



PEER-REVIEW REPORT

Name of journal: *World Journal of Psychiatry*

Manuscript NO: 89626

Title: Association between inflammatory bowel disease and all-cause dementia

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05232375

Position: Peer Reviewer

Academic degree: BSc, MSc, PhD

Professional title: Instructor, Lecturer, Postdoc, Research Associate

Reviewer's Country/Territory: United Kingdom

Author's Country/Territory: China

Manuscript submission date: 2023-11-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-11-09 23:27

Reviewer performed review: 2023-11-18 21:17

Review time: 8 Days and 21 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The study by Liao et al. investigates the relationship between Inflammatory Bowel Disease (IBD) and all-cause dementia using the two-sample Mendelian randomization method. The researchers utilized genetic variants from large genome-wide association studies for IBD and dementia. However, they found no evidence of a causal effect of IBD on dementia risk. This conclusion was consistent in validation analyses. Furthermore, reverse MR analysis also showed no effect of dementia on IBD. The study concludes that neither IBD nor its subentities are genetically associated with all-cause dementia or its subtypes. This suggests the need for further large prospective studies to determine whether intestinal inflammation affects dementia. Your manuscript could benefit from a more detailed flowchart in Figure 1. It would be helpful to provide more information on the processing of the Genome-Wide Association Study (GWAS) from all the databases and other tests such as the Pleiotropy test and heterogeneity test as well as the two-sample Mendelian randomisation method. A clearer flowchart would significantly improve the reader’s comprehension of your methodology. Additionally, a detailed figure legend for Figure 1 would be beneficial. It is also required to have the research



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code accessible as the requirement of open science. This is also crucial for understanding the methods and reproducing the results, thereby enhancing the transparency and reproducibility of your study. That would be good if the flow of the code would be the same as the Figure 1 flowchart. In Figure 2 and Figure 3, the overall summarised Odd Ratios seem to be missing for each of the forest plots. That would also be good if the discussion indicate the data from this study that would be good to give an indicator “(Figure X)” linking to the corresponding figure information, that would let readers easy to follow.



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Reviewer's code: 01587889

Position: Editorial Board

Academic degree: MD, MSc, PhD

Professional title: Academic Editor, Consultant Physician-Scientist, Professor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-11-10 13:53

Reviewer performed review: 2023-11-19 00:52

Review time: 8 Days and 10 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I reviewed this study with keen interest. There has been reported evidence supporting a connection between IBD and the development of Parkinson's disease. One meta-analysis of nine observational studies (PMID: 34269209) comprising over 12 million patients demonstrated an interesting bidirectional relationship between Parkinson's disease and IBD, where IBD as a risk factor was associated with 25–30% increase in Parkinson's disease risk and as an outcome was 40% more likely to develop among Parkinson's disease patients. Herein reported, Oulan Liao et al. indicate that IBD and subentities could be genetically associated with neither all-cause dementia nor its subtypes. Quoting Zhang et al (PMID: 35325272), who showed that IBD was associated with an increased risk of dementia, specifically Alzheimer's disease. Guo et al (PMID: 34750207) designed a Mendelian randomisation (MR) study to avoid potential confounding in observational studies, and demonstrated a genetically protective effect of IBD on AD, which is not in agreement with Zhang et al. Some concerns in their MR study should therefore be mentioned such as (i) the AD datasets from Kunkle et al (PMID: 26365416) that include older clinically diagnosed patients and selection bias may be caused by selective survival



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from IBD and the competing risk of AD. That is, reduced life expectancy in patients with IBD may be accelerated by the presence of cardiovascular disease. Participants with IBD and dead from cardiovascular disease are not included into the AD genome-wide association study (GWAS), thus diminishing or reversing MR estimates for harmful exposures (ii) Guo et al. used univariable MR to estimate causal roles of Ulcerative colitis (UC) and Crohn's disease (CD) in AD, which may lead to horizontal pleiotropy due to a high degree of instrumental variable overlap between them. Agreeably, per Oulan Liao and colleagues' conclusion further large prospective studies are required to elucidate whether intestinal inflammation affects the development of dementia. More randomized controlled trials are needed to confirm the precise association between IBD and AD. I find this study informative with controversial reporting from previous observational studies and of educational values in IBD.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Academic degree: BSc, MSc, PhD

Professional title: Instructor, Lecturer, Postdoc, Research Associate

Reviewer's Country/Territory: United Kingdom

Author's Country/Territory: China

Manuscript submission date: 2023-11-07

Reviewer chosen by: Xin-Liang Qu

Reviewer accepted review: 2023-12-05 13:01

Reviewer performed review: 2023-12-05 14:47

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



SPECIFIC COMMENTS TO AUTHORS

The manuscript needs more information to ensure reproducibility of the work. The authors should provide the full R scripts, the data sources, the functions and commands explanations, and the supplementary figures scripts for all the figures and tables. The authors should also document and share their data publicly, and include a statement of code availability and the date of data download. Revision Suggestions:

- Provide full R scripts: The manuscript only contains partial R scripts for Figure 1 and 2. The full scripts for the whole study are needed to reproduce the work. Please provide the complete R scripts for all the figures and tables in the manuscript, and explain how to run them.
- Provide data sources: The manuscript does not mention how and where the data were collected. For example, the sources of these datasets: “finngen_R7_F5_DEMENTIA.gz”, “finngen_R7_F5_ALZHDEMENT.gz”, “finngen_R7_F5_VASCDEM.gz”, “finngen_R7_F5_DEMINOTH.gz”, “finngen_R7_F5_DEMNAS.gz” from part 1, and the outcome from part 2 “harmonise_data.csv” are not specified. Please provide the URLs and/or references for these datasets, and explain how they were obtained and processed.
- Explain functions and commands: The functions and commands used in the scripts are not explained. For example, the reasons for using certain functions or commands such as read.table, merge, write.table, etc. are not clear. Please provide comments or notes in the scripts to explain the functions and commands, and their corresponding URLs if applicable.
- Provide supplementary figures scripts: You have generated a list of supplementary figures. Please provide all the scripts used to generate these figures, and explain how they relate to the main figures and tables.
- Document and share data publicly: All the data used or collected for your study should be well documented and open to the public. You may consider using a free service such as <https://osf.io/> and/or deposit on GitHub. Please



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provide the links to your data repositories in the manuscript. • Include statement of code availability: The manuscript does not include a statement of code availability. Please add a section to state whether the code used for your study is available, and where it can be accessed. • Include date of data download: The manuscript does not include the date of data download from the databases. Please specify the date of data download for each database, as they may update their data regularly. • Explain MR-PRESSO analysis: The manuscript does not explain how you performed MR-PRESSO analysis. Please provide the details of the MR-PRESSO analysis, such as the input data, the parameters, the output, and the interpretation. The key is to provide enough information for other researchers to replicate your work for ALL the figures and tables, including the corresponding information. The current information provided from the authors does not meet this requirement. Please consider these suggestions for your revision.