Author's response to reviews

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

Authors:

   Michael A Ward (maw@medicine.wisc.edu)
   Cynthia M Carlsson (cmc@medicine.wisc.edu)
   Mehul A Trivedi (mt2@medicine.wisc.edu)
   Mark A Sager (masager@facstaff.wisc.edu)
   Sterling C Johnson (scj@medicine.wisc.edu)

Version: 2 Date: 21 July 2005

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 thoughtful reviews and suggestions for our manuscript. Enclosed is a revision to the manuscript with the above (revised) title that we are re-submitting to *BMC Neurology* for publication consideration. This manuscript was submitted to and reviewed by *BMC Medicine* and Iratxe Puebla, Senior Editor stated that the manuscript may be suitable for publication in *BMC Neurology* if we were able to adequately respond to the reviews’ comments. Below please find our detailed response to the reviewer’s comments and description of changes we have made to the manuscript.

The revised manuscript describes the effect of BMI and other cardiovascular risk factors on MRI-derived global brain atrophy estimates and cognitive function in individuals between the ages of 40 and 65 years. We found that elevated BMI was associated with lesser global brain volume even after accounting for age. This study extends prior research showing that obesity in a geriatric population is associated with atrophy of the brain, cognitive decline, white matter ischemic changes, and higher incidence of dementia in elderly individuals. Our findings suggest that middle-aged obese adults may already be experiencing differentially greater brain atrophy, and raise the possibility of greater risk for future cognitive decline and dementia. Several analytical and descriptive improvements have been added to address the concerns expressed in the reviews of the original manuscript.
The major changes include: 1) the addition of education as an independent variable in the analysis of the effect of various risk factors on cognition; 2) the addition of diastolic blood pressure as a potential risk factor for decreased global brain volume and cognition; 3) a more comprehensive description of the subjects selection criteria, exclusion criteria, and medical conditions. 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: How exactly were participants recruited? Is there any reason for selection bias? Is this an MRI subsample of a larger study?

A more comprehensive description of the study participants and methods of solicitation are given in lines 4-16 of the Methods section. Greater than one-half of the study group had a family history of AD because of our a priori hypothesis that this demographic, a major risk for AD, may be associated with lesser brain parenchyma volume as compared to controls. We did not find a main effect of group on brain volume, nor were there differences on demographic or health variables. The group with family history of AD had a greater proportion of APOE e4 carriers; however, APOE status did not exert a significant effect on brain volume.

Reviewer 1: Was there any selection done on the basis of BMI?

Subjects with a BMI lesser than 18.5 kg/m² were excluded from the analysis for reasons described in the BMI Classification subsection of the Methods section (page 7 of the revised manuscript). In addition, subjects with extreme obesity (approximately anyone greater than 260 pounds) had to be excluded due to limitations of the bore size of the MRI scanner. These and other limitations of the study are described on page 12 of the revised manuscript (paragraph 6, lines 1-4 of the Discussion section).

Reviewer 1: While those with a family history of AD sample are demographically similar to those recruited from the community, was this similarity also observed for BMI? Also, was the AD group different from the community in terms of degree of atrophy?

An analysis examining differences between participants with and without a history of AD found a significant difference in education and frequency of APOE 4 genotypes, as mentioned on page 8 of paragraph 1 of the Results section. BMI was not significantly different between participants with and without a family history of AD.

Reviewer 1: Also, was the AD group different from the community in terms of degree of atrophy?
Page 9, paragraph 2, lines 9-11 of the Results indicates that only age and BMI significantly affect brain volume. Family history of AD was found to have no affect on global brain atrophy (significance summarized in Table 2).

Reviewer 1: While this is considered in the multivariate model, what were your criteria for including the covariates you did include?

The several independent variables included in the regression model (age, BMI, family history of AD, cholesterol, blood pressure, gender, education, APOE genotype), were selected a priori based on previous studies that have indicated these variables may affect brain volume and/or brain health.

Reviewer 1: The reference in the Conclusion is incorrect. The study on brain atrophy that was reported from the Swedish studies was found at mid- through later life consistently over a 24-year follow-up (not among 70-88 year olds). See Gustafson et al., Neurology, 2004;63:1876-1881.

Lines 2-4 of the Conclusions section should now accurately reflect the Gustafson et al study.

Reviewer 2

Reviewer 2: The authors should give a more detailed description of the major medical conditions used to exclude subjects from the study. Apart from diabetes, does that include hypertension and hyperlipidemia as well? Were all subjects normotensive and with normal lipid levels? If not, why exclude diabetes and keep hypertension and hyperlipidemia?

We have now added a more detailed description of the the major medical exclusions. Page 5, paragraph 2 in the Methods section, page 6, lines 5-8 of paragraph 2 in the Brain Imaging subsection, and the BMI Classification subsection of the Methods section (page 7) should give a more comprehensive description of the exclusion criteria.

In this cross-sectional study it was not our aim to recruit only extremely healthy individuals. To improve external validity we attempted to obtain a broad range of subject participants that would accurately reflect the population. Insulin dependent diabetes was an exclusion due to the small incidence rate found within our study population. This is discussed on page 12, paragraph 6 of the Discussion section. We did allow mild hypertension and hyperlipidemia in our study group, as these are generally more common in this age group and reflective of the population from which these subjects were drawn.
Reviewer 2: The sample seems to be highly selected (more than half of the persons had at least one biological parent diagnosed with AD, high ApoE4 frequency).

As touched on above, greater than one-half of the study group were selected to have a family history of AD because of our a priori hypothesis that this demographic, a major risk for AD may be associated with differentially greater brain atrophy or lesser brain parenchyma volume as compared to controls. It was hypothesized that family history of AD and APOE genotype would have the greatest effect (with the exception of age) on global brain volume. Therefore, it was our goal to obtain a demographically broad study sample in which approximately one-half of the subjects had a family history of AD. Importantly, we have found that BMI was a significant predictor of brain volume while family history and APOE status were not (in the present sample of middle aged adults). This finding is the major point of the paper.

Reviewer 2: Further, high BMI is often accompanied by diabetes and other features of metabolic syndrome, and thus, it may be very difficult to select a pure healthy high BMI study sample (such a group is very uncommon). Accordingly, the authors should discuss if it is possible to extrapolate the results and conclusions to the general population.

These results are generalizable to the general healthy population of this age demographic. The results are not generalizable to extreme obesity with other features of the metabolic syndrome since these factors were not included in this study.

To our knowledge there have not been any studies that have measured the effect of diabetes and/or extreme obesity on global brain volume. Additionally, size constraints of the MRI scanner did not permit the analysis of extreme obesity. The BMI range analyzed in our study (~19-40 kg/m²) indicated a linear relationship with global brain volume. However, it may be that at more extreme levels of obesity or underweight, the relationship to brain volume is nonlinear. The extent of generalizability of our results is now discussed in greater detail.

Reviewer 2: Methods A description of the measurement conditions for height, weight and blood pressure could be added.

Measurement conditions were added in lines 15-17 of paragraph 1 in the Methods section.

Reviewer 2: A more detailed description should be given for the neurovascular disease or structural abnormality used to exclude the persons from the study.

All scans were reviewed by a neuroradiologist for any abnormality that might be grounds for exclusion including any evidence of white matter ischemic disease or structural
abnormality. These exclusion criteria were added in lines 5-8 of paragraph 2 in the Brain Imaging subsection of the Methods section per this request.

Reviewer 2: The authors should specify the criteria used to define brain atrophy, considering the fact that the study sample is a sample of normal middle-aged subjects. Perhaps brain volume determination would be a more appropriate term. Could the variations in brain volume in this sample be within normal limits, given the very strict selection criteria? --- The authors should be more cautious in interpreting their data as indicative for a relationship between BMI and brain atrophy. There seems to be a relationship between BMI and brain volume (see point 4), but a cross-sectional study design does not allow assumptions regarding the rate of brain atrophy and BMI. As the authors mentioned, it would be very interesting to evaluate the effect of BMI on brain volume changes in a longitudinal study. Given the results, perhaps a more adequate title for this study would be The Effect of Body Mass Index on Brain Volume in Middle Aged Adults: a cross sectional study.

Our primary outcome variable was brain volume, and we had inferred that less volume was due to atrophy in these middle-aged adults. However, as the reviewer suggests, we cannot state that less volume is equivalent to atrophy. In light of this, we have taken the reviewer’s advice and now refer to reduced brain volume rather than atrophy. The term brain atrophy has been changed to brain volume in the manuscript title, lines 5, 11, and 12 of the Abstract, line 6 of the BMI Classification subsection and line 1 of paragraph 2 of the Statistical Analysis both of the Methods section, line 1 and line 1 paragraph 2 of the Discussion section, and line 1 of the Conclusions section. However, the term brain atrophy is still used in cases in which we attempt to suggest that the decrease in brain volume is due to brain atrophy. This association is based on previous longitudinal research that has indicated changes in brain volume based upon similar risk factors analyzed within our study (i.e. age, BMI, physical fitness).

Normalized brain volume (NBV) determination is defined in the Global Brain Volume Determination subsection of the Methods section. Based on the normalization methods of the brain parenchyma volume and the validity of the statistical model used to assess the correlation between BMI and NBV we feel that the variation in NBV is not within “normal limits”. The linear regression model incorporated for this analysis determined that BMI had a significant affect on brain volume even after covarying for age (see paragraph 1 of the Results section).

Reviewer 2: Education is an important factor that influences cognitive functioning; it should therefore be considered as an independent variable in the regression analysis. Also, it may not be surprising than there was no effect of the chosen independent variables on cognition (except for age), given the strict inclusion criteria (a ceiling effect cannot be excluded in this very normal middle-aged group of subjects).
Education has been added as an independent variable in the linear regression model for cognition. Education had no affect on cognition (paragraph 3 in the Results section). The reviewer may be correct in their comment regarding the possible ceiling affect of cognition within our study group. The study group is relatively young and is highly educated which may lower the variation in cognition between participants. However, the association we indicated between BMI and NBV and the research that has shown the negative effect various cardiovascular risk factors have on cognition puts BMI and other cardiovascular risk factors as potential risk factors of cognition, even for a younger, highly educated study group.

Reviewer 2: Additional data would be necessary in order to have an accurate description of the study sample (diastolic blood pressure, minimum and maximum values for BMI, cholesterol, blood pressure and neuropsychological data).

This additional data has been included in Tables 1 and 2. Minimum and maximum values for BMI have been included in lines 7-8 of the BMI Classification subsection of the Methods section.

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