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Inverse association between serum albumin and future risk of venous thromboembolism:

Interrelationship with high sensitivity C-reactive protein

Running Title: Serum albumin and venous thromboembolism

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ABSTRACT

Purpose: We aimed to assess the prospective association of serum albumin with venous thromboembolism (VTE) risk and evaluate if the association is independent of or modified by inflammation, as measured by high sensitivity C-reactive protein (hsCRP).

Design: We analyzed data of 2,176 men aged 42-61 years free from VTE in the Kuopio Ischemic Heart Disease study, with serum albumin concentrations measured at baseline using Coulter's bromcresol purple colorimetric assays. Hazard ratios (HRs) (95% confidence intervals, CI) were calculated for VTE.

Results: There were 109 validated cases of VTE recorded during a median follow-up of 24.9 years. The risk of VTE increased linearly below a serum albumin concentration of ~48 g/l. In Cox regression analysis adjusted for established risk factors and other potential confounders, the HR (95% CI) for VTE per 1 standard deviation lower serum albumin was 1.23 (1.02-1.47). The association remained persistent on further adjustment for hsCRP 1.22 (1.01-1.46). Furthermore, the association was not modified by hsCRP and persisted on exclusion of men with elevated hsCRP levels.

Conclusion: In middle-aged Caucasian men, low serum albumin is associated with an increased risk of VTE, consistent with a linear dose-response relationship. The association is independent of and not modified by inflammation.

Keywords serum albumin; venous thromboembolism; inflammation; cohort study

KEY MESSAGES

- Serum albumin may be associated with future risk of venous thromboembolism (VTE); however, the shape, nature, magnitude, and consistency of the association is uncertain.

- In a population-based prospective cohort study, low serum albumin was associated with an increased risk of VTE in a linear dose-response manner and this association was independent of and not modified by inflammation.

- Serum albumin concentrations may play a role in the development of VTE.

Introduction

Venous thromboembolism (VTE) affects several millions of people and is an important cause of preventable morbidity and premature mortality.(1, 2) Established risk factors for VTE include obesity, cancer, immobilisation, trauma, surgery, hormonal therapy, and disorders of hypercoagulation.(3, 4) Though inflammation has been suggested to play a role in the pathogenesis of VTE, the evidence is controversial.(5, 6) It appears that several unknown factors may be linked to the development of VTE, since the causes are not specific in a substantial number of VTE cases and despite the identification of several risk factors for VTE and availability of effective prophylaxis, its occurrence is not decreasing.(7) A consistent body of evidence indicates albuminuria or nephrotic syndrome (which is characterised by macroalbuminuria) to be associated with an increased risk of VTE.(8-11) Recent emerging evidence suggests that low serum albumin concentrations might be linked with an increased risk of VTE; however, the evidence has been conflicting. Whereas some studies have suggested an increased risk of VTE with low serum albumin concentrations,(12-14) other studies have shown no evidence of any associations.(9, 10, 15) In addition, majority of these studies were based on cross-sectional or retrospective designs or were conducted in populations with pre-existing diseases such as nephrotic syndrome and cancer.(12-15) However, in a recent elegant evaluation based on two population-based cohorts, Folsom and colleagues demonstrated low serum albumin to be a modest marker of increased VTE risk and speculated that the observed association might reflect a hyperinflammatory or a hypercoagulable state.(16) There were however some drawbacks of this study which included (i) inability to evaluate if inflammation might explain the findings, as there were no available measurements of C-reactive protein (CRP) in the study cohorts. Though a subject of debate, CRP - the major inflammatory marker - has been implicated in the aetiopathogenesis of VTE; (5, 6, 17) (ii) also, the study cohorts had no information on liver enzymes and hence it is uncertain if the association could be attributed to liver disease; (iii) a formal assessment of the shape of the relationship between serum albumin and VTE risk was not undertaken; hence it is uncertain if there is a dose-response relationship to the association; and (iv) finally, whether the association is

modified by relevant clinical characteristics is not certain, as no interaction analysis was conducted in this study. In this context, our main objective was to assess the shape, nature, magnitude, and consistency of the prospective association between serum albumin and risk of VTE in one comprehensive investigation using a population-based cohort of 2,176 men with no previous history of VTE from eastern Finland. A secondary objective was to evaluate if the association is independent of or modified by serum high sensitivity (hs) CRP.

Materials and methods

Study design and participants

This study was conducted in accordance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (**Supplementary Table S1**). The Kuopio Ischemic Heart Disease (KIHD) study is a population-based prospective cohort design, which was set up to evaluate established and emerging risk factors for cardiovascular disease (CVD) and other chronic disease outcomes. Detailed description of the study design and recruitment methods have been reported in previous studies.(18, 19) Briefly, a representative sample of men aged 42-61 years from the city of Kuopio and surrounding rural communities in eastern Finland were invited for screening examinations carried out in 1984-1989. The total number of randomly selected potential eligible men for the study was 3,433; of this number, 3,235 were found to be eligible. A total of 2,682 (78%) eligible men provided consent to be a part of the study; 367 declined to participate; and 186 did not respond to the invitation. In the current analysis, complete information on serum albumin, relevant covariates, and VTE outcomes was available for 2,176 men. Written informed consent was obtained from all participants and study protocol was approved by the institutional review board of the University of Eastern Finland. All study procedures were conducted according to the Declaration of Helsinki.

Assessment of serum albumin and other baseline risk markers

Baseline assessments were conducted by physical examination, blood samples, and use of self-administered questionnaires. Blood samples were taken in the morning between 08:00 and 10:00 hours after an overnight fast. Participants were also required to abstain from alcohol consumption for at least 3 days and smoking for at least 12 hours prior to blood collection. Serum samples were stored frozen at -80 °C for 0.2-2.5 years before measurements of analytes. Measurements of serum albumin concentrations were made using Coulter's bromocresol purple (BCP) colorimetric assay (Kone Specific, Kone Corporation, Espoo, Finland). Serum hsCRP measurements were made with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). Serum gamma-glutamyltransferase (GGT) activity was measured using the kinetic method (Thermo Fisher Scientific, Vantaa, Finland). Fasting plasma glucose (FPG) was measured using the glucose dehydrogenase method (Merck, Darmstadt, Germany). Plasma fibrinogen concentrations were determined in fresh plasma samples with excess thrombin using the Coagulometer KC4 device (Heinrich Amelung GmbH, Lemgo, Germany). Blood pressure was recorded by an experienced nurse with a random-zero sphygmomanometer (Hawskley, UK) after 5 and 10 minutes of rest in a seated position.(20) Body mass index (BMI) was estimated as weight in kilograms divided by the square of height in meters. Participants completed self-administered health and lifestyle questionnaires for the assessments of age, smoking, alcohol consumption, prevalent medical conditions, and medication history.(21) The energy expenditure of physical activity was assessed using the validated KIHD 12-month leisure-time physical activity questionnaire.(22, 23)

Ascertainment of incident venous thromboembolism

All first lifetime VTE events that occurred from study entry to 2013 were included. Cases were identified from ICD codes by computer linkage to the National Hospital Discharge Registry data and a comprehensive review of hospital records (discharge summaries, physician reports, and radiological

reports), health practitioner questionnaires, death certificate registers, autopsy registers, and medico-legal reports and were validated by medical record review by two physicians. The diagnosis of VTE (deep vein thrombosis or pulmonary embolism) required positive imaging tests. All participants in the KIHD study (using Finnish personal identification codes) are under continuous annual surveillance for the development of new outcomes including VTE cases.

Statistical analyses

We log transformed skewed variables (triglycerides, GGT, fibrinogen, and hsCRP) to achieve approximately symmetrical distributions. Descriptive analyses were used to summarize baseline characteristics of participants. Cox proportional hazard regression models were used to conduct time-to-event analyses after confirming the assumptions of proportionality of hazards.(24) We characterized the shape of the association between serum albumin concentrations and VTE risk by calculating hazard ratios (HRs) within quartiles of baseline serum albumin levels and plotted them against mean serum albumin levels within each quartile using floating absolute risks(25) as described previously.(26, 27) As the association showed an approximately linear shape, serum albumin was modeled continuously; per 1 standard deviation (SD) change in serum albumin levels. A 1 SD decrement was used, to ensure consistency with previous reports.(16) To further explore the shape of the relationship, we used a restricted cubic spline with knots at the 5th, 35th, 65th and 95th percentiles of serum albumin distribution in a multivariate adjusted model. Hazard ratios were also calculated by quartiles defined according to the baseline distribution of serum albumin levels in the sample. The HRs were progressively adjusted for (i) age; (ii) established risk factors and other potential confounders [BMI, systolic blood pressure (SBP), history of hypertension, prevalent coronary heart disease (CHD), smoking status, history of diabetes, total cholesterol, lipid medication, eGFR, physical activity, alcohol consumption, GGT, fibrinogen, and prevalent cancer]; and (iii) hsCRP. We selected these risk markers based on their potential as confounders as a result of their known associations with VTE outcomes and observed associations with serum albumin

using the available data(28) or evidence from previous research, as discussed in previous studies.(17) We evaluated if the association was modified by pre-specified clinically relevant characteristics including hsCRP using tests of interaction. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

Results

Baseline characteristics

Baseline characteristics of study participants by quartiles of serum albumin and by development of VTE are summarized in **Table 1 and Supplementary Table S2** respectively. The mean age of study participants was 53 (SD, 5) years. The mean (SD) serum albumin level was 42.3 (3.5) g/l. The median (interquartile range) of hsCRP was 1.27 (0.70-2.38) mg/l. Alcohol consumption was high in men with low serum albumin; GGT values were higher, whiles levels of fibrinogen and hsCRP were lower in men with high serum albumin levels. Except for serum albumin levels and smoking status, there were no significant differences in baseline characteristics between participants who developed VTE and those who did not develop VTE during follow-up. Mean levels of serum albumin were higher in the group who did not develop VTE during follow-up compared to the group with VTE during follow-up. Cross-sectional correlates of serum albumin with several risk markers are presented in **Supplementary Table S3**. Serum albumin levels were weakly and inversely correlated with age, total cholesterol, eGFR, $\log_e$ fibrinogen, and $\log_e$ hsCRP. Weak positive correlations were observed for BMI, blood pressure, $\log_e$ triglycerides, creatinine, and $\log_e$ GGT. Baseline serum albumin concentrations were lower in current smokers compared with non-smokers.

Serum albumin and risk of venous thromboembolism

During a median follow-up of 24.9 (interquartile range, 17.9-27.1) years, 109 VTE cases (annual rate 2.30/1,000 person-years at risk; 95% CI: 1.91 to 2.78) were recorded. Serum albumin was approximately

linearly associated with risk of VTE (**Supplementary Figure S1**). **Supplementary Figure S2** depicts

results of the restricted cubic spline analysis, which shows the risk of VTE increasing linearly below a

serum albumin concentration of ~48 g/l (*p*-value for non-linearity=0.161); the risk of VTE plateaus at a

serum albumin concentration of ~40 g/l. After adjustment for age, the HR for VTE per 1 SD decrement in

serum albumin was 1.22 (95% CI: 1.03 to 1.46) which remained unchanged on further adjustment for

several established risk factors and other potential confounders 1.23 (95% CI: 1.02 to 1.47). The HR

remained consistent on additional adjustment for hsCRP 1.22 (95% CI: 1.01 to 1.46). Alternatively,

comparing the bottom versus top quartiles of serum albumin levels, the corresponding adjusted HRs were

2.05 (95% CI: 1.14 to 3.70), 2.06 (95% CI: 1.13 to 3.76), and 2.01 (95% CI: 1.10 to 3.68) respectively

(**Table 2**). Except for evidence of effect modification by smoking status (*p* for interaction = 0.015), the

association between serum albumin and VTE risk was not significantly modified by several clinically

relevant characteristics including age, GGT, fibrinogen, and hsCRP (*P* for interaction ≥ 0.10 for each;

Figure 1). The association between low serum albumin and increased VTE risk was more extreme in

current smokers compared with non-smokers. To minimise the influence of an active inflammatory

process on the association, we conducted a subsidiary analysis which excluded participants in the top 5th

percentile of hsCRP and the albumin-VTE association was observed to persist (**Supplementary Table**

S4). Furthermore, the association remained and was stronger when the analysis was limited to the first 15

years of follow-up to account for the influence of regression dilution bias because of the long-term

follow-up (**Supplementary Table S4**). Finally, to minimise reverse causation bias due to pre-existing

undiagnosed conditions such as cancer and rheumatological diseases which may affect serum albumin

levels, we excluded the first two years of follow-up. Initial evidence of an association was confounded by

several established risk factors (**Supplementary Table S4**).

Discussion

Key findings

In the KIHD population-based prospective study of middle-aged Caucasian men, low serum albumin levels were associated with an increased risk of VTE. The risk of VTE increased linearly below a serum albumin concentration of ~48 g/l, with the risk plateauing at a serum albumin concentration of ~40 g/l. The association of serum albumin and VTE risk was independent of several established risk factors as well as markers of inflammation. Except for evidence of effect modification by smoking status, the associations remained generally consistent across several clinically relevant subgroups. The association was stronger in current smokers compared with non-smokers; which may reflect existing evidence that cigarette smoking lowers levels of serum albumin,(29, 30) which in turn is associated with an increased risk of VTE. Indeed, our current findings indicated that serum albumin levels were significantly lowered in current smokers. Furthermore, the association remained persistent when men with elevated hsCRP levels at baseline were excluded. However, when the first two years of follow-up was excluded, the association was less robust on adjustment for several confounders.

Comparison with previous studies

Though a broad body of evidence suggests low serum albumin to be linked to an increased risk of VTE, existing studies have mainly been based on cross-sectional and retrospective designs and in populations with pre-existing disease.(12-15) Until the publication of the findings by two large-scale population-based cohorts: the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS), no prospective cohort studies based on general population settings existed. Though the ARIC and CHS studies were large-scaled studies that provided adequate power to assess the association between serum albumin and VTE risk, there were some limitations in the published report. There was no information on CRP to ascertain if inflammation might explain the findings; no information existed on liver enzymes to account for liver disease; the shape of the relationship was not assessed; and no

subgroup analysis by relevant clinical characteristics were performed. In the REasons for Geographic And Racial Differences in Stroke (REGARDS) Cohort study which also reported evidence of an association between low serum albumin and increased VTE risk,(31) though measurements for CRP were available, no adjustment was made for it in evaluating the association between albumin and VTE. Neither were any adjustments made for liver enzymes. The current analysis therefore provides several relevant findings that have not been previously reported. Our results demonstrate low serum albumin to be associated with an increased VTE risk and this association is consistent with a dose-response relationship and is independent of inflammation. Furthermore, the association was modified by smoking status, but the levels of hsCRP did not change the observed relationship between serum albumin and VTE risk.

Possible explanations for findings

Though there is limited and unclear evidence on the aetiopathogenesis of VTE, an inflammatory hypothesis has been postulated in the development of VTE. Indeed, several markers of inflammation such as CRP, interleukins, and tumour necrosis factor alpha have been demonstrated to be associated with an increased risk of VTE.(17, 32-34) The mechanistic pathways linking low serum albumin with an increased risk of VTE is not clear; however, it has been postulated that low serum albumin levels may reflect inflammatory or hypercoagulable states,(16) which are linked to the development of VTE.(6) Serum albumin is a negative acute phase reactant which is synthesized by the liver. During inflammatory states, there is hepatic synthesis of other acute-phase proteins rather than serum albumin.(35) It therefore goes to suggest that low serum albumin is an indicator of an inflammatory response. However, our observed serum albumin-VTE association remained persistent on adjustment for several inflammatory markers such as GGT, fibrinogen, and hsCRP, as well as in analysis that excluded participants with elevated hsCRP levels, which signify an active inflammatory process. It is therefore unlikely that inflammation may explain the link between low serum albumin and increased VTE risk. It has also been suggested that low serum albumin may just be an indicator of an underlying poor general health,(16)

which may predispose to VTE risk. Health conditions such as liver disease, nephrotic syndrome, and cancer are well known risk factors for VTE;(9, 14, 15, 36) however, these conditions are unlikely to explain our findings as they are rare in the KIHD cohort. Moreover, the association persisted on adjustment for prevalent cancer. The apparent association between serum albumin and VTE was less robust when the first two years of follow-up was excluded. This may suggest that the risk of VTE could be due to underlying pre-existing undiagnosed diseases such as malignancy, liver disease, and known conditions known to predispose to the development of VTE. There have also been suggestions that atherosclerotic disease is an underlying condition and precedes the development of VTE.(37) Since low serum albumin is associated with an increased risk of atherosclerotic CVD,(30) the association between low serum albumin and high VTE risk may reflect pre-existing CVD. Our findings were however independent of and not modified by pre-existing CHD. As suggested by Folsom and colleagues, low serum albumin may be a marker of a hypercoagulable state and underlying disease conditions.(16) Consistent with their findings, we also observed low serum albumin to be associated with high fibrinogen levels. Furthermore, though the association between low serum albumin and increased VTE risk persisted on adjusting for smoking status; our subgroup analysis suggested that the association may only be evident in current smokers. It therefore appears that our findings may be due to the effects of smoking on serum albumin concentrations. Indeed, existing evidence suggests that the inverse association between serum albumin and atherosclerotic CVD may also be related to the effects of smoking on serum albumin.(30) However, given (i) that the proportion of smokers in those who developed VTE was significantly less than in those who did not develop VTE; (ii) the absence of prior studies on the relationship between serum albumin and VTE risk in non-smoking populations; (iii) the multiple statistical tests for interaction conducted; and (iv) the low event rates in these subgroups as well as the imprecise estimates, results of the subgroup analyses need to be interpreted with caution. The pathways underlying the link between low serum albumin and increased VTE risk remain controversial; therefore, future mechanistic studies are needed to clarify these uncertainties.

Implications of findings

The current data establishes an observational independent and linear dose-response relationship between serum albumin and VTE risk. Whether the association is causal remains yet to be investigated. Venous thromboembolism is under strong genetic regulation, with about 50 to 60% of the variance in its incidence being attributed to genetic effects.(38) Genetic polymorphisms that influence serum albumin levels could be employed in Mendelian randomization studies to ascertain if there is a causal relevance to the association. Taken the overall findings together suggest that serum albumin may play a role in the development of VTE. Further studies are however needed to replicate these findings and evaluate the potential relevance of serum albumin assessment in VTE prevention strategies.

Strengths and limitations

Several strengths of the current study deserve consideration. We employed a relatively large-scale population-based prospective cohort study that recruited men from the general population; there were no losses to follow-up in the cohort as participants are under continuous annual surveillance for outcome events; participants were followed up for an average period of 20 years and analysis was comprehensive which included adjustment for several established risk factors for VTE as well as markers of inflammation and coagulation, evaluation of effect modification by several clinical relevant characteristics, assessment of a dose-response relationship, as well as several sensitivity analyses. Furthermore, compared to previous studies which used the bromocresol green colorimetric assay for serum albumin measurements;(14, 16) our study employed the BCP assay which agrees with the gold standard of immunonephelometry.(39) Several limitations also deserve mention. The study is limited by the low event rate and the findings cannot be generalized to women and other populations. Though we adjusted for key confounding characteristics, residual confounding due to errors in risk marker measurements and other unmeasured potential confounders (use of medications and coagulation factors

such as Factors Va, VII, VIII, and XIII, thrombin, prothrombin, and D-dimer) cannot be ruled out. Data was only available on total VTE events which precluded the ability to conduct subgroup analyses of deep vein thrombosis and PE as well as unprovoked and provoked VTE outcomes. There was also no separate data on symptomatic and asymptomatic VTE events. We were unable to correct for within-person variability in serum albumin levels because of absence of data on repeat measurements and this could have underestimated the associations, as a result of regression dilution given the long-term follow-up of the cohort. (40, 41) Indeed, the association was stronger when analysis was restricted to the first 15 years of follow-up. Furthermore, there is evidence that serum albumin exhibits low within-individual variation; the correlation coefficient between measured levels of serum albumin several years apart has been reported to be approximately 0.70.(42) Nevertheless, studies with repeat measurements of serum albumin are still needed to assess its variability in greater detail.

Conclusions

Low serum albumin is associated with an increased risk of VTE in a linear dose-response manner in middle-aged Caucasian men. The association is independent of and not modified by inflammation. Further research is needed to replicate these findings, elucidate the mechanistic pathways involved, and assess any potential relevance of serum albumin concentrations in VTE prevention.

Disclosure of interest

The authors report no conflicts of interest

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Table 1. Baseline Participant Characteristics by quartiles of serum albumin

	Quartile 1 Mean (SD) or median (IQR) or n (%)	Quartile 2 Mean (SD) or median (IQR) or n (%)	Quartile 3 Mean (SD) or median (IQR) or n (%)	Quartile 4 Mean (SD) or median (IQR) or n (%)
Serum albumin (g/l)	38.1 (2.5)	41.5 (0.5)	43.5 (0.5)	46.5 (1.8)
Questionnaire/Prevalent conditions				
Age at survey (years)	53.8 (4.8)	53.2 (4.9)	53.1 (5.0)	52.4 (5.5)
Alcohol consumption (g/week)	33.6 (7.6-104.4)	32.4 (4.8-90.5)	28.2 (6.9-86.5)	32.1 (5.6-93.4)
History of diabetes	26 (4.4)	18 (3.6)	21 (3.8)	22 (4.2)
Current smokers	214 (36.2)	155 (30.6)	175 (31.3)	123 (23.7)
History of hypertension	159 (26.9)	148 (29.3)	170 (30.4)	170 (32.7)
History of CHD	151 (25.6)	148 (29.3)	136 (24.3)	112 (21.5)
History of cancer	8 (1.4)	5 (1.0)	16 (2.9)	7 (1.4)
Lipid medication	2 (0.3)	4 (0.8)	4 (0.7)	3 (0.6)
Physical measurements				
BMI (kg/m^2)	26.6 (3.4)	26.7 (3.4)	26.8 (3.3)	27.4 (3.8)
SBP (mmHg)	131 (16)	133 (16)	134 (16)	137 (18)
DBP (mmHg)	88 (11)	88 (10)	89 (10)	90 (11)
Physical activity (kj/day)	1151 (615-1941)	1130 (619-1893)	1220 (620-2027)	1272 (672-2126)
Lipid markers				
Total cholesterol (mmol/l)	6.04 (1.14)	5.88 (1.08)	5.84 (1.03)	5.85 (1.05)
HDL-C (mmol/l)	1.29 (0.32)	1.30 (0.28)	1.31 (0.31)	1.30 (0.29)
Triglycerides (mmol/l)	1.04 (0.76-1.45)	1.10 (0.82-1.47)	1.10 (0.78-1.59)	1.22 (0.86-1.79)
Metabolic, renal, liver, and inflammatory markers				
Fasting plasma glucose (mmol/l)	5.36 (1.39)	5.39 (1.31)	5.35 (1.26)	5.32 (1.05)
Serum creatinine (µmol/1)	88.5 (14.5)	89.2 (15.4)	89.6 (12.9)	90.6 (11.6)
Estimated GFR (ml/min/1.73 m^2)	88.0 (17.8)	87.3 (15.8)	86.9 (19.8)	85.4 (14.5)
GGT (U//L)	19 (14-29)	20 (14-33)	20 (15-30)	23 (15-37)
Fibrinogen (g/l)	3.04 (2.72-3.44)	2.96 (2.64-3.37)	2.96 (2.63-3.28)	2.88 (2.57-3.21)
High sensitivity CRP (mg/l)	1.36 (0.78-2.73)	1.38 (0.74-2.51)	1.26 (0.68-2.28)	1.09 (0.64-2.04)

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration rate; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure; VTE, venous thromboembolism;

Table 2. Association of serum albumin and venous thromboembolism

Serum albumin (g/l)	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Per 1 SD decrease	109 / 2,176	1.22 (1.03 to 1.46)	0.025	1.23 (1.02 to 1.47)	0.029	1.22 (1.01 to 1.46)	0.037
Q1 (23-40)	37 / 591	2.05 (1.14 to 3.70)	0.017	2.06 (1.13 to 3.76)	0.018	2.01 (1.10 to 3.68)	0.023
Q2 (41-42)	29 / 506	1.91 (1.04 to 3.53)	0.037	1.93 (1.04 to 3.59)	0.036	1.91 (1.03 to 3.55)	0.040
Q3 (43-44)	27 / 559	1.66 (0.89 to 3.07)	0.110	1.71 (0.92 to 3.19)	0.092	1.69 (0.91 to 3.15)	0.099
Q4 (45-60)	16 / 520	ref		ref		ref	

CI, confidence interval; HR, hazard ratio; ref, reference; Q, quartile; SD, standard deviation;

Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, systolic blood pressure, history of hypertension, prevalent coronary heart disease, smoking status, history of diabetes, total cholesterol, lipid medication, estimated glomerular filtration rate, physical activity, alcohol consumption, $\log_e$ gamma-glutamyltransferase, $\log_e$ fibrinogen, and prevalent cancer

Model 3: Model 2 plus $\log_e$ high sensitivity C-reactive protein

Figure legends

Figure 1. Hazard ratios for baseline levels of serum albumin and venous thromboembolism risk by several participant level characteristics
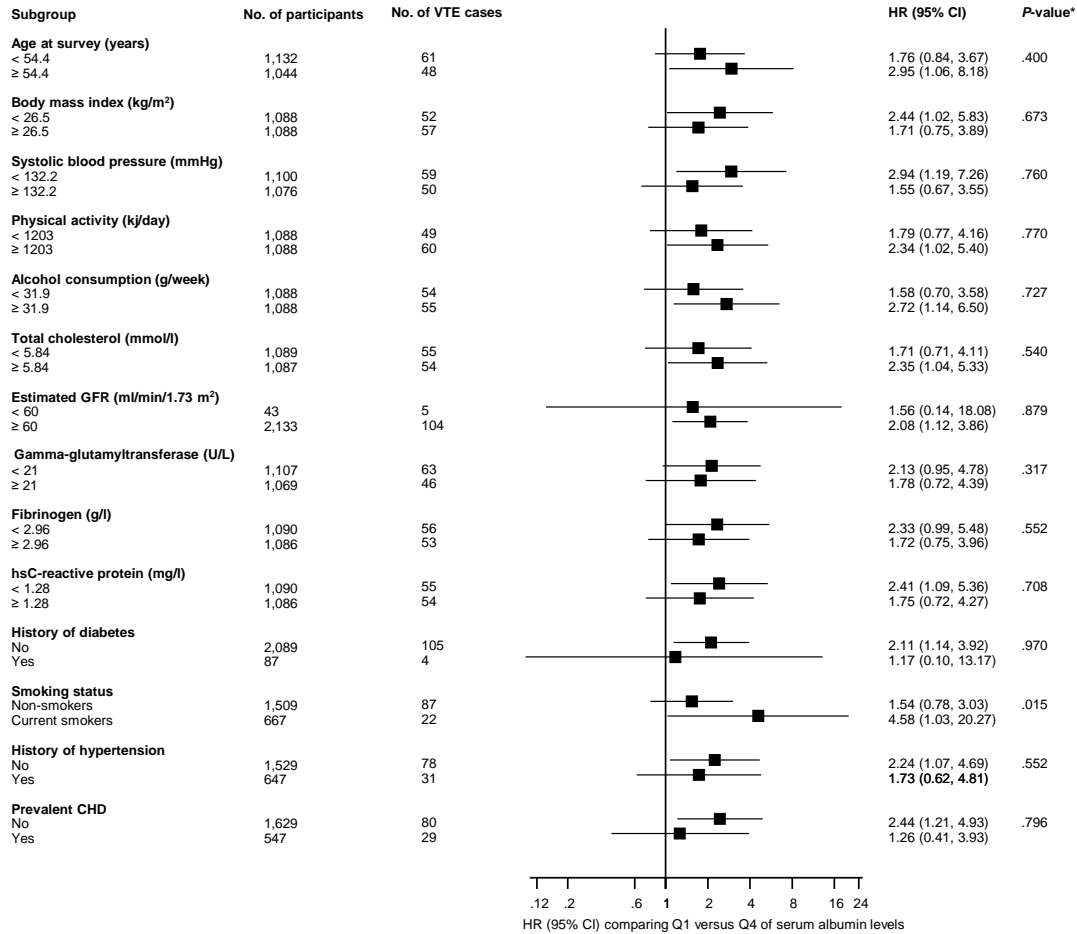
Hazard ratios are adjusted for adjusted for age, body mass index, systolic blood pressure, history of hypertension, prevalent coronary heart disease, smoking status, history of diabetes, total cholesterol, lipid medication, estimated glomerular filtration rate, physical activity, alcohol consumption, $\log_e$ gamma-glutamyltransferase, $\log_e$ fibrinogen, and prevalent cancer; CHD, coronary heart disease; CI, confidence interval; GGT, gamma-glutamyltransferase; HR, hazard ratio; hs, high sensitivity; Q, quartile; VTE, venous thromboembolism; *, *P*-value for interaction; cut-offs used for age, body mass index, systolic blood pressure, physical activity, alcohol consumption, total cholesterol, gamma-glutamyltransferase, fibrinogen, and high sensitivity C-reactive protein are median values.