PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis
AUTHORS	Zeng, Jie; Lawrence, Wayne R; Yang, Jun; Tian, Junzhang; Li, Cheng; Lian, Wanmin; He, Jingjun; Qu, Hongying; Wang, Xiaojie; Liu, Hongmei; Li, Guanming; Li, Guowei

VERSION 1 – REVIEW

REVIEWER	Bogna Grygiel-Górniak Department of Rheumatology and Internal Medicine, Poznan University of Medical Sciences, I confirm that I understand the above, and I am consent to the named publication of my review.
REVIEW RETURNED	14-Jul-2020

GENERAL COMMENTS	The manuscript titled: "Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis" presents the large long-term study describing the relationship between SUA and obesity among Chinese adults. The authors collected data at Guangdong Second Provincial General Hospital in Guangzhou City in over 15 thousand patients. The statistical analysis included LRM and GEE model to assess the association between SUA and obesity over the nine-year study period. Interestingly the subgroup analyses by gender and age show significant associations between SUA and obesity with a higher risk in females and young participants when compared to males and elderly patients. This fact can be explained by the lack of information on whether participants were prescribed medication to treat hyperuricemia, which was described as a limitation of the study. With increasing age and body fat mass, SUA became higher, and many obese patients are treated with hypouricemic medications. The baseline characteristics present in Table 1 lack the data about the female. SBP and DBP were within the recommended range, but the prevalence of hypertension in the general population is usually high. Thus, probably many patients were on hypotensive therapy. Moreover, the metabolic profile (glucose and lipid level) is generally worse in obese patients than in general populations. Analyzing the glucose level, lipid profile, and SBB/DBP, it can be suspected that some of the patients were on hypolipidemic and hypotensive therapy. It is worthy that some medications used to treat hypertension can increase uric acid levels. Therefore, this fact should also be included in the limitation of the study.

	Overall, the manuscript is well written. The text needs English correction. I believe that the work is valuable and can be published in the BMJOpen.

REVIEWER	Richard Johnson University of Colorado Anschutz Medical Campus Aurora CO 80045
REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	1. I found the paper a bit confusing as it moved from cross sectional to longitudinal presentation. These need to be separated with subheadings. Obesity is well known to be associated with hyperuricemia-- the issue is whether hyperuricemia predicts obesity or worsening BMI. They say they have a 9 year cohort, but it was unclear how many patients were followed for that period, and I cannot see that they controlled for baseline BMI or diabetes. They need to be more clear in their methods, what they controlled for, etc. The importance of the study is whether hyperuricemia at baseline predicts the development of obesity independent of baseline BMI or diabetes. It would be important, for example, to know how many developed obesity over the 9 year period, and what were the baseline uric acid levels in those who ended up with new obesity versus those who did not. It would be strengthened if there is some type of relationship as serum uric acid increases from low to high levels (such as quartiles) and whether there is a threshold level at which the risk for obesity accelerates. 2. It also seems like they only had data on a minority of their patients, questioning how well this represented the population, and I also did not see any consent signed

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Bogna Grygiel-Górniak
Institution and Country

Department of Rheumatology and Internal Medicine,
Poznan University of Medical Sciences,
Please state any competing interests or state 'None declared':
I confirm that I understand the above, and I am consent to the named publication of my review.

Please leave your comments for the authors below
The manuscript titled: "Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis" presents the large long-term study describing the relationship between SUA and obesity among Chinese adults. The authors collected data at Guangdong Second Provincial General Hospital in Guangzhou City in over 15 thousand patients. The statistical analysis included LRM and GEE model to assess the association between SUA and obesity over the nine-year study period.

Interestingly the subgroup analyses by gender and age show significant associations between SUA and obesity with a higher risk in females and young participants when compared to males and elderly patients. This fact can be explained by the lack of information on whether participants were prescribed

medication to treat hyperuricemia, which was described as a limitation of the study. With increasing age and body fat mass, SUA became higher, and many obese patients are treated with hypouricemic medications.

Response: Many thanks for the reviewer's thoughtful comment.We have carefully discussed this limitation in the revised manuscript as suggested (See page 12, Lines 238-239).

The baseline characteristics present in Table 1 lack the data about the female. SBP and DBP were within the recommended range, but the prevalence of hypertension in the general population is usually high. Thus, probably many patients were on hypotensive therapy. Moreover, the metabolic profile (glucose and lipid level) is generally worse in obese patients than in general populations. Analyzing the glucose level, lipid profile, and SBB/DBP, it can be suspected that some of the patients were on hypolipidemic and hypotensive therapy. It is worthy that some medications used to treat hypertension can increase uric acid levels. Therefore, this fact should also be included in the limitation of the study.

Response: Thank you for providing us with this insightful comment. We addressed this in the limitation (See page 12, Lines 239-240).

Overall, the manuscript is well written. The text needs English correction. I believe that the work is valuable and can be published in the BMJ Open.

Response: We thank the reviewer for their kind words. We further examined the manuscript for grammatical errors with the help of a native English speaker.

Reviewer: 2
Reviewer Name
Richard Johnson
Institution and Country

University of Colorado Anschutz Medical Campus
Aurora CO 80045

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
1. I found the paper a bit confusing as it moved from cross sectional to longitudinal presentation. These need to be separated with subheadings.

Response: Thanks for the reviewer's insightful comment and pointing this out. Our research is mainly based on longitudinal presentation for the data collection and analytical methods. Especially for the repeatedly measured .In this study, we used logistic regression model (LRM) for baseline participants and then utilized generalized estimating equations (GEE) models with unstructured correlation structures to quantify their longitudinal association between SUA and obesity over the 9-year study period. We have added more detail avoid confusion in the method (See page 8, Lines 128-132).

Obesity is well known to be associated with hyperuricemia-- the issue is whether hyperuricemia predicts obesity or worsening BMI.

Response: We thank the reviewer's insightful comment on this. Obesity is well known to be associated with hyperuricemia. We have added some relevant studies into the introduction section to explain that hyperuricemia may predict obesity or worsening BMI.

##Reference:

[1]Johnson RJ, Lanaspa MA, Gaucher EA. Uric acid: a danger signal from the RNA world that may have a role in the epidemic of obesity, metabolic syndrome, and cardiorenal disease: evolutionary considerations. Seminars in nephrology 2011; 31(5): 394-9.

[2]Masuo K, Kawaguchi H, Mikami H, Ogihara T, Tuck ML. Serum uric acid and plasmanorepinephrine concentrations predict subsequent weight gain and blood pressure elevation.Hypertension. 2003; 42:474–80.

They say they have a 9 year cohort, but it was unclear how many patients were followed for that period, and I cannot see that they controlled for baseline BMI or diabetes. They need to be more clear in their methods, what they controlled for, etc.

Response: We thank the reviewer's comments. During the 9-year cohort, 15959 patients were followed during this period. The baseline participants were selected with medical checkup ≥2 times in our analyses. Whether a patient develops into obese in each year is a dynamic process. As for how to control for baseline BMI and diabetes, we set a specific inclusion and exclusion criteria, as well as added more detailed information to clearly explain the methods on what was controlled for in this analysis(See page 7, Lines 98-100).

The importance of the study is whether hyperuricemia at baseline predicts the development of obesity independent of baseline BMI or diabetes. It would be important, for example, to know how many developed obesity over the 9 year period, and what were the baseline uric acid levels in those who ended up with new obesity versus those who did not.

Response: Thanks for reviewer's suggestions. Our study was based on baseline data to predict the development of obesity. The study revealed that a total of 1078 participants developed obesity over the 9-year period. The baseline uric acid levels in those who ended up with new obesity were greater than 429.5 mmol/L in men and 326.9 mmol/L in women, respectively. It might be more intuitive to express the risk for obesity in different levels of SUA. Therefore, most of the results are presented as OR in this manuscript. We emphasized this in the results (See page 9, Lines 160-161).

It would be strengthened if there is some type of relationship as serum uric acid increases from low to high levels (such as quartiles) and whether there is a threshold level at which the risk for obesity accelerates.

Response: We appreciate the reviewer's thoughtful comment. Our study have calculated the cut-off values of SUA for risk of obesity. The purpose of this study is mainly to calculate the threshold of the normal and high levels of SUA. The quartiles method mentioned by reviewers is another classification method. And we have carefully calculated the threshold level for risk of obesity into the quartiles method of SUA. The conclusion is consistent with dichotomy of SUA (normal and high levels) that the higher levels of SUA would accelerate the risk of obesity. Considering the repeatability of the method and the purpose of this study for SUA classification, we mainly reported the threshold level for SUA into two levels (normal and high SUA). Thanks again for your thoughtful suggestions.

2. It also seems like they only had data on a minority of their patients, questioning how well this represented the population, and I also did not see any consent signed.

Response: Thank you for bringing this to our attention. Our study included a total of 15959 participants, where nearly1078 developed obesity over the study period. The data is sufficient enough to calculate by estimating the sample size according to the sample size software PASS. Therefore, it may well represent the Chinese population in the present study. Because of the nature of this research, the IRB approved the ethical waiver of informed consent for this study. We added this information to the methods section (See page 9, Lines 146-147).

REVIEWER	Richard J Johnson University of Colorado, United States I have equity in a company developing xanthine oxidase inhibitors (XORTX) and I also consult for Horizon.
REVIEW RETURNED	30-Aug-2020

| GENERAL COMMENTS | This is an interesting paper that shows that baseline serum uric acid can predict the development of obesity. I think a few additional analyses can add to the strength of the paper.
1. First, it would also be beneficial to do an analysis of baseline uric acid values vs obesity at 9 year mark in males and females respectively where one eliminates baseline cases with hypertension, diabetes or elevated BS, dyslipidemia, normal kidney function, baseline obesity. In other words, one could look at individuals at baseline who did not have any comorbidities and see if in that group that hyperuricemia vs normouricemia predicts obesity. This would be a great way to validate the data.
2. It would also be interesting to take baseline uric acid and plot it against endpoint(9 year) increase in BMI to see if there is a correlation with higher baseline uric acid with risk for increasing BMI.

These types of analyses would add significantly to our understanding. For example, is there a level of uric acid where the increased risk for increasing BMI suddenly occurs (ie. a threshold effect) |

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2 Reviewer Name
Richard J Johnson
Institution and Country
University of Colorado, United States

Please state any competing interests or state 'None declared':
I have equity in a company developing xanthine oxidase inhibitors (XORTX) and I also consult for Horizon.

Please leave your comments for the authors below
This is an interesting paper that shows that baseline serum uric acid can predict the development of obesity. I think a few additional analyses can add to the strength of the paper.

1. First, it would also be beneficial to do an analysis of baseline uric acid values vs obesity at 9 year mark in males and females respectively where one eliminates baseline cases with hypertension, diabetes or elevated BS, dyslipidemia, normal kidney function, baseline obesity. In other words, one could look at individuals at baseline who did not have any comorbidities and see if in that group that hyperuricemia vs normouricemia predicts obesity. This would be a great way to validate the data.

Response: Thanks for reviewer's insightful comment. We have added the analysis of baseline uric acid values vs obesity at the 9-year mark in males and females, respectively. In this analysis, we excluded the baseline cases with hypertension, diabetes or elevated BS, dyslipidemia, normal kidney

function or baseline obesity. This result was consistent with the conclusion with our previous analysis and be presented in the results section (See page 10, lines176-179). Many thanks!

2. It would also be interesting to take baseline uric acid and plot it against endpoint (9 year) increase in BMI to see if there is a correlation with higher baseline uric acid with risk for increasing BMI. These types of analyses would add significantly to our understanding. For example, is there a level of uric acid where the increased risk for increasing BMI suddenly occurs (ie. a threshold effect)

Response: We appreciate the reviewer's thoughtful comment. In this revision, we have provided a scatter plot to show the relationship between baseline uric acid and endpoint (9 year) increase in BMI (SFig.1). The BMI showed an increasing trend by the increase of SUA. However, it is difficult to determine the abrupt cutoff value of BMI from SUA through this plot. Therefore, we calculated the cut-off values for SUA of obesity using the receiver operating characteristic curves (ROC) technique in our manuscript (See Supplemental Figure 1 and Supplemental Figure 2). Thanks again for your thoughtful suggestions.

VERSION 3 – REVIEW

REVIEWER	Richard Johnson University of Colorado USA I have equity in XORTX Therapeutics that is developing novel uric acid lowering treatments. I also have consulted for Horizon and Astra Zeneca.
REVIEW RETURNED	07-Oct-2020

GENERAL COMMENTS	The authors have addressed my concerns-- I appreciate their response

VERSION 3 – AUTHOR RESPONSE

Reviewer: 2
Richard Johnson
University of Colorado
USA

Please state any competing interests or state 'None declared':
I have equity in XORTX Therapeutics that is developing novel uric acid lowering treatments.
I also have consulted for Horizon and Astra Zeneca.

Comments to the Author
The authors have addressed my concerns-- I appreciate their response
Response: Thank you very much for reviewer's thoughtful comments and kindly help.