Author's response to reviews

Title: Serum gamma-glutamyltransferase and uric acid levels are associated with impaired fasting glucose in adults from Inner Mongolia, China

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Version: 2 Date: 11 February 2013

Author's response to reviews: see over
Dear editors and reviewers,

Thank you for all of your hard work on our manuscript which we really appreciated. We now would like to send the newly revised manuscript entitled “Serum γ-glutamyltransferase and uric acid levels are associated with impaired fasting glucose in adults from Inner Mongolia, China” for publication in BMC Public Health. Current manuscript has been revised point by point according to the professional comments and constructive suggestions from you. The main points of the revision have been highlighted with yellow. Other modifications have also been carried out to make our manuscript conform the request of BMC Public Health. In addition, we have had the language in our manuscript edited by the Edanz editing. The following are our specific responses to the two reviewers’ concerns and comments.

Reviewer's report
Title: Serum Gamma-Glutamyltransferase and Uric Acid Levels are associated with Prediabetes in Adults from Inner Mongolia, China

Version: 1 Date: 10 December 2012
Reviewer: Yong-Jae Lee

Reviewer's report:
12. BMC Public Health_GGT/UA and IFG_2012_12_10

Response to the Author
The study by Wu and colleagues aimed at investigating whether gamma-glutamyltransferase (GGT) and uric acid (UA) were associated with impaired fasting glucose in Inner Mongolian Chinese adults. The authors found that high resting heart rate was associated with arterial stiffness independently of other variables. The large number of subjects is a major strength of this study, but this manuscript could be improved by addressing the following points.

I. Major comments
1. Originality
This study has shown that there is a graded-positive association of GGT and with IFG in both men and women. The authors also found a significant relationship between uric acid and IFG only in women. However, many previous studies, even in Chinese population, demonstrated these associations between two variables. Sun et al. suggested that GGT is a predictive marker for not only IFG but IGT in apparently health Chinese adults (The association of gamma-glutamyltransferase and C-reactive protein with IFG/IGT in Chinese adults in Qingdao, China. Clin Chim Acta. 2011 Aug 17;412:1658-61). Kawamoto et al. also demonstrated that high MPV is an independent risk factor for coronary atherosclerosis and myocardial infarction (Serum gamma-glutamyl transferase within its normal concentration range is related to the presence of impaired fasting glucose and diabetes among Japanese community-dwelling persons. Endocr Res. 2011;36(2):64-73). Moreover, Krishnan et al. have shown that hyperuricemia in the mid-twenties is an independent marker for predicting diabetes and prediabetes among young adults in the subsequent 15 years (Hyperuricemia in young adults and risk of insulin resistance, prediabetes, and diabetes: a 15-year follow-up study. Am J Epidemiol. 2012 Jul 15;176(2):108-16.). Thus, I recommended including more subjects with DM and without CAD in your study and reanalysis. In this regard, the authors should describe the originality of the current manuscript in more details.

Thank the reviewer for the comments. In this study, we actually found a significant relationship between uric acid and IFG not only in women. As shown in table 3, the association
between UA and IFG is significant in men after adjustment for age, ethnicity, smoking, alcohol consumption, physical labor, BMI, WC, SBP, DBP, TC, TG, HDL-C, LDL-C (P for trend = 0.027). As we known, p=0.027 means that the association between serum GGT levels and IFG could be considered as statistical significant, so we think it is reasonable to draw the conclusion that a significant relationship between uric acid and IFG in both men and women.

Indeed some previous studies have reported the relationship between GGT or UA and IFG, so it is not suitable to say that “Currently there is little data available on the association between serum GGT, UA levels and clinically relevant blood glucose categories earlier in the disease continuum when diabetes prevention efforts may be applicable.”, and we have changed it into “Therefore, recent studies that examined the associations of serum GGT and UA levels with clinically defined blood glucose categories corresponding to early stages of diabetes have received considerable attention in terms of diabetes prevention.” (page 4, the last sentence in first paragraph of Background) Actually in China, the study about this is relatively less. As mentioned by reviewer, Sun et al. suggested that GGT is a predictive marker for IFG/IGT in apparently health Chinese adults in Qingdao, a coastal city of China. So we have described the originality of this study as follows: “The associations of serum GGT and UA levels with plasma glucose levels were reported recently among Chinese adults in Qingdao, a coastal city of China [16, 17]. However, China is a multi-ethnic country with marked regional differences, and little is known about the associations of serum GGT and UA levels with prediabetes among individuals living in areas inhabited by Chinese ethnic minorities.” (page 4-5); “To our knowledge, this was the first study to examine the possible associations of GGT and UA with prediabetes in areas inhabited by Chinese ethnic minorities.” (page 9, the last sentence in first paragraph of Discussion). Thank the reviewer reminding us several important literature and we have quoted them in the newly revised manuscript (see reference 14, 15, 17). In addition, we are very appreciate your recommendation that including more subjects with DM and without CAD in our study, but our another unpublished paper on association between GGT, UA and DM has included these data. Moreover, we mainly focus on the associations of serum GGT and UA levels with clinically defined blood glucose categories corresponding to early stages of diabetes. Thus, I am afraid that we could not include these subjects in the present study.

2. Title
The title of this manuscript is misleading. This is NOT “Serum gamma-glutamyltransferase and uric acid levels are associated with prediabetes in adults from inner Mongolia, China”. The authors have adopted only IFG rather than IGT in the current manuscript. Thus, the title should be changed as follows: “Serum gamma-glutamyltransferase and uric acid levels are associated with impaired fasting glucose in adults from Inner Mongolia.

We agree and therefore change the title to: Serum γ-glutamyltransferase and uric acid levels are associated with impaired fasting glucose in adults from Inner Mongolia, China.

3. Abstract
3.1. Results of the Abstract
The authors have documented a graded-positive association of GGT with IFG in both men and women, whereas a significant relationship between uric acid and IFG only in women. However, the authors have presented as follows: “A clear positive association between GGT/UA
and prediabetes was present among both men and women, independent of age, ethnicity, smoking, drinking, blood pressure, labor activity and other confounders.” Thus, the authors should correct the errors in the Results of the Abstract.

As mentioned above, table 3 showed a clear positive association between uric acid quartiles and IFG among both men and women in the multivariable-adjusted models. The association is considered as statistical significant if p for trend <0.05 and as shown in table 3, corresponding models evaluating trend in association of UA and IFG were statistically significant (P for trend =0.027) in men after adjustment for age, ethnicity, smoking, alcohol consumption, physical labor, BMI, WC, SBP, DBP, TC, TG, HDL-C, LDL-C. However, we realized that the differences of association between UA and IFG in men and women could not be ignored, so we discussed the differences in the Discussion section, “In addition, we found that women had higher OR values for IFG among each UA quartile than did men, after adjusting for confounding factors. Therefore, compared with men, women with high UA levels are at greater risk of prediabetes. Similar results were found in a cross-sectional survey of non-diabetic adults in Taiwan [28]. A recent study reported that UA is more strongly associated with impaired glucose regulation in women than in men [29], which further supports our conclusion.”(page 11, line 1-6)

3.2. Conclusion of the Abstract
“Gradually elevated serum GGT, UA levels within their normal ranges can significantly …” should be changed, because ranges of Q4 in Table 3 show above normal range of GGT and UA.

We have changed this sentence into “We found that serum GGT and UA levels were positively associated with prediabetes in men and women living in areas inhabited by Chinese ethnic minorities. As elevated GGT and UA levels were associated with significantly increased risk of prediabetes, they may be used as sensitive biological markers of prediabetes.”(page 2-3)

4. Definition of prediabetes
The definition of prediabetes in this manuscript is somewhat confusing, because you have adopted only the definition of IFG in your manuscript. Thus, PreDM or prediabetes should be in the entire manuscript.

Thank you for your suggestion. We have deleted the definition of prediabetes and Diagnosis criteria of prediabetes section of Method and added a sentence “The participants were classified according to FBG as having normal FBG (<5.6 mmol/L; NFG) or IFG (FBG 5.6–6.9 mmol/L) according to the American Diabetes Association criteria” in Laboratory measurements section of Methods (page 6, the last two lines). Prediabetes is defined as impaired fasting glucose (IFG) and/or glucose tolerance (IGT), so subjects with IFG belong to prediabetes population. Of course it will be more accurate if subjects with IGT could be included, but unfortunately in this study oral glucose tolerance tests were not performed, so we could not identify participants with IGT, which is a limitation of this study as mentioned in Discussion.(page 11, line 4-6 in the last paragraph).

5. Study population
Did you include the study subjects within normal range of GGT and UA in your work? However, Q4 in Table 3 shows above normal range of GGT and UA. How do authors explain these discrepancies between the description of the Abstract and Discussion and Table 3.
Yes, the study subjects within normal range of GGT and UA were included, but we did not exclude the subjects above normal range of GGT and UA in this study, so Q4 in Table 3 shows above normal range of GGT and UA. Actually, in table 3 the OR (vs Quartile 1) for Quartile 3 was higher than that for Quartile 2, so in the previous manuscript we proposed that higher serum GGT levels within normal range are positively associated with increased risk of prediabetes in Abstract and Discussion. Now we realized that the expression is inappropriate and easy to misleading, so we deleted “within normal range” and rewrite sentences in Abstract and Discussion. The sentence “Gradually elevated serum GGT, UA levels within their normal ranges can significantly increase the risk of prediabetes….” has been changed to “We found that serum GGT and UA levels were positively associated with prediabetes in men and women living in areas inhabited by Chinese ethnic minorities. As elevated GGT and UA levels were associated with significantly increased risk of prediabetes, they may be used as sensitive biological markers of prediabetes.’(page 2, the conclusion of Abstract). The sentence “In this study, among the healthy adults (both men and women) in Inner Mongolia of China, higher serum GGT levels within normal range are positively associated with increased risk of prediabetes…” has been changed to “In the present study, among healthy men and women in Inner Mongolia, we found that higher serum GGT levels were positively associated with increased risk of prediabetes…”(page 9 line 2-4 in the second paragraph of Discussion).

6. Statistical analysis
6.1. Weighted data are important.
Are the statistics in all Tables unweighted or weighted data?, For example table 1, I guess that they are unweighted data, in that case it might not be appropriate. Although, the target population was selected though a stratified, multistage, probability-sampling design based on geographic area, sex, and age group, Weights indicating the probability of being sampled should be assigned to each participant, to represent the entire Inner Mongolian adult population.

The data in table 1 were not weighted. A stratified, multistage, probability-sampling design based on natural populations meets a self-weighted sampling design, so it is not necessary to consider weighted as long as there is a sufficient sample size when estimating the total mean and proportion. Here, we have a sufficient amount of samples included, which could basically represent the maximum range of the adult population of Inner Mongolia.

6.2. All P-values in Table 3 are P-value for trends?
Yes, they are P-value for trends. Thank you for reminding us to realize the unclear expression and we have changed P-value into $P$ for trend in table 3.

6.3. Please describe specific methods of statistical analyses in Table 2 and Table 3.
It should be indicated below the tables which statistical analyses you used, - not only generally stated in the section on Statistical analyses.

We have added specific statistical methods below the table 2 and table 3. The following statements now appear as footnotes of table 2 and table 3 respectively, “Correlation and linear regression analyses were used to estimate the correlations between each variable and FBG” and “Multivariable logistic regression models were used to estimate the ORs and 95% CIs”.

7. Discussion
The authors have described as follows: “Furthermore, logistic regression analysis demonstrated that GGT and UA quartile subgroup levels were positively correlated with prediabetes and the correlations were still exist after adjustment for age, gender, ethnicity, smoking, drinking, BMI, WC, BP, TC, TG, HDL-C, LDL-C and other important confounders.” However, they presented gender-specific results in Table 3.

Thank the reviewer for the comments. We’ve recognized that we made a mistake and the word “gender” has been deleted in the newly revised manuscript.

II. Minor comments
1. Table 2
   Is it the result of simple correlation analysis or multivariate linear regression analysis? You should carefully explain it.
   Table 2 showed the results of correlation and linear regression analyses. As we mentioned in Results, the results showed that GGT and UA levels were significantly and positively associated with FBG levels in both sexes. ALP and CK were associated with FBG in females, and the association disappeared after adjusting for age and other factors using logistic regression analysis. (page 8 Correlations between liver enzymes, UA, and FBG levels)

2. References
   2.1 Citation references 3, 10, 13, 14, 19 need to be re-checked in the form of the BMC Public health.
   We have re-checked and revised the references to conform to the journal style.

3. Abbreviations and acronyms
   Please ensure that abbreviations and acronyms are given on first mention in text.
   We have reviewed throughout the manuscript and ensure that abbreviations and acronyms are given on first mention in text.

4. Please supply manufacturer’s name, city, state, country for all devices and software mentioned throughout.
   The manufacturer’s name, city, state, country for all devices and software mentioned in our manuscript has been supplied.

Level of interest: An article of limited interest
Quality of written English: Not suitable for publication unless extensively edited
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Reviewer's report
Title: Serum Gamma-Glutamyltransferase and Uric Acid Levels are associated with Prediabetes in Adults from Inner Mongolia, China
Version: 1 Date: 21 November 2012
Reviewer: Jialiang Li

The analysis results are interesting. The effects of GGT on the pre-diabetes outcome seem to be non-linear for male. That is, the OR for Q3 vs Q1 is higher than that for Q2 vs Q1, but also higher than that for Q4 vs Q1. Then you cannot conclude that the effects of GGT become stronger in a linear pattern. Please discuss on this. Similar pattern was observed when studying the association

Another suggestion is to show results by treating GGT as continuous variable. For a few GGT-related analysis, some authors also proposed to create an Odds plot to show the nonlinear dependence by using the well-known statistical smoothing technique. See Circulation Journal (2007).71: 1567-1572 and European Journal of Epidemiology (2009). 24(7): 369-373.

The reviewer is correct and we could not simply say that the effects of GGT on prediabetes become stronger in a linear pattern. We have revised the manuscript accordingly. In the revised paper, the sentence “We observed that OR value for prediabetes presented a gradual upward trend with increase of GGT and UA quartile subgroup levels, showing obviously "dose-dependent" ” has been changed to “Among men and women, GGT and UA quartiles were associated with IFG in all three models after accounting for the effects of confounding factors.”(page 9, line 4-6); “The OR of prediabetes increased in a dose-dependent manner with increasing quartiles of serum GGT and UA in both male and female” was deleted from Discussion. According to reviewer’s suggestion, we have discussed on this as follows, “In our study, we found that the OR (vs Quartile 1) for Quartile 3 was higher than that for Quartile 2, and was slightly higher than that for Quartile 4 (Table 3) in males, which suggests the effects of GGT on prediabetes outcome is non-linear among males. A similar pattern was observed for the association between GGT and peripheral arterial disease [23]. The possible reason for the non-linear association between GGT and IFG in this study is as follows: In adult males, increased GGT is often accompanied by dyslipidemia, probably because of the adverse eating habits (for example, people especially men from Inner Mongolia prefer drinking wine and eating meat). So the OR(vs Quartile 1) for Quartile 4 of serum GGT was slightly lower than that for Quartile 3 in Model 3 after ruling out lipid factors(including TC, TG, HDL-C, LDL-C), suggesting that the effect of lipids on FBG is the most obvious when GGT>57 U/L.(page 9-10)

We have described the effects of GGT on prediabetes outcome among males in detail and discussed the possible cause according to reviewer’s first suggestion, so we would not adopt the second suggestion and thank reviewer for the suggestions. The references supplied by reviewer are useful for us and we have quoted them in the newly revised manuscript.

Minor comments:
1. Page 6, 4th line in Statistical Analysis, add “F-test” after “analysis”.
2. 5th line, change to “A correlation and linear regression”.
3. 6th line, change to “study the relationship”.
4. 7th line, change “as quartiles” to “according to the distribution quartiles”.
5. 8th line, use lower case for logistic.
6. 9th line, change “comparison” to “effects”.

Thank reviewer for reminding us the improper description and syntax errors. We have changed them as the reviewer indicates.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests

Thank you very much for your kind consideration.

Sincerely yours,

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