Author’s response to reviews

Title: HYPERTENSION AND COGNITIVE DYSFUNCTION IN ELDERLY: BLOOD PRESSURE MANAGEMENT FOR THIS GLOBAL BURDEN

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Author’s response to reviews:

Reviewer #1:

We would like to thank you for your expert and meticulous review of our manuscript. We have accepted all your suggestions and included them in this version of the manuscript. However, we would like to explain all the changes we have made according to your previous suggestions.

1. Page 4, line 44: similar to advanced CKD, dementia may be related to small vessel diseases in the target organ; therefore, the process may be hard to revert. Early intervention in mid-life could be a better strategies and should be emphasized. However, the legacy effect of treating hyperlipidemia is more pronounced than BP (NEJM 2008;359), which may be an important issue to be considered.

We agree with you and we have added this in the introduction section.

2. Page 7, line 29: Considering the competing risk exists in elderly subjects, the effects between cognitive dysfunction and blood pressure may only be modest and even biased. In other words, only survivors of major adverse vascular events can provide the opportunities for investigators to observe the relationship between BP and cognition impairment. The competing risk could be accounted for by some statistical analysis. This may be a point worth to be addressed in the review.
This is true, but some large studies and meta-analysis showed that this relationship exists. We believe that this is not only the result of statistical analysis. However, we have added this point in the current version of manuscript.

3. Page 9, line 1: In addition, arterial stiffness may underline the association between hypertension and cognitive dysfunction (Hypertension. 2016;67:171-5) and provide explanations for the conflicting observations. Gary Mitchell provided a concept of impedance matching for the relations between pulsatile hemodynamics and cognition decline which merits to be addressed (Hypertension. 2016;67:176-82; Pulse. 2016; 4:69-77).

The references are very interesting. We have added these references and commented them in the section that you mentioned.

4. Page 10, line 34- "Hypertension induces bloodbrain barrier damage through direct effect on oxidative stress, inflammation and vasoactive substances". A reference (probable 50) is needed to be supplemented here.

Thank you for noticing this. We added the appropriate reference.

5. Page 10, line 46: a paragraph mentioning the optimal target BP for preventing cognitive dysfunction may be needed. Apparently, there is insufficient evidence for any meaningful suggestions. Discussion on the recent Sprint trial which also incorporated cognition as an important outcome!

The results from the SPRINT MIND trial will provide answers on many questions including the optimal target BP value for prevention of cognitive dysfunction. The primary objective of the SPRINT MIND trial is to determine whether intensive BP lowering with target systolic BP <120 mmHg is associated with a greater reduction in the incidence of all-cause dementia comparing with a standard treatment target of 140 mm Hg. However, to our knowledge this study has not been published jet.

6. Page 11, line 19- "[95% confidence interval: 0.02-0.07]": a point estimate should be supplemented.
Effect size 0.05, 95% confidence interval: 0.02-0.07. We have added this in the review.

7. Page 17, line 7- "However, the neuroprotective effects of β-blockers seemed to be inferior when compared to other classes." A reference should be inserted at the end of this statement.

We added this reference.

8. Page 18, line 32-"Further larger cohort studies with longer-term follow-up with appropriate BP assessments evaluating cognition with and without antihypertensive drug therapy are clearly warranted." The sentence is confusing since BP assessments issue has not been mentioned in the present review.

The sentence is omitted from this version of the article.

9. It would be very inspiring for readers if the authors can summarize current evidence gaps in this review, such as:

a) Whether mid-life antihypertensive agent can slow down future cognition function decline?

The interest for the effect of BP reduction on cognitive decline in middle-aged hypertensive patients is increasing /61/. The Syst-Eur study reported a 50% reduction in incident dementia during 2-year follow-up period in subjects older than 60 years /60/. Hypertensive middle-aged patients should be routinely tested for cognitive dysfunction because it may be an early predictor of dementia and antihypertensive treatment could slow cognitive decline in this patients.

This was added in the current version of manuscript.

b) Which is the optimal antihypertensive agents for cognition function decline?
Studies regarding the influence of different antihypertensive agents on cognitive function were mainly focused on the effect of the blockers of the renin-angiotensin-aldosterone (RAAS). These investigations showed the favorable effect of RAAS blockers on mental status, which seems to be more pronounced than in other antihypertensive groups. However, we need randomized trials that would provide answer on this important question. Possibly substudies of the SPRINT study will give satisfactory response.

We have added this in the current version of manuscript.

c) What is optimal target for preventing cognition dysfunction?

As you previously mentioned, there is no strong evidence regarding target BP values in elderly. The results from the SPRINT MIND trial, which is part of the SPRINT study, will provide answers on many questions including the optimal target BP value for prevention of cognitive dysfunction. The primary objective of the SPRINT MIND trial is to determine whether intensive BP lowering with target systolic BP <120 mmHg is associated with a greater reduction in the incidence of all-cause dementia comparing with a standard treatment target of 140 mm Hg. We mentioned this in this version of manuscript.

We hope that we have successfully changed our manuscript according to your suggestions and that it now fulfills your and the Journal criteria for publication. If you have any more suggestions please do not hesitate to send them to us. We would be very glad to improve the quality of our paper according to them.

Reviewer #2:

We would like to thank you for the detailed review of our manuscript. We greatly appreciate the effort you made concerning your critique for the review of our study. We have accepted all your suggestions and revised the article according to them.

1. Page 6, line 51: You might want to add some descriptions on the recent results from SPRINT trial in discussing optimal BP in the elderly.
Recent SPRINT trial showed that the more intensive systolic BP targets of <120mmHg in non-diabetic subjects are superior over the standard systolic BP target of <140mmHg /37/. In the elderly patients (> 75 years), intensive treatment was more effective than standard BP lowering (HR 0.67; 95%: 0.51 - 0.86) /37/. This suggests that the target systolic BP should be <120mmHg in the elderly patients. Interestingly, both the fit elderly and the frail elderly benefited from the lower systolic BP targets. However, the highest benefit was in elderly with mid fit status. In the fit elderly the HR was 0.47 (95%CI: 0.13 - 1.39), less fit elderly HR 0.63 (95%CI: 0.43 - 0.91) and the frail elderly HR 0.68 (95%CI: 0.45 - 1.01) /37/.

This is added in the new version of manuscript.

2. Page 7, line 29-39: You might want to mention that age at BP measurements may in part explain the inconsistent associations between BP and cognitive function.

We agree with you and we have added this in the current version.

3. Page 10, you might want to add some descriptions on accumulation of beta amyloid protein in the brain associated with high BP as a potential mechanistic link between BP and cognitive dysfunction.

We fully agree with you and we involved this potential mechanism in the current version.

We hope that we have successfully changed our manuscript according to your suggestions and that it now fulfills your and the Journal criteria for publication. If you have any more suggestions please do not hesitate to send them to us. We would be very glad to improve the quality of our paper according to them.