Neurology
WNL-2024-102120
Blood Pressure, Antihypertensive use, and risk of Alzheimer's and non-Alzheimer's Dementia in late-life: An IPD meta-analysis

Dear Dr. Lennon:

Thank you for submitting your paper to *Neurology*®. We require revisions before making a final decision.

The editors' and reviewers' comments must be addressed before your revision is reconsidered. With your revisions, be sure to include a 'point-by-point' response to the comments of the editors and the reviewers in the 'Response to Reviewers' document, telling us what specific changes were made to the manuscript in response to these comments. Be specific, stating the page and paragraph number where each specific change was made. If you think that a change is not warranted or disagree with the comment, explicitly state so, and explain your rationale for this decision.

When drafting your revision, use the correct reporting guideline checklist to ensure that the revised manuscript includes all the necessary information for appraisal. Use page/line numbers and not check marks. This is a requirement for the revision; you must upload a revised reporting guideline checklist **regardless** if you uploaded one with your original submission. Consult the EQUATOR Network website to identify the most recent and relevant guidelines and extensions. You may also get assistance from the EQUATOR Wizard tool.

EDITORS' COMMENTS
- Line 457 (abstract Methods): Please explain how the studies to be included in the IPD were identified. What were the criteria for inclusion in this IPD? The fact that the study includes patients from 14 countries can be stated in the Results. Spell out "Individual Participant Data (IPD)" when you use IPD for the first time.
- Line 462. Is the superscript "2" OK?
- Line 470: Is it risk of AD or of developing AD?
- Line 479: move "risk" to after "non-AD".
- Line 544: What are the criteria for being a part of COSMIC? Who is enrolled in these cohorts? It is important for readers to get a sense of who would be included (community-dwellers? Memory clinic patients?) and if there are specific criteria for initial inclusion. Also, were the diagnoses made locally or centrally adjudicated? Some of this information may be available in

prior publications but readers of this paper should be able to understand the basic structure without having to look for other papers.
- Line 551: see Author Center for instructions where to include the ethics data.

REVIEWERS' COMMENTS
Reviewer #1 Comments:

Interesting mega-analysis, trading off large numbers in follow-up studies against more or less complete confounder sets. The presentation is clear and the cautious conclusions are justified by the analyses.

Reviewer #2 Comments:

WNL-2024-1012120

MJ Lennon; D Lipnicki; BCP Lam; JD Crawford; AE. Schutte; R Peters; T Rydberg-Sterner; J Najar; I Skoog; SG Riedel-Heller; S Röhr; A Pabst; A Lobo; C De-la-Cámara; E Lobo; RB Lipton; MJ Katz; CA Derby; KW Kim; JW Han; DJ Oh; E Rolandi; A Davin; M Rossi; N Scarmeas; M Yannakoulia; T Dardiotis18; HC Hendrie; S Gao; I Carriere; K Ritchie; KJ Anstey; N Cherbuin; S Xiao; L Yue; W Li; M Guerchet; PM Preux; V Aboyans; MN. Haan; A Aiello; M Scazufca; PS Sachdev: Blood Pressure, Antihypertensive use, and risk of Alzheimer's and non-Alzheimer's Dementia in late-life: An IPD meta-analysis

This study evaluated the effect of hypertension in late-life and/or antihypertensive medication use on 1) AD or non-AD risk in late life and 2) the ideal BP for risk reduction.

This study differs from previous studies since it includes studies from developed countries and developing countries, therefore adding information. My main concern is that the authors did not consider the role of BP control sufficiently, and in their discussion section, they focused on results that excluded confounders, which is unacceptable.

Introduction:
- Line 528: I believe the authors should mention the study by Ding J et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. Lancet Neurol. 2020 Jan;19(1):61-70. doi: 10.1016/S1474-4422(19)30393-X. Epub 2019 Nov 6. PMID: 31706889; PMCID: PMC7391421.: a meta-analysis of numerous studies worldwide, including studies ranging follow-up between 7 - 25 years, which have shown that AHM did reduce all-cause dementia and AD risk in people with a history of HTN, but not without HTN.

- Line 535: It would be necessary if the authors would empathize more with how this study is different from all the previous meta-analyses (for example, the studies they have included - how the COSMIC group is different by including studies from Congo, Brazil, and China, etc.; the method used IPD, also looking non-AD dementia as an outcome, trying to define ideal BP, etc.).

Methods:
- Covariates/Line 568: Covariates - I am missing stroke/TIA and coronary artery disease as covariates. These are important ones since HTN can cause both, and both are associated with dementia risk.
- Covariates categorization/line 588: diabetes - there is diabetes mellitus and diabetes insipidus; thus, the authors should clarify which one they mean, most likely diabetes mellitus.
- Statistical analysis/Line 605: The grouping is interesting, and previous studies have been done this way. However, what is clinically relevant is whether BP is controlled. I would suggest doing a sub-analysis in group 3 (3a controlled vs 3b uncontrolled). I would compare
HTN/treated/controlled to Healthy.
HTN/treated/uncontrolled to Healthy.
HTN/treated/controlled to HTN/treated/uncontrolled.
HTN/untreated to HTN/treated/controlled.
HTN/untreated to HTN/treated/uncontrolled.
This would add a lot of information.
(I would be curious to see how many from group 4 had controlled BP?)
- Statistical analysis: I was wondering why the authors only used baseline BP. Vitals are usually measured at every visit, so it would be more informative if mean SBP and DBP over the study had been used as a definition for controlled or uncontrolled rather than baseline BP. One-time reading at baseline cannot define follow-up readings (maybe the baseline reading is normal, and all follow-ups are elevated - this way, the participant will be incorrectly assigned to a "controlled" group).
- Statistical analysis/Line 641: HT/AHT - first time used in text, needs to be spelled out. For hypertension, HTN is the generally accepted abbreviation.
- I am not clear whether sub-analyses were adjusted for covariates.

Discussion:
- Lines 767: The authors should use the fully adjusted results in the discussion; they cannot limit results to the main analysis, which excludes numerous confounders.
- Lines 776: The authors should use the results from the fully adjusted results, and based on that, there was no association, so the discussion needs to be revised.
- Lines 794: The authors use post-stroke dementia, but previously, they used VaD; please remain consistent in wording.
- Authors should point out, what this study add, and why their study is novel, not only by the

numbers, but by first study using data from developing countries.

Tables:
- Table 2 headings list n events = number; I assume it is a mistake and the authors meant events, n=number.
- Figure 2, it would be helpful to have headings over A, B -main analysis, C, D fully adjusted, and E, F > 5 years.
- Figure 3: is this main analysis or fully adjusted or followed for > 5 years?

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