

Dear Editor-in-Chief:

RE: “Causal associations between gastroesophageal reflux disease and essential hypertension: A bidirectional mendelian randomization study”

Ning Wei, Minghui Liu, Yuhu Song

Thank you very much for giving us an opportunity to revise our manuscript. These comments by the reviewers provided extremely useful opinions in rewriting this paper. The revisions are based on the reviewers' comments and here we respond to them point by point. We hope that these changes now make this paper acceptable and appropriate for publication. The changes are in yellow in the text, in the revised manuscript and tables to avoid any confusion.

Thank you for your attention and kind reply to our manuscript.

Sincerely,

Yours sincerely,

Yuhu Song

Division of Gastroenterology

Union Hospital, Tongji Medical College,

Huazhong University of Science and Technology

Reviewers' comments:

Reviewer #1:

Specific Comments to Authors: This manuscript describes a highly sophisticated method to find a correlation between GERD and hypertension. The method itself cannot be evaluated me, because I'm not familiar with these methods. However, I assume that the analysis has been performed right. From the point of view of a gastroenterologist and clinician, I have some remarks:

In the abstract, the authors use abbreviations which are less understandable, SNP, MR-Egger, IVW. How can this be avoided?

Thank you for your suggestion. We have added the full names where they first appeared.

In the text: The authors use "incidence". Instead it is prevalence

Thank you for your suggestion, and we have revised it.

Is this hypertension, as the authors demonstrate, "essential" hypertension or secondary hypertension? Essential hypertension means that no underlying cause can be found. However, as shown in this paper, there is a cause for hypertension, even if the relation is only a statistical relation. The physiological explanations of the relation are rather hypothetical. However, several studies often start with hypotheses.

It is essential hypertension in our study.

Essential hypertension is indeed a kind of hypertension in which no clear cause was found **up to now**. But with the advancement of medicine, more and more essential hypertension would be classified as secondary hypertension because a clear cause has been found.

Essential hypertension still has associated pathogenesis, such as arterial stiffness, water-sodium retention and salt-sensitive, as well as renin-angiotensin-aldosterone system[1].

As described in our penultimate paragraph, gastroesophageal reflux may increase the risk of essential hypertension by activating pathways on these mechanisms. As you said, "The physiological explanations of the relation are rather hypothetical. However, several studies often start with hypotheses". Further research is needed to further clarify the specific mechanism of the relationship between gastroesophageal reflux and essential hypertension.

1. Ma J, Chen X: **Advances in pathogenesis and treatment of essential hypertension**. *Front Cardiovasc Med* 2022, **9**:1003852.

Reviewer #2:

Specific Comments to Authors: The authors of the article proposed an interesting work design. The MR-Egger intercept test, Cochran's Q test and "leave-one-out" sensitivity analysis were performed to evaluate the horizontal pleiotropy, heterogeneities, and stability of single instrumental variable. Bidirectional mendelian randomization study found that GERD was positively associated with the risk of essential hypertension, suggesting a new prevent strategy and therapeutic perspectives of essential hypertension in patients with GERD.

Thank you for your review!

Editorial Office's comments:

Thank you for pointing out the important point. We have modified our manuscript including figures and tables.