

Peer Review File

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Reviewer A

The is a well written study with special emphasis on the genetic risk of lung cancer in GERD patients. Truly worthy of a publication.

Reply: Thank you very much for your positive feedback and recognition of our work. We are pleased that you found our study on the genetic risk of lung cancer in GERD patients worthy of publication. Thank you very much!

Reviewer B

Below is a list of my comments. I provided the line number, section, and the paragraph number. I also occasionally stated the subheading for some comments.

1. Line 67, introduction, paragraph 1- “its” is a bit confusing. Are you talking about GERD, lung cancer, or non-esophageal cancer? Reword the sentence.

Reply 1: Thank you for your detailed feedback. We have addressed the ambiguity in the sentence you mentioned. The revised sentence now reads: “Lung cancer (LC), as one of the most prevalent malignancies, remains the leading cause in both incidence rate and mortality worldwide.” (Line 84) We hope this revision resolves the confusion.

2. Line 76-78, introduction, paragraph 1- provide an example/elaborate on how “conventional epidemiological studies were susceptible to confounding factors, potential bias, or reverse causality due to the observational nature.”

Reply 2: Thank you for your comment. The limitations of conventional epidemiological studies, such as susceptibility to confounding factors, potential bias, and reverse causality, are indeed well-recognized. Unlike randomized controlled trials (RCTs), observational studies cannot randomize participants to control for all potential confounders, nor can they establish causal relationships due to the lack of temporal sequence between exposure and outcome. Mendelian randomization, on the other hand, leverages genetic variants to mitigate these issues, making it a valuable tool for causal inference. Due to these widely acknowledged limitations of conventional epidemiological studies, we did not elaborate further in the manuscript. However, we have added relevant references to support these points. We appreciate your understanding and attention to this matter.

3. Line 96-98, introduction, paragraph 4- the way the sentence is structured suggests that you should capitalize “genome-wide cross-trait analysis”. Either capitalize or reword the sentence.

Reply 3: Thank you for your feedback. We would like to clarify that "genome-wide cross-trait analysis" refers to a general method used in GWAS to study the shared genetic architecture of diseases. Based on our review of recent literature on this research method^{1,2}, we found that it is commonly written in lowercase. Thus, we have opted to maintain the lowercase format.

Reference:

1. Wu X, Xiao C, Han Z, Zhang L, Zhao X, Hao Y, et al. Investigating the shared genetic architecture of uterine leiomyoma and breast cancer: A genome-wide cross-trait analysis. *Am J Hum Genet.* 2022;109(7):1272-85.
2. Wu X, Zhang W, Zhao X, Zhang L, Xu M, Hao Y, et al. Investigating the relationship between depression and breast cancer: observational and genetic analyses. *BMC Med.* 2023;21(1):170.

4. Line 117, methods, third paragraph- mckay et al. is not capitalized.

Reply 4: Thank you for pointing this out. We have revised the manuscript to capitalize "McKay et al." as per your suggestion (Line 133).

5. Line 133, methods, paragraph under subheading “genome-wide genetic correlation analysis”- “Z-sores” is misspelled.

Reply 5: Thank you for catching that error. We have corrected the misspelling of "Z-sores" in the manuscript (Line 149).

6. Line 169, methods, first paragraph under subheading “cross-trait meta-analysis”- CPASSOC has two methods/estimates - Why did you decide to choose the S_{Het} method and not the S_{Hom} method? The justification is a bit unclear and needs further explanation.

Reply 6: Thank you for your question. We chose the S_{Het} method because it is more robust in handling heterogeneity compared to the S_{Hom} method. This allows for a more accurate correction for potential heterogeneity and ensures more reliable results. The revised sentence now reads: "For this analysis, we adopted the S_{Het} method to correct for potential heterogeneity and ensure more robust results." (Line 184-186) We hope this explanation clarifies our choice.

7. Line 189, methods, first paragraph under subheading “fine-mapping credible set analysis”- I recommend justifying or providing references on why you chose to extract variants within 500 kb. For example, this paper (<https://www.publi>

chealth.pitt.edu/Portals/0/HUGEN/journal%20club/ng.3094.pdf) also extracted variants within 500 kb.

Reply 7: Thank you for your suggestion. The 500 kb range is commonly used in GWAS studies for extracting variants. We have added relevant references to the manuscript to support this approach (Line 207). We hope this addresses your concern.

8. Line 388, discussion, paragraph 5 - start with a transition like “additionally” to make the paper flow more smoothly.

Reply 8: Thank you for your valuable suggestion. We have revised the sentence in line 388 to start with the transition word “additionally” to improve the flow of the paper (Line 403). We appreciate your feedback.

9. Line 433, discussion, paragraph 8 - the sentence “Thirdly, while we mapped identified...” has an extra verb. Either remove “mapped” or “identified”.

Reply 9: Thank you for pointing that out. We have revised the sentence in line 433 by removing the word “identified” to eliminate the extra verb (Line 449). We appreciate your feedback.

10. Overall, this paper was an interesting read. The "multi-level" aspect of the method was intriguing, and the overall objective of this paper is unique. The results were clear, significant, and provide a novel perspective on the association between GERD and LC. As long as the above comments are addressed, I believe that this is a paper worth publishing. Also, I highly recommend putting your manuscript through a grammar checker, as I may not have caught all the grammatical errors. I look forward to your future work!

Reply 10: Thank you for your positive feedback and support. We are pleased to hear that you found the multi-level aspect of our method intriguing and that our results provide a novel perspective on the association between GERD and lung cancer. We have thoroughly rechecked the manuscript for grammar and clarity to ensure it meets high standards. Thank you again for your valuable suggestions.