University of Wisconsin
SCHOOL OF MEDICINE
AND PUBLIC HEALTH

Department of Anesthesiology

October 8, 2018

Dear Dr Merino,

Many thanks for the message of provisional acceptance of our paper. We have addressed the remaining comments below.

Best wishes,

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** Comments from the external peer reviewers**

Reviewer: 1

I am satisfied that the authors have appropriately responded to the criticisms. I recommend acceptance of the manuscript as is.

Many thanks.

Reviewer: 2

The additional sensitivity analyses strengthen the authors' results and conclusions. I had only a few additional comments/suggestions.

Many thanks.

(1) It appears that the authors may have adjusted only for baseline covariates, i.e. from the 1997-1999 assessment. Shouldn't these covariates be updated over time, especially those related to cognition, e.g. diabetes, cardiovascular risk score, etc.? It's not clear what the authors mean by "occasional" missing data. It would be preferable to provide information about the amount of missing data, especially for key co-variates over time.

In our model two covariates were dynamic being updated at each cognitive wave "Additionally, measures of married/cohabitating status and Framingham primary care cardiovascular disease risk score[29] were assessed alongside the cognitive assessment." We now state:

"Additionally, measures of married/cohabitating status and Framingham primary care cardiovascular disease risk score[29] were updated alongside the cognitive assessment."

We have now run a sensitivity analysis with updating all covariates over time and the result do not change. Hence we have chosen to stay with the submitted model. We would like to emphasize that certain covariates, such as diabetes, was defined as occurring "ever" given the insidious onset of such a disease.

Apologies that in our prior response, we did not draw sufficient attention to the missing data rows in the tables where we define the quantities of missing data. To highlight this we have added the following statement to the "Missing data" section:
"The amount of missing data is stated in Table 2."

(2) Clinically, decline in cognition is observed more commonly among persons older than 70-75 years. Because only a very small subset of study participants were in this age group, the authors should explicitly indicate in the Discussion that their results may not be applicable to this increasing population of older persons.

We have now added this important caveat to the discussion.

(3) Results from Whitehall II may not be generalizable to other populations, particularly minorities. The authors should also add a statement about generalizable in the Discussion.

We agree and have now added this important caveat to the discussion.

"Finally we emphasize that the findings from this study may not be generalizable to other groups, including those with more ethnic diversity and those with greater numbers of subjects older than 70 years old, when the incidence of clinical diagnoses of cognitive decline, such as dementia, increases."

Reviewer: 3

The authors have responded very positively and at length to the reviewer comments. I have just two very minor observations.

1. The results for years equivalent cognitive impact in the tables are all presented to two significant digits. So for example in Table 3 the impact of surgery on composite score is given as 0.35 with CI 0.0077 to 0.73. Using two significant digits like this is often more appropriate than two decimal places, particularly with metrics on a multiplicative scale such as risk ratios. However here it is a linear scale in time, and there is no sense in presenting the lower limit to four decimal places. I would recommend for the years equivalent tables using two decimal places throughout, i.e. 0.01 to 0.73 in the example.

We have amended the manuscript to include only two decimal places.

2. The word surgeries crops up a lot, which the Oxford Dictionary does not recognise. Could I plead for surgery throughout instead?

We have edited the word "surgeries" as requested.

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