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ORIGINAL ARTICLE

Serum albumin, genetic susceptibility, and risk of venous thromboembolism

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Abstract

Background: Previous research on the association between serum albumin (ALB) and venous thromboembolism (VTE) has produced inconclusive results. The polygenic risk score is constructed from a set of independent risk variants associated with a disorder, enabling the identification of a larger fraction of the population at comparable or greater disease risk. It is still unknown whether ALB and genetic factors jointly contribute to the incidence of VTE.

Objectives: The present study aimed to explore ALB, genetic susceptibility, and the risk of VTE.

Methods: The present investigation was an analysis of prospectively collected data from UK Biobank, a population-based, longitudinal cohort. Cox proportional models were used to calculate hazard ratios and 95% CIs for VTE. The Kaplan–Meier curve was utilized to visualize the cumulative risk of VTE according to different serum ALB levels, and the restricted cubic spline model was leveraged to explore the exposure–response relationship among ALB levels and VTE risk.

Results: During median follow-up of 13.5 years, 11,502 cases with VTE were diagnosed among 417,113 participants in the UK Biobank. The lower ALB levels were associated with a higher risk for VTE. Individuals with both a high genetic risk and lowest ALB level had the highest risk of VTE (hazard ratio, 3.89; 95% CI, 3.41-4.43), compared with those with low genetic risk and highest ALB level. The positive joint effects of low ALB and polygenic risk score increased the risk of VTE in individuals with high genetic risk. This study excluded non-European patients and primarily focused on the European population, which may limit the generalizability of the findings.

Conclusion: Low serum ALB levels were linked to an increased risk of VTE, which was in accordance with a linear dose–response relationship. There was a positive additive effect of ALB and genetic susceptibility on the risk of VTE. ALB could serve as a biomarker for predicting the risk of VTE.

Yuyang Sun and Jun Deng contributed equally to this work.

KEYWORDS
additive interaction, cohort study, genetic susceptibility, serum albumin, venous thromboembolism

Essentials

- The joint effect of albumin and genetic factors on venous thromboembolism is unclear.
- The study was performed in the framework of the UK Biobank.
- The participants with lower serum albumin levels and high genetic risk have a higher risk of venous thromboembolism.
- Serum albumin and genetic susceptibility exhibit a significant positive additive effect on the risk of VTE.

1 | INTRODUCTION

Venous thromboembolism (VTE) is a significant global health burden, with approximately 10 million cases occurring annually [1]. It manifests as deep vein thrombosis (DVT) and pulmonary embolism (PE) and is the third most commonly occurring vascular disease after coronary artery and cerebrovascular diseases [2].

VTE is a multifactorial, episodic disease involving a range of genetic and environmental risk factors [3]. Serum albumin (ALB), synthesized in the liver, comprises approximately 50% to 60% of the serum proteins, typically between 35 and 50 g/L [4]. Several projects have shown that serum ALB may be involved in the development of VTE. Most published research on serum ALB and VTE has examined individuals with underlying conditions like cancer, chronic liver disease, and chronic kidney disease [5–7]. Some studies have shown that low serum ALB concentrations increase the risk of VTE [7,8], whereas other studies have found no evidence of an association [9–11]. A few recent studies conducted in the general population have revealed that low serum ALB is associated with long-term risk of VTE [12,13]. Also, the analysis conducted in the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban Trial revealed that hospitalized patients with severe acute illness with low baseline ALB levels experienced an elevated VTE risk through 77 days [14]. Apart from acquired factors, genetic factors are also significant contributors to the risk of VTE. The estimated heritability of VTE is approximately 50% to 60% [15,16]. Through genome-wide association studies (GWAS), researchers have identified several risk loci correlating with VTE, such as *PROCR*, *TSPAN15*, *ABO*, and *ZFPM2* [17–19]. Using VTE polygenic risk score (PRS) allowed for effective differentiation between individuals at high and low risk for VTE [20]. However, it is currently uncertain how the interaction between ALB and PRS affects the risk of VTE.

Therefore, we conducted a large population-based cohort study built upon the UK Biobank (UKB) to clarify the individual and joint association of ALB and PRS on the risk of VTE and to determine whether serum ALB and genetic risk interact in a multiplicative or additive manner.

2 | METHODS

2.1 | Data source and research population

This cohort study used data from the UKB, which included approximately 500,000 participants recruited across the United Kingdom between 2006 and 2010. Before collecting the questionnaire and biological data, participants provided written informed consent [21]. The UKB study was performed under the ethical approval granted by the UK North West Multi-Centre Research Ethics Committee. The participant selection in this study is described in Figure 1. After excluding individuals with a history of previous VTE (n = 15,150) and those with missing baseline ALB data (n = 70,133), a total of 417,113 participants were included in this study. For genetic susceptibility analysis, after excluding participants with missing PRS data (n = 5490) and of non-European descent (n = 66,423), there were 345,200 participants included in the genetic susceptibility analysis. Our study was performed under UKB application number 88159.

2.2 | PRS

The standard PRS of VTE was calculated by Genomics PLC under UK Biobank project 9659 and extracted from the UKB (data field 26289). The weights utilized in the PRS model were obtained from a meta-analysis conducted on 4 independent VTE GWAS datasets, which comprised 29,799 cases and 475,303 controls from the Electronic Medical Records and Genomics cohorts [22]. Electronic Medical Records and Genomics is a consortium of 10 participating sites collectively conducting GWAS and freely providing their respective summary statistics data [23]. These cohorts do not overlap with the participants of the UKB. All genetic variants included in the generation of PRS weight were required to have an imputation quality score >0.8. Trait-specific meta-analyses using a Bayesian approach were employed in the construction of PRS algorithms, as previously detailed [22]. The participants were categorized into 3 groups based on the 25th and 75th percentiles of standard PRS. Those with the lowest quartile standard PRS were placed in the low genetic risk group, whereas those with the highest quartile standard PRS were assigned to the high genetic risk group. Participants falling between these 2 quartiles were classified into the medium genetic risk group.

2.3 | Baseline ALB measurements

During the initial phase (2006-2010), blood samples were collected and stored at −80 °C. Serum ALB (gram per liter) concentrations were

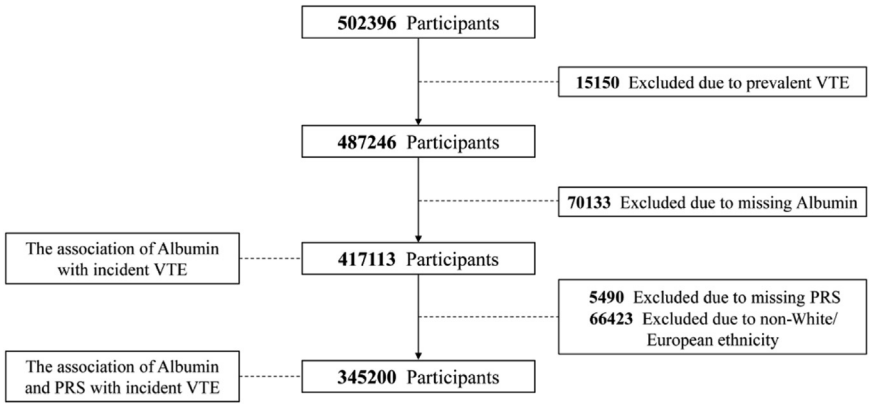

FIGURE 1 Flowchart of participants. PRS, polygenic risk score; VTE, venous thromboembolism.

measured using a colorimetric assay (Beckman Coulter AU5800). The coefficients of variation for the ALB assay were 2.1%, 2.2%, and 2.1% for concentration ranges of 27.1 to 33.5, 41.8 to 49.7, and 50.0 to 61.2 g/L, respectively. The detection range for ALB was 15 to 60 g/L.

2.4 | Identification and follow-up of VTE cases

In this study, participants who developed either DVT or PE during follow-up were defined as VTE. In UKB, diagnostic data were obtained by linking to primary care data, hospital admission data, death register records, and self-reported medical conditions. VTE diagnosis was made based on the International Classification of Diseases 10th Revision, which includes I26 (PE), I82 (DVT), and I80 (thrombophlebitis) (Supplementary Table S1). For each participant, the data field providing the earliest VTE diagnosis was identified from 1 source (Supplementary Table S2). Self-reported diseases are obtained during the initial assessment visits during which participants were asked by trained nurses if they have ever been told by doctors that they have a disease. If a participant identified both the International Classification of Diseases 10th Revision code in the registration and a self-reported medical condition, the earliest date was used. Follow-up time was calculated beginning with the enrollment date and ending with the diagnosis of disease outcome, death, loss to follow-up, or end of follow-up on July 9, 2022, whichever occurred first.

2.5 | Covariates

The related covariates, including demographic factors, socioeconomic status, lifestyle factors, and other confounders, were measured at baseline. More specific covariates include age, sex (ie, male or female) and ethnicity, body mass index (BMI), Townsend deprivation index, smoking status, drinking status, physical activity, total cholesterol (TC), systolic blood pressure (SBP), white blood cell (WBC) count, C-reactive protein (CRP), alanine aminotransferase (ALT), and serum creatinine (SCR). Townsend deprivation index was a commonly used indicator for assessing the socioeconomic situation of a particular area. Higher index values indicated poorer socioeconomic conditions or higher poverty levels in the area. BMI was evaluated as weight divided by the square of height and categorized based on World Health Organization standards into groups: <18.5 kg/m^2, 18.5 to 24.9 kg/m^2, 25.0 to 29.9 kg/m^2, and ≥ 30 kg/m^2. Smoking status was categorized as never, previous, and current. Drinking status was categorized as never, previous, and current. Physical activity was evaluated using the International Physical Activity Questionnaire, with the results reported in Metabolic Equivalent Task—minutes per week. Physical activity levels were classified as low, moderate, and high. Blood pressure was the average of 2 consecutive measurements. CRP was measured using immunoturbidimetric assays. TC, ALT, and SCR were measured using enzymatic assays (Beckman Coulter AU5800). WBC counts were measured using the Beckman Coulter LH750 instrument. The aforementioned data were collected via touchscreen, verbal interview, physical measures, and biological sampling at baseline. The distribution of time between the ALB measurements and the VTE event is shown in Supplementary Table S3.

2.6 | Statistical analysis

Baseline characteristics were summarized according to the VTE status. We described all continuous variables in terms of median and IQR and all categorical variables using absolute numbers and proportion. Missing values of covariates were imputed using interpolation. Comprehensive details on the number of missing covariates were shown in the Supplementary Table S4. For continuous variables, missing values were interpolated using the median of the variable, whereas for categorical variables, missing values were imputed as "missing." Continuous data were analyzed using the Mann–Whitney U-test. Categorical data were analyzed using the chi-squared test.

We used Cox proportional hazards regression models to estimate the hazard ratios (HRs) and 95% CIs between baseline serum ALB, PRS, and the risk of VTE. Participants were divided into 4 groups according to the quartiles of ALB levels at baseline with the highest top quartile as referent. Meanwhile, ALB was added to Cox proportional hazards regression models as a continuous variable (per SD decrement). To reduce the effect of potential confounding factors, we

TABLE 1 Baseline characteristics of participants by quartiles of albumin.

Characteristics	Total	ALB (g/L)			
		Q1 (≤43.51)	Q2 (43.52-45.21)	Q3 (45.22-46.94)	Q4 (>46.94)
No. of participants	417,113	104,692	103,885	104,489	104,047
Age, *n* (%)					
<60 y	237,937 (57.0)	51,862 (49.5)	56,515 (54.4)	61,639 (59.0)	67,921 (65.3)
≥60 y	179,176 (43.0)	52,830 (50.5)	47,370 (45.6)	42,850 (41.0)	36,126 (34.7)
Sex, *n* (%)					
Female	223,827 (53.7)	63,713 (60.9)	57,912 (55.7)	53,740 (51.4)	48,462 (46.6)
Male	193,286 (46.3)	40,979 (39.1)	45,973 (44.3)	50,749 (48.6)	55,585 (53.4)
BMI, *n* (%)					
<18.5 kg/m^2	2160 (0.5)	471 (0.4)	484 (0.5)	523 (0.5)	682 (0.7)
18.5-24.9 kg/m^2	135,953 (32.6)	29,587 (28.3)	32,618 (31.4)	35,151 (33.6)	38,597 (37.1)
25.0-29.9 kg/m^2	177,397 (42.5)	41,821 (39.9)	44,485 (42.8)	45,776 (43.8)	45,315 (43.6)
≥30.0 kg/m^2	100,000 (24.0)	32,187 (30.7)	25,928 (25.0)	22,714 (21.7)	19,171 (18.4)
Missing	1603 (0.4)	626 (0.6)	370 (0.4)	325 (0.3)	282 (0.3)
Smoking status, *n* (%)					
Never	227,452 (54.5)	55,496 (53.0)	56,085 (54.0)	57,677 (55.2)	58,194 (55.9)
Previous	143,709 (34.5)	36,646 (35.0)	36,037 (34.7)	35,807 (34.3)	35,219 (33.8)
Current	43,829 (10.5)	11,867 (11.3)	11,228 (10.8)	10,554 (10.1)	10,180 (9.8)
Missing	2123 (0.5)	683 (0.7)	535 (0.5)	451 (0.4)	454 (0.4)
Drinking status, *n* (%)					
Never	18,210 (4.4)	6140 (5.9)	4687 (4.5)	4068 (3.9)	3315 (3.2)
Previous	14,693 (3.5)	4551 (4.3)	3539 (3.4)	3361 (3.2)	3242 (3.1)
Current	383,155 (91.9)	93,651 (89.5)	95,407 (91.8)	96,825 (92.7)	97,272 (93.5)
Missing	1055 (0.3)	350 (0.3)	252 (0.2)	235 (0.2)	218 (0.2)
Physical activity, *n* (%)					
Low	63,439 (15.2)	17,184 (16.4)	15,847 (15.3)	15,328 (14.7)	15,080 (14.5)
Moderate	137,557 (33.0)	34,007 (32.5)	34,174 (32.9)	34,581 (33.1)	34,795 (33.4)
High	136,323 (32.7)	31,770 (30.3)	33,937 (32.7)	35,070 (33.6)	35,546 (34.2)
Missing	79,794 (19.1)	21,731 (20.8)	19,927 (19.2)	19,510 (18.7)	18,626 (17.9)
VTE, *n* (%)	11,502 (2.8)	4074 (3.9)	2934 (2.8)	2526 (2.4)	1968 (1.9)
Townsend deprivation index, median (IQR)	−2.2 (−3.7 to 0.5)	−2.0 (−3.6 to 0.8)	−2.2 (−3.7 to 0.5)	−2.2 (−3.7 to 0.3)	−2.2 (−3.7 to 0.3)
TC (mmol/L), median (IQR)	5.7 (4.9 to 6.4)	5.4 (4.7 to 6.2)	5.6 (4.9 to 6.4)	5.7 (5.0 to 6.5)	5.9 (5.1 to 6.6)
TG (mmol/L), median (IQR)	1.5 (1.0 to 2.1)	1.5 (1.0 to 2.1)	1.5 (1.0 to 2.1)	1.5 (1.1 to 2.2)	1.5 (1.1 to 2.2)
WBC count (10^9 cells/L), median (IQR)	6.7 (5.7 to 7.8)	6.7 (5.7 to 8.0)	6.7 (5.7 to 7.8)	6.7 (5.6 to 7.7)	6.6 (5.6 to 7.7)

(Continues)

TABLE 1 (Continued)

Characteristics	Total	ALB (g/L)			
		Q1 (≤43.51)	Q2 (43.52-45.21)	Q3 (45.22-46.94)	Q4 (>46.94)
CRP (mg/L), median (IQR)	1.3 (0.7 to 2.7)	1.8 (0.9 to 4.0)	1.4 (0.7 to 2.8)	1.2 (0.6 to 2.4)	1.0 (0.5 to 2.0)
SBP (mmHg), median (IQR)	136.5 (125.5 to 148.5)	136.0 (123.50 to 146.0)	136.5 (125.0 to 148.0)	136.5 (126.0 to 149.0)	137.0 (127.5 to 150.5)
DBP (mmHg), median (IQR)	82.0 (75.0 to 89.0)	80.5 (74.00 to 87.5)	81.5 (75.0 to 88.5)	82.5 (75.5 to 89.0)	83.5 (76.5 to 90.0)
Serum creatinine (μmol/L), median (IQR)	70.4 (61.4 to 80.9)	69.3 (60.6 to 79.9)	70.1 (61.2 to 80.5)	70.8 (61.7 to 81.1)	71.6 (62.3 to 81.9)
ALT (U/L), median (IQR)	20.1 (15.4 to 27.4)	18.6 (14.5 to 24.9)	19.6 (15.2 to 26.4)	20.6 (15.7 to 28.0)	21.9 (16.5 to 30.3)
PRS, median (IQR)	−0.04 (−0.67 to 0.63)	−0.02 (−0.64 to 0.65)	−0.04 (−0.67 to 0.63)	−0.04 (−0.67 to 0.63)	−0.07 (−0.70 to 0.60)

ALB, albumin; ALT, alanine aminotransferase; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; PRS, polygenic risk score; Q, quartile; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; VTE, venous thromboembolism; WBC, white blood cell.

constructed 3 Cox regression models. In model 1, we examined the univariate association between ALB per quartile and VTE endpoint. Model 2 is adjusted for age (as continuous), sex, BMI, Townsend deprivation index (as continuous), smoking status, drinking status, and physical activity. Model 3 included model 2, additionally adjusted for TC (as continuous), SBP (as continuous), WBC count (as continuous), CRP (as continuous), ALT (as continuous), and SCR (as continuous).

Age, sex, BMI, Townsend deprivation index, smoking, drinking, TC, SBP, WBC count, CRP, ALT, and SCR were considered when constructing Kaplan–Meier curves using the inverse probability of treatment weighting method to compare the cumulative risk of VTE at different levels of serum ALB. The association between ALB and VTE was accessed using the restricted cubic spline model that included knots at the 5th, 35th, 50th, 65th, and 95th percentiles of serum ALB distribution, adjusting for age, sex, BMI, smoking status, drinking status, physical activity, Townsend deprivation index, TC, SBP, WBC count, CRP, ALT, and SCR. We also conducted subgroup analyses based on age (<60 or ≥60 years), sex (female or male), BMI (<30.0 or ≥30.0 kg/m^2), smoking status (never smoked or other), and physical activity (low-, moderate-, or high-intensity physical activity). We compared the differences in ALB at the baseline level among different subgroups and evaluated the interaction effect between group characteristics and ALB using the likelihood ratio test.

We also used the highest top quartile of ALB and the low genetic risk group as the reference group to evaluate the combined effect of ALB and genetic risk on the risk of VTE. We also assessed the additive interaction between ALB and genetic risk using the relative excess risk due to interaction, the attributable proportion due to interaction, and the synergy index to measure the interaction.

For sensitivity purposes, we limited the population to participants with complete covariate information, excluded those diagnosed with cancer and atrial fibrillation at baseline, and eliminated participants

TABLE 2 Associations of albumin with venous thromboembolism among all participants.

ALB (g/L)	Case/*N* (%)	Person-year	Incidence density (‰)	HR (95% CI)[a]		
				Model 1	Model 2	Model 3
Per 1 SD decrease	11,502/417,113 (2.8)	5,389,551	2.1	1.35 (1.32-1.37)	1.25 (1.23-1.28)	1.23 (1.21-1.25)
Q1	4074/104,692 (3.9)	1,335,707	3.1	2.11 (2.00-2.22)	1.72 (1.63-1.81)	1.65 (1.56-1.74)
Q2	2934/103,885 (2.8)	1,345,224	2.2	1.50 (1.42-1.59)	1.31 (1.24-1.39)	1.29 (1.21-1.36)
Q3	2526/104,489 (2.4)	1,357,453	1.9	1.28 (1.21-1.36)	1.18 (1.11-1.25)	1.17 (1.10-1.24)
Q4	1968/104,047 (1.9)	1,351,166	1.5	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
P for trend[b]				<.001	<.001	<.001

ALB, albumin; HR, hazard ratio; Q, quartile; ref., reference.

[a]Model 1 was not adjusted for any covariates. Model 2 was adjusted for age, sex, body mass index, Townsend deprivation index, smoking status, drinking status, and physical activity. Model 3 was further adjusted for total cholesterol, systolic blood pressure, white blood cell count, C-reactive protein, and serum creatinine.

[b]Tests for trend were based on the median value in each quartile.

with <1 year follow-up. Additionally, we performed an analysis using multiple imputations by chained equations to impute missing covariate values.

All analyses were performed in R software (version 4.2.2, R Foundation for Statistical Computing). A 2-sided *P* value <.05 was regarded as statistically significant.

3 | RESULTS

3.1 | Baseline characteristic of participants

Baseline characteristics of participants by quartiles of ALB and by development of VTE are summarized in Table 1 and Supplementary Table S5. The median (IQR) age of participants was 58.0 (50-63) years and 193,286 (46.3%) were males. With a median follow-up duration of 13.4 years, VTE was reported in 11,502 attendees. Participants who developed incident VTE were elderly, male, overweight, smokers, or obese; were more predisposed to perform less physical activity and have lower serum ALB levels; and had higher TG level, SBP, WBC count, CRP level, SCR level, and Townsend deprivation index (Supplementary Table S5). Baseline characteristics of participants by quartiles of PRS are shown in Supplementary Table S6.

3.2 | Associations of ALB with incident VTE

A lower serum ALB level was associated with a higher risk of VTE (Table 2). In the unadjusted model, the HR for participants in the lowest quartile of ALB was 2.11 (95% CI, 2.00-2.22). After adjustment for age, sex, BMI, Townsend deprivation index, smoking, drinking, physical activity, WBC count, SBP, CRP, ALT, and SCR (model 3), the lowest level of ALB remained significantly associated with increased risk of VTE (*P* for trend < .001). The HRs of VTE were 1.65 (95% CI, 1.56-1.74), 1.29 (95% CI, 1.21-1.36), 1.17 (95% CI, 1.10-1.24), and 1.00 (reference) from lowest to highest quartiles of ALB. When performed as a continuous variation for analysis, the HR for VTE increased by 1.23 (95% CI, 1.21-1.25) times per 1 SD decrease in ALB (2.62 g/L) after adjusting for potential confounders.

The cumulative risks of VTE were differentiated at different levels of ALB (log-rank *P* < .0001), as depicted by the Kaplan–Meier curves in Figure 2. The restricted cubic spline was used to demonstrate the relationship between ALB and VTE (Figure 3); a significant overall association was observed between ALB levels and VTE risk (*P* < .001), and no significant nonlinear association was observed (*P* = .09). Linear association and decreasing trends with VTE risk were demonstrated for serum ALB. As serum ALB levels exceeded 45 g/L, the risk of VTE gradually decreased. Conversely, when serum ALB level was <45 g/L, we observed a significant increase in the risk of VTE.

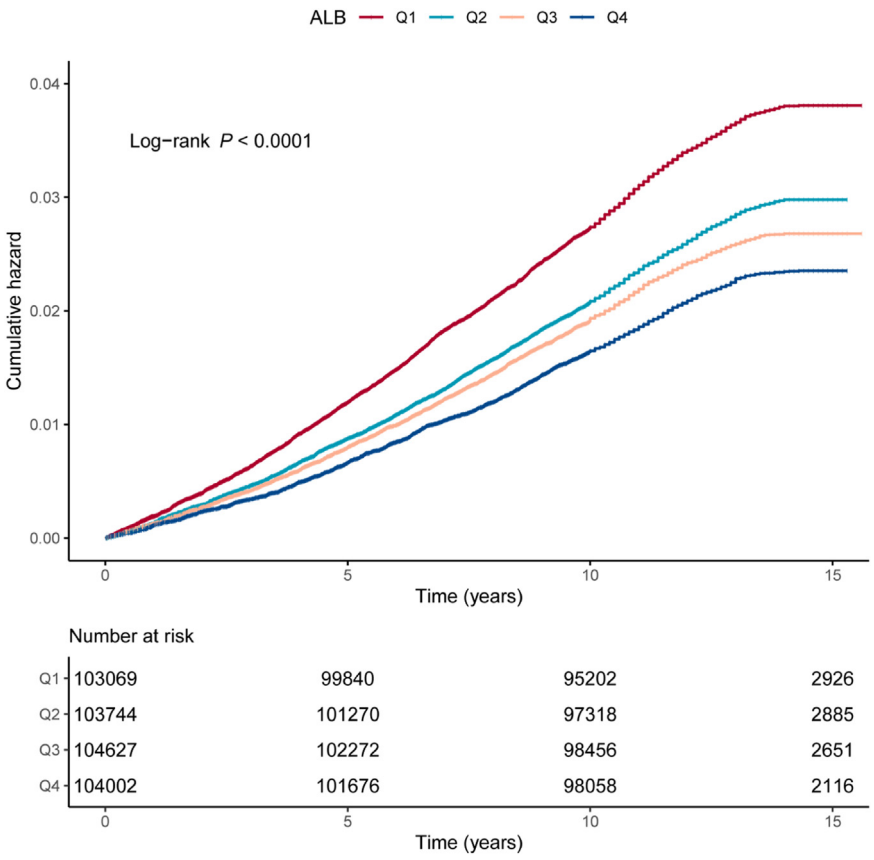

FIGURE 2 Kaplan–Meier curves for venous thromboembolism in participants according to serum albumin (ALB) levels. The inverse-variance weighting method was used and adjusted for age, sex, body mass index, Townsend deprivation index, smoking status, drinking status, physical activity, white blood cell count, systolic blood pressure, total cholesterol, C-reactive protein, alanine aminotransferase, and serum creatinine. Q, quartile.

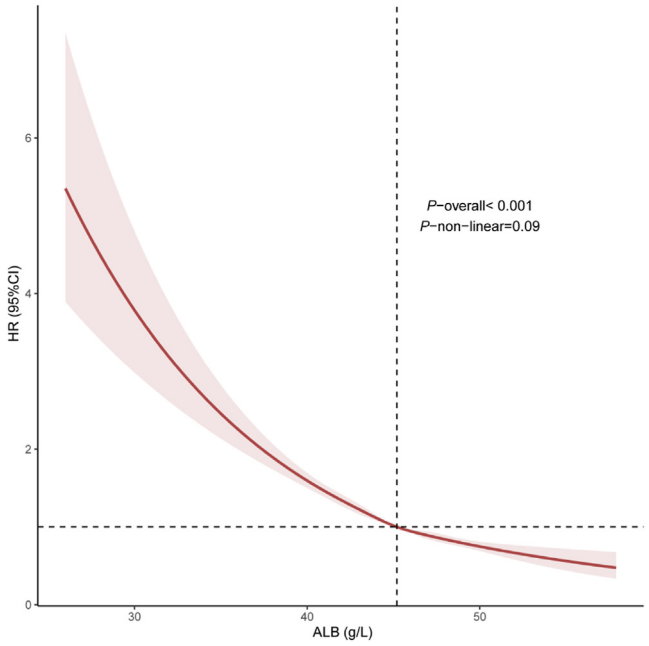

FIGURE 3 Exposure–response relationships of serum albumin (ALB) with the risk of venous thromboembolism. Hazard ratios (HRs) were adjusted for age, sex, body mass index, Townsend deprivation index, smoking status, drinking status, physical activity, white blood cell count, systolic blood pressure, total cholesterol, C-reactive protein, alanine aminotransferase, and serum creatinine.

3.3 | Associations of PRS with incident VTE

As the genetic risk increased, the HR of VTE increased gradually (Table 3). The HRs of the high and medium genetic risk groups were 2.61 (95% CI, 2.46-2.77) and 1.55 (95% CI, 1.46-1.64), respectively, in comparison with the low genetic risk group (P for trend < .001). Meanwhile, as a continuous variable, each unit increase in PRS was associated with 45% higher risk of VTE. The unit is a 1 SD increase.

3.4 | Joint effect of ALB and genetic susceptibility

After grouping the entire cohort based on genetic risk and the ALB levels, the HR of VTE increased with decreasing ALB and increasing genetic risk (Figure 4). The lowest ALB level and high genetic risk group had an HR of 3.89 (95% CI, 3.41-4.43) in comparison with the highest ALB level and low genetic risk group. Positive additive interaction was found between ALB and high genetic risk (Table 4). The additive interactions between the lowest level ALB and high genetic risk on VTE risk were significant after adjusting for potential confounders. Relative excess risk due to interaction was 0.80 (95% CI, 0.48-1.12), indicating an excess risk of 0.80 attributable to the additive interaction between the risk factors. Attributable proportion due to interaction was 0.21 (95% CI, 0.13-0.29), suggesting that 21% of the VTE risk associated with exposure to both risk factors was attributed to the additive interaction; synergy index was 1.38 (95% CI, 1.19-1.61). Additionally, there was no statistically significant multiplicative interaction detected.

3.5 | Subgroup and sensitivity analyses

Stratified analyses were performed based on age, gender, BMI, smoking status, and physical activity (Supplementary Table S7), and the results were consistent in the subgroups. In younger participants, males, nonsmokers, those with a BMI ≥30 kg/m^2, and individuals with low physical activity, lower ALB levels were associated with a higher risk of VTE. However, no significant interaction was observed between these variables (P for interaction > .05).

In the sensitivity analysis, when restricting participants to those with complete covariates and using multiple imputations by chained equations to imputed missing covariate values, no substantial changes were observed in the results. Compared with participants with higher levels of ALB, those with lower ALB levels exhibited a higher risk of VTE (Supplementary Tables S8 and S9). We reanalyzed our data in participants after excluding those with cancer and atrial fibrillation at baseline, and the patterns of VTE risk remained similar in both the unadjusted and the multivariable-adjusted models (Supplementary Tables S10 and S11). Furthermore, the association between ALB levels and VTE risk still remained consistent after excluding participants with a follow-up time of <1 year (Supplementary Table S12).

4 | DISCUSSION

This large population-based cohort study investigated the relationship between serum ALB levels, genetic susceptibility, and risk of VTE using data obtained from the UKB. We observed that serum ALB and PRS were both associated with the risk of incident VTE, with the former demonstrating a linear exposure–response relationship. Participants characterized by both high genetic risk and lowest levels of ALB were found to have the greatest relative risk increase in VTE events, compared with their counterparts with low genetic risk and high ALB levels.

To investigate the extent to which any attrition bias from the missing data affected our results, we excluded participants with missing covariates and conducted an analysis employing multiple imputations by chained equations to imputed missing covariate values. However, the association between ALB levels and VTE risk did not change. To minimize the effects of reverse causality, we excluded participants with cancer and atrial fibrillation at baseline, and the association exhibited no substantial change. Then, after excluding participants with a follow-up time of <1 year, similar results were obtained. These results suggest that the current findings are less likely to be attributed to reverse causality.

Various interpretations have been put forward to elucidate the association between decreased ALB levels and elevated risk of VTE. First, ALB can bind arachidonic acid, preventing its metabolism into potent aggregating substances, endoperoxides and thromboxane A_2,

TABLE 3 Associations of polygenic risk score with venous thromboembolism among all participants.

PRS	Case/*N* (%)	Person-year	Incidence density (‰)	HR (95% CI)[a]		
				Model 1	Model 2	Model 3
Continuous	9811/345,200 (2.8)	4,467,171	2.2	1.45 (1.42-1.47)	1.45 (1.42-1.48)	1.45 (1.42-1.48)
Low genetic risk	1467/86,300 (1.7)	1,122,809	1.3	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Medium genetic risk	4563/172,600 (2.6)	2,236,492	2.0	1.56 (1.47-1.66)	1.55 (1.46-1.65)	1.55 (1.46-1.64)
High genetic risk	3781/86,300 (4.4)	1,107,870	3.4	2.61 (2.46-2.77)	2.61 (2.46-2.77)	2.61 (2.46-2.77)
P for trend[b]				<.001	<.001	<.001

HR, hazard ratio; PRS, polygenic risk score; ref., reference.
[a]Model 1 was not adjusted for any covariates. Model 2 was adjusted for age, sex, the genotyping batch, body mass index, Townsend deprivation index, smoking status, drinking status, and physical activity. Model 3 was further adjusted for total cholesterol, systolic blood pressure, white blood cell count, C-reactive protein, alanine aminotransferase, and serum creatinine.
[b]Tests for trend were based on the median value in each quartile.

thereby inhibiting platelet activation and aggregation [24]. Furthermore, it exhibits the concentration-dependent capability to induce inducible nitric oxide synthase in macrophages, resulting in increased production of the potent platelet inhibitor nitric oxide [25]. Second, low ALB levels may also indicate the presence of underlying diseases, such as nephrotic syndrome, chronic kidney disease, and cancer, which are known risk factors for VTE [26]. Third, lower ALB levels, acting as an acute-phase reactant, can indicate the existence of inflammation and are potentially implicated in the development of VTE [27].

Although substantial evidence suggests that low ALB level is associated with an increased risk of VTE, most previous studies have been small-scale, mainly focusing on populations with preexisting diseases [7,8,28]. Several subsequent prospective cohort studies in the general population have shown similar results. Folsom et al. [13] demonstrated that ALB tended to be associated inversely with VTE in both studies after adjustment for confounding factors; the adjusted HR per SD lower ALB was 1.18 (95% CI, 1.08-1.31) in Atherosclerosis Risk in Communities (ARIC) and 1.10 (95% CI, 0.94-1.29) in Cardiovascular Health Study (CHS). A similar inverse association and dose–response

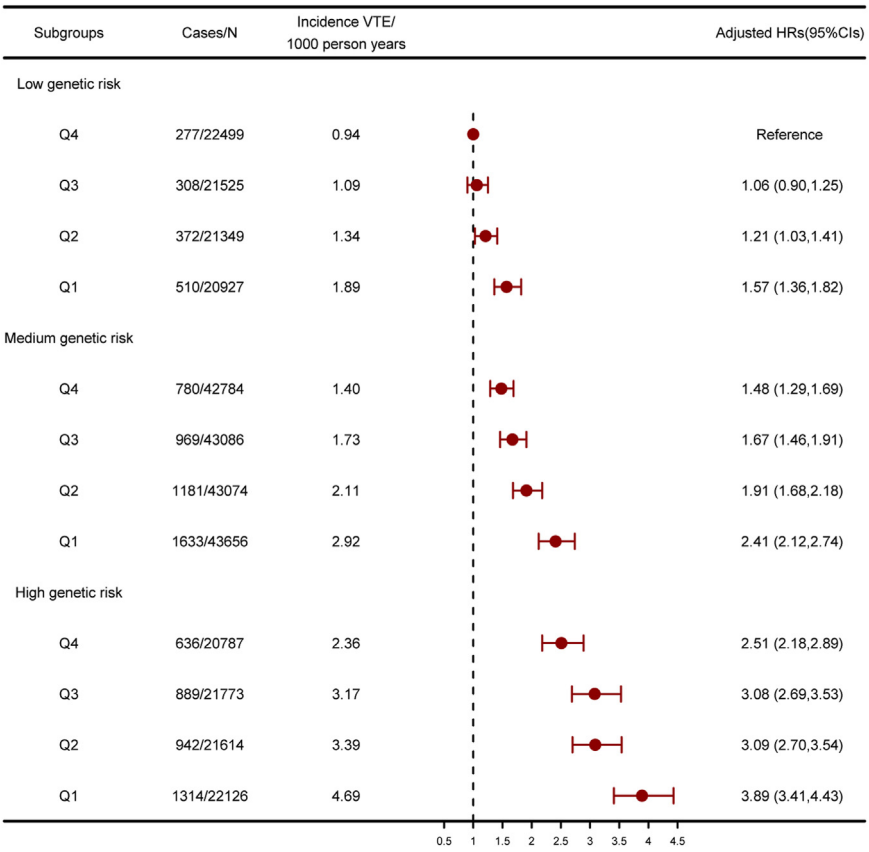

FIGURE 4 Joint effects of serum albumin and polygenic risk score on the risk of venous thromboembolism (VTE). Hazard ratios (HRs) were adjusted for age, sex, body mass index, Townsend deprivation index, smoking status, drinking status, physical activity, white blood cell count, systolic blood pressure, total cholesterol, C-reactive protein, alanine aminotransferase, serum creatinine, the genotyping batch, and the first 10 genetic principal components. Q, quartile.

TABLE 4 Effect of additive and multiplicative interactions between albumin and polygenic risk score on the risk of incident venous thromboembolism.

	Medium genetic risk[a]			High genetic risk[a]			*P* for interaction
ALB	RERI (95% CI)	AP (95% CI)	SI (95% CI)	RERI (95% CI)	AP (95% CI)	SI (95% CI)	
Q3	0.13 (−0.08 to 0.35)	0.08 (−0.05 to 0.21)	1.25 (0.82 to 1.91)	**0.51 (0.20 to 0.82)**	**0.17 (0.07 to 0.27)**	**1.33 (1.09 to 1.62)**	
Q2	0.23 (0.02 to 0.45)	0.12 (0.00 to 0.24)	1.34 (0.95 to 1.88)	**0.37 (0.06 to 0.69)**	**0.12 (0.02 to 0.22)**	**1.22 (1.01 to 1.46)**	.24
Q1	**0.36 (0.14 to 0.58)**	**0.15 (0.05 to 0.25)**	**1.34 (1.06 to 1.69)**	0.80 (0.48 to 1.12)	0.21 (0.13 to 0.29)	**1.38 (1.19 to 1.61)**	

The values in bold denote significant differences ($P < .05$).

ALB, albumin; AP, attributable proportion due to interaction; Q, quartile; RERI, relative excess risk due to interaction; SI, synergy index.

[a]Models were adjusted for age, sex, body mass index, Townsend deprivation index, smoking status, drinking status, physical activity, total cholesterol, systolic blood pressure, white blood cell count, C-reactive protein, alanine aminotransferase, and serum creatinine.

relationship between ALB and VTE risk was confirmed in the Kuopio Ischemic Heart Disease (KIHD) study with 2176 middle-aged Caucasian males. In the present study, after adjusting for several identified risk factors and other underlying confounders, the risk of VTE increased by 23% per SD decrement in the baseline. Further adjustment for CRP, the HR was 1.22 (95% CI, 1.01-1.46), which suggested that the relationship between low ALB and increased VTE risk was independent of inflammation. However, this result was limited to only males and could not be generalized to women and other populations. In our cohort, we examined whether the association between ALB and the VTE risk was influenced by confounding factors, such as leukocyte count and CRP, considered relevant markers of inflammation. After accounting for both factors in a multivariate model, the association between ALB and VTE still remained significant. Therefore, it was less likely that the inflammation explained the relationship between ALB and VTE. Moreover, our study found an exposure–outcome relationship between ALB levels and the risk of VTE in our study. Although our observation might be affected by confounding factors or reverse causation, our model included adjustments for known confounding factors as much as possible. Recent results from a 2-sample Mendelian randomization study confirmed the causal effects of lower serum ALB levels on the risk of VTE [29], proving the reliability and credibility of our observational study.

Consistent with prior studies [30,31], our research findings demonstrate a significant positive correlation between PRS and the incidence of VTE, indicating that PRS can be used to identify individuals with a high risk of developing VTE. Moreover, in individuals with high genetic risk, an additive interaction was found between PRS and ALB, resulting in a combined effect that was stronger in influencing the risk of VTE than considering each factor separately. Twenty-one percent of VTE cases could be attributed to the additive interactions, suggesting that interactive effect of high genetic risk and lower ALB levels was greater than the sum of the 2 individual effects. The observed additive interaction between genetic risk and serum ALB has public health implications because it can be used to identify people who are more likely to benefit from targeted interventions designed to focus on the serum ALB levels. Specifically, in this study, people with high genetic risk should pay more attention to serum ALB level. Therefore, by combining the readily available clinical laboratory parameter of serum ALB with PRS, it is possible to identify individuals at heightened risk of VTE at an earlier stage and to initiate early intervention.

Our research has several notable advantages. Being a large-scale population cohort study based on the UKB, we were able to leverage the participation of 417,113 individuals, providing robust statistical power. This study allowed us to effectively detect subtle associations, setting us apart from studies with limited sample sizes. The extensive collection of demographic and laboratory data by the UKB enabled us to comprehensively measure covariates, improving our ability to control for confounding factors. Additionally, we elucidated the joint effect of serum ALB and genetic susceptibility, revealing a significant positive additive effect on the risk of VTE.

Our study has several limitations. First, we only obtained data on overall events of VTE and did not perform subgroup analysis for DVT and PE. Second, because ALB measurements were taken at baseline, VTE events occurred several years after the initial measurement in most cases. Over an extended follow-up period, ALB concentrations may fluctuate, which may not accurately reflect the actual levels during VTE occurrence. Third, even though we made adjustments for the primary confounding factors, we could not exclude adjustments for measurement errors and other confounding factors, such as use of anticoagulation medications, prothrombin, and D-dimer. Therefore, we could not consider the possible influence of hypercoagulability on the relationship between ALB and the risk of VTE. Fourth, low levels of serum ALB may be correlated with malnutrition and specific disease states, and these conditions may also be associated with the occurrence of VTE. Meanwhile, because serum ALB is an extremely volatile biomarker, serum ALB levels in this study were measured at baseline and no further measurements were taken during follow-up. Therefore, we cannot assess the impact of serum ALB levels at different time points on the study outcomes. Finally, this study primarily focused on the European population, and it remains uncertain whether the exposure–outcome association holds in other racial groups. Therefore, given the limitation of our sample, future research needs to be conducted on a global scale to investigate this relationship further among other ethnicities to enhance the generalizability of our findings.

In conclusion, the results of this large population-based cohort study provided evidence that low serum ALB levels and high genetic risk were associated with an increased risk of VTE. Additionally, joint effects analysis revealed a positive additive interaction between the lowest ALB level and high genetic risk. Future research could explore the feasibility of using serum ALB levels as a basis for developing VTE prediction and treatment strategies.

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AUTHOR CONTRIBUTIONS

X.H. and Y.H. designed and supervised the manuscript. Y.S. and J.D. wrote the main manuscript and prepared the tables and figures. S. Li, Y.G., X.C., and X.H. offered advice and help with statistics. Y.D. and S. Luo interpreted the data. All authors have reviewed the manuscript and given their final approval for its submission.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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