ORIGINAL RESEARCH

The Interaction Between Venous Thromboembolism and Socioeconomic Status on the Risk of Disability Pension

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Background: Venous thromboembolism (VTE) is associated with increased risk of disability pension. How socioeconomic status (SES) impacts the risk of disability pension after a VTE is unknown. The aim of this nationwide population based cohort study to investigate the interaction between SES and incident VTE on the risk of subsequent disability pension.

Methods: Using Danish national medical and administrative databases, we established a nationwide cohort of 41,781 individuals aged 25–65 years with incident VTE during 1995–2016 and a comparison cohort (n=208,905) from the general population matched on year of birth, sex, and calendar year of VTE. We computed incidence rates (IRs) as the number of disability pension events per 1000 person-years at risk and measured the interaction between VTE and levels of SES (high, medium, low) on an additive scale by calculating interaction contrasts (difference in IR difference).

Results: Among individuals with high SES, the disability pension IR per 1000 person-years was 5.4 (95% CI: 4.8–6.1) in the VTE cohort and 1.6 (95% CI: 1.5–1.7) in the comparison cohort (IR difference 3.8). The corresponding disability pension IR in individuals with low SES was 55.1 (95% CI: 52.1–58.1) in the VTE cohort and 26.1 (95% CI: 25.1–27.1) in the comparison cohort (IR difference 24.0). An interaction contrast of 25.1 indicated that interaction accounted for 45.6% (25.1/55.1) of the disability pension IR in individuals with VTE and low SES.

Conclusion: SES and VTE interact to increase the risk of disability pension after VTE beyond their independent effects.

Keywords: education, employment, income, deep-vein thrombosis, pulmonary embolism, burden of illness

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of lost disability-adjusted life-years worldwide.[1] VTE is common in the working-age population,[2] and as the workforce is ageing, more individuals will be faced with chronic diseases causing health problems that may hamper the ability to maintain employment.[3] Even though effective treatments enable patients to continue working after a VTE,[2] the risk of losing a substantial number of years in paid employment remains high among individuals with VTE.[1]

Recent studies have shown that individuals with VTE have an increased risk of work-related disability pension compared to the general population.[4,5] Also, socioeconomic inequalities have been found to be associated with risk of VTE.[6–10] However, it remains unclear whether the impact of socioeconomic status (SES) on the risk of disability pension among individuals with VTE is due to SES and VTE separately, or whether an interaction exists.

To prevent early exit from the labour market among individuals with VTE, a better understanding is needed not only of the risk factors, but also of the interaction between factors that affect the risk of disability pension beyond the factors' independent effects. Therefore, the aim of this nationwide population-based cohort study was to investigate the interaction between incident VTE and categories of SES on the risk of subsequent disability pension.

Methods

Setting and Data Sources

All Danish residents have free and equal access to universal tax-funded health care and education.[11] The Danish Civil Registration System (CRS) assigns a unique personal identifier (CPR number) to all Danish residents upon birth or immigration and this number enables linkage of information between nationwide health and administrative registers.[11]

We used the Danish National Patient Registry (DNPR) to collect data on VTE and comorbidities and the Danish Psychiatric Central Research Register (DPCCR) to collect data on psychiatric diagnoses.[11] The DNPR contains records of all Danish hospital discharges since 1977 and emergency room and outpatient visits from 1995 onwards. Records include CPR number, admission and discharge dates, one primary diagnosis and one or more secondary diagnoses coded according to ICD-8 codes (from 1977 until 1994) or ICD-10 codes (from 1994 onwards).[11] Information on demography, vital status, and migration was collected from the CRS, while disability pensions, income, and employment status was collected from the Integrated Database for Labour Market Research (IDA), and educational level was collected from the Educational Attainment Register.[11]

Study Population

We identified 41,781 hospital or outpatient clinic patients with a primary or secondary discharge diagnosis of DVT and/or PE from January 1, 1995 through December 31, 2016. We defined the VTE date as the date of the first hospital admission/outpatient visit (Supplementary Table 1). For DNPR data, positive predictive values of 86% for DVT and 90% for PE have been reported.[12] VTEs reported solely in emergency room departments were not included due to a high proportion of clinical misclassification.[13] If a DVT and PE occurred concurrently, we registered the event as a PE due to its higher mortality rate.[14] We classified VTE events as provoked or unprovoked according to the presence of provoking factors at the time of diagnosis, such as a preexisting cancer diagnosis, fracture, trauma, surgery, and/or pregnancy within 90 days prior to VTE diagnosis (Supplementary Table 1).[15]

For each individual with VTE, we used the CRS to match five individuals, with replacement,[16] from the general working-age population by sex, year of birth, and calendar year of VTE. The date of VTE was used as the index date for the matched comparison cohort members (n=208,905). Comparison cohort members subsequently experiencing a VTE were censored on the date of the event.

Individuals with a VTE diagnosis before 1995 were excluded. To avoid potential bias and ensure that the VTE was the cause and not a consequence of another condition leading to disability pension, we also excluded individuals already receiving a disability pension and those receiving a disability pension in the same year as the VTE. Further, individuals aged <25 years or >65 years at study inclusion were excluded as they would either likely still be in school/university and lack a stable income or employment, or be retired from work due to advanced age, and therefore not meet the requirements for disability pension.

Socioeconomic Status

We defined SES as the combined measure of educational level, employment status, and annual income. Information on the highest level of completed education was extracted the year prior to the VTE/index date and categorized as low, medium, or high according to the distribution of education in age-specific groups (Supplementary Tables 2 and 3). To account for salary changes over calendar years and avoid the impact of inflation, income values were re-calculated using the new gross domestic product deflators downloaded from the World Bank's website (www.worldbank.org). Based on the deflated income values of the study population, we calculated income quartiles and merged the two middle quartiles to get three categories (ie high, medium, and low income). We measured employment status the year prior to the VTE/index date and categorized employment status as high (ie employed), medium (ie outside the workforce) and low (ie unemployed), where persons included in an educational program, those in early retirement, and those receiving other types of public support were considered being outside the workforce.

Based on the categorical distribution "low, medium, and high" described above, we established a score of 1–3 for each of the SES indicators education, income, and employment status. These scores were then combined in a composite

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SES score with values ranging from 3 to 9. Based on the distribution in the composite SES score, we calculated tertiles of low SES (scores of 3 and 4), medium SES (scores of 5, 6, and 7), and high SES (scores of 8 and 9).

Disability Pension

The outcome was receipt of disability pension. In Denmark, persons with permanent Danish residency who have lived in the country for at least three years since their 15th birthday until receipt of disability pension or public retirement age, can be granted disability pension if her/his work capacity is reduced permanently or to such a degree that he/she is incapable of providing for himself/herself through regular or flexible work.[17]

For each year, we identified disability pension yearly at the end of November and set the disability pension date as January 1 that year. Direct transition from work to disability pension is rare as most persons experience a period of sick leave prior to receipt of disability pension. Furthermore, Danish regulations require that measures to improve the working ability must be performed before disability pension can be granted.[17]

Covariates

Diagnoses of comorbidities prior to the VTE were obtained from the DNPR and the DPCCR using ICD-8 and ICD-10 codes for cancer, obesity, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), mental diseases, diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure, and chronic kidney disease, and remaining diseases included in the Charlson Comorbidity Index.[18] In addition, we retrieved information on surgery, pregnancy, and trauma/fractures three months prior to the VTE/index date. ICD codes are provided in Supplementary Table 1.

Statistical Analysis

We followed the study population from the VTE/index date until receipt of disability pension, turning 66 years of age, emigration, death, or December 31, 2016, whichever came first. Within categories of SES score (low, medium, high), we conducted a complete case analysis where we estimated incidence rates (IRs) per 1000 person-years with 95% confidence intervals (CIs) for disability pension.

We examined the presence of interaction between VTE and SES on disability pension by calculating interaction contrast (IC) using individuals with no VTE and high SES as the reference category. As previously described,[19,20] the IC measures the difference in IR differences indicating the excess or deficit disability pension IR beyond or below the baseline IR among individuals with no VTE and high SES, the individual effect of SES on the disability pension IR and the effect of VTE on the disability pension IR (Figure 1). We calculated the attributable proportion of the disability pension IR that could be explained by interaction by dividing IC with the disability pension IR among individuals with VTE with low SES.

We used the Cox proportional hazards regression model to compute hazard ratios (HRs) as estimates of the combined effect conferred by VTE and SES using individuals with no VTE and high SES as the reference category. We tested the proportional hazards assumption using log-log plots and found no violation of this assumption. HRs were adjusted for a priori defined potential confounders by two different models. Model 1 was the unadjusted model controlling for matching factors by study design (age as a continuous variable, sex in the analyses not stratified by sex, and calendar year of VTE); Model 2 also included prior cancer, obesity, coronary heart disease (atrial fibrillation, myocardial infarction, and heart failure), mental diseases, diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, and other diseases included in the Charlson Comorbidity Index, as well as surgery and trauma/fractures three months prior to the VTE/index date.

The analyses described above were conducted in the overall cohort and within strata of age (age groups 25–34 years, 35–44 years, 45–54 years, and 55–65 years on the date of inclusion) and sex.

To examine the significance of VTE subtypes and the underlying causes of VTE, we performed subgroup analyses with PE, DVT, unprovoked VTE, and provoked VTE as exposure variables. As comorbidities may be more prevalent in individuals with VTE than in the general population comparison cohort, we also performed analyses stratified by Charlson Comorbidity Index score of 0 and of ≥1.
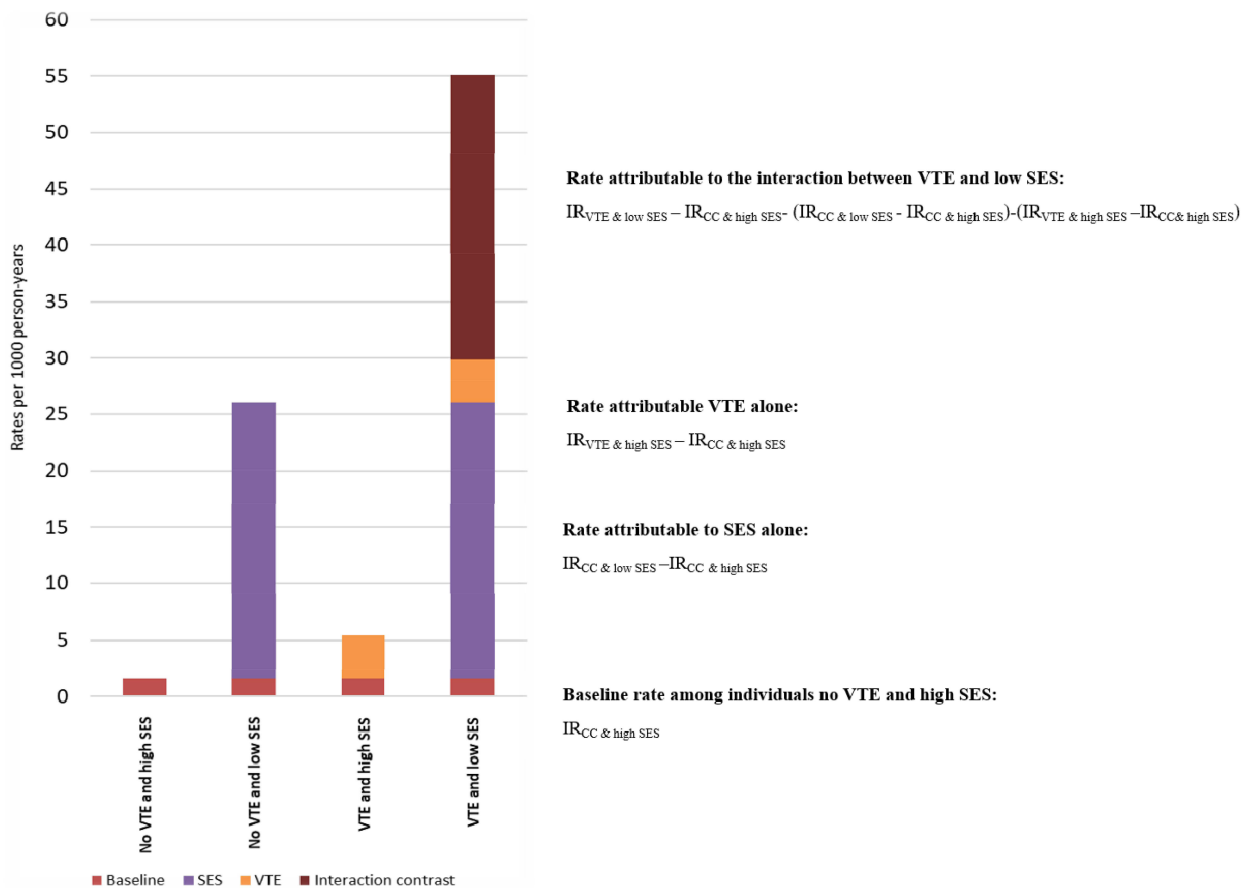
Figure I Proportion of the total disability pension incidence rate attributable to venous thromboembolism, low socioeconomic status, and their interaction.
Abbreviations: SES, socioeconomic status; VTE, venous thromboembolism; IR, incidence rate.

To account for a potential overestimation of disability pension IRs due to competing risk of death, cumulative incidence functions were estimated by the methods proposed by Fine and Gray[21] and visualized according to VTE/no VTE and level of SES score.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Ethics Declaration and Accordance Statement

According to Danish legislation, studies based entirely on registry data do not require patient consent or approval from an ethics review board. The study was approved by the Danish Data Protection Agency, record number 2016-051-000001-811. All methods were performed in accordance with relevant guidelines and regulations.

Results
Characteristics

Baseline characteristics of the study participants (46.2% women) are presented in Table 1. We identified 41,781 individuals with VTE and 208,905 matched individuals from the general population. A subsequent disability pension was granted to 4203 (10.1%) individuals in the VTE cohort and 8637 (4.1%) individuals in the comparison cohort during a median follow-up of 4.4 years for the VTE cohort and 6.0 years for the comparison cohort (Table 2). The proportion of individuals with low SES was higher in the VTE cohort than in the comparison cohort (12% vs 8%), while the proportion of individuals with high SES was lower in the VTE cohort (21% vs 25%). There were 1215 (2.9%) individuals with missing SES in the VTE cohort and 5740 (2.7%) individuals with missing SES in the comparison cohort (Table 1). Individuals with VTE also had a higher prevalence of comorbidities such as surgery 3 months prior to the VTE date,

Table 1 Baseline Characteristics of Individuals with Venous Thromboembolism (VTE) and Members of the General Population Comparison Cohort

	VTE (N=41781)	Comparison Cohort (N=208905)
Female sex	19,303 (46.2)	96,515 (46.2)
Pulmonary embolism	14,172 (33.9)	–
Deep vein thrombosis	27,609 (66.1)	–
Socioeconomic status score		
Low	4991 (11.9)	17,625 (8.4)
Medium	26,958 (64.5)	133,487 (63.9)
High	8617 (20.6)	52,053 (24.9)
Missing	1215 (2.9)	5740 (2.7)
Comorbidities		
[a]High-risk cancer prior to VTE/index date	2064 (4.9)	907 (0.4)
[a]Low-risk cancer prior to VTE/index date	2793 (6.7)	5534 (2.6)
Coronary heart disease	2926 (7.0)	8441 (4.0)
Diabetes	2213 (5.3)	7625 (3.6)
Chronic obstructive pulmonary disease	2356 (5.6)	6235 (3.0)
Obesity	2578 (6.2)	5329 (2.6)
Stroke	695 (1.7)	1824 (0.9)
Moderate to severe renal disease	710 (1.7)	1128 (0.5)
Surgery 3 months prior to VTE/index date	6071 (14.5)	4987 (2.4)
Trauma/fracture 3 months prior to VTE/index date	1858 (4.4)	1284 (0.6)
Mental disorders	3527 (8.4)	7947 (3.8)
Charlson comorbidity index		
[b]CCI score: 0	37,296 (89.3)	198,532 (95.0)
[b]CCI score: 1	3749 (9.0)	9315 (4.5)
[b]CCI score:≥2	736 (1.8)	1058 (0.5)

Notes: [a]Categorized according to 5-year mortality as high-risk cancer (>70%) and low-risk cancer (≤70%). [b]Modified CCI excluding ICD codes used in the covariate definition. Values are numbers, with percentages in brackets.

history of cancer, mental disorders, and coronary heart disease, compared to the comparison cohort (Table 1). Baseline characteristics according to VTE and SES are shown in Supplementary Table 4.

Interaction Between Venous Thromboembolism and Socioeconomic Status

The IR of disability pension per 1000 person-years among individuals with VTE and high SES was 5.4 (95% CI: 4.8–6.1) compared to 1.6 (95% CI: 1.5–1.7) in individuals with no VTE and high SES, compromising a IR difference of 3.8 (Table 2, Figure 1). The corresponding IR of disability pension in individuals with VTE and low SES was 55.1 (95% CI: 52.1–58.1) and 26.1 (95% CI: 25.1–27.1) in individuals with no VTE and low SES (IR difference of 24.0 (Table 2, Figure 1). In individuals with VTE and low SES an IC of 25.1 (95% CI: 21.9–28.4) corresponded to an attributable proportion of 45.6% of the total disability pension IR being explained by interaction between VTE and SES (Table 2). The disability pension IR in individuals with VTE and medium SES was 15.9 (95% CI: 15.3–16.5) and 5.4 (95% CI: 5.3–5.6) in individuals with no VTE and medium SES (IR difference of 10.5) (Table 2). For individuals with VTE and medium SES the attributable proportion of the disability pension IR explained by interaction was 41.6% [IC 6.6 (96% CI 5.7–7.5)] (Table 2).

The interaction was generally higher for DVT where the attributable proportion explained by interaction between DVT and low SES was 47.8% compared to 38.8% for PE and low SES (Table 3, Figure 2). In subcategories of provoked and unprovoked VTE, the attributable proportion explained by interaction between VTE and low SES was 37.8% for provoked VTE and 47.2% for unprovoked VTE (Table 3, Figure 2).

The interaction was lowest in the highest age group of 55–65 years and was higher in men than in women (Tables 2 and 3, Figure 3). The attributable proportion of the disability pension IR explained by interaction between VTE and low

Table 2 Incidence Rates, Interaction Contrast, and Hazard Ratios with 95% Confidence Intervals of Work-Related Disability Pension According to Combined Categories of Socioeconomic Status Score and Venous Thromboembolism Status

SES	Cohort	DP	PY	IR per 1,000 PY (95% CI)	IC (95% CI)	Adjusted HR[a] (95% CI)	AP[b]
Overall							
High SES	Comparison	558	350,042	1.6 (1.5–1.7)		Reference	
	VTE	277	51,069	5.4 (4.8–6.1)	–	3.0 (2.6–3.4)	
Medium SES	Comparison	5437	1,005,939	5.4 (5.3–5.6)		3.1 (2.9–3.4)	
	VTE	2649	166,994	15.9 (15.3–16.5)	6.6 (5.7–7.5)	7.7 (7.0–8.4)	41.6%
Low SES	Comparison	2642	101,065	26.1 (25.1–27.1)		11.6 (10.6–12.7)	
	VTE	1277	23,180	55.1 (52.1–58.1)	25.1 (21.9–28.4)	18.8 (17.0–20.8)	45.6%
Age 25–34							
High SES	Comparison	9	33,940	0.3 (0.1–0.4)		Reference	
	VTE	8	5222	1.5 (0.5–2.6)	–	5.5 (2.1–14.3)	
Medium SES	Comparison	413	196,676	2.1 (1.9–2.3)		8.1 (4.2–15.8)	
	VTE	220	33,391	6.6 (5.7–7.5)	3.2 (1.8–4.6)	22.8 (11.7–44.5)	48.6%
Low SES	Comparison	320	29,414	10.9 (9.7–12.1)		42.0 (21.6–81.7)	
	VTE	292	7686	38.0 (33.6–42.3)	25.8 (21.2–30.5)	99.2 (50.8–193.8)	68.0%
Age 35–44							
High SES	Comparison	70	88,352	0.8 (0.6–1.0)		Reference	
	VTE	27	12,029	2.2 (1.4–3.1)	–	2.6 (1.7–4.1)	
Medium SES	Comparison	1265	271,792	4.7 (4.4–4.9)		5.4 (4.2–6.8)	
	VTE	603	46,287	13.0 (12.0–14.1)	6.9 (5.5–8.3)	13.2 (10.3–17.0)	53.0%
Low SES	Comparison	596	20,972	28.4 (26.1–30.7)		29.6 (23.1–38.0)	
	VTE	380	6051	62.9 (56.5–69.2)	33.0 (26.2–39.8)	45.8 (35.2–59.5)	52.4%
Age 45–54							
High SES	Comparison	252	126,782	2.0 (1.7–2.2)		Reference	
	VTE	100	18,971	5.3 (4.2–6.3)	–	2.2 (1.8–2.8)	
Medium SES	Comparison	2356	332,816	7.1 (6.8–7.4)		3.2 (2.8–3.7)	
	VTE	1141	53,985	21.1 (19.9–22.4)	10.8 (9.1–12.4)	7.4 (6.4–8.5)	51.2%
Low SES	Comparison	793	20,972	37.8 (35.2–40.5)		14.1 (12.2–16.2)	
	VTE	326	4331	75.3 (67.1–83.4)	34.2 (25.5–42.8)	19.2 (16.2–22.7)	45.4%
Age 55–65							
High SES	Comparison	227	100,967	2.3 (2.0–2.5)		Reference	
	VTE	142	14,847	9.6 (8.0–11.1)	–	3.5 (2.9–4.4)	
Medium SES	Comparison	1403	204,667	6.9 (6.5–7.2)		2.4 (2.1–2.8)	
	VTE	685	33,318	20.6 (19.0–22.1)	6.4 (4.1–8.6)	5.8 (5.0–6.8)	31.2%
Low SES	Comparison	933	29,707	31.4 (29.4–33.4)		7.7 (6.6–8.9)	
	VTE	279	5124	54.5 (48.1–60.9)	15.8 (8.9–22.7)	9.6 (8.0–11.5)	29.0%

Notes: [a]Adjusted for: age, sex, calendar year of VTE, obesity, cancer, coronary heart disease (including atrial fibrillation and heart failure), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, mental diseases, surgery and trauma/fractures 3 months prior to the VTE/index date, and modified Charlson Comorbidity Index score. [b]The proportion of the IR explained by interaction is calculated as the interaction contrast divided by the disability pension IR in patients with VTE and low/medium SES.
Abbreviations: IR, incidence rate; IC, interaction contrast; HR, hazard ratio; CI, confidence intervals; DP, disability pension; SES, socioeconomic status; VTE, venous thromboembolism; PY, person years; AP, attributable proportion.

SES was 68.0% [IC 25.8 (95% CI 21.2–30.5)] in the age group 25–34 years and 29.0% [IC 15.8 (95% CI 8.9–22.7)] in the age group 55–65 years (Table 2, Figure 3). For individuals with VTE and low SES, the attributable proportion of the disability pension IR explained by interaction was 55.8% of in men and 35.2% in women. (Table 3, Figure 3). This sex difference was particularly pronounced in the youngest and oldest age groups with interaction explaining 78.6% of the

Table 3 Incidence Rates, Interaction Contrasts and Hazard Ratios with 95% Confidence Intervals of Work-Related Disability Pension According to Combined Categories of Socioeconomic Status Score and Venous Thromboembolism Status Stratified by Sex and Type of Venous Thromboembolism

SES	Cohort	DP	PY	IR (95% CI)	IC (95% CI)	HR[a] (95% CI)	AP[b]	DP	PY	IR (95% CI)	IC (95% CI)	HR[a] (95% CI)	AP[b]
				Women						**Men**			
High	Comparison	193	104,469	1.9 (1.6–2.1)		Reference		365	245,562	1.5 (1.3–1.6)		Reference	
	VTE	102	15,482	6.6 (5.3–7.9)	–	3.2 (2.5–4.0)		175	35,587	4.9 (4.2–5.7)	–	2.8 (2.4–3.4)	
Medium	Comparison	2838	5 42,717	5.2 (5.0–5.4)		2.6 (2.3–3.0)		2599	463,222	5.6 (5.4–5.8)		3.4 (3.0–3.8)	
	VTE	1285	89,084	14.4 (13.6–15.2)	4.5 (2.9–6.0)	6.3 (5.4–7.3)	31.2%	1364	77,909	17.5 (16.6–18.4)	8.5 (7.3–9.7)	8.5 (7.5–9.5)	48.6%
Low	Comparison	1643	63,769	25.8 (24.5–27.0)		9.4 (8.1–10.9)		999	37,308	26.8 (25.1–28.4)		12.7 (11.3–14.3)	
	VTE	673	14,323	47.0 (43.4–50.5)	16.5 (12.5–20.4)	13.4 (11.4–15.8)	35.2%	604	8857	68.2 (62.8–73.6)	38.0 (32.2–43.7)	23.8 (20.8–27.3)	55.8%
				PE						**DVT**			
High	Comparison	173	108,153	1.6 (1.4–1.8)		Reference		385	241,889	1.6 (1.4–1.8)		Reference	
	VTE	107	15,018	7.1 (5.8–8.5)	–	4.0 (3.1–5.1)		170	36,051	4.7 (4.0–5.4)	–	2.6 (2.1–3.1)	
Medium	Comparison	1704	300,803	5.7 (5.4–5.9)		3.2 (2.8–3.8)		3733	705,148	5.3 (5.1–5.5)		3.1 (2.8–3.4)	
	VTE	871	46,409	18.8 (17.5–20.0)	7.6 (5.7–9.4)	9.2 (7.8–10.8)	40.4%	1778	120,585	14.8 (14.1–15.4)	6.3 (5.3–7.3)	7.1 (6.3–7.9)	42.8%
Low	Comparison	794	30,622	25.9 (24.1–27.7)		11.0 (9.3–13.0)		1848	70,455	26.2 (25.0–27.4)		11.9 (10.7–13.3)	
	VTE	311	6063	51.3 (45.6–57.0)	19.9 (13.7–26.0)	18.6 (15.4–22.6)	38.8%	966	9	56.4 (52.9–60.0)	27.0 (23.2–30.9)	18.7 (16.5–21.1)	47.8%
				Provoked VTE						**Unprovoked VTE**			
High	Comparison	135	81,264	1.7 (1.4–1.9)		Reference		423	268,778	1.6 (1.4–1.7)		Reference	
	VTE	108	9272	11.7 (9.5–13.8)	–	5.9 (4.6–7.6)		169	41,797	4.0 (3.4–4.7)	–	2.4 (2.0–2.9)	
Medium	Comparison	1258	233,691	5.4 (5.1–5.7)		3.0 (2.5–3.6)		4179	772,248	5.4 (5.3–5.6)		3.2 (2.9–3.5)	
	VTE	668	33,135	20.2 (18.6–21.7)	4.8 (2.1–7.5)	9.5 (7.9–11.5)	23.8%	1981	133,846	14.8 (14.2–15.5)	6.9 (6.0–7.8)	7.6 (6.9–8.5)	46.6%
Low	Comparison	602	24,217	24.9 (22.9–26.8)		10.3 (8.5–12.5)		2040	76,848	26.5 (25.4–27.7)		12.1 (10.8–13.4)	
	VTE	249	4453	55.9 (49.0–62.8)	21.1 (13.5–28.6)	19.7 (15.9–24.4)	37.8%	1028	18,272	54.9 (51.5–58.2)	25.9 (22.3–29.5)	19.4 (17.3–21.8)	47.2%

Notes: [a]Adjusted for: age, sex, calendar year of VTE, obesity, cancer, coronary heart disease (including atrial fibrillation and heart failure), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, mental diseases, surgery and trauma/fractures 3 months prior to the VTE/index date, and modified Charlson Comorbidity Index score. [b]The proportion of the IR explained by interaction is calculated as the interaction contrast divided by the disability pension IR in patients with VTE and low/medium SES.
Abbreviations: IR, incidence rate; IC, interaction contrast; HR, hazard ratio; CI, confidence intervals; DP, disability pension; SES, socioeconomic status; VTE, venous thromboembolism; PY, person years; AP, attributable proportion.
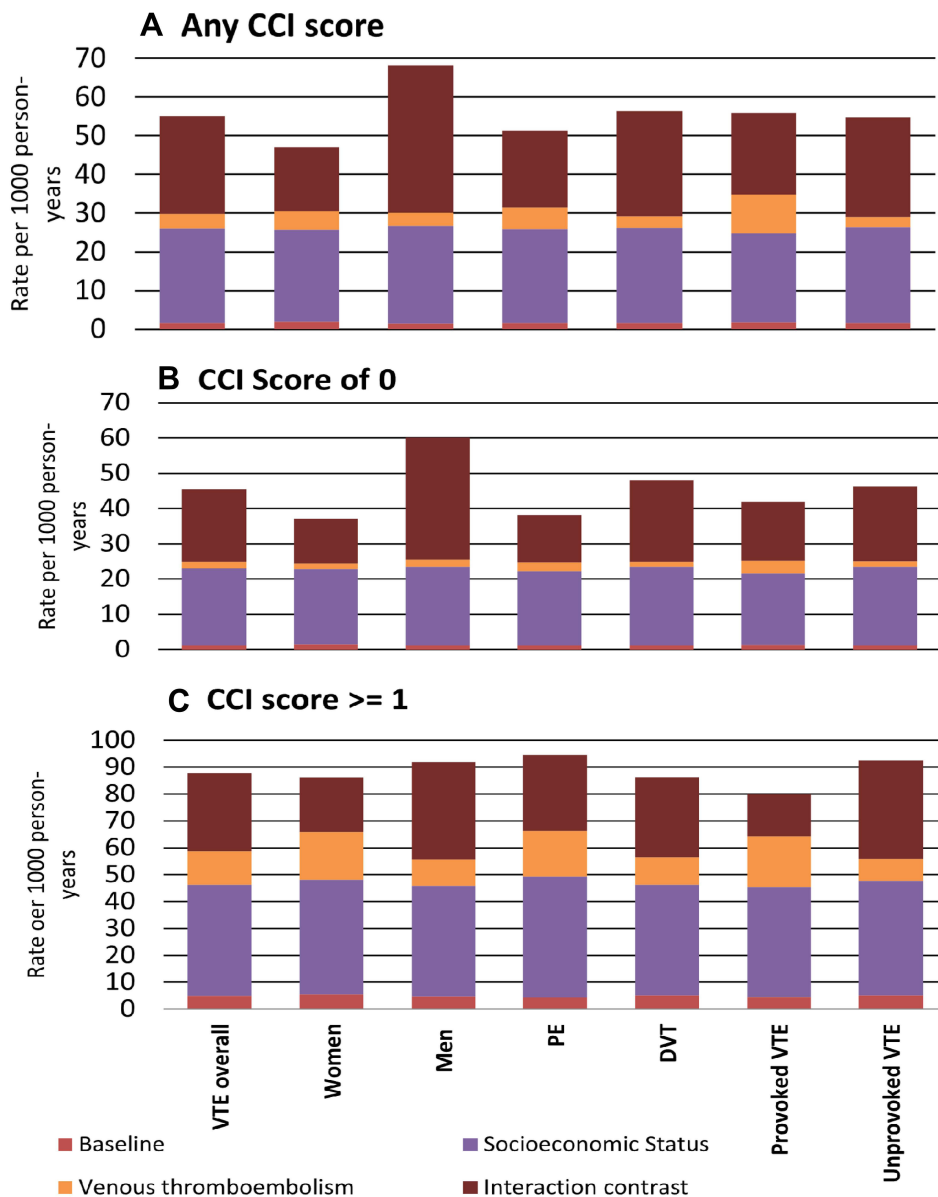
A Any CCI score

B CCI Score of 0

C CCI score >= 1

Legend:
- Baseline
- Socioeconomic Status
- Venous thromboembolism
- Interaction contrast

Figure 2 Proportion of the total disability pension rate attributable to venous thromboembolism, low socioeconomic status and their interaction in relation to men, women, pulmonary embolism, deep vein thrombosis, provoked and unprovoked venous thromboembolism in (**A**) main analysis, (**B**) analysis restricted to a Charlson Comorbidity Index score of zero, and (**C**) analysis restricted to a Charlson Comorbidity Index score of one or more.
Abbreviations: SES, socioeconomic status; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; CCI, Charlson comoribity index.

disability pension IR in men aged 25–34 and 46.6% of the disability pension IR in men aged 55–65, while the corresponding attributable proportions were 59.8% and 8.2% in women, respectively (Supplementary Table 5, Figure 3).

In an analysis stratified on Charlson Comorbidity Index score, the interaction for those with a Charlson Comorbidity score of 0 remained essentially similar to that observed in the main analysis, while it was somewhat divergent for those with a Charlson Comorbidity score of ≥1. (Supplementary Table 6, Figure 2).

In individuals with VTE and low SES, the cumulative incidence of disability pension, after taking competing risk of death into account, was 18.7% (95% CI 17.6–19.9%) after three years, 25.6% (95% CI 24.2–26.9%) after six years, and 35.0% (95% CI 33.3–36.8%) after 12 years (Supplementary Figure 1). In the adjusted Cox proportional hazards regression model, VTE combined with low SES was associated with a HR of 18.8 (95% CI: 17.0–20.8) for disability
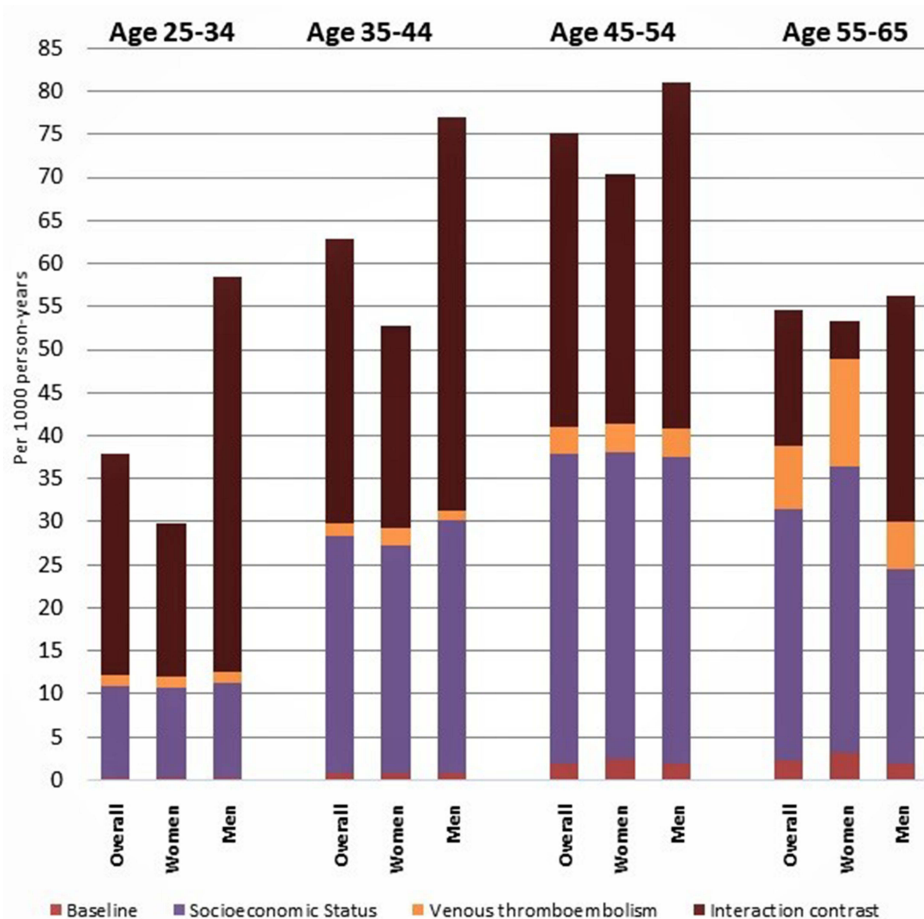
Figure 3 Proportion of the total disability pension incidence rate attributable to venous thromboembolism, low socioeconomic status, and their interaction by age and sex.

pension, while VTE combined with medium SES yielded an adjusted HR of 7.7 (95% CI: 7.0–8.4) when compared with individuals with no VTE and high SES. (Table 2).

Discussion

In this nationwide population-based cohort study we found a large interaction on the additive scale between SES and VTE on the risk of disability pension. Even though the individual effects of lower SES and VTE increased the risk of disability pension, interaction accounted for 45.6% of the disability pension IR in individuals with low SES and VTE. The interaction between SES and VTE was present in both sexes, all age groups, and for all subtypes of VTE. Competing risk of death analyses and analyses within the strata of Charlson Comorbidity Index score suggested that VTE-related comorbidities or increased mortality in individuals with VTE might only explain a minor part of the observed interaction.

Our results confirmed those of previous reports on associations between SES and VTE,[6–10] VTE and disability pension,[4,5] and SES and disability pension.[22–24] However, data on the interaction between VTE and socioeconomic gradient on the risk of disability pension have been lacking previously. A few studies have investigated the joint effect of occupational status and arterial cardiovascular disease on disability pension.[24,25] A prospective cohort study of 44,516 survey respondents from the Finnish Public Sector found that the combination of low occupational status and cardio-vascular disease were associated with a 4.5-fold increased risk of disability pension compared to high occupational class without cardiovascular disease. The combination of low occupational class and cardiovascular disease gave a Synergy Index of 1.55 suggesting a greater than additive effect.[25] Another Finnish registry based study on 258,428 individuals of working age reported IRs per 1000 person-years of disability due to cardiovascular diseases of 3.3 in male manual

workers aged 35–54 years and 2.4 in male manual workers aged 55–64 years.[24] The reported incidence was somewhat lower for women.[24]

We found an interaction between low SES and incident VTE on the risk of disability pension. However, the observed interaction between VTE and SES was much stronger than the previously reported interaction with cardiovascular disease.[24,25] Several factors may explain the large interaction observed in the current study. We measured SES by combining the SES indicators education, income and employment status in a composite SES score, and we measured SES close to the VTE. Our inclusion of multiple SES indicators is supported by several studies arguing that SES is innately multidimensional and therefore should be measured by more than one single indicator.[26,27] The interaction between VTE and SES likely influences the risk of disability pension through several factors such as physical capacity, access to healthcare, legislation, lifestyle, labour market possibilities, work characteristics and psychosocial work environment.[28,29] Therefore, a composite SES score enabled us to include a broader aspect of the socioeconomic dimension and capture both the different ways SES indicators influence each other and the temporal causation among the indicators. Moreover, by measuring SES close to the VTE, we lowered the chance of misclassifications and spurious associations that might dilute the findings. Low education and low income might imply reduced working possibilities and flexibility at work. Work-related stress, less control and decision latitude are factors that are known to generate both health problems and problems retaining employment.[3,30] Furthermore, unfavorable working conditions through unfavorable psychosocial and physical work demands have been found to be more prevalent in individuals with low levels of education.[30,31] Moreover, as individuals with VTE often suffer from reduced physical functioning due to recurrences, the post-thrombotic syndrome and the post PE-syndrome,[32–34] typical industrial professions, or occupations with manual and tedious tasks, might be challenging to retain. In contrast, a high educational level and income might provide less physically stressful and more flexible life- and working conditions, making it easier to stay in employment despite reduced physical function.[3,30]

The interaction was especially pronounced in young men. Our findings are in line with previous data indicating that socioeconomic factors are strong determinants of disability among the young.[10,22,35] Moreover, men have a higher risk of recurrence, post-thrombotic syndrome, and the post-PE syndrome[32,33,36] and they are more prone to engage in behaviours leading to higher rates of injury and disease.[37,38] These factors might contribute to the elevated risk of disability in male individuals with VTE.

Our study has several strengths. We used a large population-based cohort consisting of the entire general working-age Danish population, with highly accurate and validated data for exposures, outcome and comorbidities.[12] Furthermore, we conducted the study in a setting with government-funded and free of charge education and health care services for all residents, thus reducing selection and referral bias. This allowed a detailed interpretation of the interaction between VTE and SES on the risk of disability pension, including the measurement of several SES indicators jointly and analysis stratified on age and sex.

The study also had some limitations. Disability can vary in duration and severity, and not necessarily lead to a permanent exit from work life. With receipt of permanent disability pension as the outcome, (and not including periods of sick leave etc.) we might have underestimated the actual incidence of disability pension related to VTE and SES. We also excluded individuals with missing SES values which might have somewhat biased our results.

Further, disability pension schemes vary between countries and time-periods. The transferability of our results to other countries may therefore be limited to countries with a similar generous tax-financed social benefit, - and health care system, such as in the Nordic region.

As the study was based on information available from medical and administrative registers, we lacked information relevant to receipt of a disability pension such as categories of occupation, life-style factors, like physical activity and body mass index, quality and outcome of post-VTE care, and workplace factors. Neither did we have information on the incidence of recurrence, the post-thrombotic syndrome, or the post-PE syndrome in our individuals with VTE during follow-up.

In conclusion, low SES interacts with VTE to increase the risk of disability pension beyond what could be explained by the additive effect of SES and VTE as separate components. Consequently, SES influences disability pension risk after VTE to a substantial proportion. Our results emphasise SES as a risk factor for disability pension in individuals with VTE and can help occupational and healthcare professionals to identify individuals at risk of an early exit from the workforce after a VTE.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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