

# Letter to the editor: “uric acid’s influence on venous thromboembolism in East Asia”

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To the Editor:

We read with interest the study “Association between uric acid and risk of venous thromboembolism in East Asian populations: a cohort and Mendelian randomization study” by Weng H et al.<sup>1</sup> The authors’ diligent investigation into the association between serum uric acid (SUA) levels and venous thromboembolism (VTE) in East Asian populations has yielded noteworthy findings that hold potential implications for VTE prevention and management. We express our support and commendation for the authors’ valuable contribution.

The association between SUA levels and the risk of VTE has been subject to inconclusive findings. In an effort to address this gap in knowledge, the authors conducted an extensive investigation employing both a large cohort analysis and a two-sample Mendelian randomization (MR) study in East Asian populations. The results of the study revealed a significant positive correlation and indicated a potential causal link between SUA levels and the risk of VTE. It is noteworthy that a recent MR study based on a European population, conducted by our team, yielded null genetically causal correlations between SUA levels and VTE risk.<sup>2</sup> This discrepancy in findings might be attributed to the population stratification, as previous studies have observed the different prevalence and genetic architecture of VTE in European and East Asian populations.<sup>3,4</sup>

We commend the authors for employing a propensity-matched analysis statistical model in their cohort study, which effectively minimizes the influence of potential confounding factors. Additionally, the use of a cubic-spline model to establish the relationship between exposure and outcome further enhances the credibility of the observational conclusions drawn. The MR approach adopted by the authors, as a form of natural randomized controlled trial, significantly reduces confounding factor interference and mitigates concerns related to reverse causation. The authors’ judicious choice to utilize both univariate and multivariate MR methods to investigate the causal relationship is noteworthy. However, there are several salient issues that warrant consideration. Firstly, it should be clarified that in the authors’ MR study, the outcome variable was

specifically “pulmonary embolism (PE),” whereas VTE encompasses both deep vein thrombosis (DVT) and PE. This omission of information in the original article may potentially lead to misinterpretation by readers.

Secondly, the authors employed a wider threshold for the instrumental variable clumping process ( $R^2 < 0.2$ , window size = 500 kb), which differs from the threshold commonly used in conventional MR studies ( $R^2 < 0.001$  or 0.01, window size = 10,000 kb). While this decision has certainly improved the statistical power of the study, with reported values of 92.5% for BBJ-UA and 80.4% for META-UA, it is crucial to acknowledge that it may introduce some degree of bias. Therefore, it would be prudent to discuss the implications of this methodological choice in the limitations section and acknowledge its potential impact on the results.

Lastly, while the authors addressed the limitation of the cohort study in the discussion section by recognizing that it could not account for the confounding effects of smoking history and alcohol consumption, we concur that smoking history might indeed be a significant confounder in the study. The omission of smoking as a covariate may have led to potential misdirection of the association observed. We posit that the authors’ article conclusions could potentially have garnered heightened conviction had they opted to incorporate smoking history as a covariate within the framework of the multivariate MR analysis.

In summary, this article’s findings have provided valuable insights into the association between SUA levels and VTE risk in East Asian populations. Addressing the mentioned issues and considering the suggestions provided will enhance the study’s rigor and quality, facilitating a more comprehensive and accurate understanding of the research. Furthermore, future investigations utilizing larger GWAS datasets will continue to shed light on this complex relationship, ultimately advancing our knowledge of VTE prevention and management in East Asian populations.

Yours sincerely.

## Contributors

LX.J: Conceptualisation, Writing—Original Draft Preparation; P.S: Conceptualisation, Writing—Review & Editing, Supervision.

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Not applicable.

**Declaration of interests**

The authors declare that they have no conflict of interest regarding the publication of this letter to the editor.

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