Author's response to reviews

Title: Gender differences in the association between socioeconomic status and hypertension incidence: the Korean Genome and Epidemiology Study

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Detailed Response to Reviewers

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Reviewer

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Title: Gender differences in the association between socioeconomic status and hypertension incidence: the Korean Genome and Epidemiology Study

Author: Tae-Hwa Baek, Hae-Young Lee, Nam-Kyoo Lim and Hyun-Young Park

Dear Reviewers:

We would like to thank you and the reviewers of the BMC Public Health for taking the time to review our article. We have made some corrections and clarifications in the manuscript after going over the reviewers’ comments.

We revised the manuscript and blue highlighted lines were marked in revised text. Here we have addressed the concerns of the reviewers on separate pages, as well as our response to specific comments. All page and line numbers refer to the revised text, which has been submitted through the online site (http://www.biomedcentral.com/bmcpublichealth/manuscript).

I hope that the revised manuscript will better meet the requirements of your journal for publication. We thank the editor and the reviewers for the BMC Public Health once again for the constructive review of our paper.

Sincerely,
Reviewer #1 (sam-ang seubsman)

Reviewer's report:

General comments:
The questions posed by authors are well defined. Since the data are obtained from the KoGES it is reasonable to anticipate that they are sound. Tables containing analytic data appear to be of good quality. Overall the manuscript appears to be coherent. Limitations of the work are clearly stated.

However, I have minor comments that need authors’ attention.

1. Methods
Study sample
Participant numbers are confusing. Line 30, indicated 3897 men and 4197 women without hypertension from KoGES baseline. Line 85, said that initial number included 10,038 participants but in line 91, mentioned participants original number were 10,030. Moreover, when sum up with those omissions, the number was different from 5,287 participants. It will be of help to develop a flow diagram of total participants and exclusions that were drawn from KoGES database so that will give clearer picture of the sample structure and size.

Authors’ response>

1) Thank you for these points. In the revision, as the reviewer pointed out, we have corrected the number of subjects throughout the manuscript.

- The sentence “Data for 3897 men and 4197 women aged 40-69 years ~” was changed to “Data for 2,596 men and 2,686 women aged 40-69 years ~” (Abstract, page 2, lines 31)
- The sentence “Of the original 10,030 participants ~” was changed to “Of the original 10,038 participants ~” (Methods, page 4, lines 91)
- The sentence “In addition, those with hypertension (n = 1,646) and missing covariates (n = 337) were excluded.” was changed to “In addition, those with hypertension (n = 1,646) and missing covariates (n = 332) were excluded.” (Methods, page 4, lines 93-95)
- The sentence “Thus, 5,287 participants remained eligible for analysis” was changed to “Thus, 5,282 participants remained eligible for analysis” (Methods, page 4, lines 94-95).
- The sentence “Data from a total of 5,287 individuals (2597 men, 2690 women) were analyzed.” was changed to “Data from a total of 5,282 individuals (2,596 men, 2,686 women) were analyzed.” (Result, page 7, lines 151).

2) In addition, as the reviewer suggested, we have added a flow diagram as a Figure 1 and mentioned this Figure in the Method section as follows;

“Thus, 5,282 participants remained eligible for analysis (Figure 1).” (page 4, lines 94-95)

![Figure 1. Study flow and participants at baseline and follow-up](image)

Validation and reliability test
Authors applied standard questionnaire from KoGES which is unknown to readers. It would be helpful if the paper provided some ideas about validation and reliability of variables captured from the KoGES standard questionnaire.
Authors’ response

As the reviewer suggested, we have added the sentence to the Methods section (page 5, lines 101-102).

“The study protocol and questionnaire were standardized after assessing the inter- and intra-validity of questionnaire and interviewers during the preliminary examination in 2001.”

2. Discussion and conclusions are well balanced. However, the KoGES questionnaire provided life style factors (line 98-99) and the authors indicate that life style behaviors may cause the SES disparities (line 248), why it was not included in the adjusted model.

Authors’ response

As the reviewer pointed out, we have considered your comments carefully. We mentioned ‘alcohol intake’ and ‘smoking’ as examples of lifestyle behavior in the manuscript (line 248) and alcohol intake and smoking were already included in the models. To avoid confusion, we clarified the following sentence:
- the sentence “A standard questionnaire was used to obtain information on demographic characteristics, life style factors, socioeconomic status, medical history, smoking status, and alcohol consumption at baseline.” was changed to “A standard questionnaire was used to obtain information on demographic characteristics, socioeconomic status, medical history, smoking status, and alcohol consumption at baseline.” (line 99-101)

Even though the paper is focused on Korean society and not to be generalized, I think this paper contributes to knowledge and should be acceptable to be published.

Authors’ response

Thank you for your kind comments.
Reviewer's report:

This is an interesting paper reporting sex differences in the association between the incidence of hypertension and socioeconomic status (SES), measured by education and household income, in Korea.

Major compulsory revisions

1. In my opinion, one of the main issues of the manuscript is related to how the role of adiposity is defined in the objective and how this analysis has been performed. It is well known that body mass index (BMI) and/or waist circumference (WC) are confounders or that they may play a role as mediators or modifiers in the relationship between SES and hypertension, in addition to the fact that this relationship could differ between men and women. On the one hand, the authors have analysed the association between SES and hypertension stratified by sex; while on the other hand, and in a different model, the association between SES and adiposity has been analysed without taking into account hypertension. It seems that adiposity, either defined as obesity (BMI) or central obesity (WC), shows different patterns according to sex and SES. Sex and SES are also related in different ways with the incidence of hypertension. Thus, I think it would be more suitable to analyse all these relationships in just one model. I suggest that the authors evaluate the association between SES and hypertension into different strata of BMI (ie: normal, overweight or obese) or WC (central obesity, yes/no) by sex. Consequently, BMI in continuous form would no longer be necessary in the model. The authors could probably show a more integrated picture of the role of adiposity as mediator in the association between SES and hypertension.

Authors’ response>

Thank you for this valuable comment. As the reviewer pointed out, we have considered your comments carefully and replied in comment 3.2.

2. Some of the issues of the methods section should be clarified and better explained.
Methods section. Study participants.

2.1 Is the KoGES study representative of the Korean population?

Authors’ response>
We have added the sentence to the Methods section.
- “The enrollment of the study was based on the characteristics of the community and on the efficient method for recruiting representative samples of the Korean population.” (page 4, lines 82-84).

2.2 Were participants with previous cardiovascular disease excluded from the study?

Authors’ response>
Individuals with previous cardiovascular disease were not excluded from this study. Many of previous studies also have not excluded those with cardiovascular disease.

2.3 Excluding individuals with missing covariates could result in selection bias. Please, clarify if these individuals differed somehow from those who participated in the study. Could you also describe the main characteristics of those who refused participate in the follow-up?

Authors’ response>
We agree with you. This data was from community-based prospective cohort study which minimized the sampling bias effect.

1) Individuals with missing covariates were older (52.3 ± 8.8 vs 51.0 ± 8.5, P=0.01) and had a significantly higher SBP (114.1 ± 12.1 vs 111.1 ± 12.4, P < 0.001), but the increase in DBP (72.3 ± 7.9 vs 71.7 ± 9.0, P=0.164) was not significant compared with individuals in study group. Because the sample size is large and the proportion of missing data is small, we expect that the absence of these data has not affected the main findings.
2) The main characteristics of individuals who refused participate in the follow-up were similar to the findings of those who enrolled in the follow-up as follows:

Table. Baseline characteristics of study and refused group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Enrolled participant (n=7,260)</th>
<th>Refused or died (n=2,778)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Women</td>
<td>3,790 (52.2)</td>
<td>1,485 (53.5)</td>
<td>0.2611</td>
</tr>
<tr>
<td>Age</td>
<td>52.30 ± 8.8</td>
<td>52.3 ± 9.2</td>
<td>0.9758</td>
</tr>
<tr>
<td>SBP</td>
<td>117.5 ± 17.8</td>
<td>118.0 ± 19.0</td>
<td>0.1709</td>
</tr>
<tr>
<td>DBP</td>
<td>75.2 ± 11.4</td>
<td>75.0 ± 11.8</td>
<td>0.6033</td>
</tr>
<tr>
<td>BMI</td>
<td>24.6 ± 3.1</td>
<td>24.5 ± 3.2</td>
<td>0.0291</td>
</tr>
<tr>
<td>WC</td>
<td>82.9 ± 8.8</td>
<td>82.1 ± 8.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Education (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest (≥10)</td>
<td>3,194 (44.3)</td>
<td>1,122 (40.8)</td>
<td>0.0021</td>
</tr>
<tr>
<td>Mid-low (7-9)</td>
<td>1,649 (22.9)</td>
<td>635 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Lowest (≤6)</td>
<td>2,362 (32.8)</td>
<td>993 (36.1)</td>
<td></td>
</tr>
<tr>
<td>Monthly income (*10^4 KRW)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest (≥200)</td>
<td>2,510 (35.2)</td>
<td>930 (34.1)</td>
<td>0.5705</td>
</tr>
<tr>
<td>Mid-low (100-199)</td>
<td>2,086 (29.3)</td>
<td>806 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Lowest (≤99)</td>
<td>2,532 (35.5)</td>
<td>991 (36.3)</td>
<td></td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5,803 (79.9)</td>
<td>2,335 (84.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>1,457 (20.1)</td>
<td>443 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Current smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5,412 (75.5)</td>
<td>1,937 (70.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>1,761 (24.6)</td>
<td>795 (29.1)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5,887 (83.7)</td>
<td>2,257 (83.6)</td>
<td>0.8703</td>
</tr>
<tr>
<td>Yes</td>
<td>1,144 (16.3)</td>
<td>443 (16.4)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or number (percentage). Comparisons performed with independent two-sample t-test for continuous variables and with χ²-test for categorical variables. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference.
Methods section. Data collection.

2.4 Report measurements in the second and fourth year of follow-up.

2.5 Related to the previous comment (2.4), give a clearer definition of the main outcome. Incidence of hypertension was measured in the second and fourth year but the authors probably took into consideration the cumulative incidence at the end of the study as a main outcome. If so, please, clarify.

Authors’ response>

We agree with you. In our study, the main outcome is cumulative incidence of hypertension at the 4-year follow-up. As the reviewer pointed out, we have modified the sentences in the manuscript as follows:

- The sentence “The main outcome was the cumulative incidence of hypertension at the 4-year follow-up.” was added in the Methods section. (page 6, line 131-132)
- The sentence “This study was based on the baseline and first (year 2) and second (year 4) follow-up data.” was changed to “This study was based on the baseline and second (year 4) follow-up data.” (page 4, line 87-88)
- The sentence “The incidence of hypertension was 10.5% (565 cases) and 18.4% (971 cases) at the 2- and 4-year follow-ups, respectively.” was changed to “The cumulative incidence of hypertension was 18.4% (971 cases) at the 4-year follow-up.” (page 7, line 151-152)

2.6 What were the criteria for censoring participants in the follow-up? How did the authors deal with individuals with incident cardiovascular disease (CV)? Treatments for CV disease could modify blood pressure levels and, consequently, the incidence of hypertension

Authors’ response>

1) The follow-up loss and study participants have explained in Figure 1 as the reviewer 1 suggested.

Of 10,038 participants in a baseline survey, 286 participants died and 2,492 lost to follow-up. Of those, we excluded 1,646 and 332 participants with prevalent hypertension and missing covariates, respectively. As a result, 5,282 participants were included in this study.
2) The reviewer pointed out appropriate and important point. Unfortunately, we did not take into account the incident cardiovascular disease in this study, because the number of incident CV disease was limited due to short (4 years) follow-up period. For evaluation of the influence of incident CV disease, longer follow-up period and larger sample size will be needed.

Methods section. Statistical analysis.

2.7 Why did the authors not adjust for baseline pressure levels? Baseline pressure levels are an important risk factor for incidence of hypertension.

Authors’ response>
Thank you for this suggestion. As the reviewer suggested, we added “blood pressure levels” to the model in Table 2 and Table 3.

2.8 Did the authors check for collinearity between BMI and WC in the logistic models?

Authors’ response>
Because both BMI and WC were not incorporated in the same model, we did not check for collinearity between BMI and WC.
Model 2 adjusted for the model 1 variables with additional adjustment for BMI and Model 3 adjusted for the model 1 variables with additional adjustment for WC.

3. Results
3.1 Could the authors give an overall measure of the incidence of hypertension and calculate its 95% confidence interval? (see comment 2.5).

Authors’ response>
As we replied in 2.5, the cumulative incidence of hypertension was 18.4% (971 cases) at the 4-year follow-up and 95% confidence interval was 17.4 to 19.4.

3.2 In relation to the comment in point 1, I suggest that table 3 should be left out and that results should be shown taking into consideration different strata of BMI (obesity) and WC (central obesity) in both men and women in just one model.

4. Discussion
- It would be better to rethink the discussion taking into consideration the integrated approach proposed above. It would lead to a better understanding of the complex relationships between SES, adiposity and hypertension, in both men and women.

Authors’ response>
Thank you for this great suggestion. In the revision, we have attempted to conduct re-analyses as suggested and the results of re-analysis are shown in Table 3 and the related contents are changed throughout the manuscript.
During the analyses, educational attainment and household income were re-classified into three categories (line 102-107) and Cox’s proportional hazard regression analyses were performed instead of logistic regression analyses.

- Overall, the authors presented a discussion on the reasons for the sex-related differences between SES and hypertension. In the same way, it would be of interest to comment on the sex-related differences found depending on whether either education or income were taken into account. According the authors, what would be the best index to assess the relationship between SES and hypertension in Korea?

Authors’ response>
To date, only a few studies have been reported with inconsistent results in Korea. We think that education is better index to assess the relationship between SES and hypertension than income so far.
- Please, give some thoughts to the magnitude of the potential residual confounding of the variables not measured. The authors could also have mentioned physical exercise.

**Authors’ response**

*In our original submission, we mentioned that briefly in the Discussion as one of limitations - “First, we were unable to obtain comprehensive information on ‘conventional’ risk factors, such as salt intake, which are recognized as important risk factors for hypertension.” (line 266-268).*

- Giving some highlights related to public health implications of these findings could be worth looking into.

**Authors’ response**

*As the reviewer suggested, the following statements were newly added in Conclusion section.*

- The sentence “Thus, a stratified approach for Women of low socioeconomic status, especially those with low educational attainment, is needed for prevention and treatment of hypertension.” was changed to “Because the prevalence of hypertension is high and the adverse cardiovascular consequences are frequently accompanied by untreated and uncontrolled hypertension, optimal BP control is important public health concern. Thus, a stratified approach for Women of low socioeconomic status, especially those with low educational attainment, may be helpful for prevention and treatment of hypertension.” (line 276-281).

**Minor compulsory revisions**

- Table 1. Footnote: "...Comparisons performed with one-way ANOVA...". Make sure you are consistent with the methods stated in Statistical analysis section (T-Student).

**Authors’ response**
As the reviewer pointed out, we have corrected the error in the footnote of Table 1.
- The sentence “Comparisons performed with one-way ANOVA...” was changed to “Comparisons performed with independent two-sample t-test...”.

- Discussion. Third paragraph: "...economic level positively associated with hypertension...” Perhaps did you miss "in men" somewhere?

Authors’ response>
As the reviewer pointed out, we have corrected the error in the manuscript as follows:
- The sentence “Additionally, economic level was positively associated with hypertension but inversely associated in women” was changed to “Additionally, economic level was positively associated with hypertension in men, but inversely associated in women” (line 218-219)