

Reply to author: “uric acid’s influence on venous thromboembolism in East Asia”

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We appreciate the insightful comments and commendations expressed by Lixian Ji and Peng Shu regarding our study titled “Association between uric acid and risk of venous thromboembolism in East Asian populations: a cohort and Mendelian randomization study”.¹ Their supportive remarks have both encouraged our team and reaffirmed the importance of our research within the broader scientific discourse.² We would like to address the specific points raised by Lixian Ji and Peng Shu as follows:

- 1. Regarding the PE and VTE distinction:** We acknowledge this oversight in our study and agree that it is crucial to specify that our study primarily focused on pulmonary embolism (PE) or PE with deep vein thrombosis (DVT).^{3,4} By providing this clarification, we can prevent potential misconceptions and ensure that the implications of our findings are appropriately understood within the relevant context.
- 2. On the instrumental variable clumping process:** It should be noted that similar to GWAS studies, there is currently no standardized criterion for determining the appropriate clumping thresholds in Mendelian randomization (MR) research. The selection of thresholds is contingent upon the specific circumstances of the study. In our study, we employed slightly relaxed thresholds to retain a greater number of instrumental variables (IVs), thereby enhancing the statistical power of our study. Notably, previous studies have demonstrated that incorporating multiple weakly correlated variants as IVs can explain a larger proportion of the variance

in the risk factor, thereby strengthening the statistical power of the MR analysis.^{5,6} However, it is essential to acknowledge the potential consequences of weak linkage disequilibrium (LD), as the IVs utilized in the analysis, which are associated with the causal variant, may influence other confounding factors. That would lead to violations of the second or third IV assumptions, akin to pleiotropy-induced violations. To address this concern, we employed multivariate MR analysis and conducted tests for pleiotropy to reduce bias. Moreover, we performed a leave-one-out analysis, which demonstrated that the exclusion of any individual IV did not significantly impact our results.

- 3. Incorporation of smoking history as a covariate:** We appreciate the suggestion and concur that smoking history might indeed be a significant confounder.⁷ Due to limitations in the available data, we were unable to include smoking as a covariate in our analysis. Nonetheless, we acknowledge its potential impact and intend to consider it in future investigations and analyses.

In light of the constructive feedback provided, we are committed to further exploring these areas and providing more comprehensive data in our subsequent publications. Collaborative discussions, such as this, not only enhance the quality and rigor of scientific research but also contribute to a more holistic understanding of complex medical phenomena. We eagerly anticipate future collaborations and discussions with peers in the field. Together, as we continually refine our



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methodologies and share insights, we strive towards a deeper comprehension of venous thromboembolism and its association with serum uric acid levels, ultimately benefiting populations worldwide.

Contributors

Haobo Li, Zhu Zhang, and Haoyi Weng wrote the reply. Wanmu Xie, Peiran Yang, Zhenguo Zhai, and Chen Wang reviewed and edited the reply.

Declaration of interests

The authors have no relevant conflicts of interest to declare.

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