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Causal association between circulating α-Klotho levels and venous thromboembolism: a two-sample Mendelian randomization study

Yanmin Song[1], Liping Cao[1] and Hui Long[1*]

Abstract

Background α-Klotho may involve in the occurrence and development of venous thromboembolism (VTE). However, the underlying relationship between circulating α-Klotho levels and VTE is still unclear.

Methods This two-sample Mendelian Randomization (MR) study aims to explore the causal associations of circulating α-Klotho levels with different types of venous thromboembolism. Data of exposure and outcomes were extracted from the genome-wide association study (GWAS) of the MRC Integrative Epidemiology Unit (MRC-IEU). The fixed inverse variance weighted (IVW), MR-Egger, MR-Robust Adjusted Profile Score (RAPS) and the weighted-median methods were utilized to investigate the causal associations of circulating α-Klotho levels with different types of VTE. The effect size was expressed as odds ratios (ORs) and 95% confidence intervals (CIs), and the False Discovery Rate (FDR) test was used for correction. The MR scatter plot and leave-one-out test were used for sensitivity analysis. In addition, reverse causal associations were assessed.

Results IVW estimates suggested that an elevated circulating α-Klotho level was associated with lower odds of deep vein thrombosis (DVT) of lower extremities (OR = 0.992, 95%CI: 0.986–0.998, $P = 0.0074$), pulmonary embolism (PE) (OR = 0.474, 95%CI: 0.255–0.881, $P = 0.0183$), and DVT of lower extremities combined with PE (OR = 0.984, 95%CI: 0.971–0.997, $P = 0.0175$). However, after the FDR correction, only negatively causal association between circulating α-Klotho level and increased odds of lower-extremity DVT was statistically significant (FDR $P = 0.0296$). Also, there were no reverse causal associations between the circulating α-Klotho levels and different types of VTE (all $P > 0.05$). Additionally, both the MR scatter plots and leave-one-out test results showed that these causal associations were relatively robust.

Conclusion An elevated circulating α-Klotho levels was associated with lower risk of DVT of lower extremities, PE, and DVT of lower extremities combined with PE, indicating α-Klotho has the potential to act as a target for early screening or treatment for VTE. However, the specific mechanism that α-Klotho influencing the occurrence of VTE still needed further exploration.

Keywords α-Klotho, VTE, DVT of lower extremities, PE, Mendelian randomization

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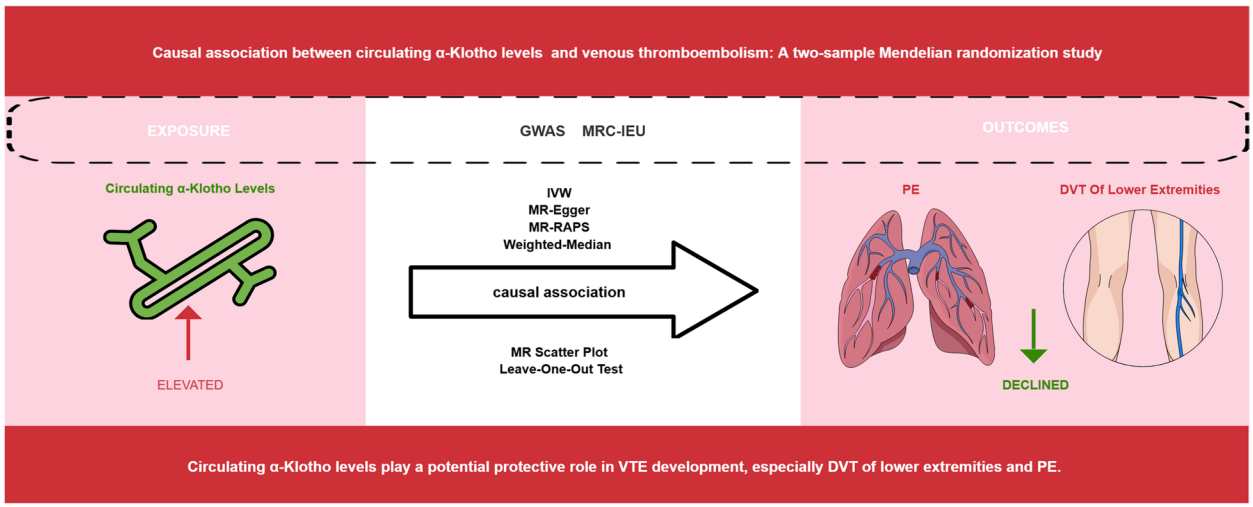
Graphical Abstract



Introduction

Venous thromboembolism (VTE) is the third most common acute cardiovascular syndrome after myocardial infarction and stroke, and mainly includes deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. Up to half of survivors have post-thrombotic syndrome, pulmonary hypertension, and other sequelae, and patients with VTE are more likely to have myocardial infarction and stroke [2–4]. Owing to the growing global population and prolonged life expectancy, the disease burden of VTE has continued to increase. Therefore, active prevention of VTE is highly valuable for reducing the burden of the disease.

α-Klotho is a membrane-binding protein that acts as a receptor for fibroblast growth factor 23 (FGF23) and characterizes the state of aging [5]. Recently, α-Klotho has received attention in cardiovascular health research because of its anti-inflammatory and antioxidant activities, and low levels of α-Klotho have been linked to susceptibility to cardiovascular disease (CVD) and related risk factors [6–9]. Multiple studies have showed that inflammation and oxidative stress are involved in the occurrence and development of VTE [10, 11]. However, the relationship between α-klotho levels and VTE remains unclear.

Mendelian randomization (MR) analysis has become a widely used approach in recent years that utilizes single nucleotide polymorphisms (SNPs) as unconfounded instrumental variants (IVs) to explore the potential causal relationships between environmental exposure and diseases [12]. Compared with traditional observational epidemiological studies, MR can avoid reverse causality inferences and reflect the long-term effects of exposure on outcomes [13]. To date, no studies have used the MR method to investigate the causal association between circulating α-klotho levels and VTE.

This study aimed to explore the causal association between circulating α-Klotho levels and VTE via a two-sample MR to provide evidence-based evidence for the prevention and exploration of potential therapeutic targets for VTE.

Methods

Data sources

Figure 1 shows the process of two-sample MR analysis. Data on study exposure (circulating α-Klotho levels) and outcomes, including VTE, deep venous thrombosis (DVT), DVT of lower extremities, pulmonary embolism (PE), and DVT of lower extremities combined with PE, were extracted from genome-wide association studies (GWASs) in the MRC Integrative Epidemiology Unit (MRC-IEU) (https://gwas.mrcieu.ac.uk/). The detailed data sources are presented in Table S1. Each GWAS involved obtaining ethical approval from the respective institution and all participants provided informed consent. Because these databases are publicly available, ethical approval was waived by the institutional review board of our hospital.

Single nucleotide polymorphism selection

The IVs were SNPs that were significantly associated with circulating α-Klotho levels, with a selection threshold

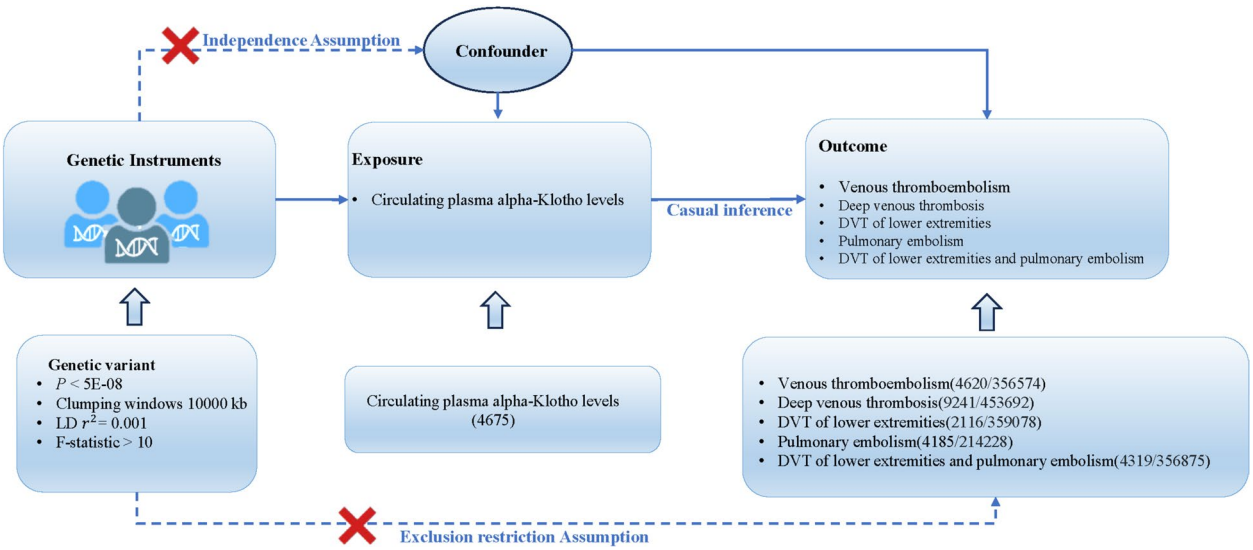


Fig. 1 Flowchart of the study process. The study exposure was circulating α-Klotho; study outcomes were different types of VTE. The main process included IVs selection, MR three assumptions, MR analysis and sensitivity analysis

of $P<5.0\times10^{-8}$. SNPs with linkage disequilibrium (LD) were deleted with a threshold of $r^2=0.001$ and clumping distance of 10,000 kb. Palindromic SNPs were also removed because the MR principle ensures that the same allele corresponds to the effects of SNPs and exposure and to the effects on the outcome.

The assumptions of MR analysis

The MR analysis must conform to three significant assumptions to minimize the impact of bias on the results. First, the IVs must be independent of confounders related to the exposure and outcome. Second, IVs were significantly associated with exposure. The MR-Egger regression test was used to monitor the potential horizontal pleiotropic effects that may have violated the second assumption of MR, which was a confounding effect caused by other diseases. The significant intercept item of the MR-Egger test indicated the existence of pleiotropy. In addition, the association between exposure and IVs was evaluated using the following formula:

$$F=\frac{N-K-1}{K}\times\frac{R^2}{1-R^2}$$

$$R^2=2\times(1-MAF)\times MAF\times\beta^2$$

where, β is the effect size of the SNP on exposure, k is the number of IVs, n is the sample size of the exposure, and MAF is the minor allele frequency. Weak associations between the IVs and exposure were observed when $F<10$. Third, IVs influence outcomes through exposure only; there is no horizontal pleiotropic effect of IVs on the outcomes.

Statistical analysis

Causal effect values were calculated using the fixed inverse variance weighted (IVW) test, which is the primary method used to obtain unbiased estimates when horizontal pleiotropy is absent. The effect size was expressed as odds ratio (ORs) and 95% confidence interval (CIs). Also, the False Discovery Rate (FDR) test was used for correction. The Statistical significance of evidence for potential causal effects was set at $P<0.05$. MR-Egger, MR-Robust Adjusted Profile Score (RAPS), and weighted median were also used to assess the causal associations between circulating α-Klotho levels and different types of VTE. The MR-RAPS offers a good opportunity to probe the issue of weak instrument bias and efficiency gain by including many weak IVs. The weighted median method provides a robust and consistent estimate of the effect, even if nearly 50% of genetic variants are invalid instruments [14]. The test for heterogeneity was performed using the Cochrane Q test with the following formula:

$$Q=\sum_j se\left(\widehat{\theta}_j\right)^{-2}\left(\widehat{\theta_{IVW}}-\widehat{\theta}_j\right)^{-2}$$

IVs ($P<0.05$) were recognized as heterogeneous. The MR scatter plot and leave-one-out test were used for sensitivity analysis. In addition, reverse causal associations were assessed. Statistical analyses were performed using

the R version 4.2.0 (Institute for Statistics and Mathematics, Vienna, Austria). The R package "TwoSampleMR" was used for the MR analysis of the causal associations between circulating α-Klotho levels and different types of VTE, as well as between circulating α-Klotho levels and multiple inflammatory factors.

Results

IVs selection

Initially, using the selection threshold, we selected 297 SNPs as potential IVs. After removing LD or palindromic SNPs, 6 of them were eligible. Also, those significantly related to the outcome variables were deleted. Finally, 3 SNPs were used as IVs in the MR analyses for causal association between circulating α-Klotho levels and VTE; 4 SNPs were used as IVs in those for causal association between circulating α-Klotho levels and other types of VTE, respectively (Table 1). Additionally, the R^2 values of selected IVs correlations were shown in the Table S2.

Table 2 shows the results of the tests for horizontal pleiotropy, heterogeneity, and the strength of the selected IVs. After quality control, according to the MR-Egger intercept values, no potential horizontal pleiotropy was observed in the association of circulating α-Klotho levels related IVs with different outcomes (all $P > 0.05$). The selected IVs also showed no heterogeneity (all $P > 0.05$), and all F values were > 10.

Causal associations between circulating α-Klotho levels and different types of VTE

As shown in Table 3, IVW estimates showed that an elevated circulating α-Klotho level was associated with lower odds of lower-extremity DVT (OR = 0.992, 95%CI: 0.986–0.998, $P = 0.0074$), PE (OR = 0.474, 95%CI: 0.255–0.881, $P = 0.0183$), and DVT of the lower extremities combined with PE (OR = 0.984, 95%CI: 0.971–0.997, $P = 0.0175$). However, after the FDR correction, only negatively causal association between circulating α-Klotho level and increased odds of lower-extremity DVT was statistically significant (FDR $P = 0.0296$).

Causal associations of α-Klotho with multiple inflammatory-related factors, including interleukin (IL)−1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-13, IL-16, IL-17, IL-18, and tumor necrosis factor (TNF)-α were also investigated. The results showed that IL-4 (OR = 0.926, 95%CI: 0.866–0.989, FDR $P = 0.0461$) and IL-6 (OR = 0.916, 95%CI: 0.857–0.979, FDR $P = 0.0192$) have causal association with circulating α-Klotho, respectively (Table S3).

We further explored the reverse causal associations between circulating α-Klotho levels and the different types of VTE (Table 4). The results showed that there were no significant causal associations between the different types of VTE and circulating α-Klotho levels (all $P > 0.05$), indicating that the associations of circulating

Table 1 Process of IVs selection

Exposure	Outcomes	Selected SNPs ($P < 5 \times 10^{-8}$)	Omitted LD SNPs	Dropped palindromic SNPs	Removed SNPs associated with outcomes
Circulating plasma α-Klotho levels	VTE	297	6	6	3
	DVT	297	6	6	4
	DVT of lower extremities	297	6	6	4
	PE	297	6	6	4
	DVT of lower extremities and PE	297	6	6	4

SNP single nucleotide polymorphism, *LD* linkage disequilibrium, *VTE* venous thromboembolism, *DVT* deep vein thrombosis, *PE* pulmonary embolism

Table 2 Test for horizontal pleiotropy, heterogeneity and strength between IVs and exposure

Outcomes	Strength		Horizontal pleiotropy test		Heterogeneity test			
	F value	R^2 (%)	Egger intercept	*P*	Egger regression		IVW	
					Egger Q	*P*	IVW Q	*P*
VTE	45.291	0.959	−0.00002	0.9861	2.2887	0.1303	2.2898	0.3183
DVT	63.413	1.334	−0.00036	0.5890	0.2055	0.9024	0.6119	0.8937
DVT of lower extremities	63.413	1.334	0.00001	0.9829	0.975	0.6142	0.9756	0.8072
PE	63.413	1.334	−0.01215	0.7950	0.5731	0.7508	0.6609	0.8824
DVT of lower extremities and PE	63.413	1.334	0.00011	0.8534	2.2203	0.3295	2.2691	0.5185

IV instrumental variant, *IVW* inverse variance weighted, *VTE* venous thromboembolism, *DVT* deep vein thrombosis, *PE* pulmonary embolism

Table 3 Causal associations between circulating α-Klotho levels and different types of VTE

Outcomes	SNPs	Methods	OR (95% CI) [a]	*P*	FDR *P*
VTE	3	IVW fixed	0.991 (0.968–1.014)	0.4183	0.9144
		MR-Egger	0.992 (0.902–1.090)	0.8885	0.9680
		MR-RAPS	0.989 (0.960–1.019)	0.4572	0.9144
		Weighted median	1.001 (0.945–1.060)	0.9680	0.9680
DVT	4	IVW fixed	0.993 (0.986–1.001)	0.0988	0.3951
		MR-Egger	1.011 (0.955–1.070)	0.7428	0.7683
		MR-RAPS	0.993 (0.970–1.017)	0.5643	0.7683
		Weighted median	0.994 (0.957–1.033)	0.7683	0.7683
DVT of lower extremities	4	IVW fixed	0.992 (0.986–0.998)	**0.0074**	**0.0296**
		MR-Egger	0.991 (0.957–1.027)	0.6702	0.6702
		MR-RAPS	0.991 (0.977–1.006)	0.2346	0.3894
		Weighted median	0.992 (0.976–1.007)	0.2921	0.3894
PE	4	IVW fixed	0.474 (0.255–0.881)	**0.0183**	0.0732
		MR-Egger	0.839 (0.015–45.476)	0.9390	0.9390
		MR-RAPS	0.456 (0.073–2.871)	0.4031	0.5900
		Weighted median	0.444 (0.056–3.529)	0.4425	0.5900
DVT of lower extremities and PE	4	IVW fixed	0.984 (0.971–0.997)	**0.0175**	0.0702
		MR-Egger	0.979 (0.928–1.032)	0.5059	0.5059
		MR-RAPS	0.982 (0.962–1.003)	0.0937	0.1873
		Weighted median	0.985 (0.964–1.007)	0.1710	0.2280

VTE venous thromboembolism, *SNP* single nucleotide polymorphism, *OR* odds ratio, *CI* confidence interval, *IVW* inverse variance weighted, *MR-RAPS* MR-Robust Adjusted Profile Score, *DVT* deep vein thrombosis, *PE* pulmonary embolism

[a] OR values of exposure were reduced by 10 units

Table 4 Reverse causal associations between circulating α-Klotho levels and different types of VTE

Exposures	Methods	SNPs	β (95% CI) [a]	*P*
DVT of lower extremities	IVW fixed	4	1.275 (0.720–2.260)	0.4044
	MR-Egger		0.943 (0.042–21.130)	0.9737
	MR-RAPS		1.275 (0.096–16.942)	0.8537
	Weighted median		1.150 (0.072–18.305)	0.9211
PE	IVW fixed	5	1.002 (0.994–1.009)	0.6617
	MR-Egger		1.006 (0.937–1.080)	0.8741
	MR-RAPS		1.002 (0.975–1.029)	0.9014
	Weighted median		1.003 (0.972–1.034)	0.8631
DVT of lower extremities and PE	IVW fixed	7	1.158 (0.841–1.594)	0.3689
	MR-Egger		1.046 (0.114–9.632)	0.9696
	MR-RAPS		1.158 (0.240–5.590)	0.8551
	Weighted median		1.052 (0.176–6.304)	0.9558

VTE venous thromboembolism, *SNP* single nucleotide polymorphism, *CI* confidence interval, *DVT* deep vein thrombosis, *IVW* inverse variance weighted, *MR-RAPS* MR-Robust Adjusted Profile Score, *PE* pulmonary embolism

[a] β values of outcomes were reduced by 10 units

α-Klotho levels with DVT of the lower extremities and PE and DVT of lower extremities combined with PE were unidirectional.

Sensitivity analysis

We confirmed the impact of relatively accurate MR results; that is, the potential causal associations between circulating α-Klotho levels and DVT in the lower

extremities, PE, and DVT in the lower extremities combined with PE by sensitivity analysis. Specifically, the MR scatter plots showed a consistent trend of a causal association between the circulating α-Klotho level and DVT of lower extremities, between the circulating α-Klotho level and PE, and between the circulating α-Klotho level and DVT of lower extremities combined with PE evaluated using different MR methods (Fig. 2). In addition, the leave-one-out test (Fig. 3) indicated that there were no significant outliers and that the potential causal associations were relatively robust.

Discussion

This two-sample MR analysis investigated the causal associations between circulating α-klotho levels and the different types of VTE. The results showed that an elevated circulating α-Klotho level was associated with lower odds of DVT of lower extremities, PE, and DVT of lower extremities combined with PE. These potential causal associations were unidirectional.

To the best of our knowledge, few studies have explored the causal associations between α-klotho levels and various diseases. Sun et al. [9] identified five SNPs associated with circulating α-Klotho levels and found evidence of a protective effect of circulating α-Klotho in the prevention of atrial fibrillation (AF) risk. α-Klotho has been identified as an aging suppressor gene. In recent years, scientists have focused on the role of circulating α-Klotho in CVD risk, and the protective role of α-Klotho has been reported to be inversely associated with the risk of coronary artery disease (CAD) and AF [15, 16]. Based on these findings, an in-depth exploration of the protective role of α-Klotho levels may help identify potential targets for the prevention and treatment of vascular diseases. VTE, a common acute cardiovascular syndrome that occurs after myocardial infarction and stroke, causes enormous disease burden. Therefore, we discussed the causal association between circulating α-Klotho levels and VTE and found negative associations between circulating α-Klotho levels and the two most common types of VTE, namely, DVT of the lower extremities and PE.

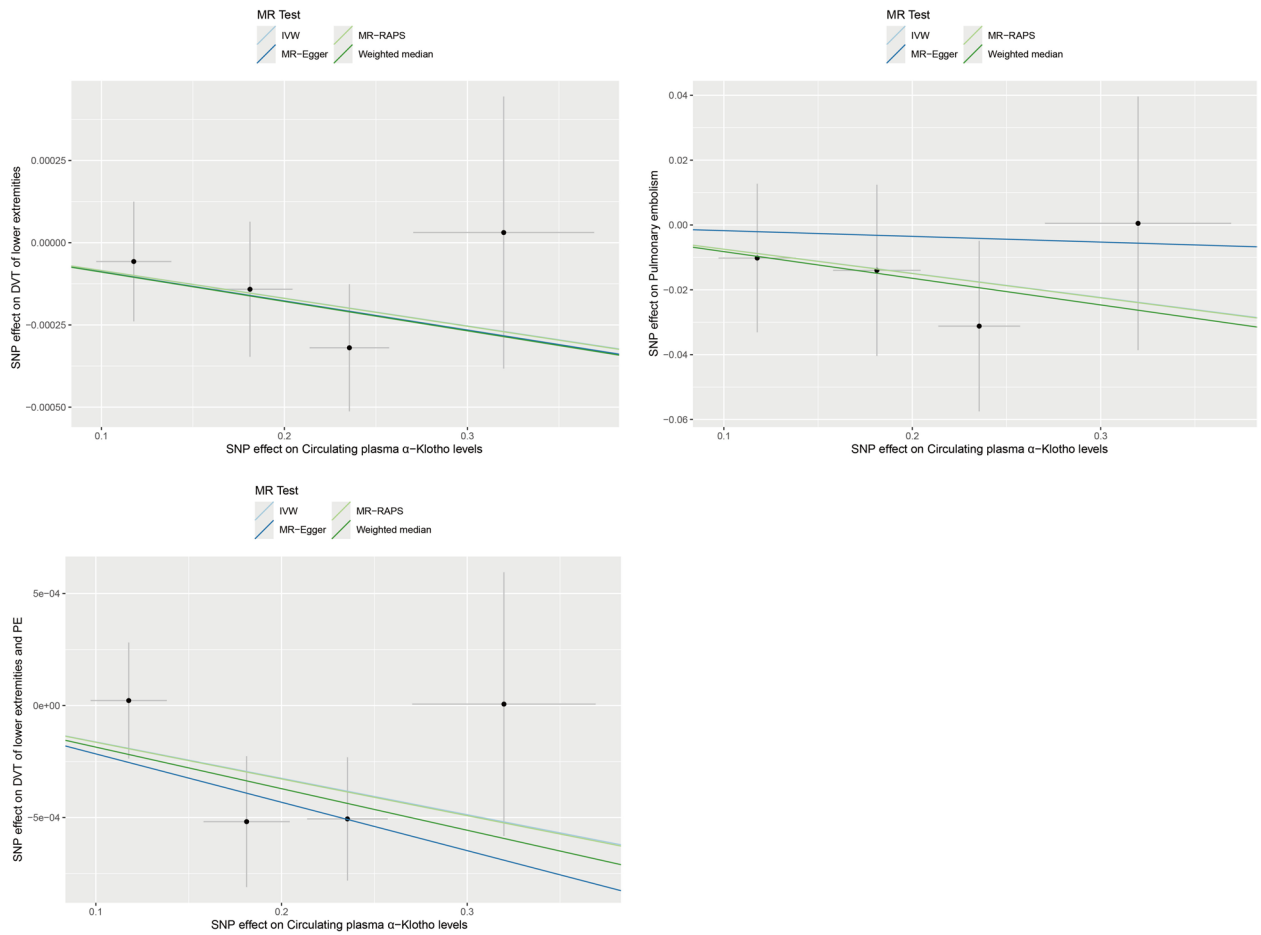


Fig. 2 The MR scatter plots of causal associations between the circulating α-Klotho levels and different types of VTE

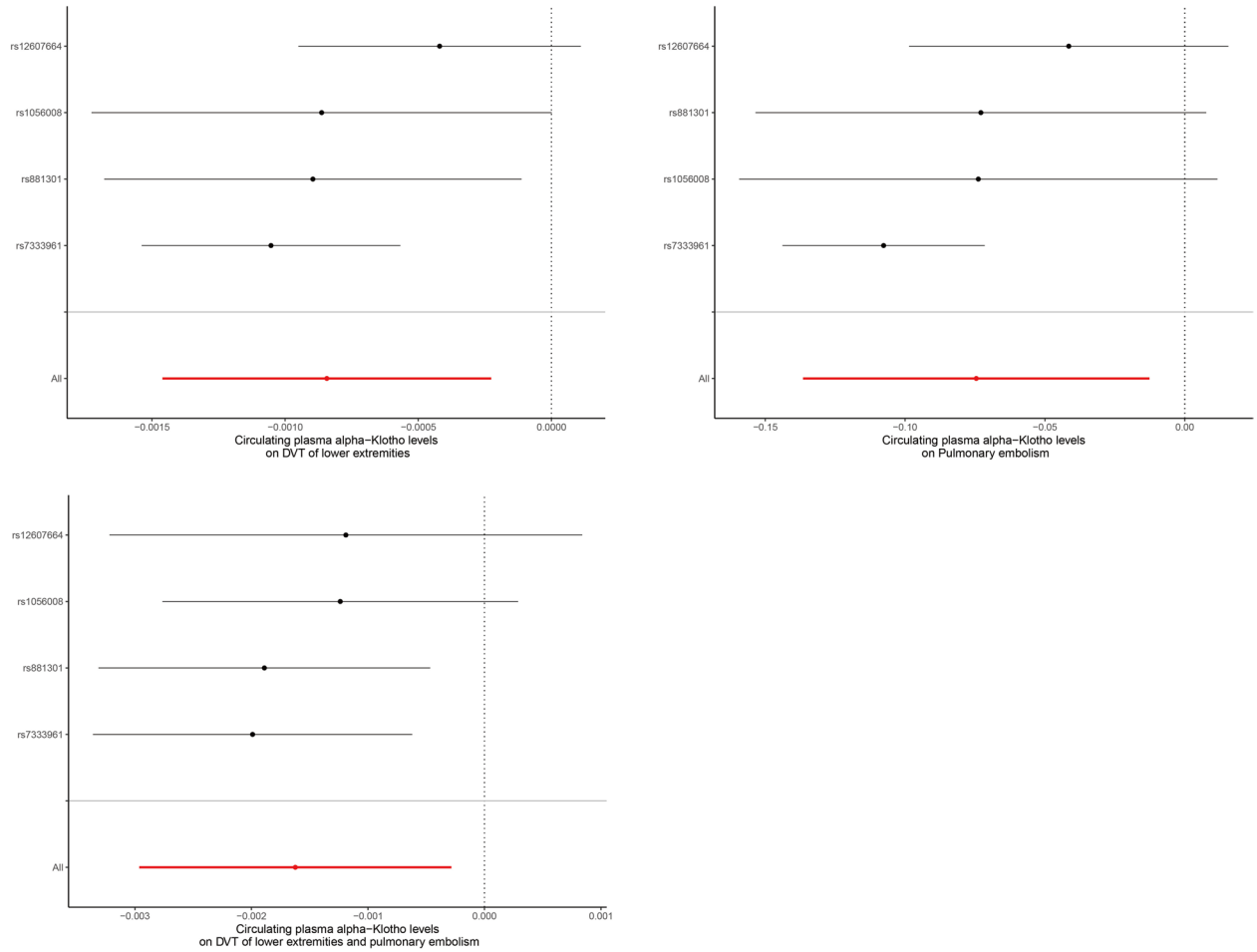


Fig. 3 The MR leave-one-out test of causal associations between the circulating α-Klotho levels and different types of VTE

In addition, a soluble form of α-Klotho is generated by the cleavage of transmembrane α-Klotho, which is readily detected in circulation and henceforth referred to as circulating α-Klotho [17]. This also suggested the clinical significance of our study, namely that circulating α-Klotho may serve as a cheap and convenient indicator for early screening of VTE or a potential target for subsequent treatment, especially in DVT of the lower extremities and PE.

Although the mechanisms by which circulating α-Klotho levels play a potential protective role in the occurrence of VTE are currently unclear, some of the reported conclusions regarding the association between aging and VTE can provide speculations. Klotho possesses multiple pleiotropic activities, including inhibition of major signaling pathways, reduction of oxidative stress, and suppression of inflammation [18]. A cross-sectional single-center case–control study in patients with CVD showed that in peripheral blood circulating cells and vasculature, α-Klotho gene expression correlated inversely with pro-inflammatory markers and directly with anti-inflammatory markers, including tumor necrosis factor (TNF)-α, interleukin (IL)−10, nuclear factor-kappa-B (NFκB)−1, DNA methyltransferase (DNMT)−1 and DNMT-3A [19]. Inflammation generally functions as a double-edged sword and can be both a cause and consequence of VTE [20]. Active IL-1β and IL-18 which produced by NLRP3 inflammasome, contributing to the inflammatory pathogenesis of VTE. Recent preclinical studies have shown that inhibition of IL-1 signaling reduces venous thrombogenesis and may favor vein wall healing, suggesting that these therapeutic approaches may have the potential to reduce the occurrence and recurrence of VTE [21–23]. In addition, α-Klotho acts as a transmembrane co-receptor for fibroblast growth factor 23 (FGF23) and is a key regulator of phosphate homeostasis. In an experimental study on airway inflammation, downregulation of klotho expression resulted in FGF23 signaling, which ultimately led to an increase in IL-1β secretion [24]. MR evidence of α-Klotho

levels suggested regulation by mechanisms other than phosphate homeostasis and raised the possibility of cross-talk with FGF19- and FGF21-dependent pathways [25]. In the present study, we explored the causal associations of α-Klotho with multiple inflammatory-related factors, and the results suggested that IL-4 and IL-6 both have causal associations with α-Klotho, which may help explain the potential inflammatory status in causal association between α-Klotho and VTE risk. Nevertheless, since mediation effect analysis or multivariate MR analysis could not be conducted due to the limitation of SNPs, whether α-Klotho influencing the occurrence of VTE through inflammation pathways in this relationship is unclear. Also, Federico et al. [26] reported that FGF-21 was not associated with incident VTE, stroke, or CVD-related mortality. In addition, aging related process, including the telomere length, DNA methylation, histone modification and mitochondrial DNA copy number, may also be involved in the pathway that α-Klotho affecting VTE [27, 28].

As mentioned previously, MR is a relatively superior study design for clarifying the causal effect of potential risk factors on diseases of interest. By exploring the potential causal associations of circulating α-Klotho levels with different subtypes of VTE risk, this study may provide a new idea for a potential target of prevention and intervention for VTE, especially DVT of the lower extremities and PE, which may further reduce the incidence and social burden of VTE. Compared to previous studies, the current study supplemented the literature and provided evidence for further exploration of the specific mechanisms by which circulating α-Klotho levels unidirectionally influence VTE risk. Sensitivity analyses using MR scatter plots and leave-one-out tests also suggested robust potential causal associations between circulating α-Klotho levels and VTE. However, limitations in this study limited the conclusions to some extent. As the included GWASs included only European populations, the study results cannot be extended to non-European populations. Other influencing factors, such as genetic heterogeneity or unknown functions of SNPs, may also influence the causal association between circulating α-Klotho levels and VTE. Additionally, the possible nonlinear association between α-Klotho and VTE could not be assessed because of the lack of individual data.

Conclusion

Circulating α-Klotho levels play a potential protective role in VTE development, especially DVT of lower extremities and PE. These findings may provide information for further exploration of the specific mechanisms in this pathway and on target indices for VTE prevention and treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12959-025-00691-2.

Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

Statistical analysis: Writing–original draft, YMS, HL; Conception–writing–reviewing and editing, YMS, LPC,, HL. All authors have read and approved the final version of the manuscript.

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Data availability

Our study used publicly available summary-level data from GWAS. It is possible to download summary statistics on circulation α-Klotho level and different types of venous thromboembolism at the following website: https://gwas.mrcieu.ac.uk/.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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