

The effects of coagulation factors on the risk of Alzheimer's disease: A Mendelian randomization study

Journal of Alzheimer's
Disease Reports
Volume 9: 1–9
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DOI: 10.1177/25424823251327674
journals.sagepub.com/home/alr



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Abstract

Background: Observational studies indicate a complex relationship between coagulation factors and Alzheimer's disease (AD). However, the current findings are inconsistent, and it remains uncertain whether a causal relationship exists.

Objective: This study utilizes a Mendelian randomization analysis to investigate the causal relationships between blood levels of coagulation factors and AD risk.

Methods: Eleven coagulation factors with valid instrumental variables available were evaluated. Two independent cohorts of European ancestry with AD genome-wide association study (GWAS) summary statistics were used: UK Biobank (UKB, N=472,868) and the International Genomics of Alzheimer's Project (IGAP, N=63,926). We primarily conducted Mendelian randomization (MR) analyses using the Inverse variance weighted (IVW). Meanwhile, the MR-Egger intercept test is used to detect horizontal pleiotropy, the Residual Sum of Squares observed (RSSobs) is used to assess the model's goodness of fit, and the leave-one-out analysis is employed for sensitivity analysis.

Results: Using IVW analysis, the UKB database shows positive correlations of Protein C (PC, $p = 0.002$), Activated Partial Thromboplastin Time (aPTT, $p = 0.019$), and coagulation factor X (FX, $p = 0.032$) with AD, and a negative association for coagulation factor XI (FXI, $p = 0.021$). The IGAP database mirrors these findings for PC and FXI but not for the others. Leave-one-out analysis showed an anomaly after a single single nucleotide polymorphism (SNP) driving, yet the overall results remained stable.

Conclusions: This study demonstrates that elevated levels of PC, FX, and aPTT, along with reduced levels of FXI, are causally associated with an increased risk of AD. These findings might pave the way for the diagnosis and treatment of AD.

Keywords

Alzheimer's disease, coagulation factor, genome-wide association study, two-sample Mendelian randomization

Received: 15 October 2024; accepted: 21 February 2025

Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, impacting over 35 million individuals worldwide.¹ Coagulation function is critical in forming thrombi upon vascular injury to prevent bleeding and chronic dysregulation of coagulation, which can lead to severe consequences.² Previous research indicates that coagulation dysfunction can lead to microvascular injury and cerebral microbleeds, accelerating the progression of AD.³ Meanwhile, other studies have found that coagulation abnormalities can promote amyloid-beta (A β) deposition

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and neuroinflammatory responses, which likewise ultimately accelerate the progression of AD.⁴

Coagulation factors are a series of proteins that play a critical role in activating the coagulation cascade, ensuring the rapid and effective formation of fibrin clots in response to injury.⁵ Indeed, previous studies have demonstrated that coagulation factors also play an important role in the pathogenesis of AD via regulating cerebrovascular lesions and neuroinflammation.⁶ For instance, knocking out specific coagulation factor XII (FXII) has been shown to improve cognitive impairment in AD.⁷ Protein C (PC), a natural anticoagulant primarily regulating the coagulation process, exerts anti-inflammatory and neuroprotective properties via the PC-related pathways in AD.⁸ Furthermore, observational studies showed that the levels of coagulation factor XI (FXI) and activated partial thromboplastin time (aPTT) were significantly increased in AD patients compared to healthy controls.^{9,10} However, results from other studies suggested that FXI levels were significantly decreased in AD patients,⁴ while no significant change was observed in aPTT.¹¹ Since traditional observational studies are susceptible to confounding factors and reverse causation,¹² which may distort the observed relationships, it remains largely unknown whether the associations between coagulation factors and AD are truly causal.

Mendelian randomization (MR) study has currently been widely applied to infer the etiology in epidemiology.¹³ This approach leverages the random and independent distribution of genetic alleles during the process of inheritance from parents to offspring, leading to a stochastic genetic variation among the progeny.¹⁴ In MR analysis, this inheritance variation is often employed as the instrumental variable (IV) for the exposure.¹⁵ As genetic variants are distributed like the random assignment of individuals in randomized controlled trials,¹⁶ MR supports an intuitive deduction of causality between potential risk factors and diseases while diminishing the influence of confounding factors. Although the relationship between coagulation factors and AD has been widely explored, most studies are observational, significantly limiting the exploration of causal relationships.^{4,7,9,10} Thus, we conducted a two-sample MR study to determine whether there was a causal link between blood levels of coagulation factors and AD risk.

Methods

Study design and instrument variable selection

Three assumptions need to be satisfied for a valid MR analysis.¹⁷ Assumption 1 (Relevance): The IV is significantly associated with coagulation factors at the genome-wide level. Assumption 2 (Independence): The IV is not correlated with potential confounding factors that could influence both coagulation factors and AD. Assumption 3

(Exclusion restriction): The IV does not directly cause AD, and it can only affect AD through its impact on coagulation factors. The overall design of this study is shown in Figure 1.

To investigate the causal relationship between coagulation factors and AD, we searched for GWASs of coagulation factors in European populations to curate genetic variants associated with coagulation factors. The selection of IVs was based on the following criteria. Initially, single nucleotide polymorphisms (SNPs) significantly associated with specific coagulation factors ($p < 5 \times 10^{-7}$) were identified as candidate IVs for MR analysis. The F-statistic was calculated to assess the strength of the selected IVs.¹⁸ An F-statistic greater than 10 indicates a strong IV, helping to rule out bias from weaker IVs. Subsequently, we clustered IVs in linkage disequilibrium (LD, $r^2 < 0.001$ within 10 Mb). Finally, 11 coagulation factors, including von Willebrand factor (vWF), coagulation factor VIII (FVIII), PC, coagulation factor X (FX), plasminogen activator inhibitor-1 (PAI-1), A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13), Plasmin, FXI, aPTT, endogenous thrombin potential (ETP), and coagulation factor VII (FVII) of European populations with valid IVs available as reported in the previous study,¹⁹ were used to explore the causal relationship between coagulation factors and AD. SNPs with inconsistent alleles and palindromic SNPs with unclear haplotypes were also excluded, and the SNPs used in the final MR analysis were archived in Supplemental Table 1. All operations were performed using the R package TwoSampleMR (v0.5.7).²⁰

Data sources

Genome-wide association study (GWAS) data on the 11 coagulation factors, including vWF, ADAMTS13, aPTT, FVII, FXI, FVII, FX, ETP, PAI-1, protein C, and plasmin, were from previously published studies with data publicly available,^{21–29} which was summarized in a recent study by Li and colleagues.¹⁹ Subsequently, to clarify the causal relationship between coagulation factors and the risk of AD, we searched for AD GWAS summary data from two cohorts, including the UK Biobank (UKB) and the International Genomics of Alzheimer's Project (IGAP). UKB is a large-scale biomedical database and research resource containing de-identified genetic, lifestyle, and health information and biological samples from half a million UK participants. The UKB contains a total of 472,868 samples and 10,602,762 SNPs, among which 53,042 individuals were diagnosed with AD or had parents or siblings with dementia (GWAS ID: ebi-a-GCST90012877). These patients were diagnosed according to the NINCDS-ADRDA clinical criteria or

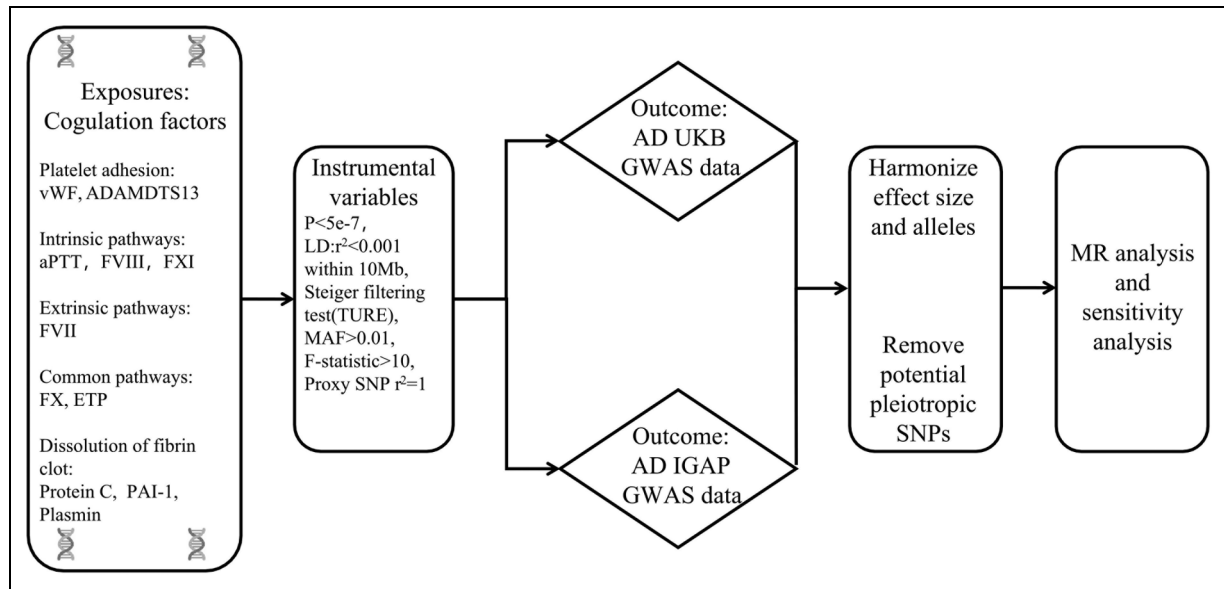


Figure 1. Study design for this Mendelian randomization study. AD, Alzheimer's disease; SNPs, single nucleotide polymorphisms; LD, linkage disequilibrium; MAF, minor allele frequencies; MR, Mendelian randomization; UKB, UK Biobank; IGAP, International Genomics of Alzheimer's Project.

DSM-IV guidelines. Another database comes from the meta-analysis conducted by the IGAP, including 63,926 samples and 10,528,610 SNPs (GWAS ID: ieu-b-2). IGAP is an international collaborative effort aimed at identifying genetic variations associated with AD through large-scale genomic analyses. All detailed information can be found in Table 1.

Mendelian randomization analysis

The causal link between the coagulation function and AD was primarily evaluated using the random-effects inverse variance weighted (IVW) method, a widely applied approach in MR analysis.³² IVW provides a weighted average effect estimate based on the statistical precision of all instrumental variables.³³ We also employed Maximum likelihood, MR Egger, Simple median, Weighted median, and Weighted mode to verify the stability of the MR estimates. Additionally, the MR-Egger method is primarily used to detect and correct for horizontal pleiotropy, and the Residual Sum of Squares observed (RSSobs) assesses the fit of the model predictions to the observed data.^{34,35} Cochran's Q test was used to assess the heterogeneity of the MR study. Moreover, to evaluate the impact of each SNP on the overall MR estimate, a leave-one-out sensitivity test was implemented via conducting permutation analysis by eliminating one IV each time. When the number of SNPs is less than five, a leave-one-out analysis will not be performed. Statistical power for the MR analysis was calculated as previously described.³⁶ All statistical analyses were conducted using the TwoSampleMR

package (version 0.5.7) in R software.²⁰ A p-value of less than 0.05 was considered statistically significant.

Results

Following the selection process, the number of SNPs available as IVs in the UKB and IGAP datasets ranges from 2 to 14 (Supplemental Table 1). Using the IVW method in the UKB dataset, we found that PC (OR = 1.092, 95% CI = 1.033 to 1.155, $p = 0.002$), FX (OR = 1.057, 95% CI = 1.005 to 1.112, $p = 0.032$), and aPTT (OR = 1.010, 95% CI = 1.002 to 1.019, $p = 0.019$) are positively correlated with AD, while FXI (OR = 0.970, 95% CI = 0.946 to 0.996, $p = 0.021$) is negatively associated with AD (Figure 2). In the IGAP dataset, similar results were obtained for PC (OR = 1.134, 95% CI = 1.044 to 1.232, $p = 0.003$) and FXI (OR = 0.959, 95% CI = 0.927 to 0.991, $p = 0.014$). However, no causal relationship with AD was found for aPTT (OR = 1.012, 95% CI = 0.999 to 1.025, $p = 0.062$) and FX (OR = 1.016, 95% CI = 0.941 to 1.096, $p = 0.688$). Other coagulation factors showed no significant causal relationship with AD, with all results presented in Figure 2. The Maximum likelihood, Simple median, Weighted median, and Weighted mode methods yielded similar results with the same trend as IVW (Figure 3), although not all results were statistically significant (Supplemental Table 2). There was no significant heterogeneity observed in Cochran's Q test. No obvious horizontal pleiotropy was observed in the MR-Egger intercept and MR-PRESSO test. Additionally, there was no outlier found in the MR-PRESSO test (Table 2). The results of the

Table 1. GWAS summary data on coagulation factors and Alzheimer's disease were used in this study.

Exposure/outcome	Author	Year	Sample size (N)	PMID	Ancestry
vWF	Sabater-Lleal M et al. ²¹	2019	42,256	30586737	European
ADAMDT513	Ma Q et al. ²²	2017	2304	29296746	European
aPTT	Tang W et al. ²⁷	2012	9240	22703881	European
FVIII	Sabater-Lleal M et al. ²¹	2019	29,573	30586737	European
FXI	Suhre K et al. ²⁸	2017	997	28240269	European
FVII	de Vries PS et al. ²³	2019	27,495	30642921	European
FX	Sun BB et al. ²⁴	2018	3301	29875488	European
ETP	Rocanin-Arjo A et al. ²⁵	2014	1967	24357727	European
PAI-I	Huang J et al. ²⁹	2012	19,599	22990020	European
Protein C	Tang W et al. ²⁶	2010	8048	20802025	European
Plasmin	Sun BB et al. ²⁴	2018	3301	29875488	European
Alzheimer's disease (UKB)	Schwartzentruber et al. ³⁰	2021	472,868	33589840	European
Alzheimer's disease (IGAP)	Kunkle et al. ³¹	2019	63,926	30820047	European

UKB, UK Biobank; IGAP, International Genomics of Alzheimer's Project; MR, Mendelian randomization; N, number.

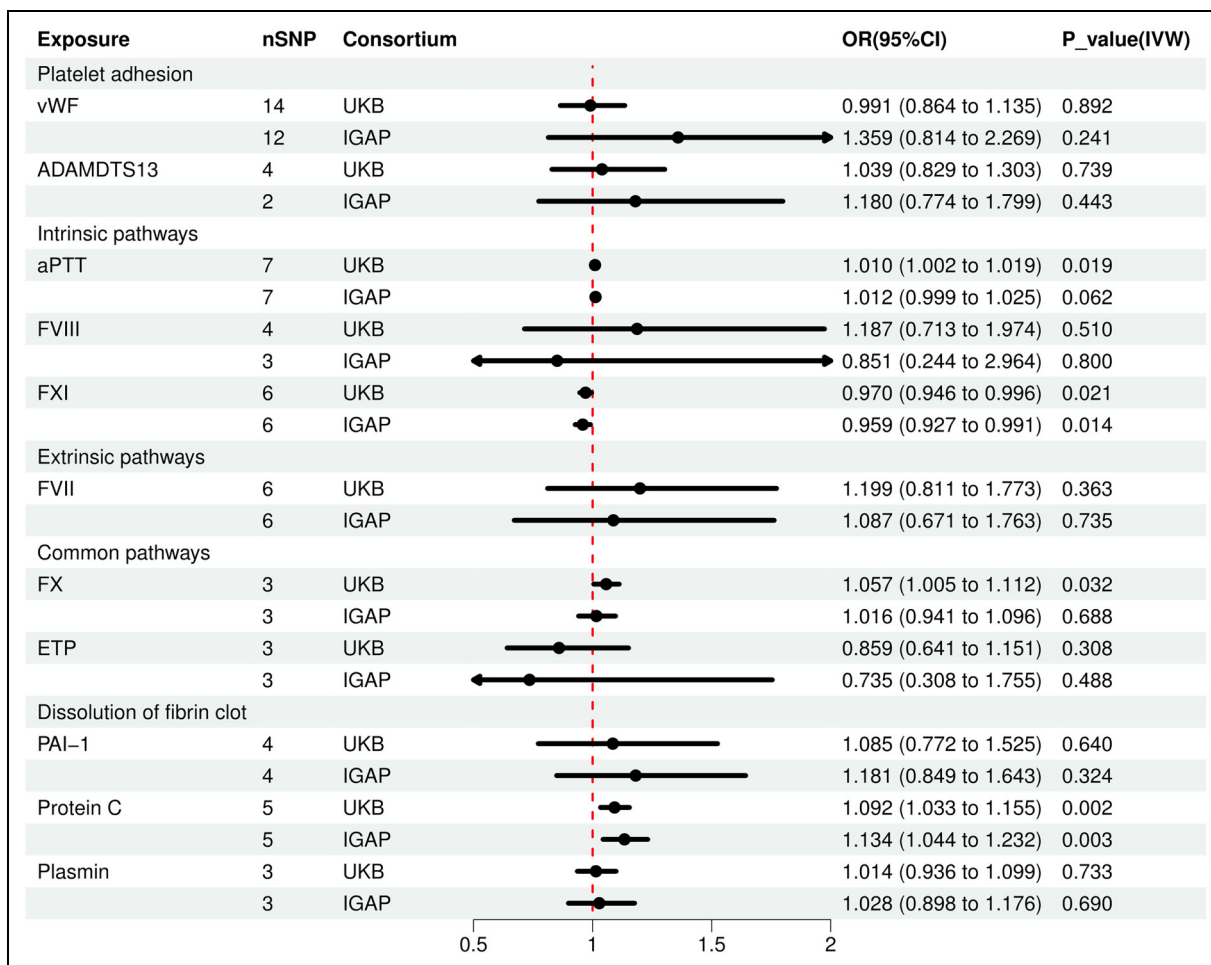


Figure 2. The forest plot illustrates the assessment of causal relationships between II coagulation factors and AD across the UKB and the IGAP databases. nSNP denotes the count of single nucleotide polymorphisms. The odds ratio (OR) was calculated using the IVW method. The horizontal bars indicate 95% confidence intervals (CI). IVW, inverse variance weighting; SNP, single nucleotide polymorphism; UKB, UK Biobank; IGAP, International Genomics of Alzheimer's Project; N, number.

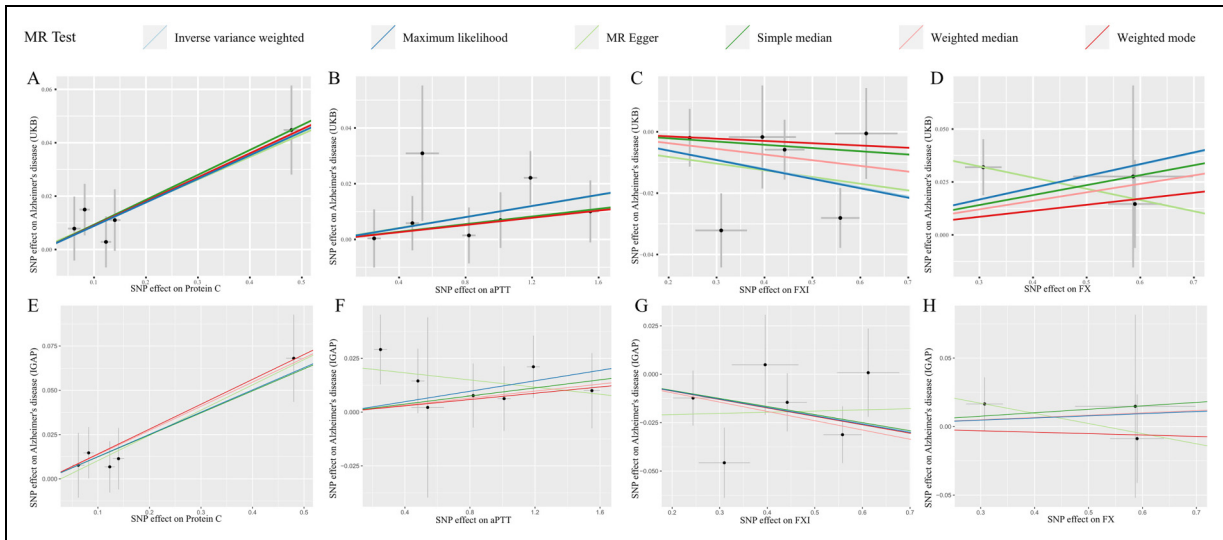


Figure 3. The scatter plot delineates the causal impact of the coagulation factors on AD within this MR study. Various methodologies, including Inverse Variance Weighting (IVW), Maximum Likelihood Estimation, MR Egger regression, Simple Median, Weighted Median, and Weighted Mode, were utilized to assess the causal relationship between coagulation function and AD. (A-D) The causal relationship between Protein C, aPTT, FXI, and FX in the UKB dataset. (E-H) The causal relationship between Protein C, aPTT, FXI, and FX in the IGAP dataset. UKB, UK Biobank; IGAP, International Genomics of Alzheimer's Project; MR, Mendelian randomization.

heterogeneity and pleiotropy test for other coagulation factors are presented in Supplemental Table 3. Leave-one-out analysis indicated potential estimated biases caused by individual SNP within the UKB database for PC, aPTT, and FXI (Figure 4). However, due to the limited number of SNPs for FX, no leave-one-out analysis was conducted for this factor. The results of the leave-one-out analysis using the AD dataset from the IGAP are presented in Supplemental Figure 1.

Discussion

Previous observational studies have investigated the association between blood levels of coagulation factors and the risk of AD, but the results are inconclusive.^{4,10} Utilizing the MR approach to minimize the impact of confounding factors and reverse causation, our study indicates that higher blood levels of PC, FX, and aPTT are causally associated with an increased risk of AD, while FXI is causally linked to a decreased risk of AD. In contrast, other coagulation factors, including vWF, FVIII, PAI-1, ADAMTS13, Plasmin, ETP, and FVII do not show a significant causal relationship with AD risk.

PC, a vitamin K-dependent plasma zymogen,³⁷ exerts its effects through activation into activated protein C (APC) via endothelial protein C receptor (EPCR).³⁸ The present MR study showed a positive relationship between PC levels and AD risk. However, previous studies did not observe a significant elevation of PC levels in AD patients, which might be due to the inclusion of patients on anticoagulants like rivaroxaban and apixaban.¹⁰ Indeed, recent

studies have shown elevated levels of soluble EPCR (sEPCR) in the serum of AD patients, with sEPCR levels positively correlated with increased cognitive impairment,³⁹ which might inhibit the activation of PC into APC, leading to higher PC levels in AD patients compared to controls. It is worth noting that the leave-one-out analysis indicated that rs8119351, an SNP closely associated with EPCR,²⁶ is vital for the MR estimate between PC and AD, suggesting that PC function is influenced by EPCR. Furthermore, previous studies have shown that APC treatment effectively improved cognitive function in 5xFAD transgenic mice by reducing A β burden and neuroinflammation in the hippocampus and cortex.⁴⁰ Thus, the reduction in PC to APC conversion might also diminish the protective effects of APC on AD. These results suggest that the PC pathway has great potential for the treatment of AD, and further research is needed to explore the underlying mechanisms driving this association.

FXI plays a significant role in the coagulation pathway by facilitating thrombin generation.⁴¹ Previous studies have reported decreased plasma levels of coagulation factor XI in AD patients,⁴ which is consistent with our findings. However, a study by EdinBecic and colleagues reported contrasting findings, showing increased levels of the coagulation factor XI in the plasma of AD patients compared to healthy controls.¹⁰ This discrepancy may be attributable to the inclusion of MCI patients and undiagnosed potential AD patients in their study, introducing confounding factors that could have influenced their results.¹⁰ aPTT is a crucial clinical test that assesses the integrity of the intrinsic coagulation pathway, playing a significant role in

Table 2. Tests for heterogeneity and pleiotropy of the causal estimates between coagulation factors and AD within the UKB and IGAP databases.

Exposure	Outcome	Cochran Q test		MR-Egger Intercept		RSSobs	
		MR-Egger (P)	IVW(P)	Intercept_Egger	Intercept_P	RSSobs	RSSobs_P
aPTT	AD(IGAP)	0.926	0.733	0.022	0.198	4.273	0.799
aPTT	AD(UKB)	0.689	0.800	1.86E-04	0.985	4.649	0.788
FX	AD(IGAP)	NA	0.753	NA	NA	NA	NA
FX	AD(UKB)	NA	0.788	NA	NA	NA	NA
FXI	AD(IGAP)	0.312	0.338	-0.022	0.431	7.504	0.441
FXI	AD(UKB)	0.108	0.176	-3.80E-03	0.866	11.519	0.219
Protein C	AD(IGAP)	0.904	0.954	-3.96E-03	0.762	1.715	0.910
Protein C	AD(UKB)	0.704	0.842	7.33E-04	0.932	1.908	0.876

UKB, UK Biobank; IGAP, International Genomics of Alzheimer's Project; MR, Mendelian randomization; IVW, Inverse variance weighted; RSSobs, Residual Sum of Squares observed; P, P value; N, number.

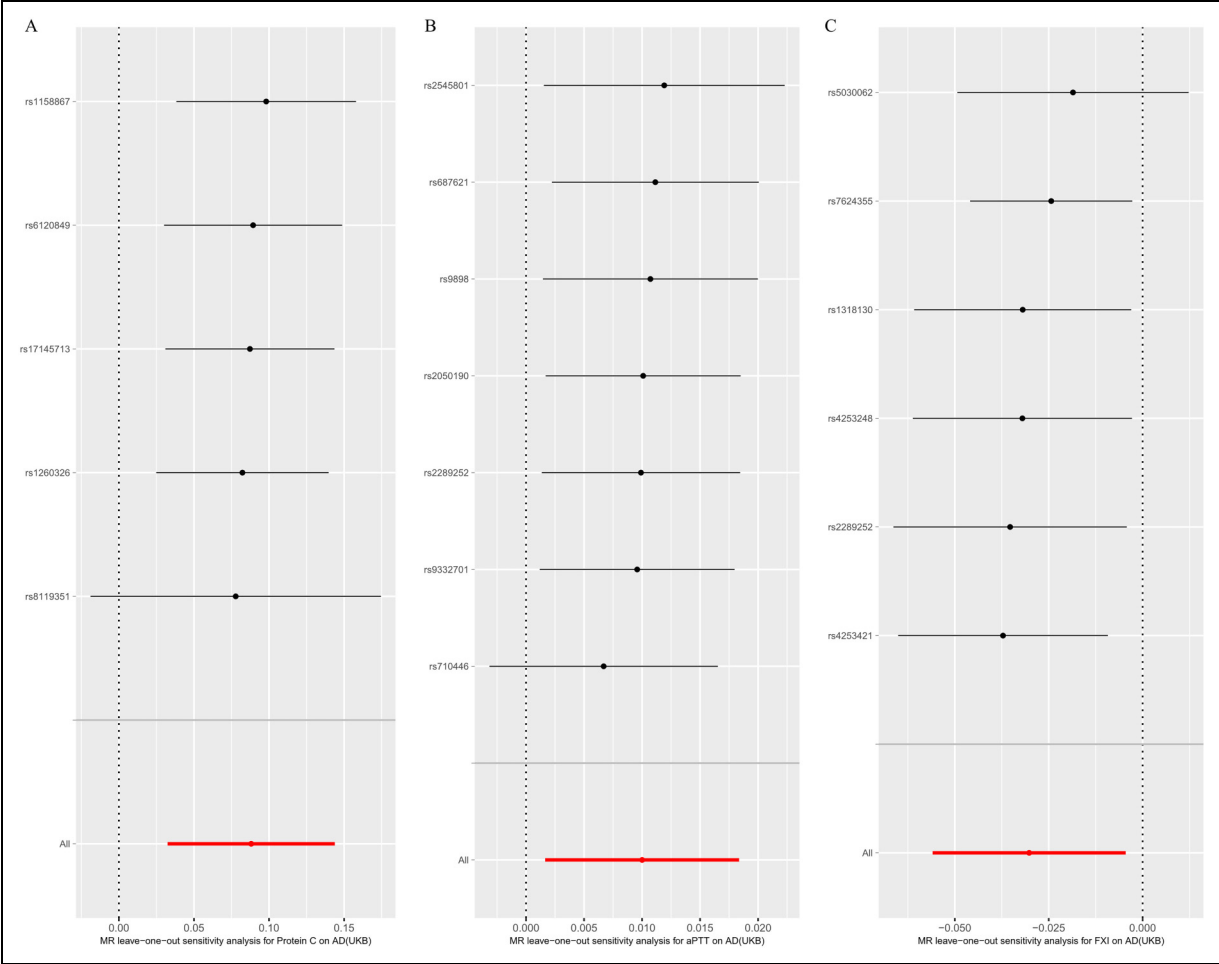


Figure 4. The leave-one-out plots for the causal association between the coagulation factors and AD in the UKB database. (A-C) Showed the leave-one-out plots for the causal effect between PC, aPTT, FXI, and AD. AD, Alzheimer's disease; UKB, UK Biobank; MR, Mendelian randomization.

the diagnosis of coagulation disorders.⁴² Previous studies have shown significantly prolonged aPTT in AD patients compared to age-matched controls, which is more

pronounced in younger AD patients.⁹ This is consistent with our findings based on the UKB dataset but was not replicated in the IGAP dataset ($p=0.062$) due to the

smaller sample size. Notably, the leave-one-out analysis revealed that SNP rs710446 and SNP rs5030062 contributed to bias in the MR estimates for aPTT and FXI respectively, while both of these two SNPs are closely associated with Kininogen 1 (KNG1).⁴³ Previous studies have indicated that KNG1 is detected with high confidence in the cerebrospinal fluid of AD patients and is tightly associated with AD risk,⁴⁴ potentially explaining the anomalous findings.

Coagulation factor X/Xa occupies a central position in the coagulation cascade, playing a critical role across the three primary pathways: intrinsic, extrinsic, and the common pathway.⁴⁵ Although previous studies did not observe a significant change of FX levels in AD patients,¹⁰ our results suggested that higher FX levels were causally linked to an increased risk of AD using the UKB dataset. In contrast, previous studies have suggested that plasma levels of vWF are higher in AD patients compared to controls, while PAI-1 levels are lower in AD patients than in controls.⁴⁶ However, the present MR study did not identify any significant causal relationships between them. These discrepancies may be due to the following reasons: first, this study included only 95 AD patients, and the small sample size may have limited the power to detect significant associations;⁴⁶ this study did not exclude individuals taking medications that influence coagulation,⁴⁷ which might confound the results. Therefore, further research with a larger sample size is warranted to confirm the relationship between vWF, PAI-1, and AD. Notably, previous studies have demonstrated that FXII depletion alleviates brain pathology and enhances cognitive function in AD mouse models.⁷ However, due to the absence of FXII-related GWAS data, we were unable to explore this further in our study. Additionally, the relationships between coagulation factors such as ADAMTS13, ETP, FVII, and FVIII and AD have not yet been adequately explored, highlighting the need for further investigation into these factors.

Utilizing this two-sample MR study, we validated the causal impact of multiple coagulation factors on the risk of AD. However, several limitations need to be addressed here. First, the number of IVs for each coagulation factor is relatively small, and some IVs might be discarded during the MR analysis, which might affect the final MR estimates. Second, our study assumes a linear relationship between coagulation-related factors and AD. However, due to the lack of individual-level data, we were not able to investigate potential nonlinear relationships between coagulation factors and AD. Third, the coagulation cascade is a complex process that involves numerous coagulation factors.⁴⁸ However, only 11 coagulation factors with valid GWAS data publicly available were included in this MR study, which could not comprehensively reflect all coagulation-related elements. The limited availability of relevant GWAS data

prevented us from conducting a more comprehensive causal analysis between other coagulation factors and AD, and we cannot exclude the possibility that other unexamined coagulation-related factors might be associated with AD. Fourth, the positive associations observed for FX and aPTT in the UKB dataset were not significantly replicated in the IGAP dataset, which might be attributed to the smaller sample size of the IGAP dataset (n=63,926) compared to the UKB dataset (n=472,868), potentially limiting statistical power in detecting significant associations. Fifth, the leave-one-out analysis indicated that certain SNPs were driving bias in the MR estimates, which might be attributed to the limited number of IVs used in the MR analysis (<7), potentially affecting the robustness of the results. Lastly, since there is a lack of high-quality publicly available GWAS data on coagulation factors and AD in non-European populations, our study is based on individuals of European ancestry.⁴⁹ Future studies based on multi-ethnic populations are needed to validate whether these associations exist in other ethnic groups.

Conclusions

Overall, our MR study suggests that elevated blood levels of PC, FX, and aPTT are causally associated with an increased risk of AD, while higher FXI levels are linked to a reduced risk. These findings underscore the potential role of coagulation dysfunction in the pathophysiology of AD and may offer novel insights into the diagnosis and treatment of AD.

Acknowledgments

The authors acknowledge all the participants, researchers, and consortia who contributed to this study.

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Statements and declarations

Ethical considerations

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Wenzhi Shi (Data curation; Investigation; Methodology; Project administration; Validation; Writing – original draft); Juanjuan Lu (Investigation; Methodology; Writing – original draft); Peiyao Wei (Data curation; Methodology; Writing – original draft); Pingping Ning (Conceptualization; Funding acquisition; Methodology; Resources); Jiaxin Fan (Conceptualization; Data curation; Methodology; Project administration); Shan Huang (Conceptualization; Data curation; Funding acquisition; Supervision); Xingzhi Guo (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization); Rui Li (Conceptualization; Funding acquisition; Project administration; Supervision; Validation).

Funding

This work was supported by the Shaanxi Province Natural Science Basic Research Program (No. 2024JC-YBQN-0799, 2022JQ-795, 2024JC-YBQN-0822) and the Shaanxi Provincial Innovation of Healthcare Program (No. 2024PT-02).

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

The GWAS summary statistics data used in this study are all publicly available in Open GWAS.

Supplemental material

Supplemental material for this article is available online.

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