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Association between venous thromboembolism and atrial fibrillation: a Mendelian randomization study

Caijing Dang[1], Wenkai Liao[2], Lin Xu[2], Wenshu Zhao[2] and Yuxia Lu[1*]

Abstract

Background Although previous observational studies have shown an association between venous thromboembolism (VTE) and atrial fibrillation (AF), the underlying causal relationship between them remains uncertain.

Methods and results This two-sample bidirectional Mendelian randomization (MR) analysis was performed to investigate the causal relationship between VTE and AF. The VTE dataset were obtained from FinnGen, including 9,176 cases and 209,616 controls. Meanwhile a genome-wide association study (GWAS) of 60,620 individuals with AF and 970,216 control subjects identified genetic variations associated with AF. The principal MR analytic approach used in this study is the inverse-variance weighting (IVW) method. Furthermore, we performed complementary MR analyses, including the MR-Egger, Weighted median (WM), and Weighted Mode. MR pleiotropy residual sum was applied to identify pleiotropy. The MR analysis showed suggestive causal associations between VTE and the risk of AF ($p=0.0245$, OR [95%CI]: 1.027 [1.003, 1.051]). The reverse MR analysis found that genetic susceptibility to AF was not significantly associated with VTE, as determined by the IVW method ($p=0.7773$). The robustness of these findings was corroborated through MR sensitivity analyses.

Conclusions There is a unidirectional causal relationship between VTE and AF, meaning that VTE is a causal risk factor for AF, whereas no effect of AF on VTE was identified.

Keywords Venous thromboembolism, Atrial fibrillation, Mendelian randomization, Association, Genetics

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Introduction

Venous thromboembolism (VTE), a common thrombotic vascular disease, primarily affects older individuals and increases global burden of disease [1]. On a global scale, approximately 10 million cases are reported annually, making VTE the third most prevalent vascular disease following myocardial infarction and stroke [2].

Atrial fibrillation (AF) is the most prevalent cardiac atrial tachyarrhythmia, with its prevalence increasing with age. AF increases the risk of heart failure, strokes, and dementia, resulting in disability and even death [3]. Moreover, given its high prevalence, AF causes a considerable burden to the healthcare system [4].

VTE and AF often occur together, leading to significant levels of morbidity and mortality [5]. Some studies have revealed that conditions like hyperlipidemia, diabetes mellitus, and hypertension, along with other risk factors for atherosclerosis, are also linked to a higher risk of VTE [6, 7]. However, the exact relationship between them remains uncertain. In many instances, the connections may not be causative, but rather attributed to the co-occurrence of two chronic conditions in individuals with poor health. Moreover, the associations deduced by observational studies might be biased by confounders. Herein, our current study aimed to illustrate causal effects between VTE and AF by using a bidirectional Mendelian randomization (BMR) approach. The concept of an instrumental variable (IV) from econometrics, as applied in Mendelian Randomization (MR) design, is a tool used in statistical analysis and econometrics to estimate causal relationships when controlled experiments are not feasible, and there is concern about the endogeneity (including omitted variable bias, measurement error, et al.) of the explanatory variables [8]. MR treats genetic variation as IVs to study exposure factors [9].

Methods

Study design

MR is a widely employed method for exploring causal relationships between an exposure and an outcome. The random assortment of genetic variants during meiosis renders the MR design a natural counterpart to randomized controlled trials (RCT), thus mitigating potential biases compared to observational research. In MR analysis, genetic variations, typically single nucleotide polymorphisms (SNPs), are used as IVs to explore the causal relationship between exposure factors and outcomes. We conducted a two-sample BMR analysis to examine the causal relationship between VTE and AF, based on summary-level data from independent, nonoverlapping populations. The approach bases on the three fundamental assumptions: (I) IVs must be significantly correlated with exposure; (II) IVs is independent of confounding factors; and (III) IVs only affect the outcomes through the exposures. Fig 1 shows a detailed workflow of the study.

Data sources and SNP selection for VTE

In this two-sample BMR study, summary-level data for VTE were obtained from FinnGen (Dataset ID: finn-b-I9_VTE), including 9,176 cases and 209,616 controls, predominantly from European individuals [10]. We selected independent significant SNPs reaching the genome-wide significance level ($p<5\times10-^{8}$, linkage disequilibrium (LD) $R^2<0.001$ and a distance of 10 Mb) as IVs for VTE [11]. To mitigate potential pleiotropic effects, we retrieved the secondary phenotype of each SNP in the PhenoScanner database using a threshold of $p<1\times10-^{5}$. SNPs associated with confounders were identified and removed. Additionally, we removed SNPs for palindromic and incompatible alleles to ensure consistent effect of each SNP align with the same effect allele.

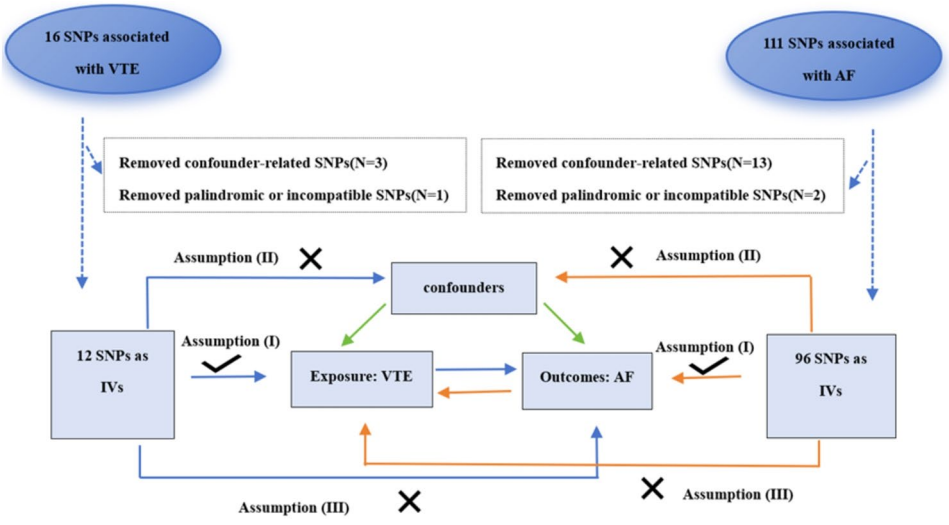

Fig. 1 Study flow diagram. AF = atrial fibrillation; VTE = Venous thromboembolism; IVs = instrumental variables; SNPs = single nucleotide polymorphisms

These SNPs showed no correlation with the outcome. The strength of each SNP was measured by F-statistics ($F=R^2/(1-R^2)\times[(N-2)/K]$) to verify the strength of instruments for exposures ($F>10$ suggested a low probability for weak instrument bias), where R^2 indicates the proportion of variance explained by the SNPs in the exposure, K is the number of SNP-exposure association and N represents the sample size [12].

Data sources and SNP selection for AF

The selection process of IVs for AF followed the same methodology as described above. To mitigate bias from overlapping samples, we selected independent datasets for two-sample MR analysis. Summary dataset for AF (Dataset ID: ebi-a-GCST006414) were obtained from the most extensive meta-analysis of GWAS conducted to date [13]. The research encompassed a total of 60,620 individuals with AF and 970,216 control subjects, sourced from six collaborative studies: The Nord-Trøndelag Health Study (HUNT), deCODE, the Michigan Genomics Initiative (MGI), DiscovEHR, UK Biobank, and the AFGen Consortium. Nearly all of the genotyped samples were from individuals of European ancestry, comprising 98.6% of the study population. SNPs associated with AF reached the genome-wide significance level ($p<5\times10-^8$) and were selected as IVs in the reverse-direction MR analysis.

All GWAS summary data used in the analyses were retrieved from the IEU Open GWAS project with approved informed consent. Proxy SNPs (LD at $r^2>0.8$) were used when SNPs available for predicting exposure were absent in the outcome GWAS. An overview of the demographics and GWAS included in this study is shown in Table 1.

Statistical analysis

The principal MR analytic approach performed in this study is the inverse-variance weighting (IVW) method. Additionally, we conducted the MR-Egger, weighted median (WM), and weighted mode as complementary MR analyses. MR pleiotropy residual sum and outlier test (MR-PRESSO) analysis were applied to detect pleiotropy and heterogeneity in the following analyzes. The global test of MR-PRESSO assessed overall horizontal pleiotropy across all genetic variants. If the test was statistically significant ($p<0.05$), outlier SNPs were excluded, and the MR analysis was rerun to correct for horizontal pleiotropy. A leave-one-out analysis was carried out to assess the influence of individual variants on the overall results. In addition, reverse MR analysis was conducted to estimate the causal effect between the exposure and outcome. The Bonferroni-corrected p-value of 0.025 (0.05 divided by 2) was set for each causal direction. All analyses were performed using the package TwoSample MR in R software (version 4.3.1).

Table 1 Details of data sources included in the study

Diseases	Data source	Sample size(cases/controls)	Ethnicity	Year
Venous thromboembolism	FinnGen	218 792(9 176/209 616)	European	2021
Atrial fibrillation	six contributing studies	1 030 836(60 620/970 216)	European(98.6%)	2018

Results

MR results from summary-level data of VTE on AF

We identified 16 SNPs as IVs with significant associations to VTE from the GWAS data. Subsequently, we conducted a search in the PhenoScanner database and excluded SNPs (rs495203, rs5896, rs2885055) that showed associations with potential confounding factors, including coronary artery disease (CAD), myocardial infarction, hyperlipidemia. Additionally, we removed SNPs that were palindromic and unavailable in the outcome dataset. The total R^2 value of the instrumental SNPs is 0.154. The F-statistics of these SNPs were all above the threshold of 10 (the mean F-statistic is 2890).

The genetically predicted risk of VTE demonstrated a causal association with AF according to summary-level MR analysis, as determined by the IVW method ($p=0.0245$, OR [95%CI]: 1.027 [1.003, 1.051]). The significant associations were enhanced in MR-Egger ($p=0.0137$, OR [95%CI]: 1.054 [1.018, 1.091]), WM analysis ($p=0.0064$, OR [95%CI]: 1.044 [1.012, 1.076]), and weighted mode analysis ($p=0.0203$, OR [95%CI]: 1.045[1.012, 1.078]) (Fig. 2). Cochran's Q Test revealed no evidence of diversity or variation ($p=0.556$). Figure 3 displays scatter plots with regression lines derived from various MR methods. MR-PRESSO test iteratively detects outlier SNPs and adjusts the causal estimates to account for their influence. In our study, the MR-PRESSO test was conducted with 10,000 iterations to ensure precise detection and correction of pleiotropy. The MR-Egger regression analysis did not indicate any evidence of pleiotropy (intercept $p=0.0754$). Figure 4 showcases forest plots illustrating the individual SNP effects in a leave-one-out analysis, from the VTE trait to the AF trait. The power of the study is 80%.

MR results from summary-level data of AF on VTE

111 independent SNPs that reached genome-wide significance ($p<5\times10-^8$) were identified. 13 SNPs were removed due to their association with confounders (e.g., hypertension, CAD and treatment with warfarin). After excluding palindromic (rs6790396) and incompatible

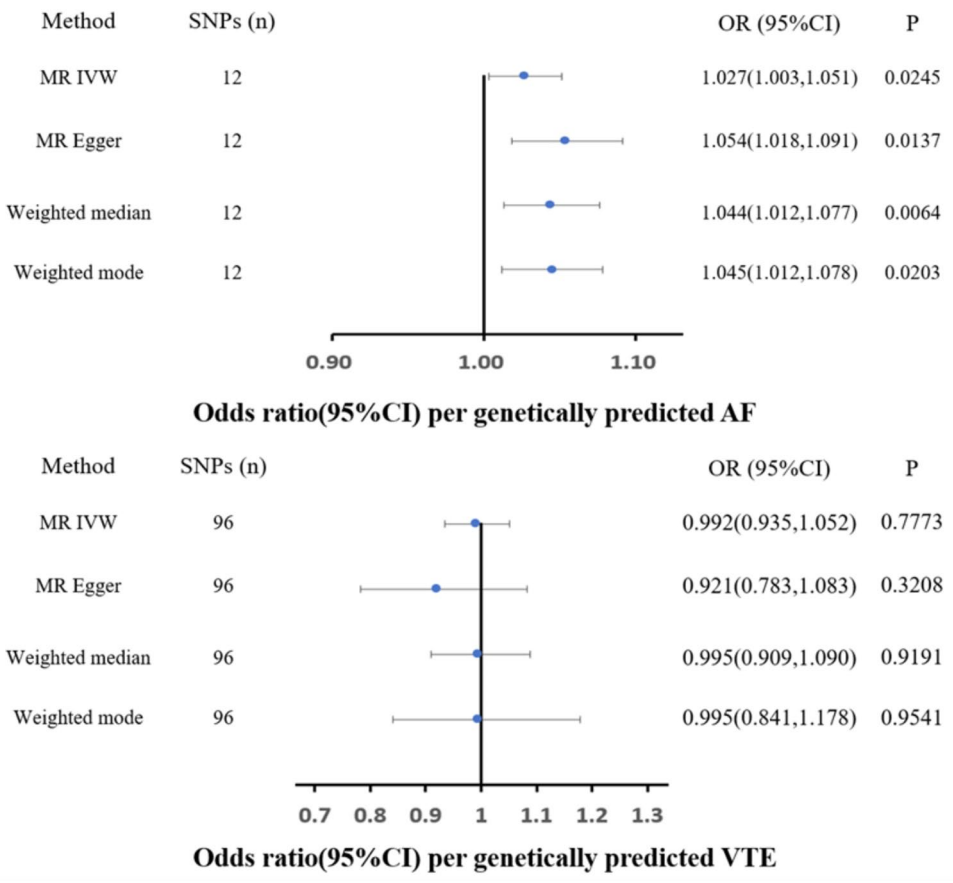

Fig. 2 Forest plot for the Mendelian randomization. OR = odds ratio; CI = confidence interval; IVW = inverse variance weighted; AF = atrial fibrillation; VTE = Venous thromboembolism

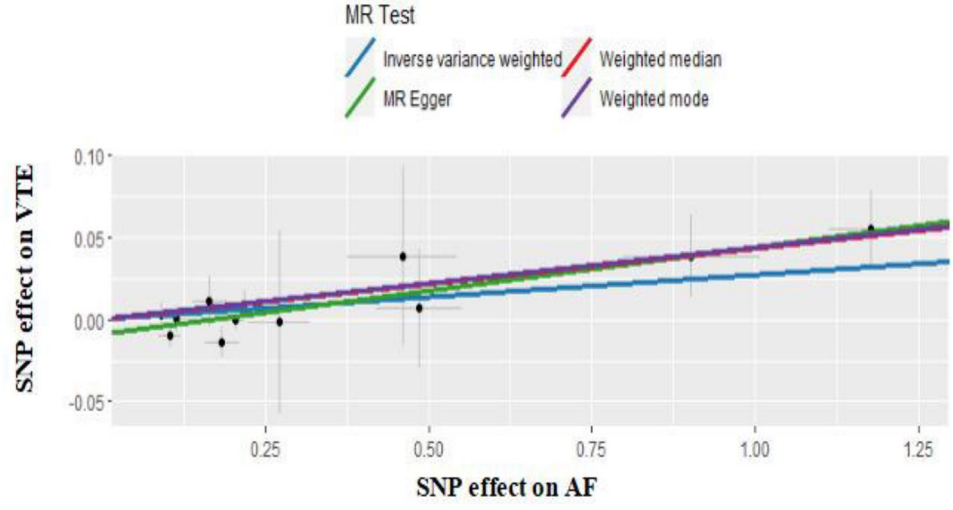

Fig. 3 Scatter_plot in the Mendelian randomization analysis of VTE and AF

(rs2739197) SNPs, we selected 96 SNPs as the IVs in the analysis of the causal effects of AF on VTE. The total R^2 value is 0.159. Each SNP was additionally filtered based on F-statistics greater than the typically accepted value of 10, indicating strong instruments (the mean F-statistic is 1709).

The MR analysis revealed no significant association between genetic predisposition to AF and the risk of VTE, as determined by the IVW method (p=0.7773).

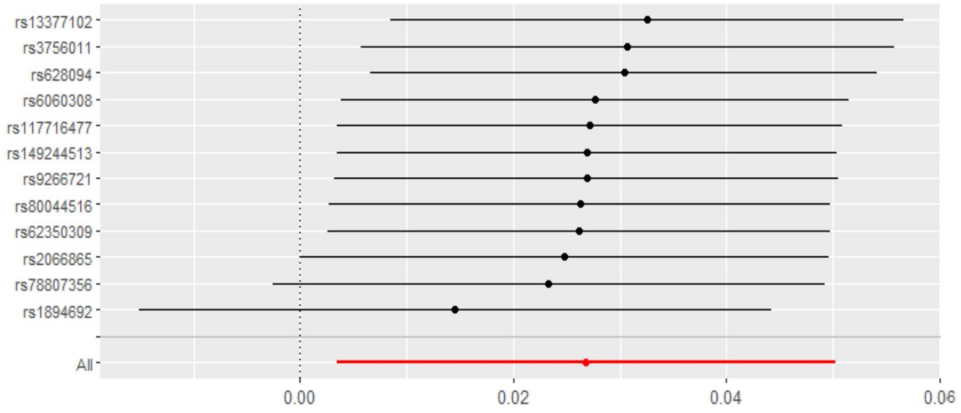

Fig. 4 Leave-one-out sensitivity analysis in the Mendelian randomization analysis of VTE and AF

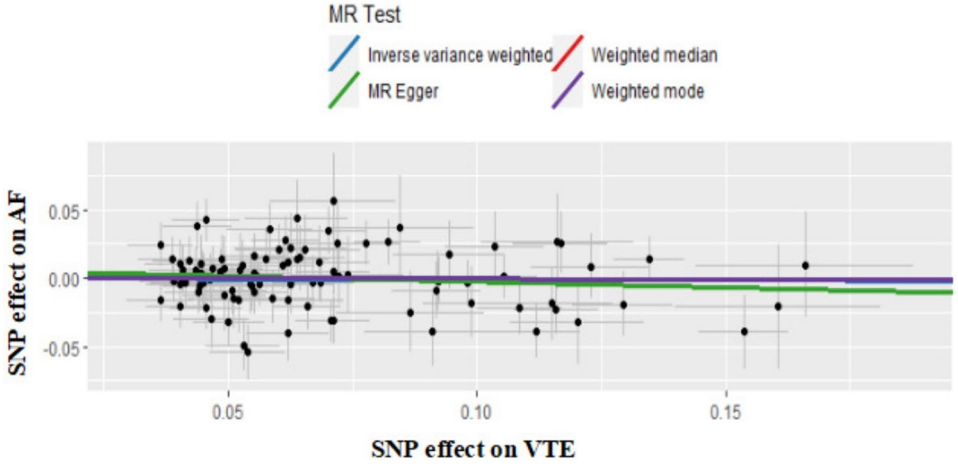

Fig. 5 Scatter_plot in the Mendelian randomization analysis of AF and VTE

MR-Egger (p=0.3208), WM (p=0.9191), and weighted mode (p=0.9541) methods show the same results (Fig. 2). Heterogeneity was not detected, as indicated by Cochran's Q p-value>0.05. No outlier SNPs were detected in the MR-PRESSO analysis. The pleiotropy (p=0.3389) were not statistically significant. Scatter plots using different MR methods are presented in Fig. 5. Sensitivity analyses, including forest plots from leave-one-out analysis of each SNP effect, further confirmed the lack of associations (Fig. 6).

Discussion

Through the utilization of genetic instruments, this study employed causal inference methods to uncover the relationship between VTE and AF. Our findings indicate that VTE is a causal risk factor for AF, while AF does not appear to increase the likelihood of developing VTE.

Previous observational studies demonstrated that patients with VTE increased risk of developing AF [14, 15], this phenomenon being particularly pronounced within the first six months following the initial diagnosis [15]. After adjusting for additional cardiovascular risk factors, this relationship still persists. Pulmonary embolism (PE) and deep vein thrombosis (DVT) are commonly viewed as two clinical manifestations of VTE. Acute PE is considered the most serious form. In a retrospective cohort study of patients diagnosed with acute PE, the incidence of new-onset AF was 9.2% (54 out of 590). Among these, 4.0% (23 patients) had massive PE [16]. Massive PE was identified as an independent risk factor for new-onset AF (OR 2.67; 95% CI: 1.19 to 5.99; p=0.017) [16]. PE can induce AF by elevating pulmonary vascular resistance and increasing the workload on the right ventricle due to obstruction of the pulmonary arteries. Additionally, AF can trigger the release of vasoconstrictive substances and inflammatory cytokines [17, 18]. The pathophysiological mechanisms leading to thrombosis are traditionally explained by the Virchow's triad: stasis, vascular wall damage or dysfunction, and hypercoagulability. Stasis and vascular wall damage or dysfunction can cause hypoxia or inflammation [19]. Hemodynamic stress, inflammation, and oxidative stress

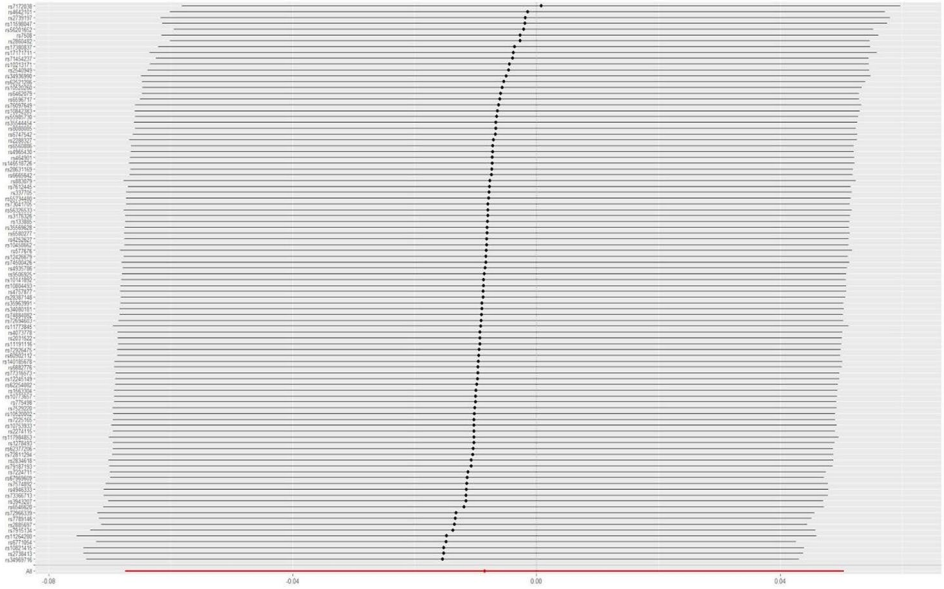

Fig. 6 Leave-one-out sensitivity analysis in the Mendelian randomization analysis of AF and VTE

are considered to play significant roles in the pathogenesis of VTE and AF [19, 20]. Animal model studies propose that blocking coagulation could potentially halt the progression of atrial fibrosis [21], thereby preventing AF. Our study further confirmed the causal relationship between VTE and AF using MR method, consistent with the aforementioned research findings. Therefore, administering anticoagulant therapy for VTE may also lower the occurrence of AF. It is crucial to intensify monitoring and preventive measures for AF in patients with VTE.

AF is widely recognized for its potential to cause blood clots to form in the left atrium, thereby raising the risk of systemic embolism, notably ischemic stroke [5]. AF is associated with an increased risk of VTE, although literature indicates a time-dependent decrease in this risk [14, 15, 22, 23]. However, several factors should be considered for this phenomenon. Firstly, the results could potentially be confounded by circumstantial conditions such as age, concomitant hospitalization and other comorbidities. Moreover, these studies did not take into account oral anticoagulant (OAC) therapy or lacked data on adherence to OAC treatment. Registry studies showed that adherence to guidelines for antithrombotic therapy was low, with only 61% of patients receiving appropriate treatment. Additionally, 17.3% of patients were undertreated, while 21.7% received excessive treatment [24]. In addition, the precise initiation of AF may not necessarily align with the date of initial diagnosis, as symptoms may be subtle, leading to potential delays in diagnosis. Finally, delays in implementing rhythm and rate control, coupled with a cautious approach to promptly initiating anticoagulant treatment, may expose individuals to an increased risk during the early stages following the diagnosis of AF.

Previous research has demonstrated a heightened risk of PE in individuals with AF [14, 23]. The mechanism involves AF facilitating the direct embolization of thrombi formed in the right atrium due to stasis or possibly through a hypercoagulable state [25, 26]. If AF leads to PE, thereby increasing the incidence of VTE, the association between AF and risk of PE without DVT should be stronger than the association between AF and risk of events including DVT. However, this phenomenon was not observed in the study by P L, Lutsey et al. [15]. Meanwhile, AF and PE share several common risk factors, including advanced age, obesity, heart failure, inflammatory states [18], and both conditions are characterized by a procoagulant state [27, 28]. Friberg L et al. showed that the presence of AF did not demonstrate an increased risk of PE after adjusting for comorbidities, medications, and age [29]. An MR study also found no substantial evidence to support a causal role of AF in the development of PE [30]. In addition, strong transient provoking risk factors such as major surgery, prolonged immobilization, and major trauma, along with the most common strong persistent risk factor, active cancer, each contribute to approximately 20% of incident venous thromboembolism episodes [31, 32]. These risk factors are potent enough to lead to VTE even in the absence of other risk factors, but they are relatively uncommon in patients with AF. In our reverse MR analysis, AF does not seem to elevate the probability of developing VTE. Nevertheless, clinicians should be aware that AF and VTE often coexist in individuals with poor health. Patients with AF and concomitant VTE should undergo a comprehensive assessment of thromboembolic risk, with a proactive approach to anticoagulant therapy. Further studies are needed to validate

the relationship and the underlying mechanisms between VTE and AF.

In this study, we further demonstrated that VTE is a causal risk factor for AF. Our findings are likely more robust and reliable due to the use of data from large-scale GWASs, with no significant horizontal pleiotropy, heterogeneity, or outliers detected. Moreover, the MR approach minimizes the influence of confounders and helps prevent reverse causality [33]. However, this study has some limitations. The summary data for GWAS primarily comprised individuals of European genetic heritage. It might restrict the applicability of the results to diverse populations. In our study, we identified statistically significant associations between SNPs and the targeted diseases. The specific contributions of individual SNPs remain unclear [34, 35]. Future investigations are crucial to elucidate the precise mechanisms and causative links between SNPs, pathophysiological alterations, and diseases. Lastly, the results should undergo further validation in robust RCT to demonstrate the existence of a causal relationship.

In Conclusion, there is a unidirectional causal relationship between VTE and AF, meaning that VTE is a causal risk factor for AF, whereas no effect of AF on VTE was identified in this study.

Abbreviations

AF	Atrial Fibrillation
VTE	Venous Thromboembolism
IV	Instrumental Variable
SNPs	Single Nucleotide Polymorphisms
MR	Mendelian Randomization
BMR	bidirectional Mendelian Randomization
GWAS	Genome-Wide Association Study
IVW	Inverse-Variance Weighting
WM	Weighted Median
RCT	Randomized Controlled Trials
MR-PRESSO	MR Pleiotropy Residual Sum and Outlier Test
LD	Linkage Disequilibrium
CAD	Coronary Artery Disease
OR	Odds Ratio
CI	Confidence Interval
PE	Pulmonary Embolism
DVT	Deep Vein Thrombosis
OAC	Oral Anticoagulant

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Author contributions
Caijing Dang designed research and wrote the paper. Caijing Dang, Wenkai Liao and Wenshu Zhao performed research and analyzed the data. Lin Xu and Yuxia Lu reviewed and checked the manuscript.

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Data availability
All the GWAS summary data used in the analyses are accessible through the IEU Open GWAS project. The summary statistics for AF have been downloaded from http://csg.sph.umich.edu/willer/public/afib2018/. The summary statistics for VTE were are available from https://gwas. mrcieu.ac.uk/datasets/finn-b-I9_VTE/.Please contact the corresponding author for any data-related inquiries.

Declarations

Ethics approval and consent to participate
Since the study utilized the public GWAS database or summary-level data, no additional ethics approval was needed. All primary investigations included in this study received ethical approval from the relevant review boards, and all participants provided informed consent. Moreover, this study did not use any individual-level data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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