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Association Between High Blood Pressure and Long-term Cardiovascular Events in Young Adults: A systematic review and Meta-analysis

Dear Dr. Chen

Thank you for sending us your revision. We continue to recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

When you return your revised manuscript, please note that The BMJ requires an ORCID ID for corresponding authors of all research articles. If you do not have an ORCID ID, registration is free and takes a matter of seconds.

Thank you for your time; I look forward to reading your second revision.

Yours sincerely,
Dr Tim Feeney
Associate Research Editor
The BMJ
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To start your revision, please click this link or log in to your account: *** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

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****Report from The BMJ's manuscript committee meeting****

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Decision: Put points

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 response to both editorial and reviewer comments. However, we are still a bit concerned about 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.

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?

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 stratified 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

We had initially asked for NNT for 1 year based on reasonable assumption of effectiveness of a drug. Instead it 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 it 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 mortality attributable to hypertension. This should be the NNT that you focus on in the results in order to better contextualize these findings.

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.

*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."

*. 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). Regarding secondary outcomes, why the exclusion 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"

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.

Additional Questions:

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