Author's response to reviews

**Title:** Relationship between metabolic syndrome and knee osteoarthritis; data from the Korean National Health and Nutrition Examination Survey (KNHANES)

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**Author's response to reviews:** see over
Resubmission of Manuscript ID 1510936328275037: Relationship between metabolic syndrome and knee osteoarthritis; data from the Korean National Health and Nutrition Examination Survey (KNHANES)

Dear Editor:

Thank you for the opportunity to revise and resubmit our paper, entitled “Relationship between metabolic syndrome and knee osteoarthritis: data from the Korean National Health and Nutrition Examination Survey (KNHANES),” to BMC Public Health. We would deeply appreciate it if you would consider our responses to the reviewers’ comments and our revised manuscript for publication. We carefully considered all the suggestions given by the editors and reviewers, and we are extremely grateful for the opportunity we were given to improve our manuscript.

Overall, we copy edited our manuscript, and we tried to make our manuscript simpler and clearer. We removed redundant parts of the manuscript, making it shorter.

In addition to these changes, we tried our best to make corrections considering the editors’ and reviewers’ recommendations, as shown below.

All of the authors agreed to the changes and approved the revised manuscript. We look forward to receiving and considering any other suggestions you may have. Constructive responses from you and your esteemed journal are always deeply appreciated. Thank you again for allowing us to resubmit our manuscript.

Sincerely,

Kwan Kyu Park,
Corresponding author.
This manuscript concerns the association in 270 subjects with knee osteoarthritis with MetS and its components in 1964 middle-aged controls from the Korean NHANES. Knee osteoarthritis was 1.8-fold more likely in MetS but this association disappeared after adjusting for confounders including BMI. Of the MetS components, waist circumference (WC) was 1.69-fold (CI 1.27; 2.26) more likely associated with knee osteoarthritis when adjusted for sex, age, and sociodemographic factors. Authors concluded that, except for WC, MetS was not significantly associated with knee osteoarthritis among Koreans.

Following points need to be addressed.

1. Some terms are used not quite accurately. In the Introduction, dyslipidemia should be replaced by atherogenic dyslipidemia; association has been described as correlation. Impaired glucose tolerance is not a MetS component, impaired fasting glucose is. WC is measured during “minimal respiration” needs correction.

   → Thank you for your comments. We changed several terms as recommended.

2. Data analysis should specify that the association between knee osteoarthritis and MetS was sought using multiple logistic regression.

   → We tried to specify the description of data analyses in the Results (the 3rd paragraph) and Discussion sections (the 2nd paragraph).

3. Since 11 years’ difference exists across subjects with knee osteoarthritis and MetS, authors might present age-adjusted estimated marginal means in patients with osteoarthritis for comparison with MetS.

   → Thank you for your comment. We fully agree with the reviewer’s opinion that age is a very important factor in this study. We already adjusted for age in the logistic regression analyses conducted under the supervision of a statistician, and we are concerned, as we presented quite lot of data, that it would make our manuscript more complicated and thereby more difficult for readers to comprehend. If the reviewer or the editor insists, we will consider making the necessary corrections.

4. It is misleading to adjust for BMI the association between osteoarthritis and WC since the two variables are collinear. This adjustment (Model 3) is better deleted. Furthermore, the analysis could be divided into two panels: one seeking the association of MetS with sex, exercise, alcohol and smoking as independent variables; and the other, with the 5 MetS components along with similar confounders (but without MetS). The discussion and conclusion of the study should therefore be modified.

   → We agree with the reviewer’s comment. We deleted Model 3 as recommended. For the second recommendation, we believe we analyzed the data as the reviewer recommended in the binary logistic regression models (Table 3), and we modified the Discussion by adding the points the reviewer recommended (the later part of the 2nd paragraph of the Discussion)

5. Several grammar mistakes await correction.

   → We copyedited our manuscript.
<Reviewer 2>

The authors investigate here the correlation between Knee Osteo Arthritis (OA) and the components of the Metabolic Syndrome (MetS) in a representative sample of the South Korean population. The topic is relevant, thoroughly explained and the data is rich and well organized. However, the sample selection criteria are debatable to me, there are some redundancies and too many details as some parts of the article could be shortened, and the English should be revised.

Major Compulsory Revisions:
1-In the Abstract, the conclusion, especially the first sentence of it, is unclear to me. It needs to be written again.

→ Thank you for the comment. We rewrote the Conclusion part of the Abstract.

2- In the Introduction, the last sentence of the first paragraph suggests that other factors may contribute to increased incidence of knee OA. Name some of these factors in order to link this idea to the next paragraph which immediately talks about MetS.

→ We added other factors and added citations.

(The 1st paragraph of the Background section: "However, it is suggested that other factors such as genetic, metabolic, and neuroendocrine factors may also contribute to increased incidences of knee OA”

3- In the Patients and Methods, Data source and subjects, it is not clear why the 2001 patients who either did not respond or responded by saying “No” to the question "Have you had knee pain recently for one month or longer?” have been excluded. If OA is considered as a chronic disease, in terms of medicine, does the fact of not suffering from the knee for one month or longer exclude the positive OA diagnosis? Moreover, the question in itself is not that obvious as “recently” is opposed to “more than one month” in my opinion.

→ Thank you for your comment. It was a very good point which all of us authors were concerned about as well. We fully agree with the reviewer’s comment. The reason we excluded these subjects is that we wanted to exclude the subjects with recent knee trauma. We agree with that in those excluded subjects, there could be many knee OA patients whose knee pain has been subsided by medication, physical therapy, and so on. But as we mentioned in the Limitations (the 4th paragraph of the Discussion section), KNHANES comprises data we could not change. Among this data, we tried to lessen the bias. As mentioned, we had to exclude those subjects for the possibility of recent trauma. In regards to the last of the reviewer’s comments, the question was “Have you had knee pain recently for one month or longer?” (Data source and subjects section and Methods section) We used this pre-made survey data.

4- In the Patients and Methods, Data source and subjects, in the 797 subjects group, those who replied “Yes” and were excluded from the control subjects could have been pooled with the 634 subjects of the former group (the OA patients) who also responded “Yes” to this same question, thus increasing your sample number. Moreover, the remaining subjects who were categorized as controls should be 3100 because 3897 – 797 = 3100. How do you account for the 4 remaining subjects since the figure stated in the text is 3104?
There was a miscalculation. We rechecked all numbers carefully and revised the manuscript (Data source and subjects section in Methods section) and Figure 1.

5- In the Patients and Methods, covariates, why did you measure Blood Urine Nitrogen, Serum Creatinine, Hemoglobin, Hematocrit, Aspartate Aminotransferase and Alanine Aminotransferase? How does it relate to MetS or OA? It is not mentioned in the manuscript. Instead, if the authors still have some frozen serum left at -80 degrees C, it will be interesting to measure Uric Acid (associated with MetS) and CRP (associated with inflammation) and see how it correlates with OA and MetS.

We wanted to include a brief introduction of KNHANES. We fully agree with the reviewer that these examinations are not related to MetS or OA and could make readers confused. We, authors, decided to remove this part from the manuscript. We removed uric acid as well, because there are chronic gout patients with normal uric acid level and because we did not use results of the blood test; however, we did use the survey for exclusion of subjects with gouty arthritis.

6- In the Discussion, the paragraph before the last one, the authors talk about much smaller numbers of male subjects with OA, not only in their study, but also in the literature as well. This idea deserves to be expanded: does OA occur more in females because of a hormonal difference, of menopause, or because of the higher muscular mass in males? How do steroids interact with inflammation caused by OA?

Thank you for your comment. We modified Table 4 to emphasize the differences between male and female subjects, and modified the Results and Discussion sections as recommended. Although it is not well known, this could be the reason for high flexion activities of female subjects in Korea. We thought this could be from the small number of male knee OA subjects, as noted in the Discussion section (the 4th paragraph). We modified and emphasized this point in the Discussion section and added citations.

Minor Essential Revisions:
1- In the Abstract, avoid "longer WC". Use “high” for instance.

We revised the Abstract section.

2- In the List of abbreviations and acronyms, be careful with the letter M which is used at the same time to indicate “month” and also to indicate “male”.

We revised the list of abbreviations.

3- In the Introduction, second paragraph, second sentence “….. has rapidly increased [4]” do you mean in US adults? The sentence before the last one “Studies involving various populations are inadequate at best. ” is unclear to me. In the last sentence, be careful with tenses (past or present) and avoid using the 1 and 2 figures in the text (figures have also been used twice in the text of the Discussion section).

Yes, it is data of from the US. We revised and modified the manuscript as recommended (Introduction section).

4- In the Discussion, the last part of the second paragraph should be written in a
simpler and shorter way. It is not clear from the text whether Gandhi et al. apply a common standard of BMI >30 kg/m² to the Asian ethnicity as a whole or to all ethnicities. Moreover, there is a redundant idea in the last part of the fourth paragraph and the first part of the fifth one. Try to shorten it.

→ We tried to make it simpler and shorter. We revised the manuscript as recommended (the 2nd paragraph of the Discussion section)

5- In the Discussion, the paragraph before the last one, there is a repetition of “current study” within one line in the first two sentences. The last sentence of this same paragraph is unclear and needs to be written again.

→ We revised the first sentence and rewrote the last sentence.

6- In the Discussion, the last paragraph, what does the abbreviation TKA stand for? I did not find it in the List of abbreviations and acronyms.

→ We added “TKA” as an abbreviation.

7-In the title, use the word "Correlation" instead of "Relation".

→ We revised as recommended.

Discretionary Revisions:

1- Be careful, in Figure 1, it is mentioned that 4,307 subjects were excluded because of their age <40M. It should be years.

→ We revised to “years”.

2- In Table 3, no need for the * sign.

→ We removed the * sign. (Please see together with an answer of #3 below)

3- Try to simplify your tables which are loaded with figures, so that it becomes more reader friendly. For instance, remove the 95% CI in Table 3 and avoid the figures ratio in Table 4 as this table is the most relevant one in your results.

→Because we removed the * sign (please see #2, above), it would not be possible for readers to notice the significance if there is no 95% CI. As we removed Model 3 as reviewer 1 recommended, we believe that Table 3 became a bit simpler. If the reviewer or editor insists on the removal of ‘95% CI’, we will consider it again. Thank you.