

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Is a body mass index of less than 18.5 kg/m² associated with an increased susceptibility to mild cognitive impairment? A cross-sectional study conducted in China.

Authors

Li, Wei; Sun, Lin; Yue, Ling; Xiao, Shifu

VERSION 1 - REVIEW

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| Reviewer | 1 |
| Name | Ando, Takafumi |
| Affiliation | National Institute of Advanced Industrial Science and Technology |
| Date | 24-Jul-2023 |
| COI | No competing interests |

I think the entire document is well-organized and easy to understand.

I also believe that the description of the background is appropriate.

However, the following points, if not critical, are worth pondering.

Major comments:

1. Why did you not include MCI and dementia as cohort 2 in brain imaging analysis, as only cognitive normal was included, making the simultaneous interpretation of this cohort 1 and 2 difficult? More specifically, the results of cohort 2 can provide a reference but cannot support the results of cohort 1, can it? In that sense, you should report them in separate papers or report the results of cohort 2 with a little less significance.

2. I think it is necessary to include a more careful discussion of the fact that BMI was an independent factor of MCI but not considered an independent factor of dementia, unlike in the Cao et al. study. Various factors have been shown to be inherent in the relationship between BMI and cognitive function, but why, specifically, was there a relationship in Cao et al. but not in this study?

3. Also, in this relationship, in particular, previous studies have pointed out that the causal relationship may be reversed. Is there any possibility that this issue could explain the above? Please mention that as well.

Minor comments:

1. The p-values of the differences between the three groups for each variable in 4.1 are difficult to cross-reference, so please provide them in brackets or similar near the variable. Alternatively, you can write it as a summary ($P < 0.01$) since the information already exists in Table 1.

2. In some BMI units, the superscript for squared needs to be corrected.

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| Reviewer | 2 |
| Name | Gedik, Tugce Emiroglu |
| Affiliation | İstanbul Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, geriatric |
| Date | 27-Oct-2023 |
| COI | There is no competing interests |

Dear Author

Thank you for this article. It was a very understandable article. I recommend you make the following small improvements.

1) The keywords 'lipid disorders' on the BMJ Open cover page are not appropriate for this article. It is appropriate to write keywords in the summary section.

2) In the second paragraph of page 8, you should make explanations about OR in the statistics section.

2) The words 'Jiatong University' in section 7.1 on page 12 should be written in capital letters.

| | |
|--------------------|--|
| Reviewer | 3 |
| Name | Haroon, Muhammad |
| Affiliation | The University of Queensland, Faculty of Medicine |
| Date | 07-Nov-2023 |
| COI | No competing interests. |

This manuscript addresses a very important issue. Establishing a link between body-mass index and MCI is challenging due to the multitude of variables at play. The study design is well-suited to accomplish its objective.

The authors have adeptly presented the research's background and rationale, and the problem statements are very clear. This reviewer could not find any vague statements. The manuscript is very easy-to-read as well as easy-to-understand. Although at times it feels that some more of the previous studies on BMI and MCI could be cited, however, that might make the manuscript unnecessarily lengthy without adding any more value to the quality of the research.

No major research flaws were identified by this reviewer.

VERSION 1 - AUTHOR RESPONSE

Responses to the comments from the reviewer 1

Comment 1: Why did you not include MCI and dementia as cohort 2 in brain imaging analysis, as only cognitive normal was included, making the simultaneous interpretation of this cohort 1 and 2 difficult? More specifically, the results of cohort 2 can provide a reference but cannot support the results of cohort 1, can it? In that sense, you should report them in separate papers or report the results of cohort 2 with a little less significance.

Response: This is because we found no significant differences in BMI and target brain regions between age -, sex -, and education-matched adults with MCI and normal adults.

Supplementary table 1. Differences in BMI and MRI between MCI and normal elderly

| Variables | MCI (n=55) | Normal (n=62) | X ² or T | p |
|--|---------------|------------------|---------------------|-------|
| Age, years | 70.25 ± 8.59 | 69.89 ± 5.83 | 0.273 | 0.785 |
| Education, years | 8.88 ± 2.13 | 9.58 ± 2.46 | -1.574 | 0.118 |
| BMI, kg/m ² | 24.33 ± 3.29 | 24.54 ± 3.49 | -0.263 | 0.794 |
| Male, n(%) | 28(50.9) | 26(41.9) | 0.944 | 0.358 |
| Left hippocampus, cm ³ | 3.59 ± 0.43 | 3.52 ± 0.36 | 0.954 | 0.342 |
| Right hippocampus, cm ³ | 3.86 ± 0.44 | 3.72 ± 0.44 | 1.687 | 0.094 |
| Left amygdala, cm ³ | 1.51 ± 0.20 | 1.46 ± 0.21 | 1.239 | 0.218 |
| Right amygdala, cm ³ | 1.67 ± 0.24 | 1.62 ± 0.23 | 1.133 | 0.260 |
| Left thickness of paracentral lobule, cm ³ | 3.12 ± 0.36 | 3.18 ± 0.46 | -0.769 | 0.443 |
| Right thickness of paracentral lobule, cm ³ | 3.44 ± 0.52 | 3.52 ± 0.52 | -0.846 | 0.399 |

Comment 2: I think it is necessary to include a more careful discussion of the fact that BMI was an independent factor of MCI but not considered an independent factor of dementia, unlike in the Cao et al. study. Various factors have been shown to be inherent in the relationship between BMI and cognitive function, but why, specifically, was there a relationship in Cao et al. but not in this study?

Response: We will discuss our results further in the revised article.

Comment 3: Also, in this relationship, in particular, previous studies have pointed out that the causal relationship may be reversed. Is there any possibility that this issue could explain the above? Please mention that as well.

Response: In the revised article, we will further discuss the relationship between MCI and BMI.

Comment 4: 1. The p-values of the differences between the three groups for each variable in 4.1 are difficult to cross-reference, so please provide them in brackets or similar near the variable. Alternatively, you can write it as a summary ($P < 0.01$) since the information already exists in Table 1.

Response: We will make corresponding modifications according to the reviewer's comments.

Comment 5: In some BMI units, the superscript for squared needs to be corrected.

Response: In the revised article, we will correct inappropriate spelling.

Responses to the comments from the reviewer 2

Comment 1: The keywords 'lipid disorders' on the BMJ Open cover page are not appropriate for this article. It is appropriate to write keywords in the summary section.

Response: In the revised article, we will write keywords in the summary section.

Comment 2: In the second paragraph of page 8, you should make explanations about OR in the statistics section.

Response: In the revised article, we will make explanations about OR in the statistics section.

Comment 3: The words 'Jiatong University' in section 7.1 on page 12 should be written in capital letters.

Response: In the revised article, the words 'Jiatong University' in section 7.1 on page 12 will be written

in capital letters.

Responses to the comments from the reviewer 3

Comment 1: No major research flaws were identified by this reviewer.

Response: We thank the reviewers for their valuable comments

VERSION 2 - REVIEW

| | |
|--------------------|---|
| Reviewer | 1 |
| Name | Ando, Takafumi |
| Affiliation | National Institute of Advanced Industrial Science and Technology |
| Date | 17-Jan-2024 |
| COI | No competing interests for this paper. |

General comment:

In common with the following responses, please add the page number and line number of the section of text you have revised. We do not know where you have changed.

Comment to the response 1:

You provided data on MCI and cognitively normal, but from which dataset is this data? Please explain in detail. If it was from COHORT2, I still need to understand why you did not include the MCI brain data in this study. Also, if there is no change in brain structure between normal and MCI, is it necessary to include them in this study?

Comment to the response 2:

I comment without fully understanding what has been revised.

In the revised paper, on page 39, you mentioned the age difference, but why would the age difference explain the difference in the relationship between MCI and dementia? Since there is no description of the mechanism, we are unable to understand the present status in the article.

For example, it has been noted in prior papers that weight gain occurs when people get dementia. Perhaps some consideration of this is needed?

Comment to the response 3:

I comment without fully understanding what has been revised. I have yet to find any discussion of the previous study I pointed out that says the opposite about causality. Where can I find it?

VERSION 2 - AUTHOR RESPONSE

Responses to the comments from the reviewer 1

Comment 1: In common with the following responses, please add the page number and line number of the section of text you have revised. We do not know where you have changed.

Response: In the revised article, we will add the page number and line number of the section of text that we have revised.

Comment 2: You provided data on MCI and cognitively normal, but from which dataset is this data? Please explain in detail. If it was from COHORT2, I still need to understand why you did not include the MCI brain data in this study. Also, if there is no change in brain structure between normal and MCI, is it necessary to include them in this study?

Response: In the revised article, we will explain the data source in more detail. All data involving magnetic resonance were from cohort 2. The reason why MCI data were not included is that although there are many differences in MRI between MCI and normal elderly people, there is no correlation between MCI and BMI. Therefore, we did not include the above data. In contrast, we found a correlation between BMI and specific brain regions in cognitively normal older adults.

Responses to the comments from the reviewer 2

Comment 1: I comment without fully understanding what has been revised. In the revised paper, on page 9, you mentioned the age difference, but why would the age difference explain the difference in the relationship between MCI and dementia? Since there is no description of the mechanism, we are unable to understand the present status in the article. For example, it has been noted in prior papers that weight gain occurs when people get dementia. Perhaps some consideration of this is needed?

Response: In fact, in our subsequent analysis, we have controlled for differences in the samples themselves, such as age, gender and education, etc. As for whether BMI increases after dementia, this is exactly the conclusion we found, and the content of this part has been described in the discussion section.

Responses to the comments from the reviewer 3

Comment 1: I comment without fully understanding what has been revised. I have yet to find any discussion of the previous study I pointed out that says the opposite about causality. Where can I find it?

Response: We will mark the exact location of the revision in the revised article. It can be found on page 13, marked in light blue.

VERSION 3 - REVIEW

| | |
|--------------------|---|
| Reviewer | 1 |
| Name | Ando, Takafumi |
| Affiliation | National Institute of Advanced Industrial Science and Technology |
| Date | 14-Apr-2024 |
| COI | No competing interests |

In the manuscript, you concluded that MCI and BMI have an association using Cohort 1 data, but in your response letter, you mentioned that they are not associated for Cohort 2. Is my understanding correct?

If so, that would be essential data for the conclusion of this paper, but why would you leave out the data that says it is not relevant for cohort 2? I wonder why you would leave out the data that you claim is not relevant for cohort 2.

I am sorry to keep repeating this. It seems that the data showing that MCI and BMI are related is only possible because MCI is included in the data, and it would be a logical fallacy to use it as support data just because BMI and brain imaging are related in CN. If you can do this with data that includes MCI, then even more so.

Nothing more if there was a proper discussion.

In a minor point, the perinent in the abstract is missing a T.

VERSION 3 - AUTHOR RESPONSE

Responses to the comments from the reviewer 1

Comment 1: In the manuscript, you concluded that MCI and BMI have an association using Cohort 1 data, but in your response letter, you mentioned that they are not associated for

Cohort 2. Is my understanding correct? If so, that would be essential data for the conclusion of this paper, but why would you leave out the data that says it is not relevant for cohort 2? I wonder why you would leave out the data that you claim is not relevant for cohort 2. I am sorry to keep repeating this. It seems that the data showing that MCI and BMI are related is only possible because MCI is included in the data, and it would be a logical fallacy to use it as support data just because BMI and brain imaging are related in CN. If you can do this with data that includes MCI, then even more so.

Nothing more if there was a proper discussion.

Response: In the revised paper, we added the MCI data and matched it with the normal control. Meanwhile, we made new statistics and discussions, and the relevant content has been marked in red

Comment 2: In a minor point, the pertinent in the abstract is missing a T.

Response: In the revised article, we have corrected the wrong spelling.