Author's response to reviews

Title: The Effect of Body Mass Index on Global Brain Volume in Middle-Aged Adults: a cross sectional study

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Author's response to reviews: see over
RE: Manuscript 388190162653729: The Effect of Body Mass Index on Global Brain Volume in Middle-Aged Adults: a cross sectional study

Dear Editors,

Thank you for the additional reviews of our manuscript. Enclosed is a revision of the manuscript that we are re-submitting to *BMC Neurology* for publication consideration. Reviewer 1 requested some clarifications within the Methods portion of the manuscript in addition to some minor editorial revisions. Reviewer 2 has accepted the manuscript without comment. Below please find our detailed response to the reviewer’s comments and description of changes we have made to the manuscript.

The major changes include: 1) a clarification of the method of recruitment for the study; 2) a more comprehensive description of the study size; 3) a clarification of the study sample included within the statistical models. Listed below, we have separated into sections the major and minor paraphrased concerns of the reviewers followed by descriptions of our attempts to mitigate these concerns and strengthen the manuscript.

Reviewer 1

*Reviewer 1: It is difficult to understand your study design. Are you describing a baseline cross-sectional analysis of a case-control study, where caseness is having a family history of AD? As part of this, you ‘matched’ WRAP participants to community participants on the basis of ‘demographics’, yet also refer to ‘age-matched controls’. Can you please explain the matching? In addition, if this is a case-control study of some sort, you basically combine the 2 groups, and adjust for caseness and other potential differences between the groups. This is OK, but you need to do a better job of describing...*
what exactly you are doing, and the study design for the reader. In addition, your ‘control’ (and I do not like using this term) group is not a community-based group, but rather a convenience sample of UWM non-faculty staff (born XX? etc.).

This study was not a case-control study; rather it was a cross-sectional study examining the effect of various factors on global brain volume and cognition. This is now clarified and better described on pages 4 and 5 (in the description of participants) and on pages 7 and 8 (in the description of the statistical analyses) incorporating the suggested wording and comments of the reviewer. As the reviewer alluded to, our reason for recruiting the way we did was to determine whether having a family history of AD was a predictor of brain volume in middle age. We recruited the groups on the same general parameters in somewhat simultaneous fashion. They were quite similar on age, gender, cognitive function and BMI; nevertheless we treated family history as a factor in the stepwise regression analyses.

Reviewer 1: In addition, in a case-control study, usually participants are recruited somewhat simultaneously over time. When were your study group participants in relationship to each other recruited?

The participants in this study were recruited somewhat simultaneously over time, which is now mentioned on page 4, paragraph 1 of the Methods section.

Reviewer 1: It is difficult to understand the sample size. In Methods, there are n=116. Then on page 8 there is a listing those who had incomplete data for various assessments. I am assuming these individuals were subtracted from the 116, but there are no sample numbers presented in the tables. In fact, the number of individuals included in the BMI classification in Table 1, totals 114.

Page 8, paragraph 3 of the Statistical Analysis subsection of the Methods section now clarifies the study size for both the brain volume analysis and the cognition analysis. In addition, the captions for Table 1 and 2 now include study size for each analysis. From the initial pool of subjects, 3 were excluded from the brain volume analysis, and 9 were excluded from the cognition analysis (this excluded set of 9 consisted of the 3 above as well as 6 others who had high scores on a depression inventory or missing data)

Reviewer 1: Eligibility requirements mentioned on p. 5, 4th line -are these the same as the criteria for inclusion in the paragraph at the bottom of page 5? If so, put these things together.

The eligibility requirements have been consolidated in paragraph 1 of the Methods section on pages 4 and 5 as suggested.
Reviewer 1: Given the above discussion, an optional first sentence of the Results: ‘116 participants with a mean age of.... and cognitive testing for a cross-sectional study analyzing the brain and cognitive effects associated with risk factors for AD.’

We have now added a sentence to this effect at the beginning of the Results section as suggested.

Reviewer 1: Discussion, 2nd sentence. ‘.... the possible effect of on cerebral atrophy had not influenced cognition in participants with a high BMI.’ Not obese subjects. The analytical description suggests that BMI is entered as a continuous variable in regression models, and not categorical.

Line 5 of paragraph 1 of the Discussion section now uses the term ‘high BMI’ in place of obesity as recommended.

Reviewer 1: Table 1. Title could be clearer. E.g., Demographic and Cognitive Measures in 116 Men and Women.

The title of Table 1 has been changed to the following; Demographic and Cognitive Measures in Men and Women. The sample size was added to the notes section of Table 1.

Reviewer 1: Table 2. Why is age not included in Table 2? Also, why is BMI asterisked? Again, a better title would help to clarify contents of the table, and perhaps state that these results are based on a stepwise model.

Age was not included in the Table because the Beta values in the table are adjusted for age in the regression analysis. To clarify this, the title of Table 2 has been changed to the following: “Age-Adjusted Associations between each predictor variable and NBV.” Age is strongly correlated with NBV; therefore we examined the associations between the predictor variables and NBV adjusting for age.

An asterisk was placed after BMI simply to indicate a significant relationship between BMI and age-adjusted NBV. Because the p-values are also presented the asterisk is not needed and was removed.

Reviewer 1: Figure 1. Can you include the r and p-values?

The caption for Figure 1 on page 18 now includes both r and p values per this request.
Reviewer 1: Please use the term participants or subjects. Both are used in the current version.

All relevant terms have been changed to participants.

We thank the reviewers for their helpful critique of this manuscript. We believe the actions we have taken in response to the reviewers’ have enhanced the quality of the paper.

Sincerely,

Sterling Johnson, Ph.D.
Michael Ward