BMJ - Decision on Manuscript ID BMJ-2020-054316

Body: 02-Mar-2020
BMJ-2020-054316 entitled "Association Between High Blood Pressure and Long-term Cardiovascular Events in Young Adults"

Dear Dr. Chen,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We 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.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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.

Sincerely,
Dr Timothy Feeney
Associate Research Editor
The BMJ
tfeeney@bmj.com

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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.

Members of the committee were: Helen Macdonald (chair), Tim Cole (statistician), Timothy Feeney, Wim Weber, Elizabeth Loder, Tiago Villanueva, John Fletcher, Joseph Ross

Decision: Put points

Detailed comments from the meeting:

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.

Please also respond to these additional comments by the committee:

*The editors were very concerned about secular trends. Particularly we are interested in understanding how the pooling of studies from the 60s and 70s and more recent studies impacts the conclusions. We strongly suggest a sensitivity analysis examining this effect.

*What are the implications of pooling studies that are all male or predominantly male with other mixed studies? Are the male studies mostly studies of military members? A sensitivity analysis of this might also be useful.

*The spline curves have no confidence intervals graphed so interpretation is challenging. Please update that figure and included error estimates.

*Please ensure that your interpretation is more in line with the results of the review. You have shown a lower relative risk from mild hypertension in younger people than older people and the absolute risk of events is also lower in younger people. In combination the attributable risk to hypertension, is much lower for younger adults than older adults. Your conclusion to lower thresholds for treatment (based on older people) in younger adults does not follow well from this.

*Please do not make recommendations about treatment. Your review contains only observational studies and while you have shown there are risks associated with mild hypertension you cannot provide clear recommendations about treatments.

*To give some perspective please calculate a representative number needed to treat for mild hypertension to prevent one event in a year based on a realistic relative risk reduction with an anti-hypertensive drug. If this runs into the thousands it might suggest caution in suggesting active intervention.

*Is it possible to provide more absolute risks in the manuscript to get a sense of absolute impact and not just relative effects?

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 Reviewers

Reviewer: 1

Comments:
Thank you for inviting me to review the paper entitled: "Association Between High Blood Pressure and Long-term Cardiovascular Events in Young Adults". In this systematic review and meta-analysis of observational studies, the authors evaluate the "future risk" of cardiovascular events in young adults (18-45 y) with high BP. They found associations between BP categories for the risk of cardiovascular events. Compared to those with optimal BP, young adults with normal BP (RR 1.26, 1.11-1.43), high-normal BP (RR 1.39, 1.24-1.55), grade 1 hypertension (RR 2.01, 1.73-2.35), and grade 2 hypertension (RR 3.21, 2.19-4.69) had elevated risks of cardiovascular events. They conclude that "young adults with high BP sustain an increased risk of cardiovascular events, even at a level of 'normal' and 'high-normal' BP. Thus, a lower diagnostic threshold may be considered for this age group, as defined by the 2017 AHA/ACC guideline, to help identify young adults at increased risk".

I have the following specific comments (on methods and interpretations of findings) which may be useful for the Editors and authors:
Comments
Please, report methods and results according to PRISMA statement reporting guidance.

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).

2. 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?).

3. 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?

4. Methods. Page 6. Information sources and search strategy.
Please, describe all information sources (not only electronic databases, but also contact with study authors, trial registers or other grey literature sources) with dates of coverage (e.g. from inception to June 30, 2019). In my opinion, the authors should update their searches (some recent studies could be missing e.g. a recent JAMA Cardiology study could be eligible? https://jamanetwork.com/journals/jamacardiology/article-abstract/2759256) In addition, the search strategy (lines 24-29, page 6) should be revised and included as supplementary material. I think a full strategy for PubMed should be reported, including limits such that it could be repeated/reproduced.

5. Page 7. Data extraction. Please, list and define all variables for which data were sought (such as PICO items, funding sources), any data assumptions and simplifications.

6. Page 7. Risk of bias/Quality assessment. Please, specify and describe any assessment of risk of bias/quality assessment of individual studies. In addition, please clarify whether this was done at the outcome or study level, or both; and state how this information was used in data synthesis (meta-analysis). Some information is reported in p.9 (missplaced). Please, revise.

7. Could you please consider to report the evaluation of confidence of evidence from meta-analyses (e.g. by using the GRADE approach)?

8. Small study bias (or "publication bias). The authors have not explored small study effects (e.g. funnel plots, Egger's tests) for most analyses involving at least 10 studies. Why? Please, clarify/revise.

9. Discussion. There is very little to no discussion on clinical and methodological heterogeneity. The study populations (e.g. comorbidities?), design and quality of studies may be very heterogeneous. In the main text (page 11-13), it is not immediately clear where statistical heterogeneity (I-2 squared, Cochran Q) was presented. P values for Cochran Q could be reported, together with 95%CI for I2 squared tests. These data, together with clear discussions of conceptual and methodological heterogeneity, would be helpful to have a better understanding of the data. A potential concerning issue is the high statistical heterogeneity found in subgroups/interventions presented (e.g. primary outcome analyses in Figure 2A, with I2 values ranging from 77% to 95%, with "only" 13 studies).

10. Discussion. Interpretation/conclusions. The authors conclude: "Young adults with high blood pressure sustain an increased risk of cardiovascular events, even at a level of 'normal' and 'high-normal' BP. Thus, a lower diagnostic threshold may be considered for

this age group, as defined by the 2017 AHA/ACC guideline, to help identify young adults at increased risk."
I do not think this interpretation is correct and fully supported by the overall analyses and findings, considering most of the evidence base came from observational studies, uncertainty persists about primary outcomes, etc..
Previous meta-analyses, in my opinion, have been more informative to guide recommendations in hypertension guidelines. For example:
Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016 Mar 5;387(10022):957-967. doi: 10.1016/S0140-6736(15)01225-8. Epub 2015 Dec 24. Review. PubMed PMID: 26724178.

Other comments
5. Abstract. Page 3. Line 29. Authors mention "Thirteen (13) studies (…) were included". However, the Flow diagram reports a different figure (e.g. n= 14 articles/studies?) .
Please, revise/clarify.
Please, consider the inclusion of a populated checklist of PRISMA statement (as supplementary material).

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

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Institution: National School of Public Health, Institute of Health Carlos III, Madrid, Spain

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Reviewer: 2

Comments:
Dangling Luo et al present a meta-analysis of studies which included a very large population and a wide range of follow up years. This meta-analysis aims to assess the impact of increasing BP across the range from 'optimal' to 'Grade 2 hypertension' on CV morbidity and overall mortality of young individuals (18-45 years). The concept is novel and very interesting. The analysis seems to have been conducted appropriately. The results are well presented/discussed and are very interesting. Namely, increasing BP above the optimal levels may be associated with significantly increased risk of CV events in young subjects. This risk seems to be significant even at the normal BP group and increasing with the rise in BP levels. Also, it seems to be more relevant to young subjects aged > 30 years and those who are overweight. These results have important public health implication as for the thresholds of 'normal BP' and the optimal BP targets in this population. These issues are very nicely discussed at the Discussion section.
I am a little unclear as for the type of studies included in the analysis (design and population) as very little information is provided.
Please see below my comments on this manuscript:

Major comments:
1] Some more information on the design of studies included (e.g. prospective, randomised, intervention, epidemiological studies, populations included) is needed. A list of study-specific inclusion / exclusion criteria would be ideal.

2] Were BPs evaluated in all studies all clinic readings or were there data from ABPM or HBPM as well? Was BP included in the analysis baseline BP or on-treatment BP for hypertensive populations?

3] 'median follow-up of 4.3 to 56.3 years'. What was the median follow up of the studies included in the analysis?

Minor comments:
1] define acronyms wherever they first appear in the manuscript, e.g. MORGAM.
2] Please cite references in Table 1.
3] Table 3 is difficult to read. Could authors please align it better?
4] Mixed gender = overall population?

Additional Questions:

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Institution: Dr

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