Reviewer's report

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

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Reviewer: Miia Kivipelto

Reviewer's report:

General

This is an interesting manuscript, with some important strengths. Most notably, the availability of BMI and MRI data at mid-life likely represents the only valid way to explore the relationship between BMI and brain volume and cognitive change, given that BMI in later life is probably a marker of disease. A follow-up study would allow some very important observations.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Methods - selection of the sample
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?
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). 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.

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

3. Brain Imaging - A more detailed description should be given for the neurovascular disease or structural abnormality used to exclude the persons from the study.

4. Global Brain Atrophy Determination 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?

5. Statistical analysis 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).

6. Results 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).
7. Discussion and conclusions 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.

Statistical analysis: effect of BMI instead of affect of BMI; page 8, paragraph 2, line 2, the same; in Discussion, line 5: BMI affects brain atrophy instead of BMI effects brain atrophy; in Table 2 the same

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.