

Point-by-point response for Manuscript ID: 88755

Title: Causal associations between inflammatory bowel disease and anxiety: A bidirectional Mendelian randomization study

Thank you so much for reviewing our original manuscript and providing constructive comments. We have now addressed all concerns and revised the manuscript. The point-by-point response is provided below. The revised manuscript with trackable changes in yellow color has been up-loaded as a Supplementary file in the online submission system.

Reviewer #1:

I find the manuscript well written. The abstract summarizes and reflects the work described in the manuscript appropriately. The key words reflect the focus of the manuscript appropriated. The manuscript describes the background and presents status and significance of the study adequately. The authors describe methods well. The manuscript interprets the findings adequately and appropriately, and the findings and their relevance to the literature stated are written in a clear manner. The manuscript meets the requirements of biostatistics. The manuscript meets the requirements of use of SI units. The manuscript appropriately cites the latest, important, and authoritative references in the Introduction and Discussion sections. I would just suggest that authors standardize how to cite scientific journals. I noticed that some are in capital letters and others are in normal letters.

Reply: Thanks for your review and comments. We have corrected the references as required by *World Journal of Gastroenterology*.

Reviewer #2

I truly congratulate the study team for writing such a good manuscript, for their idea and design. The manuscript is the first of its kind. Results are of crucial importance for our practice, in order to benefit our patients. All paragraphs

contain the necessary data. The manuscript is well-written, with attention to details. I just have some minor comments:

1. Abstract: please mention the population included – adults, children or both. Same in the whole manuscript (databases).

Reply: Thanks for your review and comments. All the population in the GWAS statistics used in this study are adults. The population information has been added in the Abstract section and the whole manuscript. In addition, the number of sample size was added in the Abstract.

2. Discussion: Please remove the studies that you already inserted in Introduction. This paragraph is otherwise nicely conceived. Strengths and limitations are also included. Maybe some proper directions for future research could be included, it would be very interesting. References that could be added in Discussion: *Cooney R, et al. Inflamm Bowel Dis 2023 Aug. Children and Young Adults With IBD Have an Increased Incidence and Risk of Developing Mental Health Conditions: A UK Population-Based Cohort Study * Arp L, et al. JCC 2022 dec. Psychiatric Disorders in Adult and Paediatric Patients With IBD - A Systematic Review and Meta-Analysis.

Reply: Good suggestions. The studies cited in the Introduction have been removed from the Discussion. Some proper directions for future research has been added in the end of Discussion. Such as: Although this study investigated the causal relationship between IBD and anxiety, the precise biological mechanisms by which UC affects the anxiety remain unclear, such as whether and how the gut-brain axis plays a role in this process. Hence, more basic and clinical studies are needed for the identification of key regulators and pathways. In addition, the two related references have been added in the second paragraph of Discussion as follows: “A recent meta-analysis showed that the pooled prevalence of anxiety in IBD patients was 12% (95% CI, 8%-18%)^[26]. Another population-based cohort study in the United Kingdom demonstrated that young IBD patients had a significantly higher incidence and risk of anxiety (adjusted hazard ratio, 1.25; 95% CI, 1.06-1.48)^[27]”

3. Unfortunately, Supplementary Tables 1-5 were not available for the reviewer, while they would have been very useful.

Reply: So sorry for this mistake. Supplementary Tables 1-5 have now been added in the online submission system.

4. Core Tip is not included in the manuscript. Please add.

Reply: Thanks for your suggestion. Core tip has been added in the manuscript, following the Abstract.

5. The certificate for non-native English speakers is missing. Please add.

Reply: The certificate for non-native English speakers has been added.

6. Authors' ORCID Numbers are missing. Please add.

Reply: Authors' ORCID Numbers have been added in the end of the manuscript.

7. The format of the manuscript is not the one requested by the WJG, including references. Please correct.

Reply: Good suggestion. The format of the manuscript, including references, has been corrected as required by *World Journal of Gastroenterology*.

Once again, we thank the reviewers and editors for reviewing our manuscript and providing comments. We hope that our responses and revised manuscript are adequate for addressing all concerns raised by the reviewers and editors. In addition, we have also polished the language of the manuscript by the editing service to improve the readability. There is anything else we need to do to further improve the manuscript, please feel free to let us know.

Sincerely,

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