Author's response to reviews

Title: Blood pressure, body mass index and risk of cardiovascular disease in Chinese men and women

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Author's response to reviews: see over
Dear Editor and Reviewers:
Thank you very much for your careful review of our work. We believe your comments have improved our manuscript greatly. As you have suggested, we have discussed all of the points you have raised and make corresponding modifications.

Best regards,

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Responses to Reviewers

Reviewer: Dr. Yao He
1. A sensitivity analysis of excluding the incident CVD that occurred during the first 1-3 years of follow-up may be added in the results to minimize the potential bias by the presence of clinical or subclinical disease at the baseline examination and by illness-related weight loss.

Response:
Thank you for the nice suggestion. We have conducted sensitivity analysis by excluding the incident CVD that occurred during the first 3 years of follow-up and the pattern and conclusion of results did not change. We have added “Sensitivity Analysis” as follows “After excluding the incident CVD that occurred during the first 3 years of follow-up, we still found that the effects of BP on risk of CVD generally increased with the increasing BMI levels. HRs and 95% CI per 1-SD increase in systolic BP computed with Cox proportional hazards models within four BMI levels (underweight, normal, overweight, and obese) were 1.26(1.19-1.33), 1.44(1.40-1.49), 1.51(1.43-1.58) and

...
1.61(1.47-1.76), respectively. HRs and 95% CI per 1-SD increase in diastolic BP within four BMI levels were 1.25(1.18-1.32), 1.40(1.36-1.45), 1.46(1.38-1.54) and 1.48(1.35-1.63), respectively. Interactions between BMI and both systolic BP and diastolic BP in the prediction of all CVD were reached statistical significance (both P<0.001).” in our revised manuscript (please page 12, the first paragraph of results).

2. There are some verbose statements as followings:
   a) Line 11-15 in page 6 and line 18-21 in page 11 were the same statements.
   b) The description of line 13-20 in page 10 was the same as table 2 on page 25.
   c) There some verbose statements in discussion in paragraph 1 and 2 on page 13, and could be together one paragraph. The author should discuss the key findings and not the details of the results (e.g., line 12-14 on page 13).

   Response:
   Thank you very much for your careful review. We have deleted the verbose statements in our revised manuscript.
   a) We deleted the repeat statements in page 11.
   b) We deleted the repeat statements in page 10.
   c) We modified paragraph 1 and 2 on page13, delete the verbose statements and made them to one paragraph.

3. Please note the consisting with the terms “harzard ratio” and “relative risk”. For example, at line 10, 11 and 16 of page 11, you used “relative risk”, while you referred to “harzard ratio” elsewhere in this paper.

   Response:
   We have replaced “relative risk” by “harzard ratio” or “HRs” in our manuscript.

4. A few editorial suggestions:
   a) 5th line of abstract section on page 2 the word 'the data set' should be revised to 'a data set'
   b) 11th line of introduction section on page 4 the word 'an opposite results' should be revised to 'some opposite results'.
   c) 11th line of results section on page 10 the word 'all level' should be revised to 'all levels'.

   Response:
Thank you very much. We have modified the manuscript as you suggested.
Reviewer: Dr. Zhi-Jie Zheng

1) The authors indicated that participants from 13 provinces who were interviewed and examined in the original 1991 China National Hypertension Survey were excluded from the follow-up study due to the unavailability of the contact information, and the baseline characteristics of those excluded were not significantly different from those included. What baseline characteristics (variables) did the authors examine in the analyses, e.g., age, gender, ethnicity, locality (urban vs. rural, North vs. South), BMI, BP, medical history?

Response:
We examined the baseline characteristics of study participants by followed-up status. The baseline characteristics of subjects including from the remaining 17 provinces that were included age, gender, education, cigarette smoking, alcohol consumption and physical inactivity in this analysis were similar to those in the 13 excluded provinces. For supporting our statement and explanation, we have added a paper we published with relevant information as a reference in the revised manuscript.

2) With limited information available on death certificates, what measure and processes did the study use to validate a fatal myocardial infarction or other cardiovascular diseases, particularly if the case occurred out of hospital, simultaneously or unattended? What were the composition of the incident cases reported in this study (% fatal vs. non-fatal cases, incident cases vs. recurrent cases, CHD, stroke, and other forms of CVD, etc)

Response:
We obtained information on the history of disease, hospitalizations, and death, and obtained hospital records and death certificates. All death identified in interviews with participants’ proxies were verified by death certificates obtained from the local departments of public health or police. If death occurred while a participant was hospitalized, the participant’s hospital records, including medical history, findings on physical examination, laboratory findings, autopsy findings and discharge diagnosis, were abstracted by trained staff using a standard form. In addition, photocopies of selected sections of the participant’s inpatient record, discharge summary, electrocardiogram, and pathology reports were obtained. We added those into the revise version.

In our study, participants with a history of CVD had been excluded from the
analysis (please see page 5, first paragraph of methods), so all cases were incident cases. Among 10,416 CVD cases, 4,506 (43.3%) were fatal cases, 5,910 (56.7%) were non-fatal cases; 1,312 (12.6%) were CHD cases, 6518 (62.6%) were stroke cases and 2,568 (24.8%) were other CVD cases.

3) Information on the proportions of participants who were hypertensives (defined as such in the methods section), those treated with anti-hypertensives, as well as those with a history of cardiovascular disease should be included in the table 1.

**Response:**

We added data of hypertension and hypertension treatment in table 1 (please see page 25). In our study, participants with a history of CVD had been excluded from the analysis (please see page 5, first paragraph of methods), so all cases were incident cases.

4) The authors chose to use systolic or diastolic blood pressure as a continuous variable in the analyses. How would the hypertension treatment affect the analyses? Would the use of hypertension status, as defined to include the hypertensive treatment, yield similar results?

**Response:**

In our study, among 37,500 baseline hypertensive participants (defined as participants with systolic BP ≥140mmHg or diastolic BP ≥90mmHg, or having taken antihypertensive medication in last two weeks before baseline interview), 3384 (9.02%) had antihypertensive medication. Furthermore, only 868 participants which had antihypertensive medication controlled their blood pressure (SBP<140 mmHg and DBP <90 mmHg). We also examined the mean SBP and DBP of participants with hypertension treatment and those without hypertension treatment in baseline hypertensive participants, however, there were no significant difference in the two groups. Thus, considering the low percentages of treatment and control of hypertension in our study, hypertension treatment would not substantially affect the analyses when using systolic or diastolic blood pressure as continuous variables.

**Table: Blood pressure of baseline hypertensive participants**

<table>
<thead>
<tr>
<th>characteristics</th>
<th>Hypertensive participants without hypertension treatment</th>
<th>Hypertensive participants with hypertension treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>34,116</td>
<td>3,384</td>
</tr>
<tr>
<td>SBP ( mean (SD), mm Hg)</td>
<td>153.4(18.9)</td>
<td>153.8(25.0)</td>
</tr>
<tr>
<td>DBP ( mean (SD), mm Hg)</td>
<td>89.7(11.4)</td>
<td>89.5(13.0)</td>
</tr>
</tbody>
</table>
5) From the Table 1, it seems that 60% of individuals with low BMI were from the South or rural area, while 85% of those with high BMI were from the North and urban area. Do the found association of BP with incident CVD by BMI levels remains if analyses based on and stratified by the North vs. South and Rural vs. Urban.

**Response:**

Thanks for your insightful comments. We stratified our participants by the North vs. South and Rural vs. Urban accordingly, however, we found that the effects of systolic or diastolic BP on risk of CVD generally increased with the increasing BMI levels (underweight, normal, overweight, and obese) in each subgroup so the results were not substantially changed after stratification analyses. For example, in north China, HRs per 1-SD increase in systolic BP within four BMI levels (underweight, normal, overweight, and obese) were 1.20, 1.43, 1.47 and 1.64, respectively. HRs per 1-SD increase in diastolic BP in four corresponding BMI levels were 1.21, 1.42, 1.44 and 1.52 respectively. In south China, HRs per 1-SD increase in systolic BP within four corresponding BMI levels were 1.32, 1.46, 1.57 and 1.66, respectively. HRs per 1-SD increase in diastolic BP in four corresponding BMI levels were 1.29, 1.42, 1.55 and 1.63 respectively. Meanwhile, in rural region, HRs per 1-SD increase in systolic BP within four corresponding BMI levels were 1.27, 1.42, 1.47 and 1.79, respectively. HRs per 1-SD increase in diastolic BP in four corresponding BMI levels were 1.27, 1.40, 1.52 and 1.88 respectively. In urban region, HRs per 1-SD increase in systolic BP within four corresponding BMI levels were 1.25, 1.48, 1.54 and 1.58, respectively. HRs per 1-SD increase in diastolic BP in four corresponding BMI levels were 1.19, 1.45, 1.47 and 1.57 respectively. In each subgroup, the interactions between BMI and both systolic BP and diastolic BP in the prediction of all CVD remained positive (all P<0.001)