Revision for " Association Between High Blood Pressure and Long-term Cardiovascular Events in Young Adults: A systematic review and Meta-analysis (BMJ-2020-054316.R1) "

Dear editor,

Thank you for your letter and reviewers' comments concerning our manuscript entitled " Association Between High Blood Pressure and Long-term Cardiovascular Events in Young Adults: A systematic review and Meta-analysis (BMJ-2020-054316.R1) ". We have carefully modified the manuscript according to the comments from the committee and reviewers. All concerns raised have been addressed. We believe that the manuscript is significantly improved and hope that the revised version of our manuscript is now able to be considered for publication in your journal. We appreciate for Editors/Reviewers' warm work.

Looking forward to hearing from you soon.

With kindest regards,

Yours Sincerely,

Hao Chen (Email: chenhao@gdph.org.cn; ORCID: 0000-0003-4339-3441)

Caojin Zhang (Email: gdzcjpaper@163.com; ORCID: 0000-0002-4824-8991)

Weishong Sha (Email: shaweihong@gdph.org.cn; ORCID: 0000-0001-7610-3813)

Point to Point Response to Reviewers and the Committee (BMJ-2020-054316.R1)

To the committee
Comments
First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

We appreciate your revisions in reponse to both editorial and revieiwer comments. However, we are still a bit concerned about the some of the analyses. Specifically, we worry that this will provide justification to treat "normal" blood pressures in order to reduce them to "optimal".

We still find too much emphasis on relative risk throughout the manuscript and would like to see absolute event rates be consistently reported in the text, not just the RRs.

Response: Thanks for your comments. We did agree that relative risk estimates for disease incidence are of limited clinical utility given the uncertainty regarding the incidence rate in the referent group (1). Hence, except for the RRs, we also presented the event rates and absolute risk difference for young adults with different BP levels in our findings (lines 279-288, pages 13-14 & lines 316-334, pages 15-16 in the revised manuscript). Acknowledging this, we have also amended part of our discussion based on the estimation of the absolute risk in our revised manuscript (lines 440-453, page 21).

The studies that were more likely to observe large associations were longer, 20 years or more. We note that the p value on the interaction by length of follow-up is not significant, which is at least somewhat reassuring. However, the authors report an average period of follow-up of 15 years, but that should be weighted by study cohort size. Was it?

Response: It's very nice and considerate of you to point out this. We are sorry that we did not describe how we calculated the average follow-up duration clearly in our last submission. Indeed, the study cohort size should be taken into consideration when estimating the average follow-up duration. In our last submission, the calculation of the follow-up duration was based on the total person-years in our study. To enable the total person-years of observation to be calculated, we included data from reports that specified one or both of the following: total person-time of follow-up, or sample size and median follow-up per person. The result of average follow-up duration was the sum of the total person-years divided by the total sample size of the current study. Thus, we believe that this estimation has been weighted by the study cohort size. Thank you again for your valuable comments.

We are still interested in stratification by sex. While the authors have provided an interaction analysis by sex, when those data were available we also would prefer a stratfied analysis: comparing those that were over 90% male versus the others (which would mean all the aggregated studies would be used, not just those reporting sex-stratified results). Also, please highlight this breakdown of male-only studies in the text as readers may have the same question as the editors

Response: Thanks for your valuable comments. Indeed, disparity in gender proportion was speculated to be an important factor influencing the associations of high BP and cardiovascular risks. This possibility could be further explored by performing a stratification analysis based on gender proportion (i.e. male proportion). As suggested, we separated studies based on male proportion (over 90% versus below 90%) to examine the potential effect of gender distribution on the exposure-outcome associations, the detail of which was described and highlighted in our revised manuscript (lines 240-242, page 11; lines 304-306, pages 14 & lines 417-420, page 19-20). Both of the gender-related results from the stratification analyses were provided in the revised Table 3. As is shown, the risk estimates were identical in studies with different male proportion, indicating that the proportion of males in the sample did not significantly affect the associations of high BP and cardiovascular risks.

We had initially asked for NNT for 1 year based on reasonable assumption of effectiveness of a drug. Instead if appears you have only presented NNT for 15 years assuming a) all the risk is attributable to hypertension and b) it is all removed by treatment. Based on the numbers from Table S1 is appears that the NNT for 1 year do indeed run into the thousands for normal and high normal, even assuming a treatment removed all the risk of due to hypertension. The NNTs should make a reasonable assumption about the effectiveness of drug treatment and say what that assumption is. Thus, please present NNT for one year while accounting for the proportion of morbidity and moratlity attributable to hypertension. This should be the NNT that you focus on in the results in order to better contextualize these findings.

Response: It's very nice and considerate of you to point out this. We are sorry that we did not calculate the NNTs as suggested and make clear assumptions on it in our last submission. In the revised manuscript, we described more clearly on how the NNTs for one year were calculated (lines 210-215, page 10, in the revised manuscript). Since our included population were generalized healthy young adults without other overt diseases (as stated in "inclusion and exclusion criteria" of our methods section), we assumed that the absolute risk differences within different BP strata were all attributable to the elevated BP. And thus, when assessing the potential benefit of initiating or adding treatments, we assumed that the effect of treatment could help to lower the increased BP to optimal level and the event rate could be reduced to the

same level of that in the population with optimal BP. Based on these assumptions, NNT was calculated directly as the reciprocal of the absolute risk difference (RD), where RD was the difference in event rates in person-years between subjects with increased BP and optimal BP. The calculation and discussion of NNT for one year have been modified correspondingly in our revised manuscript (lines 348-352, page 17 & lines 492-496, page 23). Thanks again for your valuable comments.

To the reviewer #1
Reviewer 1 comments: ("--" = new inquiry)
***1. Registration and protocol deviations, post-hoc analyses and clarifications: Apparently, there is no review protocol. Please, indicate if a review protocol exists, if and where it can be accessed (e.g., PROSPERO web address), and, if available, provide registration information including registration number. In addition, please state any protocol deviations, post-hoc analyses and clarifications (e.g. as supplementary material).**

Your Response: This study was conducted strictly under the predefined protocol. However, small amendments were embraced for clinically logical reasons. The search end date was updated to 6th, March, 2020. Additional study outcomes were also searched to better depict the relationship of high BP and adverse outcomes. Apart from the items listed in the protocol, an unplanned calculation of population-attributable fraction and number needed to treat was implemented in the current study. The grading quality of this meta-analysis was evaluated by using the GRADE approach. These changes have been documented in the attached protocol and highlighted in red (Appendix 1).

--Have these deviations from the pre-defined protocol been highlighted in the text? IF so, where? While deviations themselves are not a fatal flaw it is good practice to be transparent about changes made in the revision process and that should be included.

Response: Thank you very much for your comment. We are sorry that we only highlighted the protocol deviations in the attached protocol during last submission. Indeed, these deviations from the pre-defined protocol should have been highlighted in the text as well. These changes made in the revision process help depict a better illustration of our findings. Following the suggestion, we have reported the protocol deviations in the revised manuscript and highlighted in red (lines 130-135, pages 6-7). Thanks again for your valuable comments.

***Introduction. Page 5. Justification. Please, describe the rationale for this review/meta-analysis in the context of what is already known (e.g. any existing systematic review of RCTs, observational studies, or both?).**

your response: Unfortunately, no systematic reviews or RCTs has been

conducted to illustrate the associations of increased BP with cardiovascular risk in young adults.

--Please consider highlighting that "Unfortunately, no systematic reviews or RCTs has been conducted to illustrate the associations of increased BP with cardiovascular risk in young adults."

Response: It's very nice and considerate of you to point out this. Highlighting the currently absence of systemic reviews or RCTs in this field helps us better illustrate the importance and rationale of our study. We totally agree with this suggestion and have included this important information in our revised manuscript (lines 106-109, page 5). Thanks again for your valuable comments.

***. Methods. Page 6. Outcomes. The authors' state: "The primary study outcome was cardiovascular events". Please, clarify and report an explicit definition of "cardiovascular events" (e.g. "classical 3-point major cardiovascular event" is defined as a composite of nonfatal stroke, nonfatal myocardial infarction, cardiovascular death. But another studies define cardiovascular events as "admission for HF, stroke, myocardial infarction, and cardiovascular death). Regarging secondary outcomes, why the exclusión of renal failure/chronic kidney disease or diabetes?**

--It appears there were no "other" outcomes, but If I am mistaken, please include what outcomes comprised "other types of cardiovascular diseases"

Response: We are sorry about not making it clear. In the last submission, we mentioned that the primary outcome was a composite of total cardiovascular events, including coronary heart diseases, stroke, heart failure, other types of cardiovascular diseases or any cardiovascular deaths. Actually, most of our included studies defined the CVD outcome using the classical definition, including coronary heart disease, stroke or any cardiovascular deaths. However, two of them included peripheral artery disease or other vascular disease in their CVD outcomes(2, 3). Therefore, "other types of cardiovascular diseases" defined in our primary outcome was referred to "peripheral artery disease/other vascular disease". In order to explore the influence of heterogeneous definition of the cardiovascular outcome, we further performed a sensitivity analysis by excluding studies using nonequivalent outcome definition (lines 245, page12). As presented in the revised Table S2, the results did not change materially after removing the two studies.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

**** Comments from the external peer reviewers****

Reviewer: 1

Comments:
Thank you for inviting me to review this revised version of the manuscript. Overall, the authors have addressed most of my previous comments. I believe the reporting of background/justification, methods and results for this systematic review and meta-analysis is much clear and transparent.

Thank you again to all your valuable and thoughtful comments! We learned a lot from your comments and the manuscript is also substantially improved after revising according to your suggestions.

We would like to express our great appreciation to the editors and reviewers. Thank you for giving us an opportunity for revision.

Reference

1. Lloyd-Jones DM, Braun LT, Ndumele CE, Smith SC, Jr., Sperling LS, Virani SS, et al. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease: A Special Report From the American Heart Association and American College of Cardiology. Circulation. 2019;139(25):e1162-e77.
2. Jee Y, Jung KJ, Lee S, Back JH, Jee SH, Cho S-i. Smoking and atherosclerotic cardiovascular disease risk in young men: the Korean Life Course Health Study. BMJ Open. 2019;9(6).
3. Yano Y, Reis JP, Colangelo LA, Shimbo D, Viera AJ, Allen NB, et al. Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. Jama. 2018;320(17).