

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	High prevalence of hyperuricemia and its impact on non-valvular atrial fibrillation: The cross-sectional Guangzhou (China) Heart Study
<b>AUTHORS</b>	Lin, Wei-dong; Deng, Hai; Guo, Pi; Liu, Fangzhou; Chen, Ruyin; Fang, Xianhong; Zhan, xianzhang; Liao, Hongtao; Huang, Wenxiang; Liu, Yang; Wang, Feng; Zheng, Murui; Liu, Huazhang; Huang, Jun; Wei, Wei; Xue, Yume; Wu, Shu-lin

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Tiffany Gill The University of Adelaide
<b>REVIEW RETURNED</b>	08-Dec-2018

<b>GENERAL COMMENTS</b>	<p>Thank you for the opportunity to review this paper. My comments are as follows:</p> <p>Abstract: Clear and appropriate.</p> <p>Introduction: First line, "ranged" should be "ranges", "showed" should be "has shown" Other issues with English throughout impact on clarity.</p> <p>Methods: Study population: How did the random selection take place, how many eligible participants were in the urban areas? Why was a street and two towns chosen as the rural areas? First sentence of the second paragraph in this section is repeated as the first sentence in the Data collection section. Cohort definition section, "has history of AF with evidence" what is the evidence? Statistical analysis section, "multivariate" should be "multivariable" Issues with English throughout this section impact on clarity.</p> <p>Results: What was the eligible sample for inclusion and what was the response rate to the study? The analysis of the prevalence risk of hyperuricemia is unclear. Was a dichotomous variable for hyperuricemia used? If so (given it is logistic regression) what cutoff was used. It is unclear what is meant by adjusted risk factors. The analysis presented appears to be covariates associated with hyperuricemia. It should be stated that "these factors are associated with hyperuricemia" or "the presence of these factors increases the risk of hyperuricemia occurring". Issues with English throughout impact on clarity of result presentation.</p>
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	<p>Discussion: Clarity is impacted by English. Page 16, line 20 "multivariate Cox regression" should be "multivariable Cox regression".</p> <p>Tables appropriate. Figures appropriate although Figure 1 title "..stepwise age categories" just needs to be "age categories"</p>
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<b>REVIEWER</b>	Yingxian Sun The First Hospital of China Medical University
<b>REVIEW RETURNED</b>	10-Jan-2019

<b>GENERAL COMMENTS</b>	<p>Dear editors,</p> <p>The association between SUA and cardiovascular diseases is interesting and important health question. Authors analyzed the prevalence of hyperuricemia, risk factors and its impact on NVAf in a large sample from both urban and rural areas of Guangzhou. They concluded that the prevalence of HUA was extremely high among citizens of southern China, and HUA was strongly related to NVAf especially in Chinese females. This study has many advantages such as its large sample from urban and rural areas, and the using of 24 hours single-lead ECG. However, I have to raise some issues regarding the study.</p> <ol style="list-style-type: none"> <li>1. The authors generally said "The association between AF and HUA has been reported a lot, but whether SUA is one of risk factors of AF remains under discussion" in the Introduction, and only cited one literature. As for the objective and highlight of this paper, there is plenty of evidence showing that SUA is one risk factor for AF including both cross-sectional and prospective studies from different countries including China. Therefore, the authors should cite more literature about this topic and redefined the key highlights of this paper, such as unique characteristics of study population, and so on.</li> <li>2. In study population, the authors said "A sample of permanent residents aged 35 and above was selected by cluster sampling in each community". I think it will be better presenting the total number of invited subjects meeting the study's criteria and the response rate, or some other information, which can reflect the representativeness of the enrolled sample.</li> <li>3. In the data collection, the references about detail methods should be cited.</li> <li>4. In the definition, how to diagnose non-valvular AF but not valvular AF? By echo, history, or other? I think it should be described.</li> <li>5. In the definition, what's the purpose for MetS? I think it's not necessary, because no analysis was conducted about the associations between MetS, SUA, and AF in the paper.</li> <li>6. In the statistical methods, I think ROC was not proper for the analysis of associations between HUA and AF. And the authors said "Receiver-operating characteristic (ROC) analyses were used to detect the cutoff value of SUA in prediction of non-valvular AF." I didn't find the results about cutoff.</li> </ol>
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	<p>7. In the results (baseline characteristics), the authors said “In contrast, the SUA value and incidence of HUA were not affected by age among men [Figure 1].” However, the statistical method and the P value were not presented. Also, the sentence “The incidence of HUA in urban areas is higher than rural areas (Table 1)” was not a result in Table 1, and this description is not proper. The authors should review it.</p> <p>8. The meaning of “incidence” was different from “prevalence”, and the authors should proofread and correct it.</p> <p>9. The language should be improved.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Tiffany Gill

1, Introduction: First line, "ranged" should be "ranges", "showed" should be "has shown". Other issues with English throughout impact on clarity.

Response: We are very sorry for our incorrect writing and we have made correction according to the Reviewer’s comments.

2, Methods:

Study population: How did the random selection take place, how many eligible participants were in the urban areas? Why was a street and two towns chosen as the rural areas?

Response: Randomized multistage cluster sampling was used in this study. We divide all the 11 districts in Guangzhou into 2 groups: urban group (Yuexiu, Haizhu Liwan Tianhe and Huangpu District) and suburban group (Baiyun, Panyu, Nansha, Huadu, Conghua and Zengchen District). Sealed envelopes with the names of all the districts written on pieces of paper were prepared before the selection. Then, we randomly selected one envelope from each group. Yuexiu District was selected to represent the urban places while Panyu District was chosen for the rural regions. We selected Xinzao Town, Nancun Town and Xiaoguwei Street to conduct the survey in Panyu District using the same methods above while Dadong Street and Baiyun Street were chosen in Yuexiu District. Finally, in the same way, 7 residential committees in Dadong Street and Baiyun Street and 17 village committees in Xinzao Town, Nancun Town and Xiaoguwei Street based on population size. Every subject who was eligible to fit the inclusive criterions in Yuexiu and Panyu District was all included for the study.

A total of 29,196 residents were eligible for inclusion, of which 12013 residents participated in the study, the response rate was 41.16%.

Nancun Town, Xinzao Town and Xiaoguwei Street chosen as the rural areas in Panyu District. Xiaoguwei Street used to be a part of Xinzao Town and was set up to be a administrative street since 2004. The residents of Xiaoguwei Street live in 2 regions : one is in Xinzao Town called Guwei New Town which belongs to Xinzao Town and the other is Xiaoguwei Island near Xinzao Town. In 2000, Two-thirds of the residents lived in the Xiaoguwei Island moved to live in Xinzao Town due to demolition from the Guangzhou government for the University City.

Original residents both in Xiaoguwei Island or Guwei New Town share the same culture and lifestyle. Most of them in both regions are from the same family. They are relatives or even brothers and sisters. We include all of them to get a general view of their disease and family history.

They all have the health care in the same village hospital, Xinzao Hospital, with Xinzao residents. The 4 village committees in Xiaoguwei Street cannot only have villagers live in Guwei New Town join our survey and have the free checkups because they have to treat all their villagers equally. If we do

not include Xiaoguwei Island in our study, the survey in Guwei New Town cannot be better conducted.

Because all above, we decided to have Xiaoguwei Street as the survey places for the research.

3, First sentence of the second paragraph in this section is repeated as the first sentence in the Data collection section.

Response: We are very sorry for our negligence of the repeat sentence, we have deleted the repeat sentence in Data collection section.

4, Cohort definition section, "has history of AF with evidence" what is the evidence?

Response: All the residents receive ECG screening in this study, therefore, we diagnosed with NVAf meeting any one criterion as following: 1) AF pattern in ECG screening; 2) No AF in ECG screening but positive AF history; and 3) AF episodes in 24 hours single-lead ECG recording. "Has history of AF with evidence" means although the residents don't find AF during ECG screening, they have previous ECG examinations suggesting atrial fibrillation.

5, Statistical analysis section, "multivariate" should be "multivariable". Issues with English throughout this section impact on clarity.

Response: We are very sorry for our incorrect writing and we have made correction according to the Reviewer's comments.

6, Results: What was the eligible sample for inclusion and what was the response rate to the study?

Response: A total of 29,196 residents were eligible for inclusion, of which 12013 residents participated in the study, the response rate was 41.16%. We have added the details in data collection section.

7, The analysis of the prevalence risk of hyperuricemia is unclear. Was a dichotomous variable for hyperuricemia used? If so (given it is logistic regression) what cutoff was used. It is unclear what is meant by adjusted risk factors. The analysis presented appears to be covariates associated with hyperuricemia. It should be stated that "these factors are associated with hyperuricemia" or "the presence of these factors increases the risk of hyperuricemia occurring".

Issues with English throughout impact on clarity of result presentation.

Response: The cutoff points of dichotomous variables for hyperuricemia have added below table2.

We are very sorry for our incorrect writing and we have made correction according to the Reviewer's comments.

Discussion:

8, Clarity is impacted by English. Page 16, line 20 "multivariate Cox regression" should be "multivariable Cox regression".

Response: We are very sorry for our incorrect writing and we have made correction according to the Reviewer's comments.

Tables appropriate.

9, Figures appropriate although Figure 1 title "stepwise age categories" just needs to be "age categories"

Response: We are very sorry for our incorrect writing and we have made correction according to the Reviewer's comments.

Reviewer: 2

Reviewer Name: Yingxian Sun

1. The authors generally said “The association between AF and HUA has been reported a lot, but whether SUA is one of risk factors of AF remains under discussion” in the Introduction, and only cited one literature. As for the objective and highlight of this paper, there is plenty of evidence showing that SUA is one risk factor for AF including both cross-sectional and prospective studies from different countries including China. Therefore, the authors should cite more literature about this topic and redefined the key highlights of this paper, such as unique characteristics of study population, and so on.

Response: It is true as Reviewer suggested that we should cite more literature about this topic and redefined the key highlights of this paper, we have re-written this part according to the Reviewer’s suggestion.

2. In study population, the authors said, “A sample of permanent residents aged 35 and above was selected by cluster sampling in each community”. I think it will be better presenting the total number of invited subjects meeting the study’s criterions and the response rate, or some other information, which can reflect the representativeness of the enrolled sample.

Response: A total of 29,196 residents were eligible for inclusion, of which 12013 residents participated in the study, the response rate was 41.16%. We have added the total number of invited subjects meeting the study’s criterions and the response rate in Data collection.

3. In the data collection, the references about detail methods should be cited.

Response: It is true as Reviewer suggested that we should cite about the detail methods, we have cited the detail methods.

4. In the definition, how to diagnose non-valvular AF but not valvular AF? By echo, history, or other? I think it should be described.

Response: All residents with atrial fibrillation underwent a cardiac ultrasonography to confirm whether they were valvular atrial fibrillation. The criterion of diagnosis of NVAf followed the 2014 AHA/ACC/HRS guideline.

5. In the definition, what’s the purpose for MetS? I think it’s not necessary, because no analysis was conducted about the associations between MetS, SUA, and AF in the paper.

Response: Central obesity, Elevated FPG, Elevated BP, Reduced HDL and Raised Triglycerides level were all the diagnostic component of MetS. Although we didn’t analyze the associations between MetS, SUA, and AF in the paper, we found that the component of MetS were strongly associated with the risk of HUA. In the discussion section we also mentioned the relationship between MetS and atrial fibrillation. So we mentioned the definition of MetS.

6. In the statistical methods, I think ROC was not proper for the analysis of associations between HUA and AF. And the authors said “Receiver-operating characteristic (ROC) analyses were used to detect the cutoff value of SUA in prediction of non-valvular AF.” I didn’t find the results about cutoff.

Response: We are very sorry for our incorrect writing, we didn’t discuss the cutoff value of SUA in prediction of non-valvular AF. We have made correction according to the Reviewer’s comments.

7. In the results (baseline characteristics), the authors said, “In contrast, the SUA value and incidence of HUA were not affected by age among men [Figure 1].” However, the statistical method and the P value were not presented. Also, the sentence “The incidence of HUA in urban areas is higher than

rural areas (Table 1)” was not a result in Table 1, and this description is not proper. The authors should review it.

Response: We are very sorry for our incorrect writing, we have rewrite the relationship between age and hyperuricemia in different gender, and we have added one more Figure (Figure2) to show the difference in the prevalence of HUA between urban areas and rural areas.

8. The meaning of “incidence” was different from “prevalence”, and the authors should proofread and correct it.

Response: We are very sorry for our incorrect writing and we have made correction according to the Reviewer’s comments.

9. The language should be improved.

Response: We are very sorry for our incorrect writing and we have made correction according to the Reviewer’s comments.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Tiffany Gill The University of Adelaide, Adelaide, Australia
<b>REVIEW RETURNED</b>	11-Mar-2019

<b>GENERAL COMMENTS</b>	<p>I thank the authors for addressing the previous comments. My remaining comments are as follows:</p> <p>Abstract: First sentence, " hyperuricemia (HUA) epidemiology." I don't think the word epidemiology is required. Perhaps it should be "There are country and regional variations in the prevalence of hyperuricemia" Abstract generally clearer.</p> <p>Introduction: Clearer.</p> <p>Materials and methods: Line 110, If the methodology of the Guangzhou Heart Study is published, it should be referred to. Line 113 "...was selected by cluster sampling.." how was this done, how was selection made? Or refer to previously published methodology. Line 115, it is unclear what "3-round mobilization" Line 158, "The role of patients in this study was residents." This sentence is not clear.</p> <p>Results: Still some minor issues with English e.g. line 185, "Larger proportion.." Should be "A higher proportion.." which impact on clarity of results.</p> <p>Discussion: Appropriate</p> <p>Tables: Appropriate. Figures: Appropriate.</p>
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<b>REVIEWER</b>	Yingxian Sun The First Hospital of China Medical University, China.
<b>REVIEW RETURNED</b>	11-Mar-2019

<b>GENERAL COMMENTS</b>	No additional suggestions.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Abstract: First sentence, " hyperuricemia (HUA) epidemiology." I don't think the word epidemiology is required. Perhaps it should be "There are country and regional variations in the prevalence of hyperuricemia"

Response: We are very sorry for our incorrect writing and we have made correction according to the Reviewer's comments.

Introduction: Clearer.

1. Materials and methods: Line 110, If the methodology of the Guangzhou Heart Study is published, it should be referred to.

Response: We have referred the methodology of the study and mentioned it. (Line 139)

2. Line 113 "..was selected by cluster sampling.." how was this done, how was selection made? Or refer to previously published methodology.

Response: Randomized multistage cluster sampling was used in this study. We divide all the 11 districts in Guangzhou into 2 groups: urban group (Yuexiu, Haizhu Liwan Tianhe and Huangpu District) and suburban group (Baiyun, Panyu, Nansha, Huadu, Conghua and Zengchen District). Sealed envelopes with the names of all the districts written on pieces of paper were prepared before the selection. Then, we randomly selected one envelope from each group. Yuexiu District was selected to represent the urban places while Panyu District was chosen for the rural regions. We selected Xinzao Town, Nancun Town and Xiaoguwei Street to conduct the survey in Panyu District using the same methods above while Dadong Street and Baiyun Street were chosen in Yuexiu District. Finally, in the same way, 7 residential committees in Dadong Street and Baiyun Street and 17 village committees in Xinzao Town, Nancun Town and Xiaoguwei Street based on population size. Every subject who was eligible to fit the inclusive criterions in Yuexiu and Panyu District was all included for the study.

Line 115, it is unclear what "3-round mobilization"

Response: We conducted a 3-round mobilization approach in order to find the residents in the list at all possible. For the first-round mobilization, we made appointments for the survey from door to door.

Responsive information was collected to identify who were eligible to join the survey and within the eligible subjects who were willing, reluctant or indecisive to come. In the second round mobilization, we promoted the residents who were not connected in the same way. At the same time, we continued to have telephone appointments for people who were willing or indecisive to join the survey but had not come yet and collected the responsive information. During the last round of the mobilization, we mainly made telephone appointments for the eligible rest of the list who still did not come and sum up the latest responsive information.

Line 158, "The role of patients in this study was residents." This sentence is not clear.

Response: Response: We are very sorry for our incorrect writing and we have made correction according to the Reviewer's comments.

Results: Still some minor issues with English e.g. line 185, "Larger proportion..." Should be "A higher proportion..." which impact on clarity of results.

Response: We are very sorry for our incorrect writing and we have made correction according to the Reviewer's comments.

Discussion: Appropriate

Tables: Appropriate.

Figures: Appropriate.