Round 1

Response to reviewers and editorial office

Dear editor and reviewers,

Thank you for giving us this opportunity to improve the quality of our manuscript (Manuscript NO.: 89626, Clinical and Translational Research). We appreciated very much the reviewers' constructive and insightful comments. We have revised the manuscript in which major changes are highlighted in yellow. These changes are summarized below, following a point-by-point response to the reviewer's comments.

Reviewer 1#

Point 1: 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 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.

Response 1: Thank you for your advice and support. We were inspired by the your analysis of some concerns in Guo et al.'s MR study. Therefore, we have mentioned these points in the discussion of our manuscript, which helps to improve the depth of the discussion and enrich the content of the manuscript.

Reviewer 2#

Point 1: 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.

Response 1: Thanks for your advice. Based on the actual MR analysis process, we have created a more detailed flowchart with a legend that explains and illustrates the contents of Figure 1 in detail.

Point 2: It is also required to have the research 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.

Response 2: Thanks for your advice. We have documented the MR analysis code in MS word, which is consistent with Figure 1 flowchart. This document will be submitted as supplementary material.

Point 3: In Figure 2 and Figure 3, the overall summarised Odd Ratios seem to be missing for each of the forest plots.

Response 3: Thanks for your advice. What is depicted in Figure 2 are the inverse variance weighted estimates of inflammatory bowel disease, ulcerative colitis, and Crohn's disease on all-cause dementia and its four main subtypes, which are the overall summarized odd ratios computed from the individual instrumental variables (refer to the forest plots in Supplementary Figure S1-15). That is, the odd ratios presented in Figure 2 are already the final summarized odd ratios, with the first odd ratios in each forest plot being the inverse variance weighted estimates of inflammatory bowel disease, ulcerative colitis, and Crohn's disease on all-cause dementia, and the second to fifth odd ratios being the inverse variance weighted estimates of inflammatory bowel disease, ulcerative colon disease, and Crohn's disease on the four subtypes of dementia. Similarly, Figure 3 depicts the inverse variance weighted estimates of inflammatory bowel disease (validation) on dementia. We very much apologize for the lack of clarity in Figure 2 and Figure 3, and for this reason we have provided further explanations in their legends.

Point 4: 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.

Response 4: Thanks for your advice. We have provided indicators accordingly in the discussion of our manuscript.

Editorial Office's comments and suggestions

Point 1: The quality of the English language of the manuscript does not meet the requirements of the journal.

Response 1: Thanks for your advice. We have invited a professional language polishing agency to improve the language quality of the full text with language certificate.

Point 2: Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response 2: Thanks for your advice. We have prepared and arranged the figures using PowerPoint.

Point 3: Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

Response 3: Thanks for your advice. We confirm that all figures are original and have add the copyright information.

Point 4: Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response 4: Thanks for your advice. We have confirmed that the table conform to the editing specifications.

Point 5: When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

Response 5: Thanks for your advice. We again searched the literature related to this study through the PubMed website and there are no recent findings to add.

Round 2

Response to reviewers

Dear editor and reviewers,

Thank you for giving us this opportunity to improve the quality of our manuscript (Manuscript NO.: 89626, Clinical and Translational Research). We appreciated very much the reviewers' constructive and insightful comments. We have revised the manuscript in which major changes are highlighted in yellow. These changes are summarized below, following a point-by-point response to the reviewer's comments.

Reviewer 1#

Point 1: 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.

Response 1: Thanks for your advice. We will respond to each of your revision suggestions in points 2 to 9.

Point 2: 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.

Response 2: Thanks for your advice. In our Mendelian randomization study, the exposure was inflammatory bowel disease and its two subtypes, and the outcome was all-cause dementia and its four subtypes. Thus, there are a total of 15 Mendelian randomization analyses in the main analysis. In addition, we performed one validation cohort analysis (a total of five Mendelian randomization analyses) and one reverse analysis. In fact, we have provided all commands in original R-code statement. However, we did not explain how to run them repeatedly for multiple Mendelian randomization analyses. To ensure reproducibility of the study, we rewrote the R scripts and added comments to the code runs. Table 1 is the details of the genome-wide association studies included in the Mendelian randomization, which does not need R scripts. The inverse variance weighted estimates of inflammatory bowel disease (both primary and validation analyses) for all-cause dementia and its four main subtypes are shown in Figures 3 and 4, and the flowchart (Figure 2) contains the inverse variance weighted estimates. As for the supplementary material scripts, we reply to you in the point 5.

Point 3: 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.

Response 3: Thanks for your advice. The sources of all genome-wide association study summary data in this study are described in the Methods of the manuscript and in the data sharing statement of the footnotes. These five datasets (finngen_R7_F5_DEMENTIA.gz, finngen_R7_F5_ALZHDEMENT.gz, finngen_R7_ F5_VASCDEM.gz, finngen_R7_F5_DEMINOTH.gz, and finngen_R7_F5_DEMNAS.gz) were from the FinnGen study (https://www.finngen.fi/en), and we read them through the function “fread” without any processing. We harmonised the alleles and effects between the exposure and outcome through the harmonise_data function, then saved them after naming them harmonise_data.csv. Therefore, the "harmonise_data.csv" in Part 2 is the result of the harmonising single nucleotide polymorphisms. We sincerely apologize for not explaining these datasets in the R scripts, which has created a barrier to understanding for you and other readers. To address this issue, we have included explanations of how the datasets were obtained and processed in the comments of the R scripts.

Point 4: 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.

Response 4: Thanks for your advice. We have provided notes in the R scripts to explain the functions and commands.

Point 5: 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.

Response 5: Thanks for your advice. We have provided scripts for generating supplementary figures in the original R-code statement, including “mr_scatter_plot”, “mr_forest_plot”, and “mr_leaveoneout_plot”. And we have explained in detail how they related to the main figures and tables in their legends.

Point 6: 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 provide the links to your data repositories in the manuscript.

Response 6: Thanks for your advice. All data used in this study are publicly available. So, we have not uploaded this data to GitHub for deposit. The links to access the data are listed in the data sharing statement.

Point 7: 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.

Response 7: Thanks for your advice. We have added a section of the code availability statement to the manuscript that describes the availability and accessibility of the code used in this study.

Point 8: 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.

Response 8: Thanks for your advice. We have provided the date of data download in the data sharing statement.

Point 9: 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.

Response 9: Thanks for your advice. We have provided a detailed description of the MR-PRESSO analysis in the Methods section of the manuscript, which includes information on input data, parameter settings, and interpretation of the output.

Point 10: 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.

Response 10: Thanks for your advice. We have taken your suggestion seriously to provide the information necessary to ensure the reproducibility of this study.