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ORIGINAL ARTICLE

Socioeconomic status and risk of incident venous thromboembolism

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Abstract

Background: Although venous thromboembolism (VTE) is a leading cause of morbidity and mortality, and socioeconomic status (SES) affects human health and health behavior, few studies have examined the association between SES and VTE.

Objectives: We aimed to investigate the association between SES, assessed individually and in a composite score by levels of education, income, and employment status, and incident VTE.

Methods: We used Danish national registries to identify 51 350 persons aged 25–65 years with incident VTE during 1995–2016. For each case, we used incidence density sampling to select five age-, sex-, and index-year-matched controls from the general Danish population (n = 256 750). SES indicators, including education, income, and employment status, were assessed 1 and 5 years before the VTE. We used conditional logistic regression to compute odds ratios (ORs) with 95% confidence intervals (CIs) for VTE according to individual SES indicators and a composite SES score in analyses adjusted for age, sex, and comorbidities.

Results: Compared with low levels, high educational level (OR 0.74; 95% CI 0.71–0.77), high income (OR 0.70; 95% CI 0.68–0.72), and high employment status (OR 0.66; 95% CI 0.64–0.68) were associated with decreased risk of VTE, even after adjusting for comorbidities. A composite SES score was superior to the individual indicators in assessing VTE risk (OR for high vs. low score: 0.61; 95% CI 0.59–0.63). In sensitivity analysis with SES indicators measured 5 years before the VTE, the risk estimates remained essentially the same.

Conclusion: High levels of both individual SES indicators and a composite SES score were associated with decreased VTE risk.

KEYWORDS
education, employment, income, socioeconomic status, venous thromboembolism

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1 | INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a serious vascular disorder associated with substantially reduced quality of life, morbidity, and mortality.[1,2] Socioeconomic status (SES) has been demonstrated to affect the risk of arterial cardiovascular diseases such as myocardial infarction and stroke,[3–5] but less is known of the importance of SES in VTE.

The few studies that have investigated associations between SES indicators and VTE risk report that stress,[6] low income,[7,8] low educational status,[7–10] low occupational class,[6,9,10] single status,[7] and neighborhood deprivation[11,12] are associated with increased VTE risk. Even though existing studies suggest that individual SES indicators play a role in the VTE risk, similar to that for other arterial cardiovascular diseases, available evidence is inconsistent and the SES indicators found to be associated with VTE vary within and between studies.[6–10] The discrepancy in current studies is likely explained by differences in composition of the study populations, study designs, time between SES and VTE assessments, and methods for monitoring SES indicators. Furthermore, because low SES is associated with VTE-related comorbidities such as cancer and cardiovascular diseases,[3–5,13] it is likely that these conditions partly explain or mediate the associations reported between SES and VTE.

To tailor VTE prevention at the population level, it is important to assess the strength of the associations between SES and VTE, measured both as individual SES indicators and as a composite SES score, and examine whether these associations are explained by confounding diseases. The aim of this population-based nationwide case-control study was therefore to investigate the impact of the major SES indicators education, income, and employment status, assessed individually and combined, on risk of incident VTE.

Essentials

- Few studies have explored the association between socioeconomic status (SES) and VTE risk.
- We assessed the association between individual SES indicators and a composite SES score, and VTE.
- High levels of SES indicators and a composite SES score were associated with decreased VTE risk.
- The combined SES score performed better than individual indicators in assessing the risk of VTE.

2 | METHODS

2.1 | Design and setting

Denmark has universal tax-funded health care and educational systems covering all legal Danish residents.[14] In addition, the Danish government maintains nationwide registries containing routinely collected administrative and health data.[14] The unique personal identifier (CPR number) assigned to every Danish resident at birth or upon immigration makes it possible to access and link the nationwide registries to obtain extensive individual-level health care information and current data on civil and vital status.[14]

In the current study we extracted demographic information and data on vital status and migration from the Danish Civil Registration System.[14] Information on VTE and comorbidities was obtained from the Danish National Patient Registry (DNPR) and the Danish Psychiatric Central Research Register both covering all Danish hospitals.[14] Furthermore, we obtained data on income and employment status from the Integrated Database for Labour Market Research, and data on education from the Educational Attainment Register.[14]

2.2 | Cases and controls

We used the International Classification of Diseases (ICD) 8 and10 codes in the DNPR to identify 51 350 VTE patients aged 25–65 years with a first-time primary or secondary discharge diagnosis of DVT or PE from January 1, 1995, to December 31, 2016. If a patient had simultaneous PE and DVT diagnoses, we categorized the event as PE because of its higher mortality rate.[15] We defined the first hospital admission/outpatient clinic visit date as the VTE date and excluded VTEs registered only in emergency room departments because they often represent working diagnoses with high rates of clinical misclassification.[16] We did not include individuals aged <25 years because they were likely to still be in school and to lack a stable income or employment. We also did not include individuals aged ≥65 years because they would be retired from work and receive an old age pension instead of work-related income.

For each VTE patient, we used the Civil Registration System to individually match five general controls from the general working age population by year of birth, sex, and calendar year (n = 256 750), with replacement based on incidence density sampling.[17] The hospital admission date for the VTE patient was used as the index date for the matched controls.[17] Individuals in the control group could not have been hospitalized for VTE before their index date. Cases and controls with missing SES values (n = 20 398) were not included in the regression analysis.

2.3 | Variables

We measured educational level, employment status, and income level 1 and 5 years before the VTE/index date. We divided the level of education (i.e., high, medium, low) into age-specific groups based on the distribution of education in each group. (Tables S1 and S2). To avoid the impact of inflation and to account for salary changes over calendar time, we recalculated income values using the new gross domestic product deflators downloaded from the

World Bank homepage (www.worldbank.org). After deflation of the income values, we calculated income in quartiles based on the VTE cases and controls and merged the two middle quartiles to obtain three categories (i.e., high, medium, and low). We divided employment status into "employed, unemployed, and outside the workforce." We considered persons pursuing an educational program, those in early retirement, and those receiving other types of public support, except work-related disability pension, to be outside the workforce. Employment status was categorized as high (i.e., employed), medium (i.e., outside the workforce), and low (i.e., unemployed and persons on permanent work-related disability pension).

We used the "low, medium, and high" categorical distributions to create a score for each of the socioeconomic indicators education, income, and employment status. The score for each indicator ranged from 1 to 3 with categories of high (score of 3), medium (score of 2), and low (score of 1), with low serving as the reference. We combined the scores from education, income, and employment status into a composite SES score ranging from 3 to 9. Based on the distribution of the total score, we divided the composite SES score into categories of high (scores of 8 and 9), medium (scores of 5 to 7), and low (scores of 3 and 4), using low SES score as the reference.

We searched the DNPR for information on comorbidities diagnosed before the VTE/index date using ICD-8 codes (1977–1994) and ICD-10 codes (from 1994 onwards) for obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infraction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases, surgery and trauma/fractures 3 months before the VTE/index date, and diseases included in the modified Charlson Comorbidity Index (CCI).[18] All ICD codes used in the study are provided in Table S3.

2.4 | Statistical analysis

We used conditional logistic regression models to compute crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) as a measure of the incidence rate ratio of VTE, both according to individual SES indicators (educational level, income, and employment status) measured 1 year before the VTE/index date and according to a composite SES score combining the three indicators. We performed age- and sex-stratified analyses (age groups 25–34, 35–44, 45–54, and 55–65 years of age at the inclusion date) and subgroup analyses of DVT and PE.

We applied three models adjusted for *a priori*-defined potential confounders. Model 1 comprised the matching variables (age and sex). Model 2 comprised model 1 plus obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, mental diseases, surgery and trauma 3 months before the VTE/index date, and CCI score excluding the comorbidities listed previously. In the analyses of individual SES indicators, we used a third model (model 3), which comprised model 2 plus the SES indicators that would act as confounding variables (i.e., in analyses with education as the exposure we did not adjust for income or employment status, with employment as exposure, we adjusted for education, and with income as the exposure, we adjusted for educational level and employment status).

To assess the risk of potential residual confounding we performed ordinary logistic regression analyses stratified on CCI score of zero, where a score of zero indicates that no comorbidities exist before the index date. To examine whether our results were influenced by recent changes in the exposure variables (as a potential result of reverse causation), we performed sensitivity analyses measuring educational level, income, employment status, and the composite SES score 5 years before the VTE/index date.

We tested potential nonlinearity in the associations between income, education, SES score, and VTE risk against a confounder-adjusted restricted cubic spline with a prespecified list of five knots. For the income analysis, we used the 5, 27.5, 50, 72.5, and 95 percentile values defined from our data. For SES score, we used the score values: 3, 4, 5, 7, 8, with 6 as reference. For education we used the Danish educational level values with primary education (=1) to doctoral degree or equivalent (=9) with four knots and postsecondary or short-cycle tertiary education (=5) as reference.

We conducted the analysis using SAS version 9.4 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency (record number 2016-051-000001). Informed consent and approval from an ethics committee are not required for Danish registry-based studies.

3 | RESULTS

3.1 | Characteristics of cases and controls

The characteristics of the 51 350 VTE patients and 256 750 population controls aged 25–65 years are presented in Tables 1 and 2. The distribution of characteristics across age groups (25–34, 35–44, 45–54, and 55–65 years of age) is presented in Table S4. Compared with men, women had a lower educational level and income, a higher prevalence of unemployment, and a lower SES score, with the greatest differences observed in the oldest age groups (Table 2). The following variables were more common among VTE patients than controls: low educational level (37% vs. 31%), low income (32% vs. 24%), and unemployment (20% vs. 11%). Furthermore, a high SES score was less frequent in VTE patients than in matched controls (18% vs. 24%), whereas a low SES score was more frequent (22% vs. 13%) (Table 2). In addition, several comorbidities were more prevalent among VTE patients than among controls: surgery and/or trauma 3 months before the VTE/index date (16% vs. 3%), history of cancer (13% vs. 4%), mental diseases (13% vs. 6%), and CCI score >2 (21% vs. 7%) (Table 1).

TABLE 1 Characteristics of cases with VTE and matched controls

	VTE (n = 51 350)	Controls (n = 256 750)
Sex (% men)	26 962 (52.5)	134 810 (52.5)
Pulmonary embolism	17 617 (34.3)	88 085 (34.3)
Deep vein thrombosis	33 733 (67.5)	168 665 (65.7)
Comorbidities		
High-risk cancer before VTE/index date[a]	2754 (5.4)	1446 (0.6)
Low-risk cancer before VTE/index date[a]	3668 (7.1)	7571 (2.9)
Coronary heart disease	4641 (9.0)	12 398 (4.8)
Diabetes	3578 (7.0)	11 273 (4.4)
Chronic obstructive pulmonary disease	4000 (7.8)	9228 (3.6)
Obesity	3816 (7.4)	7625 (3.0)
Stroke	1353 (2.6)	3328 (1.3)
Moderate to severe renal disease	1206 (2.3)	1747 (0.7)
Surgery 3 months before VTE/index date	7473 (14.6)	6511 (2.5)
Trauma/fracture 3 months before VTE/index date	2299 (4.5)	1711 (0.7)
Mental disorders	6892 (13.4)	14 491 (5.6)
Charlson comorbidity index		
CCI score: 0	33 287 (64.8)	215 092 (83.8)
CCI score: 1	7151 (13.9)	23 816 (9.3)
CCI score: ≥2	10 912 (21.3)	17 842 (6.9)
CCI score: 0[b]	43 617 (84.9)	240 096 (93.5)
CCI score: 1[b]	5940 (11.6)	14 074 (5.5)
CCI score: ≥2[b]	1793 (3.5)	2580 (1.0)

Note: Values are numbers, with percentages in brackets.
Abbreviations: CCI, Charlson Comorbidity Index; VTE, venous thromboembolism.
[a]Categorized according to 5-year mortality as high-risk cancer (>70%) and low-risk cancer (≤70%).
[b]Modified CCI excluding International Classification of Diseases codes used in the covariate definition.

3.2 | VTE risk by SES indicators

The ORs for VTE risk by SES indicators are shown in Figure 1. High educational level, high income, and high employment status were all associated with a decreased OR for VTE in analyses adjusted for age and sex (Figure 1). Further adjustment for comorbidities had a modest attenuating impact on the association between VTE and high educational level (OR 0.74; 95% CI 0.71–0.77), high income (OR 0.70; 95% CI 0.68–0.72), and high employment status (OR 0.66; 95% CI 0.64–0.68) (Figure 1, model 2). Additional adjustment for the confounding SES indicators further reduced the strength of the associations, but residual increments in ORs remained for all three exposures. When compared with low levels, the ORs for VTE by high educational level (OR 0.74; 95% CI 0.71–0.77), high income level (OR 1 OR 0.92; 95% CI 0.89–0.96), and high employment status (OR 0.69; 95% CI 0.67–0.71) remained lowered after adjustments for comorbidities and SES indicators (Figure 1, model 3).

In the composite score model, a high SES score was associated with a lower OR for VTE in analyses adjusted for age and sex. Compared with persons with a low SES score (13% of the control population), individuals with a medium SES score (60% of the control population) had an OR of VTE of 0.71 (95% CI 0.69–0.73) while individuals with a high SES score (24% of the control population) had an OR for VTE of 0.61 (95% CI 0.59–0.63) after adjustments for potential confounders (Figure 1, Model 2).

Figures 2–4 show the unrestricted quadratic spline regression models for income, education, and SES score with adjustment for comorbidities. The OECD average income in Denmark for 2016 was approximately 355 000 DKK. We found that an annual income more than 600 000 DKK was protective against VTE (Figure 2). The corresponding curve with educational level for the age group 25–44 as the exposure variable indicated that an educational level above tertiary education reduced the risk of VTE (Figure 3). With SES score as exposure, the spline curves revealed a clear association between increased VTE risk and below average SES scores (Figure 4).

3.3 | VTE risk according to age and sex

The association between VTE and the individual SES indicators, as well as the composite SES score, was strongest in the younger age groups, with the lowest ORs in the age group 35 to 44 years (Tables 3 and 4). ORs for VTE by education, employment status, and the composite

TABLE 2 Socioeconomic status of cases with VTE and matched controls overall and according to sex

	Overall		Men		Women	
	VTE (*n* = 51 350)	Controls (*n* = 256 750)	VTE (*n* = 26 962)	Controls (*n* = 134 810)	VTE (*n* = 24 388)	Controls (*n* = 121 940)
Education						
Low	19 195 (37.4)	79 102 (30.8)	9157 (34.0)	38 758 (28.8)	10 038 (41.2)	40 344 (33.1)
Medium	25 202 (49.1)	135 464 (52.8)	13 929 (51.7)	73 027 (54.2)	11 273 (46.2)	62 437 (51.2)
High	5374 (10.5)	35 152 (13.7)	2959 (11.0)	19 069 (14.1)	2415 (9.9)	16 083 (13.2)
Missing	1579 (3.1)	7032 (2.7)	917 (3.4)	3956 (2.9)	662 (2.7)	3076 (2.5)
Income level						
Low	16 415 (32.0)	60 445 (23.5)	7324 (27.2)	25 332 (18.8)	9091 (37.3)	35 113 (28.8)
Medium	24 462 (47.6)	129 260 (50.3)	11 934 (44.3)	60 749 (45.1)	12 582 (51.4)	68 511 (56.2)
High	10 403 (20.3)	66 458 (25.9)	7662 (28.4)	48 417 (35.9)	2741 (11.2)	18 041 (14.8)
Missing	70 (0.1)	587 (0.2)	42 (0.2)	312 (0.2)	28 (0.1)	275 (0.2)
Employment status						
Unemployed	10 058 (19.6)	29 245 (11.4)	4814 (17.9)	14 368 (10.7)	5244 (21.5)	14 877 (12.2)
Outside workforce	9961 (19.4)	39 798 (15.5)	4862 (18.0)	17 725 (13.1)	5099 (20.9)	22 073 (18.1)
Employed	31 117 (60.6)	185 859 (72.4)	17 141 (63.6)	101 665 (75.4)	13 976 (57.3)	84 194 (69.0)
Missing	214 (0.4)	1848 (0.7)	145 (0.5)	1052 (0.8)	69 (0.3)	796 (0.7)
SES score						
Low	11 264 (21.9)	33 745 (13.1)	4897 (18.2)	14 346 (10.6)	6367 (26.1)	19 399 (15.9)
Medium	29 038 (56.5)	153 146 (59.6)	14 693 (54.5)	74 410 (55.2)	14 345 (58.8)	78 736 (64.6)
High	9424 (18.4)	62 415 (24.3)	6422 (23.8)	41 868 (31.1)	3002 (12.3)	20 547 (16.9)
Missing	1624 (3.2)	7444 (2.9)	950 (3.5)	4186 (3.1)	674 (2.8)	3258 (2.7)

Note: Values are numbers, with percentages in brackets.
Abbreviations: SES, socioeconomic status; VTE, venous thromboembolism

SES score were lower overall in women than in men (Tables S5-S7). However, subgroup analysis indicated that the associations were stronger in men in the two youngest age groups and stronger in women in the two oldest age groups (Tables S5-S7).

3.4 | Subgroup and sensitivity analysis

Subgroup analysis showed that the ORs for DVT by the high levels of the individual SES indicators, including the composite SES score, were somewhat lower than ORs for PE (Table 5). In analysis restricted on patients with CCI score of zero, the ORs for VTE by high SES levels were slightly attenuated; however, the association remained significant (Table S8). When we assessed SES indicators 5 years before the VTE event/index date, ORs for VTE were essentially the same as in the primary analysis, except for employment status in which the ORs were somewhat lower than 1 year before the VTE event. (Table 6).

4 | DISCUSSION

In this large population-based case-control study, we found that high levels of individual SES indicators (education, income, and employment status), as well as a high composite SES score, were associated with lower odds of VTE even after adjustment for comorbid conditions. Further adjustment for confounding SES indicators, showed that each indicator had an independent effect on VTE risk. Given previous findings underscoring the multidimensional aspect of SES,[19–23] the independent effects of individual SES indicators on the VTE risk encouraged us to explore whether a composite SES score would improve discrimination between subjects at low and high risk of VTE. We found that the OR for the composite SES score (high vs. low) was consistently lower than the ORs for the individual indicators.

Previous studies have reported divergent results for the association between individual SES indicators and VTE. A Swedish cohort of 6958 men aged 45–55 years with 28 years of follow-up found that self-reported high socioeconomic occupational status measured at index date was associated with lower risk of PE, whereas no association was found with DVT.[6] A Danish cohort (Copenhagen City Health study) of men and women >20 years of age, with median follow-up of 19.5 years, found that medium vs. low household income was associated with reduced risk of VTE, but did not observe an association between education level and VTE risk.[8] A cohort study of Swedish adults (>20 years) followed for 17 years found that those with high educational level and high-status occupations measured at index date had

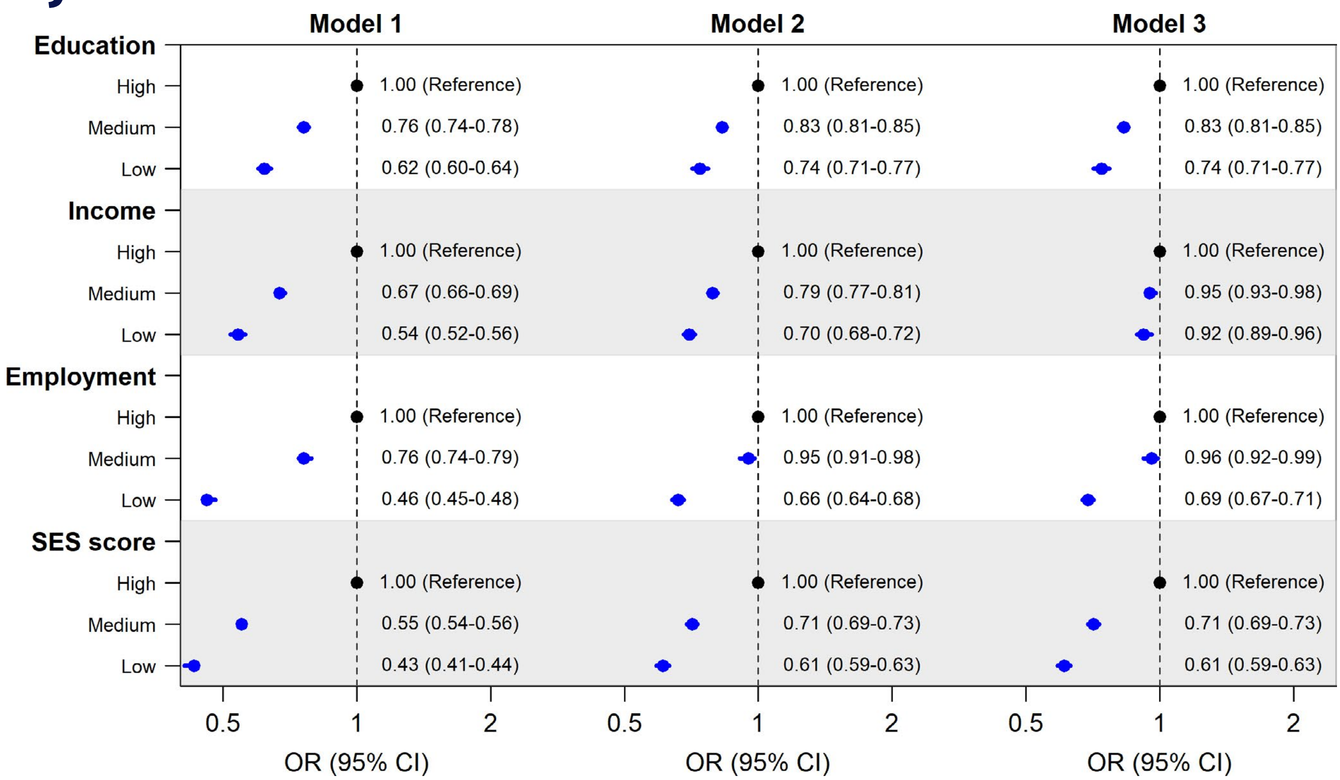

FIGURE 1 Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for venous thromboembolism (VTE), according to education, income, employment status, and SES score. Model 1: Crude model controlled for matching variables by study design. Model 2: Adjusted for obesity, cancer, coronary heart disease (including atrial fibrillation and heart failure), diabetes, stroke, chronic obstructive pulmonary disease, acute kidney failure, chronic kidney disease, mental diseases, surgery 3 months before the VTE/index date and Charlson Comorbidity Index score, excluding comorbidities already adjusted for. Model 3: Adjusted for model 2 and SES indicators. *With SES score as the exposure, there were no additional SES variables; therefore, models 2 and 3 are identical. SES, socioeconomic status

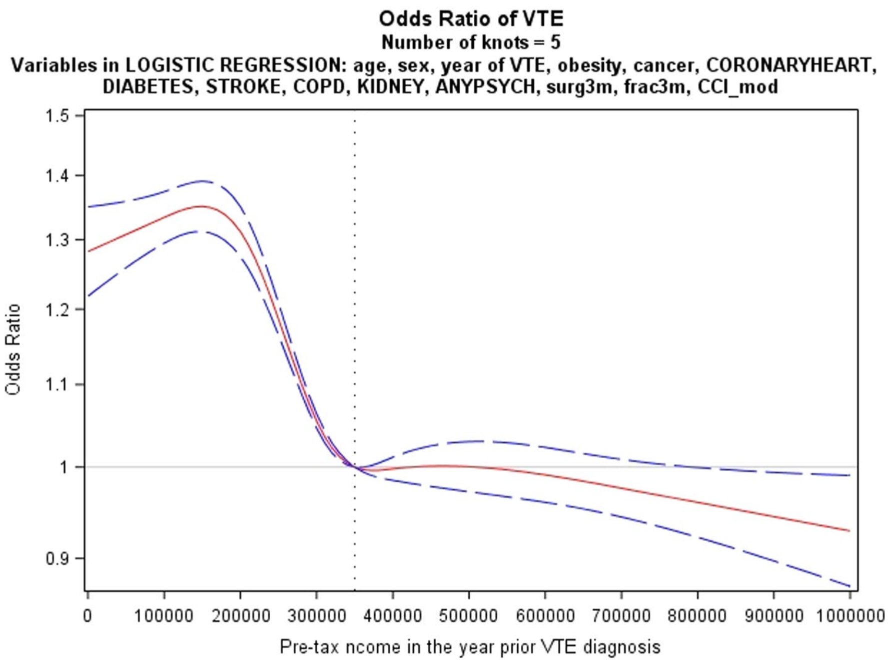

FIGURE 2 Restricted cubic spline models with adjusted odds ratios and 95% confidence intervals for venous thromboembolism (VTE), according to income

lower risk of VTE, whereas no association was found between income and VTE risk.[9] Another Swedish cohort of individuals >25 years of age at inclusion, with 13 years of follow-up, showed that low household income, single marital status, and low educational level measured at index date were associated with increased VTE risk.[7] However, there was no adjustment for comorbidities in the analyses.[7]

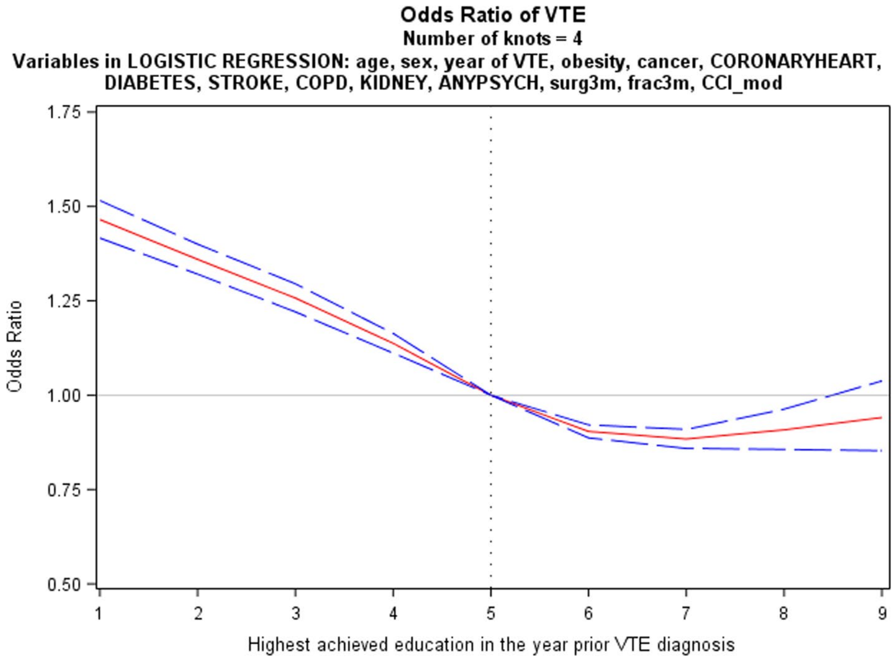

FIGURE 3 Restricted cubic spline models with adjusted odds ratios and 95% confidence intervals for venous thromboembolism (VTE), according to education

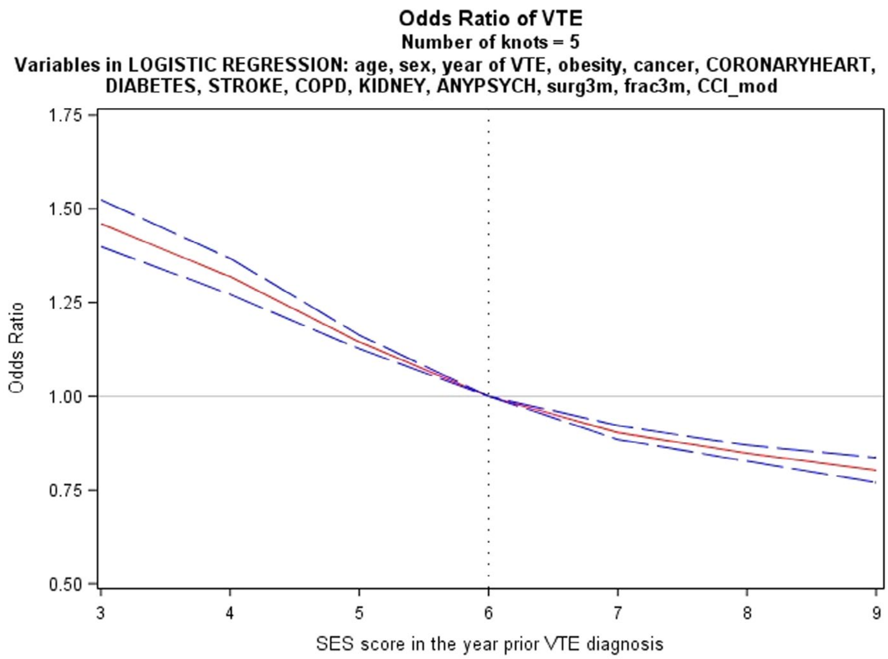

FIGURE 4 Restricted cubic spline models with adjusted odds ratios and 95% confidence intervals for venous thromboembolism (VTE), according to SES score

We found that education, income, and employment status were all associated with VTE. Education, income, and employment are correlated indicators as education often precedes and influences employment level, which in turn affects income. To capture the complexity of influences and the temporal relation among indicators, we applied a composite SES score to measure the association between SES and VTE risk. We found a positive linear relation between the SES score and VTE risk, and the OR for VTE in those with a high SES score was lower than the ORs in those with high levels of any of the individual SES indicators. This may suggest the SES score as a superior tool over individual SES indicators when assessing the risk of VTE.

In modern Western societies, work-related indicators fluctuate over time, especially during life stages such as early and midlife/mature adulthood, for instance because of transition from student to employee or advances in employment and income. The optimal lag time between assessments of SES indicators and disease outcomes, along with the question of reverse causation when good health leads a subsequent high SES,[24] remains subjects of debate. In our study, we assessed SES indicators among individuals of working age (25–65 years) 1 year before the VTE event. To ensure that our results were not influenced substantially by recent changes in SES or health status, we performed sensitivity analyses restricted to persons without comorbidities before the index date. We also performed sensitivity analyses

TABLE 3 Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for venous thromboembolism (VTE) according to education, income, and employment status

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Education			
Medium vs. low			
Overall	0.76 (0.74–0.78)	0.83 (0.81–0.85)	0.83 (0.81–0.85)
Age 25–34	0.66 (0.62–0.70)	0.73 (0.68–0.78)	0.73 (0.68–0.78)
Age 34–44	0.63 (0.60–0.66)	0.71 (0.67–0.75)	0.71 (0.67–0.75)
Age 45–54	0.74 (0.71–0.77)	0.82 (0.79–0.86)	0.82 (0.79–0.86)
Age 55–65	0.88 (0.86–0.92)	0.95 (0.91–0.98)	0.95 (0.91–0.98)
High vs. low			
Overall	0.62 (0.60–0.64)	0.74 (0.71–0.77)	0.74 (0.71–0.77)
Age 25–34	0.60 (0.54–0.66)	0.76 (0.68–0.84)	0.76 (0.68–0.84)
Age 34–44	0.43 (0.40–0.48)	0.55 (0.50–0.61)	0.55 (0.50–0.61)
Age 45–54	0.56 (0.52–0.61)	0.70 (0.64–0.76)	0.70 (0.64–0.76)
Age 55–65	0.73 (0.69–0.76)	0.84 (0.80–0.88)	0.84 (0.80–0.88)
Income			
Medium vs. low			
Overall	0.67 (0.66–0.69)	0.79 (0.77–0.81)	0.95 (0.93–0.98)
Age 25–34	0.69 (0.65–0.74)	0.73 (0.69–0.78)	0.96 (0.89–1.05)
Age 34–44	0.54 (0.51–0.57)	0.65 (0.61–0.69)	0.86 (0.80–0.93)
Age 45–54	0.63 (0.60–0.66)	0.79 (0.75–0.83)	0.97 (0.91–1.03)
Age 55–65	0.76 (0.73–0.79)	0.88 (0.85–0.92)	1.01 (0.96–1.05)
High vs. low			
Overall	0.54 (0.52–0.56)	0.70 (0.68–0.72)	0.92 (0.89–0.96)
Age 25–34	0.57 (0.51–0.63)	0.67 (0.60–0.75)	0.92 (0.81–1.05)
Age 34–44	0.41 (0.39–0.44)	0.55 (0.51–0.59)	0.81 (0.74–0.89)
Age 45–54	0.49 (0.47–0.52)	0.68 (0.64–0.72)	0.90 (0.84–0.97)
Age 55–65	0.63 (0.61–0.66)	0.81 (0.78–0.85)	1.01 (0.95–1.07)
Employment status			
Medium vs. low			
Overall	0.76 (0.74–0.79)	0.95 (0.91–0.98)	0.96 (0.92–0.99)
Age 25–34	0.89 (0.79–0.99)	0.99 (0.88–1.12)	0.98 (0.87–1.11)
Age 34–44	0.90 (0.83–0.98)	1.03 (0.94–1.13)	1.05 (0.95–1.15)
Age 45–54	0.84 (0.78–0.90)	0.92 (0.85–1.00)	0.93 (0.86–1.01)
Age 55–65	0.68 (0.65–0.71)	0.87 (0.83–0.91)	0.87 (0.83–0.92)
High vs. low			
Overall	0.46 (0.45–0.48)	0.66 (0.64–0.68)	0.69 (0.67–0.71)
Age 25–34	0.48 (0.44–0.53)	0.62 (0.55–0.69)	0.66 (0.59–0.74)
Age 34–44	0.40 (0.38–0.43)	0.57 (0.53–0.62)	0.63 (0.58–0.68)
Age 45–54	0.45 (0.43–0.48)	0.65 (0.61–0.68)	0.67 (0.63–0.71)
Age 55–65	0.51 (0.49–0.53)	0.71 (0.68–0.74)	0.72 (0.69–0.76)

Note: Model 1: Crude model controlled for matching variables (age, sex) by study design. Model 2: Adjusted model controlled for matching variables (age, sex) by study design and adjusted for obesity, cancer, coronary heart disease (including atrial fibrillation and heart failure), diabetes, stroke, chronic obstructive pulmonary disorder, acute kidney failure, chronic kidney disease, mental diseases, surgery 3 months before the VTE/index date and Charlson Comorbidity Index score, excluding comorbidities already adjusted for. Model 3: Adjusted model controlled for matching variables (age, sex) by study design and adjusted for model 2 and socioeconomic status indicators.

TABLE 4 Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for venous thromboembolism (VTE) according to SES score

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Low	1.00 (ref)	1.00 (ref)
Medium vs. low		
Overall	0.55 (0.54–0.56)	0.71 (0.69–0.73)
Age 25–34	0.48 (0.45–0.52)	0.58 (0.54–0.63)
Age 34–44	0.41 (0.39–0.44)	0.55 (0.51–0.59)
Age 45–54	0.51 (0.48–0.53)	0.69 (0.65–0.73)
Age 55–65	0.65 (0.63–0.68)	0.82 (0.79–0.86)
High vs. low		
Overall	0.43 (0.41–0.44)	0.61 (0.59–0.63)
Age 25–34	0.42 (0.37–0.46)	0.56 (0.49–0.62)
Age 34–44	0.30 (0.27–0.32)	0.44 (0.40–0.48)
Age 55–65	0.38 (0.36–0.41)	0.58 (0.54–0.62)
Age 45–54	0.52 (0.50–0.55)	0.73 (0.69–0.76)

Note: Model 1: Crude model controlled for matching variables (age, sex) by study design. Model 2: Adjusted model controlled for matching variables (age, sex) by study design and adjusted for obesity, cancer, coronary heart disease (including atrial fibrillation and heart failure), diabetes, stroke, chronic obstructive pulmonary disorder, acute kidney failure, chronic kidney disease, mental diseases, surgery 3 months before the VTE/index date and Charlson Comorbidity Index score, excluding comorbidities already adjusted for.

in which the SES indicators were measured 5 years before the VTE event. The risk estimates remained essentially unchanged in the sensitivity analyses, indicating that our findings were robust with minor risks of residual confounding, misclassification, or reverse causation. The relatively short time interval from SES measurement to VTE event (1–5 years), in addition to a study population restricted to individuals of working age, may explain why, in contrast to previous studies, we found that all measured SES indicators were robustly associated with VTE risk, even after adjustment for comorbidities.

The pathways in which SES can lead to an increased risk of VTE are likely complex and multifactorial. Low educational level might lead to limited knowledge of the harms of unhealthy and benefits of healthy behavior,[25] and low income and unemployment might lead to increased psychosocial stress and subsequent increased disease risk.[26] Low SES is associated with reduced ability to identify healthcare needs and to seek and obtain healthcare services.[27] Moreover, low SES is associated with conditions such as obesity,[7,28,29] physical inactivity,[30,31] and trauma/injury from occupational risks,[9] which are well-known risk factors for VTE. The biological mechanisms for the associations between SES and VTE most likely reflect a large range of factors acting through complex causal pathways. Of note, links have been found between chronic psychosocial stressors and coagulation and fibrinolysis variables,[6,28,32,33] and lower levels of circulating inflammatory and hemostatic markers, as well as increased fibrinolysis markers, have been found to be more prevalent in individuals of higher social class.[32–34]

TABLE 5 Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for pulmonary embolism (PE) and deep vein thrombosis (DVT) according to education, income, employment, and SES score

	PE			DVT		
	Low OR (95% CI)	Medium OR (95% CI)	High OR (95% CI)	Low OR (95% CI)	Medium OR (95% CI)	High OR (95% CI)
Education						
Model 1	1.00 (ref)	0.80 (0.77–0.83)	0.67 (0.63–0.71)	1.00 (ref)	0.74 (0.72–0.76)	0.59 (0.57–0.62)
Model 2	1.00 (ref)	0.87 (0.84–0.91)	0.79 (0.75–0.84)	1.00 (ref)	0.81 (0.79–0.83)	0.71 (0.68–0.74)
Model 3	1.00 (ref)	0.87 (0.84–0.91)	0.79 (0.75–0.84)	1.00 (ref)	0.81 (0.79–0.83)	0.71 (0.68–0.74)
Income						
Model 1	1.00 (ref)	0.70 (0.67–0.73)	0.56 (0.54–0.59)	1.00 (ref)	0.66 (0.64–0.68)	0.53 (0.51–0.55)
Model 2	1.00 (ref)	0.81 (0.78–0.85)	0.73 (0.69–0.77)	1.00 (ref)	0.78 (0.75–0.80)	0.69 (0.66–0.71)
Model 3	1.00 (ref)	0.99 (0.94–1.04)	0.96 (0.90–1.03)	1.00 (ref)	0.94 (0.90–0.97)	0.90 (0.86–0.95)
Employment status						
Model 1	1.00 (ref)	0.76 (0.72–0.80)	0.46 (0.44–0.48)	1.00 (ref)	0.76 (0.73–0.80)	0.47 (0.45–0.48)
Model 2	1.00 (ref)	0.94 (0.89–1.00)	0.66 (0.62–0.69)	1.00 (ref)	0.94 (0.90–0.99)	0.66 (0.64–0.69)
Model 3	1.00 (ref)	0.95 (0.90–1.01)	0.67 (0.64–0.71)	1.00 (ref)	0.96 (0.92–1.00)	0.70 (0.67–0.72)
SES score[a]						
Model 1	1.00 (ref)	0.57 (0.55–0.60)	0.45 (0.42–0.47)	1.00 (ref)	0.54 (0.52–0.56)	0.42 (0.40–0.43)
Model 2	1.00 (ref)	0.74 (0.70–0.77)	0.64 (0.60–0.68)	1.00 (ref)	0.69 (0.67–0.72)	0.59 (0.57–0.62)

Note: Model 1: Crude model controlled for matching variables by study design.

Model 2: Adjusted model controlled for matching variables by study design and adjusted for obesity, cancer, coronary heart disease (including atrial fibrillation and heart failure), diabetes, stroke, chronic obstructive pulmonary disorder, acute kidney failure, chronic kidney disease, mental diseases, surgery 3 months before the VTE/index date and Charlson Comorbidity Index score, excluding comorbidities already adjusted for. Model 3: Adjusted model controlled for matching variables by study design and adjusted for Model 2 and SES indicators.

[a]With SES score as the exposure, there were no additional SES variables; therefore, models 2 and 3 are identical and model 3 is not included in the table.

TABLE 6 Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for venous thromboembolism (VTE) according to education, income, employment status, and SES score 5 years before VTE/index date

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Education[a]			
Low	1.00 (ref)	1.00 (ref)	
Medium vs. low	0.78 (0.76–0.79)	0.85 (0.83–0.87)	
High vs. low	0.63 (0.61–0.65)	0.74 (0.72–0.77)	
Income			
Low	1.00 (ref)	1.00 (ref)	1.00 (ref)
Medium vs. low	0.69 (0.67–0.70)	0.81 (0.79–0.83)	0.94 (0.91–0.97)
High vs. low	0.57 (0.55–0.58)	0.74 (0.71–0.76)	0.90 (0.87–0.94)
Employment status			
Low	1.00 (ref)	1.00 (ref)	1.00 (ref)
Medium vs. low	0.93 (0.90–0.97)	1.05 (1.00–1.09)	1.05 (1.01–1.10)
High vs. low	0.56 (0.55–0.58)	0.76 (0.74–0.79)	0.79 (0.77–0.82)
SES score[a]			
Low	1.00 (ref)	1.00 (ref)	
Medium vs. low	0.58 (0.56–0.59)	0.73 (0.71–0.75)	
High vs. low	0.46 (0.44–0.47)	0.64 (0.62–0.66)	

Note: Model 1: Crude model controlled for matching variables by study design. Model 2: Adjusted for obesity, cancer, coronary heart disease (including atrial fibrillation and heart failure), diabetes, stroke, chronic obstructive pulmonary disorder, acute kidney failure, chronic kidney disease, mental diseases, surgery 3 months before the VTE/index date and Charlson Comorbidity Index score, excluding comorbidities already adjusted for. Model 3: Adjusted for model 2 and remaining SES indicators.

[a]With education and SES score as the exposure, there were no adjustments for additional SES variables; therefore, models 2 and 3 are identical and model 3 is not included in the table.

Our study has several strengths and some limitations. We conducted the study in a setting that provides government-funded educational and health care services free of charge to all citizens, thus preventing selection and referral bias. We used a large sample from the general working age population with highly accurate and validated data for exposures, outcomes,[35] and comorbidities, which allowed a detailed interpretation of the association between SES and VTE. In addition, we were able to perform repeated measurements of SES close to the VTE/index date, thereby avoiding misclassification and potential attenuation of associations. Unfortunately, we were unable to measure modifiable risk factors such as body mass index, physical activity, or diet that could act as confounders or intermediate variables for the association between SES and VTE. We also did not have access to relevant SES indicators such as occupational category, household income or length of employment. Although we found that the composite SES score might provide a common and improved measure of SES for assessment of VTE risk, the score has not been validated.

In conclusion, we found that high SES was associated with decreased VTE risk even after accounting for comorbidities. As compared with measuring individual SES indicators (education, income, and employment), we found that a composite SES score improved the risk assessment of VTE. Our findings may help healthcare providers improve preventive strategies diminishing the burden of VTE on public health and healthcare systems.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Helle Jørgensen, Erzsébet Horváth-Puhó, Kristina Laugesen, Sigrid K. Brækkan, John-Bjarne Hansen, and Henrik T. Sørensen contributed to the planning and design of the study and to the analysis and interpretation of the data. Helle Jørgensen drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version before submission.

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