Author's response to reviews

Title: An inverted J-shaped association of serum uric acid with muscle strength among Japanese adult men: a cross-sectional study

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Version: 2 Date: 16 July 2013

Author's response to reviews: see over
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Version: 2 Date: 16 July 2013

Author’s response to reviews: see over
Reviewer’s report

Title: An inverted J-shaped association of serum uric acid with muscle strength among Japanese adult men: a cross-sectional study

Version: 1 Date: 18 June 2013

Reviewer: Ailsa Welch

Reviewer’s report:

General
This is an interesting paper describing the association between serum uric acid and muscle strength. It is well written and concise.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Why were women excluded? It seems a pity to have excluded them particularly as there were a large number of them n=282.

   Actually, there were only 152 women in grip strength group and 96 women in leg extension power group after excluding the missing values of muscle strength and other relative variables. In addition, because sex differences existed in the uric acid (UA) levels and muscle strength, we considered inappropriate to perform analyses on men and women together. Thus, the information on women was not included in the final analysis due to a small sample size.

2. Can you provide the rationale for exclusion of those with renal failure – surely they would have provided information at the highest levels of uric acid? Likewise provide explanation for excluding those on anti-hypertensive or anti-diabetic agents or lipid lowering drugs - specifics of how these impact on uric acid should be provided.

   In this study, we excluded subjects who reported a history of cardiovascular disease and renal failure or who used anti-hypertensive, lipid-lowering, or anti-diabetic agents. In the fear that such diagnoses and agents may lead to changes in UA levels and/or muscular function and thus confound and obscure a true association.

   To be specific, there was only 1 subject with a history of renal failure in this study, and he had a low serum UA level 3.2 mg/dL. Adams and Vaziri [Adams and Vaziri, Am J Physiol Renal Physiol, 2006] reported that chronic renal failure contributed to skeletal muscle function decline. Furthermore, positive effect of antihypertensive [Shulman et al. Hypertension, 1989], lipid-lowering (statins) [Elisaf and Mikhailidis, Angiology, 2002], and
antidiabetic agents [Koro et al. Clinical Therapeutics, 2009] on renal function have been reported. Therefore, such diagnoses and agents were excluded from our study to guarantee the precision of results.

Page 5, line 87.

“3) having a history of cardiovascular disease and renal failure, or using antihypertensive, lipid-lowering, or antidiabetic agents (n = 146) because of the concern that such diagnoses and agents may lead to changes in UA levels and/or muscular function and thus confound and obscure a true association [19].”

3. Page 7 why was depression examined?

Previous study showed that depressive patients had lower serum UA levels [Wen et al. Clinical Biochemistry, 2012], although such an association was not found in the current study. Furthermore, our study indicated that subjects with depression had lower grip strength (means and 95% confidence intervals: 42.5 [41.9–43.1] vs. 40.9 [40.1–41.8], kg, P < 0.01) and leg extension power (18.9 [18.4–19.5] vs. 17.8 [17.0–18.7], W/kg, P < 0.05). Therefore, depression may play an important role in the association between uric acid and muscular function.

4. I think the curve described for the results of this study would be an ‘inverse U shape’ rather than a J shaped curve.

Information on the description of inverted J-shaped association in this study was insufficient. In fact, in the multivariate model (model 4), we found a high value for muscle strength in the second UA quartile as compared with the first quartile, although not significant. Meanwhile, grip strength and leg extension power were found to be significantly lower across the latter 3 quartiles of serum UA levels (P for linear trend = 0.05) (data not shown). Thus, the “inverted J-shaped curve” is more appropriate than “inverted U-shaped curve” in this study.

Page 10, line 210.

“To be specific, in model 4, we found a high value for muscle strength in the second UA quartile as compared with the first quartile, although the difference was not significant. Meanwhile, both grip strength and leg extension power were found to be significantly lower across the latter 3 quartiles of serum UA levels (P for linear trend = 0.05) (data not shown).”

5. In the discussion I think it would be helpful to compare UA levels found in this study with those found in the reference number 10.

A comparison between the current study and reference number 10 was added in the discussion part. Indeed, serum UA level in this study is higher than in reference number 10.

Page 13, line 246.
“Moreover, another explanation is that the mean level (SD) of serum UA is 6.1 (1.2) mg/dL in this study, which is higher than the 5.0 (1.2) mg/dL (in both men and women) from the previous study. It is well known that an increased UA level is related to high inflammatory cytokines [14], a contributor to poor muscle strength [33].”

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Some minor corrections to the English required.
   
   English proofreading for this paper was taken again, as you suggested.

Level of interest: An article of importance in its field.

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'
Reviewer’s report

Title: An inverted J-shaped association of serum uric acid with muscle strength among Japanese adult men: a cross-sectional study

Version: 1 Date: 20 June 2013

Reviewer: Junxiu Liu

Reviewer’s report:

General
Overall speaking, I think this is a good written and organized paper.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
None.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. I have concern about log transformation since simulations study do not support log transformation since when doing statistical inference, there will be way off the truth. Please check with statistician about this.

   We checked this point with a statistician. (Qiang Li, PhD, Department of Public Health, Xi’an Jiaotong University College of Medicine, Xi’an, Shaanxi, China)

   We think the simulations study you mentioned is from O’Hara and Kotze [O’Hara and Kotze, Methods in Ecology and Evolution, 2010], which indicated that count data should not be analyzed by log-transforming, but instead models based on Poisson and negative binomial distributions should be used.

   However, the data used in our study were continuous data (etc. muscle strength, BMI, eGFR, and daily nutrient intakes), but not count data. The log-transformation of continuous data can be used to make highly skewed distributions less skewed. This can be valuable both for making patterns in the data more interpretable and for helping to meet the assumptions of inferential statistics [Bland and Altman, BMJ, 1996; Olivier et al. Ann Allergy Asthma Immunol, 2008]. Therefore, the log-transformation used in this study would not way off the truth.

2. In the result part, the author mention about potential confounding factors. I think it needs to be spoke out which potential confounding factors were included in the analysis. (even
though they listed in the table part)

To address your concern, details on potential confounding factors were included in the result part.

**Page 10, line 192.**

“In our study, grip strength differed significantly between participants with and those without hyperuricemia (geometric mean and 95% CI: 40.3 [39.2–41.3] kg vs. 41.9 [41.3–42.5] kg; \( P = 0.01 \)) (Fig. 1) after adjustment for age, BMI, smoking status, drinking frequency, education levels, occupation, physical activity, daily energy and protein intakes, metabolic syndrome, depressive symptoms, eGFR, and hs-CRP.”

**Page 10, line 204.**

“The inverted J-shaped association between UA quartiles and grip strength (\( P \) for quadratic trend: model 1 = 0.07, model 2 = 0.09, model 3 = 0.04, and model 4 = 0.05, respectively) and leg extension power (\( P \) for quadratic trend: model 1 = 0.06, model 2 = 0.05, model 3 = 0.03, and model 4 = 0.03, respectively) were unchanged even after adjustment for potential confounding factors, including age, BMI, smoking status, drinking frequency, education levels, occupation, physical activity, daily energy and protein intakes, metabolic syndrome, depressive symptoms, eGFR, and hs-CRP in the multivariate model (Table 3).”

3. In the discussion part, due to the cross-sectional study design nature, the authors should also point out another very important limitation which is temporality which is different from causality.

As you suggest, the correction was expressed as follows.

**Page 14, line 277.**

“First, the association between serum UA and muscle strength is temporarily due to the cross-sectional nature of this study, and thus, a prospective study is necessary to confirm the causality of this association further.”

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

Quality of written English: Acceptable.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that I have no competing interests.