Title: Association between hyperuricemia and atrial fibrillation in rural China: a cross-sectional study

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Author's response to reviews: see over
Dear Editor and Reviewers,

Thank you very much for your comments on our manuscript entitled “Gender-specific association between hyperuricemia and atrial fibrillation in rural China: a cross-sectional study” (MS: 1288764110153040). According to the recommendations, we have revised carefully our manuscript with colored text (Red). The following is a detailed list of our description on revision according to the reviewers’ comments. If any question arises, please let us know.

Thank you very much for your consideration.

Sincerely yours,

Yingxian Sun

Response to Alvaro Alonso's comments:

Major compulsory reviews:

- The authors chose to present their findings as showing that hyperuricemia was associated with AF prevalence in men but not women. However, they did not test for effect modification by sex and, therefore, it is unclear whether the results between men and women are statistically different (they are not). I believe the correct interpretation of the data is that hyperuricemia is associated with AF prevalence in the entire sample. This association may be restricted to men, but the authors’ data does not provide enough evidence to indicate that’s the case.

Answer: We made a formal statistical test for the different association of AF with
hyperuricemia between men and women. As a result, $P > 0.05$ for gender difference was observed. Therefore, we revised our manuscript thoroughly by red font.

Title (Page 1, line 1-2): Revised as “Association between hyperuricemia and atrial fibrillation in rural China: a cross-sectional study”

Abstract-Results (Page 2, line 43-44): Added “However, the interaction logistic regression analyses presented $Ps > 0.05$ for gender difference.”

Abstract-Conclusions (Page 3, line 45): Revised as “SUA is positively associated with the prevalence of AF in rural China.”

Key words (Page 3, line 47): Deleted “Gender-specific association;”

Introduction (Page 4, line 67-68): Added “and analysed the effect of gender on the independent association.”

Statistical analysis (Page 8, line 157-158): Added “Interaction regression models were used to test the difference in the associations of SUA with AF prevalence between men and women.”

Results - Association between SUA and AF (Page 9, mainly line 188-189): Added “However, $P > 0.05$ was observed for the different association of AF with hyperuricemia between men and women.”

Discussion (Page 10, line 209-213): Added a paragraph “We also tested the different association of SUA with AF between men and women by interaction regression models. However, the effect of gender on the association was not statistically significant with $Ps > 0.05$. Now, we thought low AF prevalence and small sample might give up to the inconsistence, and the positive association between SUA and AF might also exist in women even not significantly.”
In addition to reporting the association between hyperuricemia and AF prevalence, the authors should consider exploring the association between serum uric acid as a continuous variable and AF prevalence.

**Answer:** We added the association between serum uric acid as a continuous variable and AF prevalence.

Tables (Page 21): Added “Table 3”.

Abstract-Results (Page 2, line 42-43): Added “Similar associations were observed between SUA as a continuous variable and AF prevalence.”

Statistical analysis (Page 8, line 156): Changed “hyperuricemia” to “SUA”, including the analysis about SUA as a continuous variable.

Results - Association between SUA and AF (Page 9, line 190-191): Added “Similar associations were found between SUA as a continuous variable and AF prevalence (Table 3).”

- The discussion needs to provide some evidence about the validity of self-reported physician-diagnosed AF.

**Answer:** We revised it.

Discussion (Page 10, line 214-217): We added “In our current study, AF was diagnosed based on a previous history of physician-diagnosed AF and/or evidence of AF on the ECG, which was similar with some previous studies [9, 22]. Therefore, self-reported AF history was a method for the diagnosis of AF. But I think it’s a limitation that might give rise to some bias.”
- The Introduction and the Discussion should clarify what this study is adding to the existing literature showing consistently that hyperuricemia is associated with higher prevalence and incidence of AF.

**Answer: We revised it.**

**Introduction (Page 3, line 60-66):** Revised as “Serum uric acid (SUA) is a risk factor for cerebrovascular and coronary artery disease, as well as for hypertension, metabolic syndrome, and kidney disease [8], though only a few cross-sectional studies in Japan [9], Turkey [10], and China [11–13] have reported a positive association between hyperuricemia and the prevalence of AF. Also, population-based prospective cohorts showed that hyperuricemia was associated with high risk of AF [14,15]. However, all these cross-sectional studies enrolled only hospital patients rather than a general population. Furthermore, only the study in Japan analyzed the effect of gender on the association between hyperuricemia and AF, reporting that the independent association was observed only in women. Therefore, the current study was designed to explore the association between SUA and AF in a general population from rural China, and analyzed the effect of gender on the independent association.”

**Discussion (Page 9-10, line 198-201):** Revised as “Our finding that hyperuricemia was positively associated with the AF prevalence in the general population was consistent with previous studies [9-13], however, in our current study, the independent association was only observed in men but not women, which was inconsistent with the findings in Japan [9].”

**Minor essential revisions:**
We revised it.

Abstract-Results (Page 2, line 35-36): We added “A total of 139 participants were diagnosed of AF, among which, 72 were self-reported, 45 were ECG-diagnosed, and 22 were both.”

We revised it.

Abstract-Results (Page 2, line 43-44): We added “However, the interaction logistic regression analyses presented $P > 0.05$ for gender difference.”

We revised it.

We revised it.

Introduction (Page 2, line 43-44): We added “Also, population-based prospective cohorts showed that hyperuricemia was associated with high risk of AF [14,15].”

We revised it.

We revised it.

Results (Page 8-9, line 176-177): We added “Among these AF cases, 72 were self-reported,”
45 were ECG-diagnosed, and 22 were both.”

- Figure 1. Instead of using a grid pattern, I suggest to the authors using flat colors (e.g. dark color and white)

**Answer:** We revised it.

Response to Weihong Tang's comments:

**Major comments:**

1) Some AF cases were diagnosed based on a history of physician-confirmed AF and the medical history was ascertained during a face-to-face interview with the participants. The accuracy of self-reported AF history is of concern especially in participants recruited from a rural area in China. Please clarify this issue.

**Answer:** We provided some previous studies using the self-reported AF history and discussed its accuracy in the discussion.

Discussion (Page 10, line 214-217): We added “In our current study, AF was diagnosed based on a previous history of physician-diagnosed AF and/or evidence of AF on the ECG, which was similar with some previous studies [9, 22]. Therefore, self-reported AF history was a method for the diagnosis of AF. But I think it’s a limitation that might give rise to some bias.”

2) Quality index for laboratory measurements (e.g. coefficient of variation and/or
repeatability), especially for serum uric acid measurement, should be provided.

**Answer:** We added the description about the quality index for laboratory measurements.

Materials and Methods-Data collection and measurement (Page 6, line 120-123): We added “The laboratory measurements were calibrated and verified during analyzing our biochemical indexes and the results met the national standards of measurement (CNAS certificate of accreditation No.L0467) with the quality index $U = 0.006 (k = 2)$.”

3) A formal statistical test should be conducted to evaluate whether the different association of AF with hyperuricemia between men and women is statistically significant.

**Answer:** We made a formal statistical test for the different association of AF with hyperuricemia between men and women. As a result, $P > 0.05$ for gender difference was observed. Therefore, we revised our manuscript throughout.

Title (Page 1, line 1-2): Revised as “Association between hyperuricemia and atrial fibrillation in rural China: a cross-sectional study”

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4) Waist circumference is included in the definition of metabolic syndrome and also correlates with serum uric acid level. Therefore, waist circumference should be included in the multivariate adjustment analysis.

Answer: We revised it.

Table 1: We added the variable “waist circumference” in Table 1.

Table 2: We renewed the results in Table 2 by red font.

Materials and Methods-Data collection and measurement (Page 5-6, line 110-112): We added “Waist circumference (WC) was measured at the umbilicus to the nearest 0.1 cm with the participants standing at the end of normal expiration.”

Results (Page 8, line 168): We added “WCs”
Results (Page 9, line 186): We added “WC”

Minor comments:

1) Page 5, line 96. It would be better to replace “should be” by “were”.
   Answer: We revised it (Page 5, line 100).

2) Page 7, line 146. Please clarify what “at each SUA level” means or use better wording.
   Answer: We changed it to ”among participants with both normal SUA level and hyperuricemia” (Page 7, line 154)

3) Page 8, line 159-160. It states that hyperuricemia group had a higher prevalence of familial AF. This is inconsistent with what’s shown in Table 1.
   Answer: We deleted “familial AF” here. (Page 8, line 170)

4) Page 9, line 183. It would read better to add “observed” between “only” and “in”.
   Answer: We added “observed” here. (Page 9, line 197).