Responses to reviewers

Editor			
No.	Reviewer Comment	Author Response	Changes Made
1	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.	Thank you for your comments throughout. Each of the studies was part of the Cohort studies of Memory in an International Consortium (COSMIC) group. Membership of this consortium required studies to be community based, longitudinal studies of aging with cognition as a major outcome measure. All studies participating in COSMIC were invited. Those that agreed to provide participant level data and had the variables needed for the analysis were included. Individual data from the COSMIC participant studies have been harmonized using standard protocols. We have tried to make this clear in the abstract while keeping within the constraints of the word limit. We have expanded out the IPD.	Abstract, Methods: "This Individual Participant Data meta-analysis included community-based longitudinal studies of aging from a pre-existing consortium"
2	Line 462. Is the superscript "2" OK?	Yes, this indicates that an age squared term was used in the models.	
3	Line 470: Is it risk of AD or of developing AD?	You are technically correct	Abstract, Methods: "The main outcomes were risk of developing AD and non-AD"
4	Line 479: move "risk" to after "non-AD".	Thank you. We have made this change.	Abstract, Discussion: "Antihypertensive use was associated with decreased AD but not non-AD risk throughout late-life in comparison to those with untreated hypertension."
5	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	The criteria for being part of COSMIC are "cohort studies that longitudinally examine change in cognitive function and the development of dementia in older individuals (60+ years)".	Methods, Contributing Studies: " This analysis incorporated 14 community-based

	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.	They are community dwelling longitudinal studies of ageing. The diagnoses are made by the investigators of each study and not centrally. We agree that this information should be available in this publication.	longitudinal studies of ageing (n=31,250) that were participants of the Cohort Studies of Memory in an International Consortium (COSMIC) group, a collaborative that has been described in prior papers[18,21]. The COSMIC consortium includes longitudinal studies that examine cognitive change and dementia diagnosis over time. To be included in this present paper, studies at a minimum had collected basic demographic, AD diagnosis and blood pressure/hypertension history data. " Methods, Dementia Outcomes: "The two main outcome variables for this study were AD and non-AD dementia. These diagnoses were made within each study rather than centrally adjudicated."
6	Line 551: see Author Center for instructions where to include the ethics data.	Thank you. We have added the ethics into the relevant section.	
Reviewer 1			
1	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.	Thank you for the time taken to review our paper and your kind comments.	
Reviewer 2			
1	This study evaluated the effect of hypertension in late-life and/or	Thank you for your comments throughout.	Methods, Statistical Analysis, Paragraph 5:

	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.	To your first point, we have attempted to consider BP control in two ways, but we accept your point that these analyses have not been sufficiently explicated throughout the paper. The first way in which we examine the moderating effect of blood pressure control on the antihypertensive use was to examine the interaction between HTN/AHTN status and natural splines SBP/DBP. We used the natural splines terms as the interaction terms as these were what we had used in the main analysis and because they allowed us to flexibly examine the moderating effect of continuous blood pressure on the relationship between HTN/AHTN status and AD/non-AD risk. We found no significant interaction between these terms indicating that a single measure of blood pressure did not moderate the relationship (eTable 15). We recognise however that using this approach was not easily comprehensible or clinically translatable. As such we employed a second method (eTable 16), in which we had done as you recommended in dividing the treated hypertension group into both controlled and uncontrolled hypertension. We recognise that in the text of the methods, results and discussion this was not made sufficiently clear and we have edited these to give more emphasis to this part of the analysis. With regards to your comment about the partially adjusted analysis, we accept that this analysis is at risk of confounding. However, the novelty of our study was that we incorporated studies from developing	"Models comprised of both continuous BP parameters and HTN/AHT status were attempted but were excluded because of poor model fit, number of excluded participants and a lack of interaction significance." Methods, Statistical Analysis, Paragraph 6: "Fifth, to assess the impact of effectiveness of blood pressure control in those with treatment, the main analyses were re-run with the treated hypertension group divided into those with BP <140/90 mmHg (controlled) and those with BP either >140 mmHg SBP or >90 mmHg DBP (uncontrolled)." Results, Paragraph 6: "There were no significant interactions between either SBP or DBP and the HTN/AHT status of participants for either AD or non-AD (eTable 15). However, when baseline BP was considered as a binary variable (controlled <140/90 mmHg or uncontrolled >140 mmHg SBP or >90 mmHg DBP), those who had treated hypertension that was uncontrolled had substantially elevated risk of non-AD (HR=1.331, 95%CI[1.04, 1.704], p=0.0233), whereas those with treated, controlled hypertension had no increased risk (eTable 16). This result was consistent in those participants restricted

		nation and in order to be inclusive of these studies, and run interaction analyses looking particularly at race, the model needed to be parsimonious. As part of our sensitivity analyses we include fully adjusted models and identified discrepancies throughout the results and discussion. We have changed the discussion to more clearly reflect the differences in the partially and fully adjusted models (see responses to comments below). We have also added this focus on the partially adjusted models as a limitation in our discussion.	to 5 years follow-up but was no longer significant in the fully adjusted analysis. There was no difference in AD risk between those with controlled or uncontrolled treated hypertension." Discussion, Limitations: " Stroke/TIA and heart disease were other potential confounders that were not controlled for because they may act as mediators rather than covariates and including them would have excluded many participants from developing countries missing those data. Similarly, the partially adjusted model was used as the main model to limit exclusion of participants but these results may be confounded and should be interpreted with caution."
2	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	Thank you for this. We have included this paper in the text.	Background, Paragraph 4: "A 2020 IPD meta-analysis[16] (n=31,090, age>55 years old) found that antihypertensive use reduced All-Cause Dementia and AD dementia risk by 12% and 16% respectively in those with elevated baseline BP"

	- 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.		
3	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.).	We have made changes to the introduction to emphasise these novel aspects of our study.	Introduction, Paragraph 4: "In the current paper, we use international data from 14 longitudinal cohorts including studies from the Republic of Congo, Brazil, China and Nigeria. We use an IPD approach to investigate how antihypertensive medication use is associated with the risk of both AD and non-Alzheimer's dementia (non-AD) and we explore ideal blood pressure for dementia risk using a flexible, non-linear model."
4	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.	These are covariates that we considered carefully but ultimately did not include for three reasons. First, the novelty of our study was that we incorporated studies from developing nations. Including stroke and TIA as covariates in the analysis would have removed these studies from the meta-analysis as they lacked these covariates. Second, as you point out HTN can cause both of these and thus they may be a mediator rather than a simple covariate in the analysis. Including them in the analysis without running the mediation analysis may remove the effect of BP. Third, we pre-specified the analysis in a registry and were attempting to keep our analysis consistent with our previous paper in which we did not include stroke/TIA or CVD. We have added this as a limitation to	Discussion, Study Limitations " There are likely to be non-random differences between those who do and don't take antihypertensives that we could not control for, including socioeconomic status, health literacy, access to medications, poorly managed comorbidities and depression and other mental illnesses that may confound the association between hypertension status and dementia risk. Stroke/TIA and heart disease were other potential confounders that were not controlled for because they may act as mediators rather than covariates and including them would have excluded many participants from developing

		our discussion.	countries missing those data."
5	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.	Thank you for this comment. We have made this change throughout the text.	Methods, BP Measures…. Covariates "The covariates used in the analyses were age, sex, years of education, racial group, body mass index (BMI), diabetes mellitus status, hypercholesterolaemia and smoking status (for details see Tables S5 to S7)."
6	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?)	Thank you for this comment. We certainly agree that this is very much clinically relevant. We had included in eTable 16 a supplementary analysis in which we did divide group 3 as you mentioned into controlled and uncontrolled hypertension. We recognise that this was not sufficiently highlighted and have as such changed the results and discussion to emphasise these results.	Statistical analysis, 6th Paragraph: "Fifth, to assess the impact of effectiveness of blood pressure control in those with treatment, the main analyses were re-run with the treated hypertension group divided into those with BP <140/90 mmHg (controlled) and those with BP either >140 mmHg SBP or >90 mmHg DBP (uncontrolled)." Results, Paragraph 6: "However, when baseline BP was considered as a binary variable (controlled <140/90 mmHg or uncontrolled >140 mmHg SBP or >90 mmHg DBP), those who had treated hypertension that was uncontrolled had substantially elevated risk of non-AD (HR=1.331, 95%CI[1.04, 1.704], p=0.0233), whereas those with treated, controlled hypertension had no increased risk (eTable 16). This result was consistent in those participants restricted to 5 years follow-up but was

			no longer significant in the fully adjusted analysis. There was no difference in AD risk between those with controlled or uncontrolled treated hypertension." Discussion, paragraph 1: "Within those with treated hypertension there was difference in risk of developing AD risk between those with and without effective BP control at baseline."
7	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).	Some of our studies had multiple waves of BP but even for those in which it was available the frequency and timing (6-monthly, annually, biannually) varied making it difficult to develop a consistent approach to using multiple measures of blood pressure. Furthermore, while some studies had in-person assessments at each wave some intermittently had waves that were conducted over telephone interviews and thus BP was not collected. We certainly appreciate the challenge of understanding effectiveness of blood pressure control, as it varies considerably even minute to minute, which is why for accurate diagnoses 24-hour BP monitoring if often recommended. We had considered using the waves of blood pressure that we did have to explore the effect of cumulative blood pressure exposure and this may form part of our future research but ultimately for this piece of work we thought that it would result in excluding too many of the participants, which we have recognised as limitation.	Discussion, Study Limitations: " Due to study heterogeneity multiple waves of BP measures were not able to be used and given the considerable variability in BP, the single baseline measure may not accurately capture those with consistently high or low BP."

8	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.	We have changed references to HT/AHT to HTN/AHT throughout the text and spelled it out in the first use instance. To clarify, for the sensitivity analyses assessing outcomes for vascular dementia (eTable 12) and assessing the differential effect of uncontrolled vs controlled treated hypertensives (eTable 16), the partially adjusted, fully adjusted and >5 year models were used. For the models assessing the interactions with age, sex and race these included covariates from the partially adjusted model.	Statistical analysis, Paragraph 1: "Hypertension history, as a dichotomous variable, was examined, but because its effect was significantly modified by treatment status (eTable 10), the main analysis focussed on a categorical variable based on both hypertension history and antihypertensive use (HTN/AHT status)." Statistical analysis, 6th Paragraph: "Fourth, to assess the putative moderating effects of age, sex and ethnoracial group, interactions between the main predictors (HTN/AHT status and baseline BP) with these variables were included in separate models. These models assessing the interaction effects were adjusted for Age, Age^2, Sex, Education, Racial group and a random intercept term for study"
9	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.	Thank you for this comment. We understand the caution required when discussing unadjusted or partially adjusted results. We have decided to include both in the sentence starting line 767 so readers can understand that the results were consistent in one direction but differed considerably in their effect estimate.	Discussion, 1st Paragraph: " In this study there were a number of key insights into the association of late-life hypertension and AD risk. We found that those with untreated hypertension had significantly higher risk of AD than "healthy controls" (main model: +36%, fully adjusted: +70%) and those with treated hypertension (main model: +42%, fully adjusted: +100%)."
10	Lines 776: The authors	Thank you we have revised this	Discussion Paragraph 2:

	should use the results from the fully adjusted results, and based on that, there was no association, so the discussion needs to be revised.	statement.	"In the current study, diagnosed hypertension, both treated and untreated, was associated with considerably greater risk of non-AD in late life compared to "healthy controls" in the partially but not fully adjusted analysis." Discussion, Paragraph 2: "The non-AD and VaD results should be considered with caution as the results of the partially adjusted analysis were not replicated in the fully adjusted analysis or when restricted to more than 5 years of follow-up, indicating that the differences may be better explained by vascular covariates."
11	Lines 794: The authors use post-stroke dementia, but previously, they used VaD; please remain consistent in wording.	We have clarified this statement. There are 4 subtypes of vascular dementia, subcortical vascular, post-stroke, multi-infarct dementia and mixed dementia. In the literature we cite in the discussion they relate specifically to post-stroke dementia and as such we wanted to be precise in the language we use when referred to what their outcomes were. We have added in the discussion that post stroke dementia is a subtype of VaD.	Discussion, Paragraph 2: "The results for VaD are also consistent with the few published clinical trials that have found that the risk of post-stroke dementia, a subtype of VaD, is significantly modified by antihypertensive use, reducing risk by up to 34%[29]"
12	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.	We edited the conclusion to add emphasis to this.	Conclusion, Paragraph 1 " To conclude, this IPD meta-analysis, with data from 14 nations, including studies from developing countries, illustrates that throughout late-life those with treated hypertension had a lower risk of AD compared to those with untreated hypertension,

			suggesting that antihypertensive use should be part of any AD prevention strategy even in late-life"
13	Table 2 headings list n events = number; I assume it is a mistake and the authors meant events, n=number.	We apologise for the confusion here. The n = indicates the total number of participants included in each analysis. n (event) indicates the total number of incident dementia cases included in that analysis. We have changed the formatting for this to make this clear.	Table 2, description " **Table 2:** Summary of Cox Proportional Hazards Models examining relationship between HTN/AHT status, baseline BP and both AD and non-AD risk. n indicates the total number of participants included in each analysis. n (event) indicates the total number of incident dementia cases."
14	Figure 2, it would be helpful to have headings over A, B - main analysis, C, D fully adjusted, and E, F > 5 years.	We have made this change.	
14	Figure 3: is this main analysis or fully adjusted or followed for > 5 years?	This analysis used the partially adjusted model.	Table 4: " **Figure 4:** The relationship between SBP, DBP and AD/non-AD risk with 95%CIs (shaded areas) showing the changing relationship with increasing age. In all models SBP and DBP was grand-mean centred (at 140 mmHg and 80 mmHg respectively) and all HRs represent within-group risk relative to this grand-mean. These models were partially adjusted and included covariates of Age, Age^2, Sex, Education, Racial group and a random effect for Study."
EDITORIAL CONTENT			
1	WORD COUNT Please ensure that the revised paper does not exceed the word count specification for your manuscript category (Npub.org/authors); this means that any changes made to address the reviewers' comments may require edits elsewhere in the manuscript.	Thank you for this comment. We have completed this.	
2	METHODS	We have made these changes.	

	Place the ethical approval/patient consent information in a subsection within the Methods labeled: "Standard Protocol Approvals, Registrations, and Patient Consents". Move the data sharing statement to the end of the Methods.		
3	REFERENCES Reduce the number of references to fifty.	We have done this.	
4	DISCLOSURES The Disclosure line is not formatted correctly. Every author should be included in the Disclosure Statement and appear in the same order as in the manuscript byline. Please use the author's initials and full last name when indicating disclosures. (For John H. Smith, use J.H. Smith.) Example: If an author has relevant disclosure(s), please state *J.H. Smith serves on the advisory board of Pfizer.* If the author has no relevant disclosures, please state *J. H. Smith reports no disclosures relevant to the manuscript.* If all authors do not have relevant disclosures, please add: *The authors report no disclosures relevant to the manuscript.* Please correct in the Disclosures field when uploading your revision.	We have made these changes to the disclosures.	
5	FIGURES	We have made these changes by	

	Limit the number of panels for one figure to a maximum of four (e.g., 1 A,B,C,D). Limit each panel to 1 item. The exception is brain images and pathologies that require multiple panels to illustrate a progression. Portions of the figures can be moved to supplemental files which has no limit on sizing.	splitting figure 2 into two different figures.	
6	SUPPLEMENTAL DATA Supplemental content should be organized in the order in which they are referenced in the manuscript text and following the naming conventions below. - Videos: Video 1, Video 2, Video 3... - Tables: eTable 1, eTable 2, eTable 3... - Figures: eFigure 1, eFigure 2, eFigure 3... - Methods: eMethods - References: eReferences; e1, e2, e3... - Study Protocol and Statistical Analysis Plan (for clinical trials): eSAP 1, eSAP 2, eSAP 3... - Appendices: eAppendix 1, eAppendix 2, eAppendix 3...	We have changed all references to supplemental content according to the style of this journal.	