Author's response to reviews

Title: Associations of alcohol consumption with diabetes mellitus and impaired fasting glycemia among middle-aged and elderly Chinese

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Author's response to reviews: see over
Previous title: Associations of alcohol consumption with diabetes mellitus and hyperglycemia among middle-aged and elderly Chinese

Current title: Associations of alcohol consumption with diabetes mellitus and impaired fasting glycemia among middle-aged and elderly Chinese

Shanghai, China, Sep. 27, 2010

Dear Dr. Gabriella Anderson:

We greatly appreciate and have carefully revised our manuscript based upon the valuable comments from the reviewers. The title of manuscript is currently changed to “Associations of alcohol consumption with diabetes mellitus and impaired fasting glycemia among middle-aged and elderly Chinese” accordingly. In the attached letter, we provided a point-by-point response to each of the comments raised by the reviewers. In addition, all the revisions in the manuscript were highlighted with yellow color.

We hope this revision makes our manuscript now suitable for publication in the BMC Public Health. Please let me know if you have additional requests or questions.

Yours sincerely,

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Comments from Reviewer 1:
This study is a cross-sectional analysis of the associations between alcohol consumption and diabetes, hyperglycemia and related markers in a study of 50 to 70 year olds in 2 areas of China. The studies strengths include detailed anthropometric and laboratory measures, dietary intake measures and what appears to be a good measure of current alcohol intake with attention to beverage type and container or drink size. Statistical measures appear to be appropriate. The results are to some extent in accord with previous findings indicating increased risk for liquor drinkers and for the heaviest drinking group and decreased risk among all drinkers for women. However, results indicating increased risk for the lightest drinking group, which includes drinkers of up to 19.9g/d, seem to differ from many previous studies.

Major Compulsory Revisions
1) The major weakness in this study is the lack of any past drinking information. While this is acknowledged, the authors should provide additional information on any studies assessing the proportion of abstainers who are likely to be former drinkers and lifetime abstainers. They should also comment on the potential biases in the results from including former drinkers in the abstainer category.

We appreciate Reviewer’s comment and agree that the lack of past drinking information might induce potential biases as we indicated in the last paragraph of Discussion section. Based upon the reviewer’s suggestion, we also cited a study which evaluated the effect of alcohol consumption on mortality in a large population-based cohort including 66,743 Chinese men aged 30-89 in Shanghai from 1996 to 2000 (Xu et al., Prev Med 2007). The data in this study showed that only 5.3% of abstainers were former drinkers. Likewise, the proportion of former drinkers among abstainers and related biases might be insignificant in our study. We emphasized this by replacing “Thirdly, due to lacking of relevant data, we could not exclude ex-drinkers from abstainers” with “Thirdly, due to lacking of relevant data, we could not exclude former drinkers from abstainers, which might confound the observed associations between alcohol consumption and risk of having altered glucose metabolism. However, according to the data from a large cohort study conducted in 66,743 Chinese men in Shanghai [35], only 5.3% of abstainers were former drinkers. Likewise, the biases driven by misclassifying former drinkers in abstainers might be negligible” (Discussion section, Paragraph 7, Page 15 Line 1).
2) Because the abstainer category is a mixed group it would also be informative to test for differences between groups of drinkers for men in order to establish increased or decreased risk as alcohol intake goes up.

We agree with Reviewer’s comment and have analyzed the associated between alcohol consumption and diabetes and/or IFG using different alcohol consumption categories as reference group. The results were presented in Supplemental Table 1 as follows:

**Additional file 1 – Multivariable adjusted odd ratios (95% confidence intervals) for diabetes mellitus and combined diabetes and IFG according to alcohol consumption categories**

<table>
<thead>
<tr>
<th>Diabetic cases/non-cases, n</th>
<th>Abstainers</th>
<th>0.1-19.9g/d</th>
<th>20.0-39.9g/d</th>
<th>≥40.0g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>95/593</td>
<td>74/312</td>
<td>13/129</td>
<td>32/187</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.79 (0.54,1.14)</td>
<td>1.0 (reference)</td>
<td>0.55 (0.29,1.07)</td>
<td>1.24 (0.75,2.06)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.42 (0.74,2.73)</td>
<td>1.81 (0.94,3.51)</td>
<td>1.0 (reference)</td>
<td>2.53 (1.09,4.64)</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.63 (0.38,1.04)</td>
<td>0.80 (0.48,1.33)</td>
<td>0.44 (0.22,0.91)</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined diabetes and IFG cases/non-cases, n</th>
<th>270/418</th>
<th>211/175</th>
<th>52/90</th>
<th>107/112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.73 (0.55,0.98)</td>
<td>1.0 (reference)</td>
<td>0.59 (0.38,0.91)</td>
<td>1.10 (0.75,1.61)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.25 (0.82,1.91)</td>
<td>1.71 (1.10,2.64)</td>
<td>1.0 (reference)</td>
<td>1.87 (1.16,3.02)</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.67 (0.46,0.96)</td>
<td>0.91 (0.62,1.33)</td>
<td>0.53 (0.33,0.86)</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>

The values are adjusted for age, geographic location (north/south), residential region (urban/rural), educational level, smoking, physical activity, family income, family history of CVD or diabetes, diet (total energy intake without alcohol, energy adjusted dietary fiber and fat intake), BMI, inflammatory markers (log-transformed CRP, IL-6 and ferritin), and adipokines (RBP4, log-transformed adiponectin and PAI-1).

Model 1, 2 and 3 were calculated using “0.1-19.9g/d”, “20-39.9g/d” and “≥40.0g/d” group as reference group respectively.

We presented the findings in the Results section as “When using different alcohol consumption categories as reference group, moderate alcohol consumption was found to be associated with a decreased risk of having diabetes and/or IFG compared with both of heavy (ORs 0.44 [95%CI: 0.22-0.91] for diabetes and 0.53 [95%CI: 0.28-0.99] for combined diabetes and IFG)”.
for combined diabetes and IFG) and light alcohol consumption (OR 0.59 [95% CI: 0.38-0.91] for combined diabetes and IFG) (Additional file 1).” (Results section, Page 10 Line18-22) We also mentioned this in the Discussion section as “However, unlike findings from previous studies, the favorable effect of moderate drinking was only evidenced when compared with heavy drinkers but not with abstainers in our study” (Discussion section, Page 12 Line8-10)

3) In the Table 4 beverage type analysis it would be of interest to divide the <40g/d group to see where the differentiation between reduced and increased risk occurs.

We appreciate Reviewer’s comment and divided the <40g/d group into two groups in Table 4: 0.1-19.9g/d and 20-39.9g/d, respectively. For liquor drinkers, light or heavy alcohol consumption was associated with combined diabetes and IFG, whereas for non-liquor drinker, none of these alcohol consumption groups was associated with diabetes and/or IFG. We have presented these findings in Results section: “Compared with abstainers, liquor drinkers had a higher likelihood of having hyperglycemia in the full model analysis (OR: 1.46, 95%CI: 1.09-1.97)” with “In the stratified analyses according to beverage types, liquor drinkers had a higher likelihood of having combined diabetes and IFG in the full model analysis (OR: 1.47, 95%CI: 1.09-1.98), and the increased risk was mainly observed in light and heavy liquor drinkers compared with abstainers. There was no association observed among non-liquor drinkers.” (Results section, Page 12 Line12-16). We also discussed this in Discussion section as “In line with these studies, we observed that an increased risk of combined diabetes and IFG was associated with light and heavy liquor drinking but not with non-liquor drinking. Given the fact of much higher proportion of liquor drinkers in Chinese than in Caucasian, the controversial results between our study and others might be attributable to the differences in the types of beverage consumption” (Discussion section, Page 13 Line 5-10).

4) Table 4 is very interesting but also raises questions regarding the increased risk among very light drinkers, <1 day a week, where there would not seem to be a plausible mechanism differentiating them from abstainers and for 5-7 day 0.1-19.9 g/d drinkers who appear to drink about 0.5 to 1.5 US standard drinks (14gram) a day, which would be considered moderate drinking in most studies.
and might be expected to have a reduced risk. The authors should comment on these findings.

We highly appreciate Reviewer’s comment. In the revised version, the association between drinking frequency and diabetes and/or IFG and also explanations regarding the inconsistency between our study and previous studies are included in the Discussion section as “Moreover, drinking frequency might also modify the association between alcohol consumption and diabetes. In the stratified analyses, individuals drinking less than 1d/wk tended to have a higher risk of combined diabetes and IFG. Although the majority subjects in this group were light and non-liquor drinkers, we could not rule out the possibility that some of them consumed excessive alcohol over a short period of time. Interestingly, inconsistent with previous reports,[23] the increased risk was also observed in regular light drinkers (5-7 d/wk, 0.1-19.9g/d). Given the cross-sectional design, it is unclear whether some of the individuals have recently changed drinking habit according to their health conditions. Certainly, prospective studies are needed to address this issue.” (Discussion section, paragraph 3, Page 13 Line 13-22)

5) The study design is a multistage sampling procedure in three areas. This design should be included in the analysis to account for the effects of clustering on standard errors.

We highly appreciate Reviewer’s comment. A multistage sampling method was used to recruit the participants from Beijing and Shanghai, the 2 large cities representing the north and the south of China, respectively. Two urban districts and 1 rural district in both Beijing and Shanghai were chosen with comparable socioeconomic statuses. In order to minimize the biases induced by the north-south difference and urban-rural differences, all our analyses were adjusted for region (north/south) and residence (urban/rural) status.

6) Particularly for women, the drinkers might differ from non-drinkers insocioeconomic status or other important characteristics. Income is included in Table 1 but is not controlled in the analysis. This should be included or it's exclusion justified. Additional comment regarding this issue is also warranted.

We agree with Reviewer’s comment and have re-analyzed all of the relevant results with further adjustment for family income (<20,000/ 20,000-39,999/ ≥40,000 rmb/y)
and the results are presented in the revised tables. Indeed, the results were not substantially changed and the inverse association between alcohol consumption and diabetes mellitus remained significant in women after additional controlling for family income.

Comments from Reviewer 2:
Chen Liu et al have conducted a cross-sectional study of 3289 50-70 years old Chinese men and women who have reported their drinking habits regarding the weekly amount of ingested alcohol, the drinking pattern and the type of alcohol. This has been compared to their prevalence of diabetes, fasting blood sugar > 5.6 mmol/l, insulin sensitivity, pancreatic beta cell function and the concentration of some circulating inflammation factors and adipokines. The study finds an inverse association between alcohol drinking and prevalence of diabetes and “hyperglycemia” in women. In men, a moderate alcohol intake of 20.0-39.9 g/day seems to protect from both diabetes and “hyperglycemia”.

General impression:
An easily read and apparently well-conducted cross-sectional study of the association of alcohol drinking and diabetes. The study is relevant and interesting as existing data in this field concerning non-caucasians is sparse.

Major compulsory revision:
1. It would be beneficial to state whether the investigated prevalence of diabetes in the Chinese population covers both type 1 and type 2 diabetes. At least, the subject should be discussed.

We appreciated reviewer’s comments and indicated as a limitation that we did not specifically distinguish type 1 diabetes from type 2 diabetes during the recruitment of our study population. However, our participants were age 50 to 70 years and most of those diagnosed as diabetes were beyond 50 years old. Therefore, the bias induced by this might be negligible. We mentioned this in Discussion section as “Fourthly, we could not distinguish individuals with type 1 diabetes from those with type 2 diabetes. Given that in the present study only 14.4% of diabetic individuals had a diagnosis when they were younger than 50 years, and the fraction of type 1 diabetes is less than 10% among diabetic patients, it is less likely that the associations of alcohol consumption and diabetic risk could be confounded with the autoimmune diabetes.”
2. The percentage numbers mentioned in the text, e.g. p 8 ln 22 and p 9 ln 4-6, seem not to be consistent with the numbers stated in Tabel 1. Please clarify.

We highly appreciate the Reviewer’s comment. The percentage numbers mentioned in the text were calculated based upon the number of male or female drinkers, whereas the percentages in table 1 were calculated based upon both abstainers and drinkers in two sexes. Therefore, different percentages were presented accordingly. In this version, we have revised these numbers as following: “Among men, 52.1% were current drinkers and 15.3% consumed alcohol more than 40g/d. Meanwhile, male drinkers were more likely to drink liquor and have alcohol more than 5 days per week, whereas only 9.8% of female participants were current drinkers and majority of them seemed to be light, occasional and non-liquor drinkers” (Results section, Paragraph 1, Page 9 Line 1-5)

Minor essential revision:

1. The definition of “hyperglycemia” is somewhat confusing. Does it comprise every subject with fasting glucose >5.6 mmol/l and therefore also the diabetic subjects? Would it not be more beneficial to use the internationally accepted terms: “diabetes” and “impaired fasting glycemia”?

We highly appreciate Reviewer’s comment. The “hyperglycemia” comprised both subjects with fasting glucose >5.6 mmol and diabetic patients. Therefore, we agree with Reviewer’s comment and used “combined diabetes and impaired fasting glycemia (IFG)” to replace “hyperglycemia” in our manuscript.

2. The term “liang” should either be explained/defined or deleted.

We agree with Reviewer’s comment. The term “Liang” has been deleted and replaced with “50ml” in the text.

Discretionary revision:

1. Perhaps it is worth mentioning under “Conclusion” that the association between alcohol intake and prevalence of diabetes found in men actually follows the most commonly found J-shape?

We highly appreciate Reviewer’s comment and the J-shape association is mentioned
in Conclusion As: “In our study, an approximately J-shaped association was observed between alcohol consumption and combined diabetes and IFG among Chinese men.” (Conclusion, Page 16 Line14-15), and also mentioned in the Abstract section by replacing “Both low and high alcohol consumption were associated with increase the risk of having hyperglycemia among Chinese men” with “An approximately J-shaped association was observed between alcohol consumption and combined diabetes and IFG among men compared with abstainers in Chinese.” (Abstract, Page 2 Line 5-7).

2. There are several mistakes and misspellings in the article. It would benefit from being corrected by a person fluently speaking English.
We appreciate the Reviewer’s comment. The manuscript has been checked by someone with fluent English and revised the manuscript carefully to reduce the linguistic errors as much as we can.