countries where the eligibility age is often 65 or older. So our study included 50-59 population, comprised large part of the general population. In addition, both age and education were included in the models as confounding variables to control their impact on frailty, and the results of table 4 indicated that age and education were both associated with frailty to make more rigorous, the title of the paper was changed to: Association between anemia and frailty in 13,175 community-dwelling adults aged 50 years and older in China.

Reviewer 1 Comment 2: Higher wealth was also associated with higher anemia rates" - if this is true (although it doesn't make sense) - the authors need to address it in the discussion (since this is not the expected finding).
Response: Thank you for the suggestion. We checked the data and code very carefully, and we also analyzed the distribution of the missing data of Hb and found that the missing data were mainly concentrated in the high income group in urban area and low income group in rural area (see below table). That is the reason we believe what led to conflicting results.

The distribution of the missing data of Hb

<table>
<thead>
<tr>
<th>Income Quintile</th>
<th>Urban(%)</th>
<th>Rural(%)</th>
<th>Total(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Lowest)</td>
<td>14.7</td>
<td>30.5</td>
<td>21.2</td>
</tr>
<tr>
<td>2</td>
<td>16.0</td>
<td>30.1</td>
<td>21.8</td>
</tr>
<tr>
<td>3</td>
<td>21.5</td>
<td>19.5</td>
<td>20.7</td>
</tr>
<tr>
<td>4</td>
<td>20.3</td>
<td>13.1</td>
<td>17.4</td>
</tr>
<tr>
<td>5 (Highest )</td>
<td>27.4</td>
<td>6.8</td>
<td>19.0</td>
</tr>
</tbody>
</table>

We noticed that we analyzed the distribution of the missing data of Hb and found that total of missing values were randomly distributed across five income groups, but there are significant differences between rural and urban across five income groups. we have mentioned in discussion part as one of limitations of our study (Discussion, line11-14, page 10).

Reviewer 1 Comment 3: With regard to place of residency - there are conflicting results (page 6, line 45 and Page 7, line 1 - Rural residents had lower levels of anemia and higher levels of frailty (which points to inverse correlation).
Response: Please see the responses to “Reviewer 1 Comment 2.”
Reviewer 1 Comment 4: Page 6, line 10 - "Covariates of interest included age, gender, education, smoking, nutrition, physical activity". Table 4 refers to additional covariates which should be mentioned (residence, income quintile. Alcohol consumption).
Responses: Thank you for the suggestion. We have amended the covariates including age, gender, residence, education, household wealth, fruit and vegetable intake, tobacco use, alcohol consumption and physical activity (Statistical methods, line 8-10, page 6).

Reviewer 1 Comment 5: In the last paragraph of the results section (page 7, lines 6-23) there are missing covariates (which can be found in the table but are not mentioned in the results without any good reason (Physical activity and nutrition).
Responses: Thank you for the suggestion. We have amended the covariates including age, gender, residence, education, household wealth, fruit and vegetable intake, tobacco use, alcohol consumption and physical activity (Results section, line 10-11, line 15-17, page 7).

Reviewer 1 Comment 6: There are several grammar issues (page 8, line 8 - "increasing" should be "increased". Page 8 line 48 - "suggesting that…..Hematocrit levels" ?, page 8 line 51 - "found mildly" - should be "found that mildly".
Responses: Noted and revised (Discussion section, line 17, page 8 and line 7-8, page 9).

Reviewer 1 Comment 7: Page 9 line 42 - "results from SAGE china Waves 2 and 3 may provide an opportunity to examine the direction of this relationship we identified" - there is no explanation for that in the text. What is it about SAGE Waves 2 and 3 that will allow for this opportunity?
Responses: SAGE is a longitudinal cohort, designed as a multiwave panel study representative of the population aged 50 and older in six low- and middle-income countries (China, Ghana, India, Mexico, Russian Federation and South Africa). Data of this study was sourced from SAGE China Wave 1 from 2007-2010, and Wave 2 data collection was completed in 2014/15, following up all Wave 1 respondents, Wave 3 was conducted in 2018. However, the data cleaning of SAGE Waves 2 and 3 is still in progress.

Reviewer 1 Comment 8: Page 9 line 49 - "Thirdly, the missing data for hemoglobin…." I didn't identify any mention of missing data earlier in the paper.
Responses: Corresponding description has been included in the result part (line 23, page 6).

Reviewer 2 Comment 1: Please describe in the methods any measures of BMI and nutritional intake more clearly.
Responses: It was noted and revised (Methods-measures, line 1-2, page 5 and Methods-other covariates, line 18, line 25, page 5).

Reviewer 2 Comment 2: Please make sure that all measures used in tables and figures are described clearly and consistently in the methods e.g. residence, income quintile, alcohol consumption.
Responses: It was noted and revised (Statistical methods, line 8-10, page 6).

Reviewer 2 Comment 3: In the results please clearly state (referred to the appropriate table) when nutritional intake of fruit and veg was included in the statistical models. This measure of fruit and veg intake is an important confounder of anemia, if data on intakes of red meat have also been gathered would also be useful.
Responses: Thank you for the suggestion. We have amended the covariates (Statistical methods, line 8-10, page 6 and Results section, line 10-11, line 15-17, page 7). SAGE have not collected the intakes of
red meat information at baseline. We would like to gather the data on intakes of red meat in next waves.

Reviewer 2 Comment 4: Page 6, line 47 -" Higher wealth was also associated with higher anemia rates" - this is counter intuitive and an unexpected finding. I would ask the authors to address this finding in the discussion please.
Responses: Please see the responses to “Reviewer 1 Comment 2.”

Reviewer 3 Comment 1: Page 3 line 15: unclear and Refs needed
Responses: The reference 3 was in line 8 page 3, which was a review about “anemia in frailty” and suggested that anemia increased the levels of fatigue, cognitive decline and weakened muscle strength.

Reviewer 3 Comment 2: Page 3 Third paragraph: The referenced meta-analysis reports that the association between anaemia and frailty differ by study designs. Would be good to include the follow-up time for the longitudinal studies which found no association between anaemia and frailty. Line 49: unclear which frailty criteria is referred to. ?
Responses: The two longitudinal studies reported the conflicting results: Hirani et al reported a significant 80% increased risk of incident frailty over 2-5 years in men with baseline anaemia. In contrast, Trevisan et al found that persons with anaemia had a lower odds of progressing from robust to prefrail/frail: 0.83 (0.72–0.96), or progressing from prefrail to frail: 0.84 (0.72-0.99) over 4.4 year follow-up. However, in the multivariate model they did not find a significant association between anaemia and improvement from prefrailty or frailty. We have added the follow-up time (page3, line22).

Reviewer 3 Comment 3: Page 4 Line 23: Unclear. The number of respondents n=13,175 and number of those responded to individual questionnaire (n=13,175?) with a response rate of 98%.
Responses: Thank you. We have revised it: SAGE China Wave 1 contacted 1,642 individual respondents aged 18–49 years and 13,367 respondents aged 50+ years (Methods section, line10-11, page 4).

Reviewer 3 Comment 4: Methods: which dietary assessment tool was used to ascertained fruit and vegetables intake? A brief description as to why limit to fruit and vegetable consumptions considering animal protein have higher level of heme-iron which is more absorbable than non-heme-iron.
Responses: Thank you for the suggestion. It was a limitation that we didn’t consider animal protein intake in the dietary assessment. We would like to gather the data on intakes of animal protein in next waves. Five or more servings of fruit and vegetable consumption were defined as sufficient daily intake (equivalent to at least 400 grams per day), fewer than five servings was categorized as insufficient according to WHO (Diet, nutrition and the prevention of chronic diseases. Report of a joint WHO/FAO expert consultation. ) (Methods section, line 25, page 5).

Reviewer 3 Comment 5: Statistical method: Why 'residence' is considered as a confounder? Is this correlated with household wealth?
Responses: It was showed that the prevalence of anemia among rural dwelling respondents (19.4 %) was lower than in urban areas (46.3%) (F=76.318, P&lt;0.001) in table 2. And compared with female urban respondents, female rural dwellers had higher levels of frailty (F=2.272, P=0.024). So “residence” is considered as a confounder.

Reviewer 3 Comment 6: Results: Page 6 second paragraph: Interesting findings. One would assume
wealth is positively correlated with education level but an inverse association between wealth and Hb level. Interesting point for discussion.

Responses: Please see the responses to “Reviewer 1 Comment 2.”

Reviewer 3 Comment 7: Page 7: would be good to synthesise findings on prevalence of anaemia across different countries instead of reporting the individual finding.
Responses: Noted and undertaken. In this section we synthesised findings on prevalence of anemia, and then described the individual results of different countries (Discussion section, line 1-3, page 8).

Reviewer 3 Comment 8: Page 8 and 9 Discussion on the association between anaemia and frailty: Need to acknowledge reverse causality, and be clear/specific about study design, i.e. association at one time point vs longitudinal study. Are there any report on anaemia predicting frailty over time?
Responses: There are few longitudinal studies on the relation between anaemia and frailty. Hirani et al (reference 20) reported a significant 80% increased risk of incident frailty over 2-5 years in men with baseline anaemia. Another longitudinal study (Trevisan et al) found that persons with anaemia had a lower odds of progressing from robust to prefrail/frail: 0.83 (0.72–0.96), or progressing from prefrail to frail: 0.84 (0.72-0.99) over 4.4 year follow-up. However, in the multivariate model they did not find a significant association between anaemia and improvement from prefrailty or frailty(reference 35).

Reviewer 3 Comment 9: Page 9, line 32: last sentence unclear, is it protective against frailty or anaemia? Is this mentioned in the result section?
Responses: Table 4 indicated that sufficient intake of vegetables and fruit and moderate to high levels of physical exercise had protective effects against frailty. It was noted and revised (Discussion section, line 3, Page 10).

Reviewer 3 Comment 10: Page 9, line 49: which type of bias may be related to missing Hb data?
Responses: The missing data may led to selection bias. We have amended it (Discussion section, line 11, Page 10).

Reviewer 3 Comment 11: Conclusion: New term "low-normal Hb" is introduced in the conclusion paragraph.
Responses: "low-normal Hb" means lower levels of Hb concentration. We have revised it in conclusion (line 21, page 10).

Reviewer 3 Comment 12: Table 1. Confusing column heading for age
Responses: We have revise the column heading for age in table1-4.

Reviewer 3 Comment 13: Table 2: would be good to include the mean (SD) of Hb level, and define what is 'low-normal Hb'
Responses: Noted and revised. We have described the mean (SD) of Hb level in results(line 22-23, page 6). "Low-normal Hb" means lower levels of Hb concentration. We have revised it in conclusion (line22-23, page 6).

Thank you for your consideration.

Sincerely,

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