PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between urbanization and the risk of hyperuricemia among Chinese adults: a cross-sectional study from the China Health and Nutrition Survey (CHNS)
AUTHORS	Yu, Xixi; Zhu, Cheng; Zhang, Han; Shen, Ziyan; Chen, Jing; Gu, Yulu; Lv, Shiqi; Zhang, Di; Wang, Yulin; Ding, Xiaoqiang; Zhang, Xiaoyan

VERSION 1 – REVIEW

REVIEWER	Eiji Oda Tachikawa General Hospital Japan
REVIEW RETURNED	26-Sep-2020

GENERAL COMMENTS	Table 3 should have a top line of urbanicity levels; low, medium and high. Limitation of the study should also be mentioned in Discussion.

REVIEWER	Arrigo Cicero Medical School, University of Bologna
REVIEW RETURNED	29-Sep-2020

GENERAL COMMENTS	I've read with attention the paper of Yu et al. that is potentially of interest. The background and aim of the study have been clearly defined. The methodology applied is overall correct, the results are reliable and adequately discussed. I've only some minor comments: - The authors should consider (if available) the fructose intake in the different social context, being fructose intake strongly associated with SUA level (Nutrients. 2019 Nov 5;11(11):2674. doi: 10.3390/nu11112674.) - The authors should limit their conclusion to China, since in other countries, the hyperuricemia prevalence could be similar in rural and in city areas (Sci Rep. 2018 Aug 1;8(1):11529. doi: 10.1038/s41598-018-29955-w.)

REVIEWER	Xianjia Ning Tianjin Medical University General Hospital, China.
REVIEW RETURNED	06-Nov-2020

GENERAL COMMENTS	1. Page 5 25-38 lines: The burden of hyperuricemia is not described enough, which can not highlight the harm of hyperuricemia. It is mentioned that hyperuricemia is associated with various diseases, but the specific association is not clear. 2. Page 6 40-42 lines: "Nine surveys have been conducted since 1989." Can you provide the references? 3. Page 7:The definition of "Urbanicity scale" is described in detail,

	but it lacks the standards of low, medium and high urbanization. 4. Page8 22-27 lines: Why is it calculated this way? 5. Page 10 4-7 lines: It is mentioned in the introduction that patients with low renal function will significantly increase their uric acid levels, so why included CKD patients? How to prove that the increase of uric acid in patients with CKD was associated with urbanization or with CKD itself? 6. Page 11 14-19 lines: Please specify the definition of BMI. Normal BMI should be less than 24. 7. Page 11 33 lines: Please specify the cut-off value of MET. 8 . Page 13 43-53 lines: Why does the conclusion drawn here contradict with Table 2? Table 2 points out that hypertension, diabetes, obesity and CKD lead to higher levels of serum uric acid. But here reported that individuals without hypertension, diabetes, obesity and CKD leads to a higher risk of HUA. 9. Page 14 17-28 lines: It is pointed out here that high urbanization brings high number of motor vehicles and high pollution, but the literature cited is from 15 years ago. Can it represent the current pollution situation? Is air pollution caused by motor vehicles at present? 10. Page 15 17-22 lines: It is pointed out here that adequate physical exercise causes higher risk of HUA, which is not consistent with the description of the results, please check. 11. Page 15 25-33 lines: Please discuss it with the results of this article. 12. Page 15 17-23 lines: In this article, only two cities and four counties are selected, which can not represent China. 13. Please describe the limitations of this article in discussion section.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

1.Table 3 should have a top line of urbanicity levels; low, medium, and high.

Response: We have added the top line in the Table 3 (Page 28).

2.Limitation of the study should also be mentioned in Discussion.

Response: We have added the limitations in the text (Page 16, Line 43-59; Page 17, Line 4-28).

Reviewer #2:

1.Please state any competing interests or state 'None declared': Non declared

Response: We have added it in the text (Page 19, Line 32).

2. The authors should consider (if available) the fructose intake in the different social context, being fructose intake strongly associated with SUA level.

Response: Thank you for your constructive suggestion, and the analysis of fructose intake must be very critical. However, the detailed data of fructose intake is not included in the design of CHNS. We have added it in the Introduction (Page 5, Line 46).

3. The authors should limit their conclusion to China, since in other countries, the hyperuricemia prevalence could be similar in rural and in city areas.

Response: We have added it in the Discussion (Page 17, Line 22-28).

Reviewer #3:

Please state any competing interests or state 'None declared': Non declared
Response: We have added it in the text (Page 19, Line 32).

1.Page 5 25-38 lines: The burden of hyperuricemia is not described enough, which cannot highlight the harm of hyperuricemia. It is mentioned that hyperuricemia is associated with various diseases, but the specific association is not clear.
Response: We have emphasized the harm of hyperuricemia (Page 5, Line 17-25) and described the association between hyperuricemia and various diseases in detail (Page 5, Line 25-33).

2.Page 6 40-42 lines: "Nine surveys have been conducted since 1989." Can you provide the references?
Response: We have added the reference (Page 6, Line 35-38).

3.Page 7 The definition of "Urbanicity scale" is described in detail, but it lacks the standards of low, medium, and high urbanization.
Response: We have described the standards in the methods (Page 8, Line 33-43).

4. Page 8 22-27 lines: Why is it calculated this way?
Response: Scoring algorithms within these components were developed based on distributions in the data, with the goal of having the median score in a middle year be close to half of the total possible points and with sufficient spread in the scores between the minimum and maximum points. Furthermore, each of the components was scaled to 0–10 based on the size or density of the area's population (Page 8,17-23).

5.Page 10 4-7 lines: It is mentioned in the introduction that patients with low renal function will significantly increase their uric acid levels, so why included CKD patients? How to prove that the increase of uric acid in patients with CKD was associated with urbanization or with CKD itself?
Response: Previous study[1] had reported that urbanization increases the risk of chronic kidney disease (CKD) and patients with CKD have high level of serum uric acid because of the decline of renal clearance of uric acid, so we need to analyze whether urbanization is an independent risk factor for hyperuricemia or whether it indirectly increases the risk of hyperuricemia by increasing the risk of CKD. We confirmed that urbanization is a risk factor of hyperuricemia independent of CKD through multivariate regression analysis (Table 3).

6.Page 11 14-19 lines: Please specify the definition of BMI. Normal BMI should be less than 24.
Response: We have revised the definition (Page 10, Line 20-25).

7.Page 11 33 lines: Please specify the cut-off value of MET.
Response: We have added the cut-off (Page 10, Line 45-48).

8.Page 13 43-53 lines: Why does the conclusion drawn here contradict with Table 2? Table 2 points out that hypertension, diabetes, obesity and CKD lead to higher levels of serum uric acid. But here reported that individuals without hypertension, diabetes, obesity and CKD leads to a higher risk of HUA.
Response: Table 2 depicted the association between hypertension, diabetes, obesity and CKD and higher levels of serum uric acid in all population we studied. But in Figure 2, we made a subgroup analysis to investigate whether the association still existed in the subgroups such as CKD or hypertension population, and we found the participants without hypertension, diabetes, obesity or CKD who lived in highly urbanized area had a higher risk of developing hyperuricemia.

9.Page 14 17-28 lines: It is pointed out here that high urbanization brings high number of motor vehicles and high pollution, but the literature cited is from 15 years ago. Can it represent the current pollution situation? Is air pollution caused by motor vehicles at present?
Response: We have added the current pollution situation in the text (Page 14, Line 20-33).

10.Page 15 17-22 lines: It is pointed out here that adequate physical exercise causes higher risk of HUA, which is not consistent with the description of the results, please check.
Response: We have revised the description (Page 15, Line 22-27).

11.Page 15 25-33 lines: Please discuss it with the results of this article.
Response: We have added the discussion in the text (Page 15, Line 30-46). Table 1 showed the highly urbanized group had the highest prevalence of CKD.span style="font-family:Verdana; background-color:#ffffff"> Table 2 showed the uric acid level of patients with CKD was higher than those without CKD, meaning CKD is closely related to HUA, which is consistent with previous studies.

12. Page 15 17-23 lines: In this article, only two cities and four counties are selected, which cannot represent China.
Response: The CHNS is a longitudinal study of nine Chinese provinces (Guizhou, Guangxi, Heilongjiang, Henan, Hubei, Hunan, Liaoning, Jiangsu and Shandong), and from each province we selected two cities and four counties randomly. So altogether 18 cities and 36 counties were selected (sampling procedure please refer to Figure 1). We have further explained in **Materials and Methods** (Page 6, Line 35-59; Page 7, Line 4-23).

13.Please describe the limitations of this article in discussion section.
Response: We have added the limitations in the text (Page 16, Line 43-59; Page 17, Line 4-28). First, a fair amount of smoking data in females was missing. Second, the real prevalence of diseases might be underestimated. Third, the population we analyzed was derived from China and global data is needed to generalize the result.

References
1. Inoue, Howard, AG, et al. The association between urbanization and reduced renal function: findings from the China Health and Nutrition Survey. *BMC Nephrol* 2017