Association between uric acid and risk of venous thromboembolism in East Asian populations: a cohort and Mendelian randomization study

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Summary

Background Serum uric acid (SUA) levels have been associated with an increased risk and recurrence of venous thromboembolism (VTE) in European populations, but the potential causal relationship remains unclear. Large-scale studies on the association between SUA and VTE in East Asian populations are lacking, despite the high prevalence of hyperuricemia in this region. To address this, we conducted a cohort analysis and a two-sample Mendelian randomization (MR) study in East Asian populations.

Methods We collected data on VTE patients from the China Pulmonary Thromboembolism Registry Study (CURES) and compared them to controls obtained from the China Health and Retirement Longitudinal Survey (CHARLS). Propensity score matching (PSM) and cubic-spline models were applied to assess the effect of SUA on VTE risk while adjusting for multiple covariates. We also performed two-sample MR analyses to infer potential causality based on summary statistics from Genome-wide Association Studies (GWAS) of SUA and VTE in the East Asian population.

Findings We found that the SUA levels were higher in VTE patients (317.95 mmol/L) compared to the general population (295.75 mmol/L), and SUA ≥ 325 mmol/L was associated with an increased risk of VTE recurrence (*P-value* = 0.0001). The univariable MR suggested a causal relationship between elevated SUA and higher VTE risk ($P_{inverse\ variance\ weighted} < 0.05$), and multivariable MR showed that elevated SUA levels continued to promote the development of VTE after adjusting for multiple covariates ($P_{multivariable\ residual} < 0.05$). Sensitivity analyses produced similar results for these estimations.

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Interpretation Our study provides evidence supporting a robust positive association between SUA and VTE in the East Asian population, and MR analyses suggest that this association is likely to be causal. Our findings underscore the importance of monitoring SUA levels in VTE prevention and call for urgent action to address the growing burden of hyperuricemia in the Asia-Pacific region.

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Keywords: Mendelian randomization; Causal relationship; Serum uric acid; Venous thromboembolism

Research in context

Evidence before this study

Prior to this study, a systematic search was conducted in Embase and MEDLINE using MeSH terms related to uric acid and venous thromboembolism (VTE) up to March 29, 2023. Thirteen relevant studies were identified, but there was insufficient evidence to support uric acid as a risk factor for VTE. Most of the cohort studies included individuals of Caucasian ancestry, with few studies considering individuals of East-Asian ancestry. A search in PubMed using MeSH terms related to Mendelian randomization (MR), uric acid, and VTE up to March 29, 2023 yielded only one relevant MR analysis. The study used summary-level data of the uric acid from the BioBank Japan cohort and the summary-level data of VTE from the FinnGen consortium, which reported no significant causal effect of genetically predicted uric acid levels with VTE. However, it remains uncertain whether uric acid is causally associated with VTE in other populations, such as the East Asian population.

Added value of this study

The present study, which utilizes cohort and two-sample MR analyses, is the largest study in East Asia investigating the association between uric acid and VTE. The key findings can be summarized into three points: (1) For Chinese adults, patients with high uric acid have a higher risk of VTE when compared to those in the general population, where causality was suggested by MR analysis in an East-Asian population; (2) In our cohort analysis, we used propensity score matching to show that VTE patients have higher uric acid compared to the general population. (3) In the MR analysis, we used the novel summary statistics of genetically predicted uric acid as an instrument variable. The genetic data of VTE was obtained from a recently published GWAS study of 18,931 Chinese subjects. Our findings support that uric acid may have a specific etiological role in VTE. The findings of this study provide evidence for potential causal associations between serum uric acid and VTE.

Implications of all the available evidence

The available evidence suggests a significant causal association between serum uric acid and VTE among the East-Asian population. Individuals with higher uric acid levels are at increased risk of developing VTE as well as VTE recurrence. Therefore, efforts aimed at improving uric acid control may represent effective strategies for improving the detection and treatment outcomes of VTE.

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), is a serious medical condition with a reported incidence rate of 3.2–17.5 per 100,000 individuals among the population of East Asian ancestry.[1,2] A series of factors, such as age, sex, body mass index (BMI), lipids, and sedentary behavior, have been identified to contribute to VTE risk.[3] In addition, genetic factors are also important in VTE development, with family-based studies showing that heritable factors account for a significant proportion of familial cases of VTE.[4] Several genetic loci have been identified by large GWAS studies to be associated with susceptibility to VTE,[5] which were included in metabolic pathways.

Uric acid (UA), the metabolic end product of purine metabolism, is mainly derived from dietary sources, such as purine-rich and glutamate-rich foods, as well as from endogenous sources, such as the breakdown of nucleic acids.[6] Elevated serum UA (SUA) levels, resulting from overproduction or under-excretion of UA, play an important role in cardiovascular diseases, heart failure and stroke.[7,8] Several observational studies have reported a positive association between SUA levels and VTE risk.[9–11] For example, a single-center prospective study found that patients with high SUA levels showed a

three-fold increase in the risk of VTE recurrence.[12] However, the underlying pathophysiological mechanism remains unclear, and the causal relationship between SUA and VTE remains to be confirmed. There is also a lack of large-scale studies on the association between SUA and VTE in East Asian populations, even in the form of observational studies.

Randomized controlled trials (RCTs) are considered the gold standard for causal inference in clinical research, but they tend to be costly and time-consuming. Moreover, ethical issues may prevent their implementation in some cases. In contrast, the Mendelian randomization (MR) approach, which uses genetic variants as instrumental variables, offers a powerful tool for identifying causal relationships between exposure and outcome, because genetic variants are theoretically randomly distributed in the population and are unlikely to be affected by any confounding factors.

The prevalence of hyperuricemia is steadily growing in China, possibly attributable to lifestyle changes such as increased red meat intake and physical inactivity,.[13] Given the high prevalence of hyperuricemia in the Asia-Pacific region and the threat of VTE on human health, it is of great importance to investigate the potential impact of this condition on VTE among East Asian populations. Therefore, this study aimed to quantify the relationship of SUA with VTE in two nationwide cohorts of East Asian individuals and use MR to estimate the causal effect between SUA and VTE (Fig. 1). The findings of this study might contribute to the prevention of VTE and its recurrence in East Asian populations.

Methods

Study data and population-based cohorts

We conducted a cohort study on Chinese individuals from two nationwide population-based cohorts to investigate the relationship between SUA and VTE risk. VTE patient data were collected from the China pUlmonary thromboembolism Registry Study (CURES), an ongoing multicenter registry of patients with PTE between 2009 and 2015.[14] The diagnosis of PTE was confirmed by helical computed tomographic pulmonary angiography (CTPA), ventilation-perfusion lung scintigraphy (V/Q scan) or pulmonary angiography. DVT was diagnosed by compression ultrasonography (CUS) or computed tomographic venography. In contrast, the data on control individuals were collected from the 2015 China Health and Retirement Longitudinal Survey (CHARLS), a national survey of Chinese adults over 45 years old.[15]

Propensity score matching and cubic-spline model analysis

To create a control group and minimize the effects of potential confounding factors, we employed a propensity score-matching strategy. Specifically, we compared the characteristics of the CURES participants to those of a subset of respondents from the CHARLS study who were similar to the CURES participants in all relevant background characteristics except for the presence of VTE. We estimated individual propensity scores by using a logistic regression model that incorporated nine potential confounding factors as covariates, including demographic characteristics (sex, age, BMI, systolic blood pressure, diastolic blood pressure, and diabetes) and serum biochemical parameters (triglycerides, total cholesterol, and creatinine). To compare SUA levels between VTE patients and the general population, we performed 1:1 propensity score matching (PSM) to balance the effects of potential confounding factors.

We used a cubic-spline model to measure the association between SUA and the risk of VTE recurrence, adjusting for multiple covariates including sex, age, BMI, systolic blood pressure, diastolic blood pressure, diabetes, triglycerides, total cholesterol, and creatinine. By using this approach, we were able to estimate the independent effect of SUA more accurately on the risk of VTE recurrence while controlling for potential confounding factors.

All *P-value*s were two-tailed, and the significance level was set at *P-value* < 0.05. All statistical analyses were performed using R software (version 4.2.2), and the cubic-spline models were generated using the R package "*Hmisc*" and "*rms*".

GWAS summary for SUA and VTE

The summary statistics for SUA were obtained from a GWAS study of the Biobank Japan Project (BBJ), which included 109,029 East Asian participants aged between 18 and 85 years old (BBJ_UA).[16] Subjects receiving urate-lowering therapy and those with renal insufficiency were excluded. To validate our results, we utilized another large-scale SUA summary statistics dataset with 121,745 Japanese subjects (META_UA).[17] We further obtained the VTE summary statistics from a GWAS study of a Chinese descent population,[18] consisting of 1,268 cases and 17,663 controls to minimize potential bias from population stratification.

Instrumental variable selection and functional analysis

To identify valid and strong instrumental variables (IVs) in MR analysis, we adopted a series of steps for IV selection. First, we selected single nucleotide polymorphisms (SNPs) that were genome-wide significant ($P < 5 \times 10^{-8}$) for the exposure. Next, we performed the clumping process ($R^2 < 0.2$, window size = 500 kb) with 1000 genomes of East Asian sample data as a reference to ensure the independence of IVs. We discarded genetic variants with ambiguous strand in the harmonizing process; we excluded SNPs that were not present

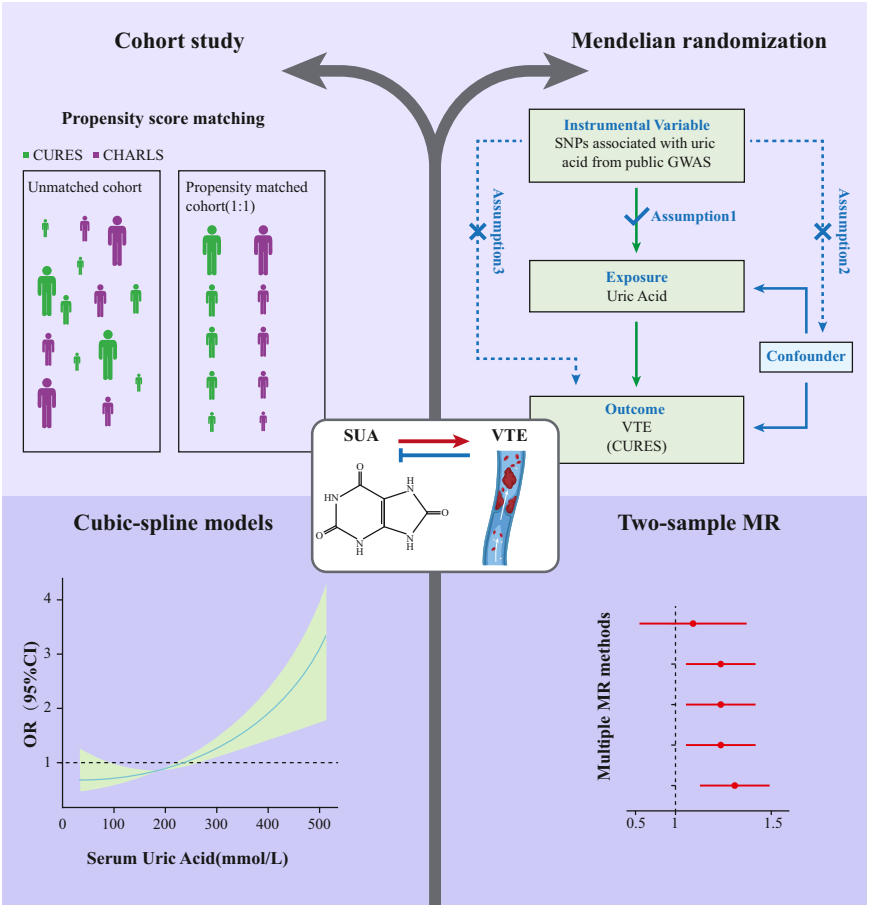

***Fig. 1:* Study workflow chart.** Association and causal effect of uric acid and venous thromboembolism.

in the outcome summary statistics. We then mapped each identified IV to corresponding genes using SNPnexus[19] and selected protein-coding genes for Gene Ontology (GO) annotations to explore the biological functions of the IVs. To test for "weak instruments", we calculated the individual and overall F statistics for two sets of instrumental variables obtained from BBJ_UA and META_UA. An F statistic exceeding the suggested threshold of 10 is considered a non-weak instrument.

Two-sample Mendelian randomization

We performed a univariable two-sample MR analysis to estimate the causal relationship between SUA exposure and VTE outcome, using summary statistics from large-scale GWAS studies. The inverse variance weighted (IVW)[20] method was used for the main MR estimate, while additional multiple sensitivity analyses such as maximum likelihood,[21] MR-RAPS,[22] and MR-PRESSO[23] approaches, were used as complementary analyses to examine the robustness of the results.

We conducted bi-directional MR analysis to detect reverse causal effect occurrence when the outcome has an effect on the exposure in addition to the exposure affecting the outcome. We also conducted leave-one-out analyses to evaluate the potential impact of excluding any IVs on the MR estimates. Additionally, we performed a power analysis to estimate the statistical power of our MR study.

Multivariable MR, a supporting analysis for univariable MR, was used to select SNPs significantly correlated with at least one exposure and present in all summary statistics. In this study, we used summary-level data from BBJ and VTE summary statistics to investigate the potential confounding effect on the association between SUA and VTE. After removing SNPs with pairwise $r^2 > 0.2$ within 500 kb windows, 596 SNPs were included in the analysis. Two common methods for multivariable MR, the residual regression method proposed by Burgess[24] and the multivariable IVW with weighting for the inverse variance of the outcome,[25] were used. In the analysis, a *P-value* < 0.05 was considered evidence of a causal effect of SUA on VTE. The R package "*TwosampleMR*" was utilized to conduct MR analysis with R software version 4.2.2.

Heritability, genetic correlation and pleiotropy

We estimated the heritability of SUA and VTE, as well as the genetic correlation between them, using the linkage disequilibrium score regression (LDSC) method.[26] The LD Score was computed using East Asian data from the 1000 Genomes Project as the reference panel. We further utilized MR-Egger,[27] MR-RAPS,[22] and MR-PRESSO[23] methods to detect pleiotropy and outlier SNPs. These complementary analyses ensured that the causal estimates were robust to heterogeneity and that the "no pleiotropy" assumption was not violated. *P-value*s < 0.05 were considered as genetically correlated between SUA and VTE. All analyses were conducted using R software.

Role of the funding source

The funding source had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

Baseline characteristics of participants in the cohort study

This study included 3,754 patients with VTE from CURES and 10,477 controls from CHARLS. The baseline characteristics were compared between the VTE and control groups (Table 1). Overall, significant differences were observed between the groups with respect to demographic characteristics and serum biochemical parameters. Specifically, the VTE patients were found to be older than the general controls (63.7 years vs. 61.48, *P-value* < 0.001), have a higher BMI (24.41 vs. 23.85, *P-value* < 0.001) and a smaller proportion of female participants (49.1% vs. 53.5%, *P-value* < 0.001). Additionally, the VTE patients exhibited higher levels of creatinine (74.02 vs. 71.61, *P-value* < 0.001) but lower levels of lipid parameters when compared to the controls (*P-value* < 0.001).

Serum uric acid levels of VTE patients and controls

Compared to the general control group, VTE patients displayed significantly elevated SUA levels (325.03 vs. 294.42 mmol/L, *P-value* < 0.001). After performing PSM, 2,751 VTE patients were matched to 2,751 general controls. The distributions of propensity scores illustrated a successful matching between groups (Supplementary Fig. S1). The characteristics of both groups were well-balanced, as demonstrated in Table 1. Notably, the SUA levels in the VTE patient group remained substantially higher than those in the control group (317.95 vs. 295.75 mmol/L, *P-value* < 0.001) after the PSM procedure.

Association between serum uric acid levels and the risk of VTE recurrence

A total of 3,754 VTE patients from the CURES were included in the cubic-spline model. A hypothetical patient with SUA of 325 mmol/L was considered as the reference (OR = 1), and the relative odds ratio (OR) was calculated for each patient with a specific SUA level. Based on these results, we estimated the non-linear relationship between SUA levels and the risk of VTE recurrence (Fig. 2). The analysis demonstrated a gradual increase in the risk of VTE recurrence with increasing SUA levels (*P-value* = 0.0001).

Selection of instrumental variables and functional analysis

Following the IV selection procedures, we identified 217 independent SNPs as instruments for the BBJ_UA dataset and 234 independent SNPs for the META_UA dataset, which exhibited significant associations with SUA levels. These selected SNPs were subsequently

	Overall			Propensity-score matched		
	CURES	CHARLS	*P-value*	CURES	CHARLS	*P-value*
No.	3,754	10,477		2,751	2,751	
Female (%)	1,843 (49.1)	5,601 (53.5)	<0.001***	1,404 (51)	1,432 (52.1)	0.447
Age	63.69 ± 14.63	61.48 ± 9.40	<0.001***	61.77 ± 14.31	62.37 ± 9.68	0.787
BMI (kg/m^2)	24.41 ± 3.78	23.85 ± 3.68	<0.001***	24.13 ± 3.57	24.24 ± 3.89	0.657
Diabetes (%)	473 (12.6)	1,082 (10.3)	<0.001***	311 (11.3)	329 (12)	0.481
Blood pressure (mmHg)						
Systolic	128.12 ± 19.53	128.86 ± 20.11	0.055	128.58 ± 19.50	129.26 ± 19.71	0.407
Diastolic	78.03 ± 12.55	75.68 ± 11.75	<0.001***	76.92 ± 11.91	76.55 ± 11.64	0.119
Triglycerides (mmol/L)	1.49 ± 0.86	1.61 ± 1.02	<0.001***	1.55 ± 0.88	1.55 ± 0.96	0.096
Total Cholesterol (mmol/L)	4.48 ± 1.21	4.77 ± 0.94	<0.001***	4.64 ± 1.09	4.63 ± 0.92	0.710
Creatinine (mmol/L)	74.02 ± 31.95	71.61 ± 26.60	<0.001***	71.70 ± 28.60	72.34 ± 30.77	0.216
Uric Acid (mmol/L)	325.03 ± 120.68	294.40 ± 84.00	<0.001***	317.95 ± 115.22	295.75 ± 84.93	<0.001***

CURES, China Pulmonary Thromboembolism Registry Study; CHARLS, China Health and Retirement Longitudinal Survey; BMI, Body Mass Index. As the result of significance test, *means *P-value* < 0.05; **means *P-value* < 0.01; ***means *P-value* < 0.001.

Table 1: **Characteristics of participants in the cohort study before and after propensity score matching.**

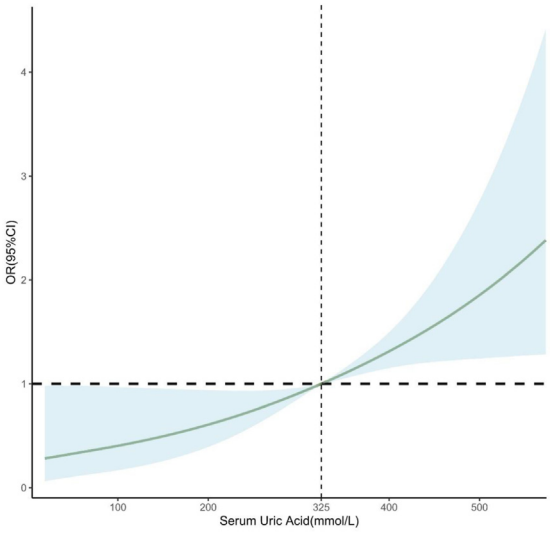

***Fig. 2:* Association between serum uric acid levels and venous thromboembolism recurrence risk.** The solid black line is the estimated odds ratio, and the shaded blue area is the 95% confidence interval.

employed in MR analyses to estimate the causal effect of exposure on the outcome. We evaluated the strength of the IVs by calculating the F statistics and overall F statistics for BBJ_UA and META_UA, which were found to be 121 and 125, respectively. These results suggested that the instruments used in our study are not considered "weak instruments". Detailed information regarding the IVs screened in our MR analysis can be found in Supplementary Tables S2–S5. Notably, there was substantial overlap in the selected SNPs between the two datasets (Supplementary Fig. S2). To elucidate the functional roles of these SNPs, we conducted functional annotation and enrichment analyses. Specifically, we mapped the identified SNPs to 46 protein-coding genes and found that these genes were predominantly enriched in the biological processes of urate metabolism and urate transport, as determined by gene ontology (GO) biological process enrichment analysis (Supplementary Fig. S2).

Univariable two-sample Mendelian randomization

The MR estimates from various methods to assess the causal effect of SUA on VTE were presented in Fig. 3 and Supplementary Table S1. The IVW method yielded a positive causal effect of SUA on VTE in both the BBJ_UA dataset (β = 0.17 [0.05–0.29], *P-value* = 0.0079) and the META_UA dataset (β = 0.14 [0.01–0.27], *P-value* = 0.025). These findings were consistent with those obtained from maximum likelihood, MR-RAPS, and MR-PRESSO analyses (Fig. 3). The consistency of the results across the two datasets suggests that the findings are robust. It is worth noting that the MR-Egger method includes an estimate of the intercept, which may have lower statistical power to detect a causal effect compared to other methods. However, the MR-Egger method is particularly useful for detecting the presence of pleiotropy. The estimated effect and standard error of the instrumental variables on both SUA and VTE are presented in scatter plots in Supplementary Fig. S3, while the causal effects of each instrumental variable on VTE are displayed in forest plots in Supplementary Figs. S4 and S5. Leave-one-out analyses indicated that the results were stable and not driven by any single SNP (Supplementary Figs. S6 and S7). The MR analysis conducted in the reverse direction did not provide any reliable evidence to suggest that VTE may be the cause of elevated SUA levels (Supplementary Table S6). Moreover, we performed a power analysis to estimate the statistical power of our MR study and found that the statistical power for BBJ_UA and META_UA were 0.925 and 0.804, respectively. These values suggest that our study has a high probability of detecting a true causal effect if one exists, and further supports the validity and reliability of our findings.

Multivariable two-sample Mendelian randomization

We also conducted a multivariable MR analysis, considering nine covariates (LDL, HDL, TG, TC, DM, DBP, SBP, CK, BMI) as covariates (Fig. 3 and Supplementary Table S7). The results provided further suggestive evidence supporting the notion that higher SUA levels increase the risk of VTE. Specifically, both the residual method (BBJ_UA dataset: β = 0.21 [0.09–0.33], *P-value* = 0.0006; META_UA dataset: β = 0.20 [0.08–0.32], *P-value* = 0.0012) and the multiple variates IVW method (BBJ_UA dataset: β = 0.18 [0.05–0.31], *P-value* = 0.0068; META_UA dataset: β = 0.15 [0.02–0.28], *P-value* = 0.02) yielded statistically significant evidence supporting a positive causal effect of SUA on VTE. Furthermore, the direction of the causal effect was consistent and positive, as observed in all other methods employed in the study.

Heritability, genetic correlation and pleiotropy

The LDSC results (Table 2) revealed moderate total heritability estimates for both SUA (h^2 = 0.14, SE = 0.044) and VTE (h^2 = 0.13, SE = 0.028). Additionally, the genetic correlation analysis indicated no significant genetic correlation (*P-value* = 0.862) between SUA and VTE, suggesting that the fraction of SNPs with an effect on both traits is small. This further implied that the IVs used in the MR analysis were less likely to have a direct effect on the outcome. The results of MR-Egger, MR-RAPS, and MR-PRESSO methods all suggested no potential horizontal pleiotropy, which indicated that our results were not biased (Table 3). Moreover, the funnel plot exhibited a symmetric distribution of the point estimate of the causal association effect when using a single SNP as an instrument (Supplementary Fig. S8). This finding further indicated

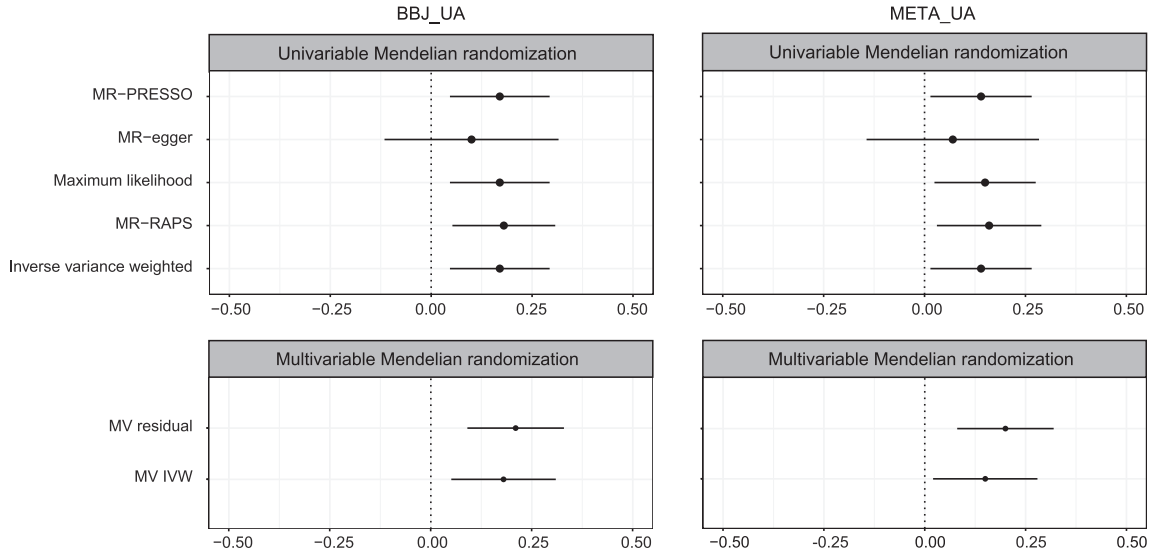

***Fig. 3:* Two-sample Mendelian randomization reveals causal evidence for SUA on VTE.** The forest plots illustrate the standardized beta (95% Confidence Interval) for each two-sample MR method.

Traits	Heritability			Genetic Correlation	
	h^2 (SE)	intercept *P-value*	ratio of stratification	Correlation (SE)	*P-value*
SUA	0.1397 (0.044)	0.000233	8.64%	0.0136 (0.0782)	0.862
VTE	0.1265 (0.028)	(intercept = 0.9938 < 1)	<0		

SUA, Serum uric acid; VTE, Venous thromboembolism; SE, Standard Error.

***Table 2:* Heritability and genetic correlation of SUA and VTE.**

DataSet	Egger-intercept	Egger-SE	Egger *P-value*	MR-PRESSO Global Test
BBJ_UA	0.0049	0.0064	0.44	0.466
META_UA	0.0053	0.0060	0.38	0.326

UA, Uric acid; SE, Standard Error.

***Table 3:* Egger regression and MR-PRESSO detect no horizontal pleiotropy.**

that the underlying bias was unlikely to influence the causal association.

Discussion

This study demonstrated that SUA is an independent predictor of VTE in the East Asian population. Our cohort analyses using two nationwide population-based cohorts showed a significant increase in the risk of VTE incidence and recurrence at higher SUA levels. Further MR analyses suggested that the relationships of SUA with VTE were likely to be causal. The MR findings were robust in the repeated analysis using different methods and sensitivity analysis, and two different datasets supported the consistent result. The finding of large F statistics for both sets of IVs provides evidence against the presence of weak instrument bias in our study. The weak and nonsignificant genetic correlation between SUA and VTE obtained by LDSC indicated no direct effect of the genetic instruments on the outcome (VTE). Furthermore, the absence of pleiotropy was suggested by MR-Egger, MR-RAPS, and MR-PRESSO, indicating that the MR results were not biased. The overall statistical power of our MR study is high enough to obtain a true causal effect if one exists. Finally, we conducted multivariable MR and obtained consistent findings after controlling for additional common traits. To the best of our knowledge, this is the first study combining evidence from large-scale cohort studies and MR studies to provide more robust causal inferences between SUA and VTE in the East Asian population.

Existing evidence has suggested a positive association between SUA and both the incidence and recurrence of VTE, indicating that elevated SUA may serve as a potential risk factor for VTE.[9,11,12] However, most cohort studies on SUA and VTE have focused on European and American populations, with few studies conducted on East Asian populations. Furthermore, classical cohort studies may fail to estimate causality due to numerous known and unknown confounders. Mendelian randomization, as a technique for exploring causal association, can effectively overcome some limitations of observational studies. Based on the evidence from both nationwide population-based cohorts and MR analyses, we confirmed that SUA is causally associated with a higher risk of VTE in the East Asian population, which is consistent with previous observational studies.

The underlying mechanism of the identified causal effect remains poorly understood. Although SUA is primarily a metabolic waste deriving from the elimination of purine, it is known to have physiological functions that are not yet fully understood. The activation of the inflammatory pathway induced by elevated SUA is a potential mechanism underlying the causal effect. For example, a cross-sectional population-based study found a strong positive association of SUA with C-reactive protein, TNF-α, and IL-6 in plasma.[28] Additional studies have reported similar findings of elevated SUA associated with inflammatory cytokines.[29,30] In vitro and in vivo studies support the hypothesis that SUA contributes to systemic sterile inflammation.[31] The intimate interplay between inflammation and coagulation activation has a key role in the development of VTE. It has been previously demonstrated that inflammatory mediators can upregulate the expression of tissue factors on the surface of circulating monocytes and neutrophils to induce activation of coagulation.[32,33] Hongyin Yu et al.[34] demonstrated hyperuricemia can induce phosphatidylserine exposure and microparticle release, leading to a thrombotic role of endothelial cells mediated through TMEM16F. Furthermore, increased uric acid levels have been shown to upregulate the expression of lethal-7c (let-7c), which has been linked to platelet dysfunction. In an animal model of hyperuricemia, elevated SUA levels were found to activate MEF2C-dependent and NF-κB pathways via let-7c, resulting in thrombosis.[35]

The elucidation of the relationship between hyperuricemia and pulmonary embolism has significant implications for clinical practice. Such understanding can aid in the development of more effective prevention and treatment strategies to reduce the risk of pulmonary embolism in affected patients. If a clear correlation is established between hyperuricemia and pulmonary embolism, controlling uric acid levels may become an important measure for preventing the occurrence of pulmonary embolism. Additionally, assessing the risk of pulmonary embolism in patients with hyperuricemia can assist healthcare professionals in identifying high-risk individuals at an early stage and implementing appropriate interventions to reduce the incidence of pulmonary embolism and related complications.

There are some limitations in the present study. Firstly, potential confounders related to VTE, such as smoking history and alcohol consumption, were not available for all patients and were not included in the cohort analysis. It is also possible that some degree of heterogeneity in our results may have been attributed to differences in the methods of sample collection and quality control employed across the cohorts. Secondly, although the causal effect of SUA on VTE was demonstrated, the pathophysiological mechanism is still unclear. Further research, such as RCTs, is warranted to investigate whether the management of SUA levels through lifestyle modifications or pharmacological interventions could potentially lower the risk of VTE. Thirdly, MR analysis assumes that the effect of a genetic variant on an outcome is solely through exposure. However, there is a potential for other unmeasured factors to influence this relationship, which might result in horizontal pleiotropic associations that could be difficult to quantify and address. Lastly, despite our efforts to address the issue of weak instruments through various statistical tests, it is important to acknowledge that this issue may still persist to some extent. As such, caution should be exercised when interpreting the results of our study, and further research is needed to confirm our findings and address potential sources of bias.

Our study exhibits notable strengths, as the largest study in East Asia to investigate the association between SUA on VTE risk, the results were derived from nationwide population-based cohort studies and MR analyses. We utilized two large genetic datasets of the SUA to establish robust causal effects, which provided sufficient power to attain a causal inference. Compared to the previous MR analysis in SUA and VTE,[36] our study is unique and specific as it was restricted to individuals of East Asian descent, reducing the potential bias from population stratification. The use of exposure and outcome data from different populations and differences in the instrumental variables may have contributed to the lack of significant causal effect observed in the previous MR study. These factors highlight the importance of conducting population-specific MR studies and using appropriate instrumental variables to ensure accurate and reliable results. We employed several methods to detect possible pleiotropy and exclude reverse causal effects, thus minimizing the likelihood of false positives due to pleiotropy. The direction of association is deterministic, and the potential influence of other common confounding variables has been effectively ruled out by multivariable MR analysis.

Conclusions

Our study has provided compelling evidence that elevated SUA levels independently increased the risk of VTE in East Asian populations, suggesting that SUA could be a causal risk factor for VTE. These findings have important clinical implications, indicating that SUA management may be an effective strategy for VTE prevention. Given the increasing prevalence of hyperuricemia in the Asia Pacific region, our study highlights the urgent need for public health initiatives to address this issue on a regional and global scale.

Contributors

Haoyi Weng and Zhenguo Zhai contributed to the study design. Haobo Li, Haoyi Weng, Yu Zhang, Linfeng Xi and Dingyi Wang contributed to the cohort study. Di Zhang, Chao Deng, Ruoyan Chen, Senwei Tang and Haoyi Weng contributed to the Mendelian randomization analysis. Haoyi Weng and Haobo Li wrote the manuscript. Zhu Zhang, Peiran Yang, Xianbo Zuo, Gang Chen, Zhenguo Zhai, and Chen Wang reviewed and edited the manuscript.

Data sharing statement

To access SUA summary statistics from Biobank Japan in this manuscript, see http://jenger.riken.jp/en/. The SUA summary statistics derived from a genome-wide meta-analysis with 121,745 Japanese subjects are available at the National Bioscience Database Center (Research ID: hum 0167.v1.meta.v1).

The summary statistics of VTE in this study were deposited in The National Genomics Data Center (NGDC, https://bigd.big.ac.cn/) under the accession number: PRJCA008276 (https://ngdc.cncb.ac.cn/gsa-human/s/96I4Q3YX).

Declaration of interests

The authors have no relevant conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100848.

References

1 Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. *Lancet*. 2021;398(10294):64–77.
2 Zhang Z, Lei J, Shao X, et al. Trends in hospitalization and in-hospital mortality from VTE, 2007 to 2016, in China. *Chest*. 2019;155(2):342–353.
3 Crous-Bou M, Harrington LB, Kabrhel C. Environmental and genetic risk factors associated with venous thromboembolism. *Semin Thromb Hemost*. 2016;42(8):808–820.
4 Zhang Y, Zhang Z, Shu S, et al. The genetics of venous thromboembolism: a systematic review of thrombophilia families. *J Thromb Thrombolysis*. 2021;51(2):359–369.
5 Ghouse J, Tragante V, Ahlberg G, et al. Genome-wide meta-analysis identifies 93 risk loci and enables risk prediction equivalent to monogenic forms of venous thromboembolism. *Nat Genet*. 2023;55(3):399–409.
6 Ndrepepa G. Uric acid and cardiovascular disease. *Clin Chim Acta*. 2018;484:150–163.
7 Cortese F, Giordano P, Scicchitano P, et al. Uric acid: from a biological advantage to a potential danger. A focus on cardiovascular effects. *Vascul Pharmacol*. 2019;120:106565.
8 Virdis A, Masi S, Casiglia E, et al. Identification of the uric acid thresholds predicting an increased total and cardiovascular mortality over 20 years. *Hypertension*. 2020;75(2):302–308.
9 Kubota Y, McAdams-DeMarco M, Folsom AR. Serum uric acid, gout, and venous thromboembolism: the atherosclerosis risk in communities study. *Thromb Res*. 2016;144:144–148.
10 Țăpoi L, Șalaru DL, Sascău R, Stătescu C. Uric acid-an emergent risk marker for thrombosis? *J Clin Med*. 2021;10(10):2062.
11 Huang CC, Huang PH, Chen JH, et al. An independent risk of gout on the development of deep vein thrombosis and pulmonary embolism: a nationwide, population-based cohort study. *Medicine (Baltimore)*. 2015;94(51):e2140.
12 De Lucchi L, Nardin C, Sponchiado A, et al. Serum uric acid levels and the risk of recurrent venous thromboembolism. *J Thromb Haemost*. 2021;19(1):194–201.
13 Zhang M, Zhu X, Wu J, et al. Prevalence of hyperuricemia among Chinese adults: findings from two nationally representative cross-sectional surveys in 2015-16 and 2018-19. *Front Immunol*. 2021;12:791983.
14 Zhai Z, Wang D, Lei J, et al. Trends in risk stratification, in-hospital management and mortality of patients with acute pulmonary embolism: an analysis from the China pUlmonary thromboembolism REgistry Study (CURES). *Eur Respir J*. 2021;58(4):2002963.
15 Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China health and retirement longitudinal study (CHARLS). *Int J Epidemiol*. 2014;43(1):61–68.
16 Kanai M, Akiyama M, Takahashi A, et al. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. *Nat Genet*. 2018;50(3):390–400.
17 Nakatochi M, Kanai M, Nakayama A, et al. Genome-wide meta-analysis identifies multiple novel loci associated with serum uric acid levels in Japanese individuals. *Commun Biol*. 2019;2:115.
18 Zhang Z, Li H, Weng H, et al. Genome-wide association analyses identified novel susceptibility loci for pulmonary embolism among Han Chinese population. *BMC Med*. 2023;21(1):153.
19 Oscanoa J, Sivapalan L, Gadaleta E, Dayem Ullah AZ, Lemoine NR, Chelala C. SNPnexus: a web server for functional annotation of human genome sequence variation (2020 update). *Nucleic Acids Res*. 2020;48(W1):W185–W192.
20 Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658–665.
21 Burgess S, Dudbridge F, Thompson SG. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods. *Stat Med*. 2016;35(11):1880–1906.
22 Zhao Q, Wang J, Hemani G, Bowden J, Small DS. Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score. *Ann Stat*. 2020;48(3):1742–1769.
23 Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698.
24 Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. *Am J Epidemiol*. 2015;181(4):251–260.
25 Adams CD, Boutwell BB. Using multiple Mendelian randomization approaches and genetic correlations to understand obesity, urate, and gout. *Sci Rep*. 2021;11(1):17799.
26 Bulik-Sullivan BK, Loh PR, Finucane HK, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet*. 2015;47(3):291–295.
27 Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512–525.
28 Lyngdoh T, Marques-Vidal P, Paccaud F, et al. Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based Colaus study. *PLoS One*. 2011;6(5):e19901.
29 Fröhlich M, Imhof A, Berg G, et al. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care*. 2000;23(12):1835–1839.
30 Ruggiero C, Cherubini A, Ble A, et al. Uric acid and inflammatory markers. *Eur Heart J*. 2006;27(10):1174–1181.
31 Oğuz N, Kırça M, Çetin A, Yeşilkaya A. Effect of uric acid on inflammatory COX-2 and ROS pathways in vascular smooth muscle cells. *J Recept Signal Transduct Res*. 2017;37(5):500–505.

32 Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood*. 1993;82(2):513–520.

33 Rivers RP, Hathaway WE, Weston WL. The endotoxin-induced coagulant activity of human monocytes. *Br J Haematol*. 1975;30(3):311–316.

34 Yu H, Wang Z, Li Z, et al. Hyperuricemia enhances procoagulant activity of vascular endothelial cells through TMEM16F regulated phosphatidylserine exposure and microparticle release. *FASEB J*. 2021;35(9):e21808.

35 Cheng X, Liu T, Ma L, et al. Prothrombotic effects of high uric acid in mice via activation of MEF2C-dependent NF-κB pathway by upregulating let-7c. *Aging (Albany NY)*. 2020;12(18):17976–17989.

36 Liu Z, Mi J. Serum albumin and circulating metabolites and risk of venous thromboembolism: a two-sample mendelian randomization study. *Front Nutr*. 2021;8:712600.