Author's response to reviews

Title: Prevalence of arterial stiffness in North China, and associations with risk factors of cardiovascular disease: a community-based study

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Author's response to reviews: see over
Response to the reviewers:

Response to the Reviewer 1

Reviewer's report:

- Wang JW et al. had improved the manuscript a lot. Although no response letters to answer the questions of reviewers, however, I can see the response in the manuscript.

Thanks for the positive comment. However, the authors are confused of the fact that Reviewer 1 could not see the letter with detailed responses to the original comments.

According to the Journal system, we understand that the downloading hyperlink of the previous response letter is [http://www.biomedcentral.com/imedia/4861649598050428_comment.pdf](http://www.biomedcentral.com/imedia/4861649598050428_comment.pdf).

Major Compulsory Revisions

- Statistical analysis, second paragraph: The authors mentioned that the backward stepwise method was used to perform multiple logistic regression. However, Table 6 showed all the OR (95% CI) and P value (including P > 0.05) in each variables in the multiple analysis. This is not the backward stepwise method. The authors should check again. (May change to “Multiple logistic regression analysis was performed to evaluate the association between risk factors for high baPWV.)

The backward stepwise method was used to perform multiple logistic regressions. Table 6 has been modified in the re-revised version, where variables not entering the last step of regression model are removed.

- Discussion, second paragraph: The authors mentioned that this suggests that decrease of estrogen in menopause should take effects on the arterial stiffness. However, no menopause age in female of this study group was reported in the Results. The authors should add the menopause age in the Results if the authors have the data, otherwise, the authors should provide the reference about the mean menopause age in North China female.

According to a cross-sectional study of 3,343 women from eight cities in China, the mean age of natural menopause was 48.7 years ([The research on the factors affecting the timing of natural menopause in Chinese city women. Maternal & Child health care of China. 2011,26(8):1191-1193](http://www.biomedcentral.com/imedia/4861649598050428_comment.pdf)). However, in the present study, no data of menopause age were collected.

Moreover, previous researches have indicated that estrogen has beneficial effects on arterial stiffness and hormone replacement therapy may improve arterial elasticity to some extent. A Japanese study reported that the menopause augments the age-related increase in arterial stiffness during the early postmenopausal phase and that this augmentation is probably related, at least in part, to estrogen deficiency (Zaydun G, Tomiyama H, Hashimoto H, Arai T, Koji Y, Yambe M, et al. Menopause is an independent factor augmenting the age-related increase in arterial stiffness in the early postmenopausal phase).

The reference has been added into the re-revised version of this manuscript.

Minor Essential Revisions
● Results, fourth paragraph: As was shown in Table 5 and 6 # As shown in Table 4 and 5
Yes, modified.

● The abbreviation was used in front of the manuscript, and they should be used afterwards (such as cardiovascular disease # CVD). Authors should carefully check again.
Yes, the manuscript has been carefully checked and modified with regard to the usage of abbreviation.

● Discussion, last paragraph: Finally, the population was from north china # North China
Yes, modified.

● Table 4: Low baPWV (baPWV > cut-off) # High baPWV.
Yes, modified.

● Discussion, fifth paragraph: The present data showed that a high SBP was a risk factor for high baPWV in both male and female. The baPWV was partially dependent on BP, so it was suggested to adjust for mean arterial pressure at the time of measurement before further analysis. Adjustment was performed by a linear regression of the two variables. The residual values were added to uncorrected baPWV to form the adjusted baPWV. Adjusted baPWV values were used for analysis.

Thanks for this comment. We understand that association between SBP and PWV has been shown in the present study as well as several previous studies. However, considering the following reasons, we did not adjust PWV for arterial pressure before further analysis.

1) No apparent or inherent association can be directly determined based on either the formula for PWV calculation or the definition of PWV.
2) Base on the evidence available, it is true that SBP is associated with BWV to some extent. However, whether the association is linear dependent or not remains not fully clear. Furthermore, results from the previous studies are in consistent on how much exactly SBP affects PWV. Therefore, adjustment for SBP based on a certain formula or model would be biased or less reliable.
3) Though there are limitations with PWV, PWV is by far a good indicator for the assessment of atherosclerosis. Also, it has been widely used in clinical practice. In some way, an “adjusted PWV” might be considered as a new indicator. If statistical analyses were all based on “adjusted
baPWV” rather than baPWV, the final results might make readers confused and be less relevant to clinical practice.

Response to the Reviewer 2

● There remain substantial issues with proper use of grammar, including verb tenses. I would recommend the authors having the manuscript be improved by an expert in written English. The basic ideas behind the communication are very good.

Yes, the manuscript has been carefully re-checked and re-modified with regard to the English writing.

● With regard to my previous comment below, I understand the authors were hesitant to include the reasons due to concerns about a word limit and that many readers will understand the reasons for exclusion. With there not being a firm word limit in BMC Cardiovascular Disorders, and that readers who are not experts in this field will likely not understand the reasons behind these exclusion criteria, please provide brief rationale for excluding these participants, using appropriate references.

Prior Comment:
Please state the reasons for excluding participants with the following factors:
a) Previous percutaneous coronary intervention and/or coronary artery bypass grafting;
b) aortic valvular heart disease;
c) aortic aneurysm;
d) serious myocardial dysfunction with an ejection fraction of <30%;
e) peripheral arteriosclerosis obliterans with an ankle-brachial index (ABI) of <0.9.

Yes, the reasons for exclusion have been added to the re-revised version of the manuscript (page 4).

● Adjustment for age: I understand the authors were hesitant to adjust for age, as the cutpoints for high baPWV were calculated based on 10-year age-specific cutpoints. In determining whether age may be a confounder in the associations between CVD risk factors and high baPWV, a confounder is associated with both the exposure (e.g. blood pressure) and the outcome (i.e. baPWV). In the case of age, this is clearly still the case even after the age-specific cutpoints are used, as shown in Tables 4 and 5, where for example in females those with baPWV > cut-off have a mean age of 58.1 years and those with baPWV< cutoff have a mean age of 52.8 years (p<0.001). This shows that there continues to be confounding by age within the 10-year categories. As an example, for participants in the age 50-59 y category, those aged 50 years likely have lower BaPWV (and other CVD risk factors) than those aged 59, even though they are in the same age category for analyses. Please adjust for age in Table 6. In interpreting the point estimates shown in Tables 4 and 5, I expect many of the associations there are also confounded by age. I don’t feel as strongly about adjusting for age in these tables as it is clearly stated age is not adjusted for here. However as a reader, I am unclear whether the differences in associations of CHD risk factors such as cholesterol with baPWV are due to confounding by age, or due to
cholesterol having an effect on baPWV. The multivariate models in table 6 (after age is included) should clarify this, so I would consider it optional about whether to adjust for age in Tables 4 and 5.

In the present study, participants were first stratified based on 10-year. Cut-off points for high baPWV were defined as the 90th percentiles in the each age group of the healthy reference sample respectively. Therefore, statistical analyses with regard to the association between high baPWV and potential CVD risk factors were all performed based on the age-specific cut-off points.

However, in the previous versions of the manuscript, age was not used as an independent variable in the multiple logistic regression analysis. After carefully reading this comment, we believe that including age into the multivariate analysis may be more reasonable to eliminate the confounding effect of age. Therefore, based on this idea, the multiple backward stepwise logistic regressions were performed once again. The present results have been shown in the Table 6 in the re-revised version of the manuscript, where significant risk factors remain the same but OR values and P values changes to some extent.

As shown in Table 6, variables positively associated with high baPWV were HR (OR = 1.029, [1.015, 1.044], p < 0.001), SBP (OR = 1.055, [1.045, 1.065], p < 0.001), fasting glucose level (OR = 1.023, [1.086 to 1.331], p < 0.001) and smoking (OR = 1.271, [0.944, 1.710], p = 0.032) in men; while in women, the variables were SBP (OR = 1.048, [1.040, 1.056], p < 0.001), diabetes (OR = 1.835, [1.299, 2.593], p = 0.001), TC levels (OR = 1.220, [1.076, 1.384], p = 0.002) and HR (OR = 1.044, [1.032, 1.056], p < 0.001).

Table 6. Associations between high baPWV* and potential risk factors based on the multiple logistic regression analyses†

<table>
<thead>
<tr>
<th>Variables‡</th>
<th>Male (95% CI)</th>
<th>p value</th>
<th>Female (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, per 1 mmHg</td>
<td>1.055 (1.045, 1.065)</td>
<td>&lt; 0.001</td>
<td>1.048 (1.040, 1.056)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HR, per 1 beats/min</td>
<td>1.029 (1.015, 1.044)</td>
<td>&lt; 0.001</td>
<td>1.044 (1.032, 1.056)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TC, per 1 mmol/L</td>
<td>—a —</td>
<td>—</td>
<td>1.220 (1.076, 1.384)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting plasma glucose, per 1 mmol/L</td>
<td>1.203 (1.086, 1.331)</td>
<td>&lt; 0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes (yes/no)</td>
<td>—</td>
<td>—</td>
<td>1.835 (1.299, 2.593)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>1.271 (0.944, 1.710)</td>
<td>0.032</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* High baPWV was defined based on age-specific cut-off points.
† The backward stepwise method was used.
‡ Only the variables that entered the final step of backward stepwise logistic regression were listed in the table. Originally, variables entering the multiple logistic regression model included SBP, DBP, HR, fasting glucose, diabetes, hypertension, CCBs usage, ACEIs/ARBs usage, and smoking in men; while in women, the included variables were SBP, BMI, HR, TC, HDL-C, TG, fasting glucose, diabetes, hypertension, CCBs usage, ACEIs/ARBs usage.

a The symbol “—” represents covariates that did not significantly contribute to the model or were not included.
If the cut-off point of high PWV was defined as the crude 90th percentiles of the health reference sample as a whole irrespective of age, it would be 1978 cm/s and 2173 cm/s in men and women respectively. In this case, using the same multivariate method with adjustment for age, we would get “new” results as listed in Table X. However, this way is obviously less valid due to the confounding effects of age on the prevalence of high baPWV.

### Table X

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>1.047 (1.036 to 1.058)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HR</td>
<td>1.019 (1.000 to 1.038)</td>
<td>0.048</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.141 (2.003 to 4.925)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>smoking</td>
<td>1.126(1.017 to 1.142)</td>
<td>0.007</td>
</tr>
<tr>
<td>CCBs</td>
<td>0.345(0.223 to 0.534)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.057(1.037 to 1.077)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>1.033(1.021 to 1.044)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CCBs</td>
<td>0.421(0.274 to 0.648)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- Discussion section, pg. 8: Please use the terms such as “study population” instead of “cohort” for this study. The term “cohort” refers to longitudinal study population. This study is cross-sectional, so does not seem to have a longitudinal component at this time.

Yes, modified.

- Pg. 9, para. 2 (starting with “The present data indicated…”): The statement “This suggests that decrease of estrogen in menopause should take effects on the arterial stiffness” appears somewhat speculative, given that rates were lower in females than males after the age of 59 years. Please provide strong rationale and references to support this statement, or modify it as needed.

Please refer to the response to the similar comment (the third one) of Reviewer 1.

- Pg. 9, para. 3 (starting with “On the basis of the age-specific…”): This paragraph was very difficult to understand. Please rephrase so that the intended meaning is very clear.

Thanks for this comment. We have deleted this paragraph for it is not an important part of the discussion.
Pg. 10, para. 4: The statement “The low response rate would lead to biased associations only when participation was associated with both arterial stiffness and the risk factors in question, which is considered to be less common.” Seems fairly speculative. For example, people with low socioeconomic position often have different CHD risk factor levels than those with higher socioeconomic position (in most Western countries, people with low socioeconomic position tend to have elevated CHD risk factors but this may not be the case in Northern China), and are less likely to participate in research studies. Please provide rigorous references for this statement, or modify as needed.

Considering this comment, we have deleted the statement “When it comes to the association between high baPWV and risk factors within the group of respondents, however, the overall response rate is less of a concern. The low response rate would lead to biased associations only when participation was associated with both arterial stiffness and the risk factors in question, which is considered to be less common.” in paragraph 4 on page 10.

Table 2: Please correct the typo in the title from “health reference sample” to “healthy reference sample”.

Yes, modified.

Table 4: The title for the third column should likely state “High baPWV” instead of “Low baPWV”. Please correct it, and also made the column headings for Tables 4 and 5 consistent with each other.

Yes, modified.

Table 6: In a footnote, please state that stepwise regression was performed and that the symbol “-“ represents covariates that did not significantly contribute to the model. Readers often jump to the tables without reading the methods section, so it is helpful for the tables to be understandable without referring to the methods section.

Yes, the information has been added into the footnote.

Once again, the hard work of both two reviewers and editors is very much appreciated.

Sincerely yours,

The authors