Author’s response to reviews

Title: Association of body mass index with amnestic and non-amnestic mild cognitive impairment risk in elderly

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Author’s response to reviews:

Dear editor

Thank you for your great effort! All questions have been carefully answered. We hope the revised article will be acceptable! Thank you very much!

Sincerely yours,

Wang Feng, Lei Ping

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Reviewer reports:

Kjeld Andersen, Ph.D. (Reviewer 1):

(1) The patients included are 240 patients with aMCI, 240 patients with naMCI, and 480 controls. The participants enrolled from a geriatric department (aMCI and naMCI) and from a department of medical examination (controls). It is stated that the participants were randomly selected but no information is provided about the procedure by which they actually were selected, thus pertaining to the generalisation of results, why not consecutive patients? How were the controls selected? By the way, no information is provided why the participants have been admitted, neither for the MCIs nor for the controls.

The selection method has been carefully revised. We hope it is clear now! In addition, MCI patients were consecutive patients, and controls were randomly selected. We are sorry for our poor English! (2.1 Subjects section)

(2) The authors then go "about 6 years back" to gather information at "baseline" collecting baseline data from medical records or medical examination reports. Thus, I assume a participant had to have "6-year-old" data available otherwise this participant was excluded, but this is not clear from the paper. No information is provided about the follow-up time (mean, standard deviation), and why a 6-year period of follow-up?

The selection method has been carefully revised. We hope it is clear now! (2.1 Subjects section)

This is a retrospective observational study. The follow-up period was 6 years for each MCI patient. (2.2 Data collection)

(3) The participants were examined by MMSE and MoCA, why both? The wording on page 8 (line 167-173) is unclear to me, does 20/24 point cut pertain to MMSE and 25/26 to MoCA or both to MMSE? The diagnosis of MCI was determined according to two psychologists (page 8, line 175-176), was that done both at baseline and admission? It is stated that subjects who had any types of cognitive disorder at baseline were excluded (page 8, line 161), thus were all participants examined by psychologists at baseline? I think this needs clarification.

MMSE and MoCA are common scales of cognitive function. They have different characteristics. MoCA is applied to detect single cognitive domain impairment, especially impaired memory. MMSE is applied to detect multiple cognitive domain impairment, especially disorientation and executive disability. Therefore, MMSE and MoCA can complement each other.
“20/24 point” pertain to MMSE and “25/26 point” pertain to MoCA. This mistake has been corrected.

Diagnostic procedure has been carefully revised. We hope it is clear now! (2.3 Diagnosis of mild cognitive impairment)

(4) Some information about BMI is also unclear to me. On page 9 (line 186-187) it is stated that the definition of increased BMI is > 4% per year (and decrease < 4% per year). Is that over the 6-year period of follow-up? And is it then 4%+4%+4%+4%+4%+4% = approx. 24% increase (decrease)?

Yes, something like that.

Average annual change rate of BMI was calculated using the formula:

\[(n=6, \ m_6 = \text{BMI of the 6th year, } m_0= \text{BMI on admission})\]

The 4% cut-off for BMI change has been defined as clinically important by several previous studies. For example:


(5) Further, analyses pertaining to this is presented in table 5. Decreased BMI for subjects with normal weight at baseline yielded an increased risk of 3.95. Is this then per 4% increase in BMI? A detail: the risk is calculated by logistic regression that provides an OR and not a RR. I also think that the authors may consider the numbers upon which the analyses are based. The multi-variate analyses include 8 variables and in some of the categories (cells) there is only one, two, three, four, and five subjects. Is the material strong enough for such elaborate model?

Yes, annual decreased rate of BMI > 4% in subjects with normal BMI at baseline showed an 295% increased risk of aMCI.

Yes, our statistical expert calculated OR using logistic regression. It was OR, not RR. This was a translation error. Our statistical expert did not participate in the translation and the final check. So, we failed to find this mistake. Now, the mistake has been corrected. We are so sorry for that.
The sample size of this study is not large. The number of the subjects with significantly changed BMI is even smaller. But we have tried our best to enlarge the sample size, and most of the subjects who met the Inclusion Criteria have been enrolled. In addition, this grouping mode was conducted according to the previous study. If we combine some groups, the results may cancel each other out and give us a negative conclusion.

Though a firmed conclusion cannot be drawn in the present study, the preliminary conclusion from this study may still helpful for future study.

(6) I think the discussion needs some revision. A baseline underweight was only related to an increased risk of aMCI but not naMCI. This is explained by weight loss may improve vascular disorders, but the sentence only state that cross-sectional baseline underweight is associated with increased risk not weight loss! (Page 12, line 254-256) Again, the numbers upon which this is stated are very small and with elaborated multivariate model with many variates in the model (table 4).

The article has been revised. Thank you! (Discussion section, Paragraph 2)

(7) On page 11-12, line 242-243, it is stated that aMCI and naMCI were more likely to develop several geriatric diseases. Does this means that this is incident geriatric disease during the follow-up? Or not, because on page 10, line 206 it is stated that aMCI and naMCI had more subjects with geriatric diseases? This pertains to the time aspect of this study, which I am unclear about. Is this a cross-sectional study or a follow-up study? Sometimes you get the impression of a cross-sectional study and sometimes an impression of a follow-up study. Therefore, it becomes unclear about the direction of "causality": does MCI affect the risk in changes in BMI or does BMI (changes in BMI) affect the risk of MCI? I am not fully convinced that "the direction of time" is fully accounted for.

This is a follow-up study. Baseline BMI and changes in BMI affect the risk of MCI. Our poor English cause these troubles. We are sorry for this. We have tried our best to improve the language in the article. We hope everything is clear now! (Discussion section, Paragraph 1)

(8) A revision of the language may also improve the paper, for example: "Subject who did not find any cognitive disorder was defined as "normal cognitive function" (page 8, line 173-174).

It has been revised. (2.3 Diagnosis of mild cognitive impairment, Paragraph 4)

The language in the article has been carefully revised. We hope it will be acceptable.
Minor points:

(9) Table 1: What is Han? (race?)

Yes, it is a race. It has been changed to “Han nationality” in Table 1.

(10) Page 6, line 115-115: "more than seven million people suffer from dementia annually all around the world". Is it incidence or prevalence, if the later I think the number is much higher than 7 mill.

The article has been revised. All around the world, dementia affected more than 45 million people in 2015. (1. Introduction, Paragraph 1)

Yong Xu (Reviewer 2):

1. This is a retrospective study that the baseline is defined as 6 years ago. How dose this baseline defined? Is there any common view on it? The authors should provide more details about the protocol.

Health data of the elderly had been collected for research since 2008. We did not have earlier data. So, the follow up period was 6 years. The details has been revised in the article. (2.1 Subjects)

2. Were the patients under some treatment? The possibility that the results may be related to treatment should be mentioned and, especially some medicine can have effect on the BMI. If possible, the author should do some analysis to exclude the effect of treatment as confounding variable?

Several drugs which may obviously affect BMI have been included in the study. (Table 1) The multivariable logistic regression analysis has adjusted by these confounding variables. (Table 4-5)

3. The statistical methods includes t-test, ANOVA, chi-square test and multivariable logistic regression analysis, and there are many comparisons among different level of weight and the subjects (naMCI, aMCI and controls). Has the author done multiple correction on the statistics? Pay attention to Table1-5.
Yes, our multivariable logistic regression analysis has adjusted by all confounding variables. The potential effect of these confounding variables on the conclusion has been avoided.

4. The level of education has definite effect on the cognitive function, so the author should describe this characteristics of the subjects in this study. If possible, the author should do some analysis to exclude the effect of education as confounding variable?

Education level has been showed in the Table 1. There was no difference in the education level among the three groups. So, education level was not much like a confounding variable.

5. The subjects enrolled 240 naMCI, 240 aMCI and 400 controls. How does the sample size calculate? What's the power of it?

The selection method has been carefully revised. (2.1 Subjects)

Actually, almost all subjects met the inclusion criteria were enrolled.

The numbers of naMCI patients and aMCI patients were the same. The numbers of three groups were integers. So, calculation and analysis were more convenience.

Sample size in the study was not large enough, and it may limit the power of test. However, we thought our study might still helpful for future research.

6. I suggest to tone down the significance of the claim and the comparison with the current methods: In particular, I think there are a few points that merit further discussion and possibly further input from the literature.

Sorry, our English was not very good. I did not fully understand the meaning of this comment. However, the Materials and Methods section, the Discussion section and the Conclusion have been revised carefully. We hope it will be acceptable.

Mohammadrasoul khalkhali, M.D. (Reviewer 3):

Introduction

(1) Line 120: Reference is needed.

A reference has been added. ([5] Dannhauser TM, Cleverley M, Whitfield TJ, Fletcher BC, Stevens T, Walker Z. A complex multimodal activity intervention to reduce the risk of dementia
in mild cognitive impairment—ThinkingFit: pilot and feasibility study for a randomized controlled trial. BMC Psychiatry. 2014;14:129.)

(2) Line 140-143: Consider rephrasing.
The text has been revised (1. Introduction, Paragraph 4)

Methods:

(3) How were the controls selected? How did you know that they had normal cognition? You have used MMSE for diagnosis of MCI and selecting the controls. MCI is a clinical diagnosis based on definite clinical evaluations. The cognitive function evaluation should be described better. What was finally the inclusion criteria? Clinical or by MMSE? What was the degree of clinical psychologist and their expertise? This part needs to be revised. More detailed information is needed. The study design is not detailed.
The text has been revised (2.1 Subjects; 2.3 Diagnosis of mild cognitive impairment)

(4) 201 -205: Delete these lines. They are easily accessible from the tables.
These lines have been deleted. (3. Results, Paragraph 1)

(5) 213: What was the difference between baseline and admission?
This was a retrospective observational study. “On admission” was defined as “January 1, 2014 and October 31, 2016”, and “at baseline” was defined as “about 6 years ago, between January 1, 2008 and October 31, 2010”.

(6) 207-218: Please rephrase the sentence. What was your reference for stable, increased or....BMI?
(7) 228-230: These sentences should be rephrased. The meaning is not clear.
The text has been revised. (3. Results)

(8) 242-244 have no meaning.
The text has been revised. (4. Discussion, Paragraph 1)

(9) 253-256: Better explanation according to references is needed.
The references have been added. (4. Discussion, Paragraph 2)

(10) 283-284: There was no information about this variable (APOE) in the methodology.
Genotyping was conducted in the subjects to determine apolipoprotein E4 (APOE4) carrier status on admission. (2.2 Data collection)

(11) The format of writing references should be changed.
The format of writing references has been revised.