UiT The Arctic University of Norway

Faculty of Health Sciences, Department of Clinical Medicine

The impact of socioeconomic status on the risk and prognosis of venous thromboembolism

Helle Jørgensen

A dissertation for the degree of Philosophiae Doctor, May 2022

Contents

Acknowledgements

The work presented in this thesis was carried out in 2020-2022 at the Thrombosis Research Center, UiT-The Arctic University of Norway and at the Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital.

I wish to express my sincere gratitude to all who have helped, supported and encouraged me during the work of this PhD. I am extremely grateful to my main supervisor John-Bjarne Hansen for providing me the opportunity to do this project. Thank you for sharing your vast knowledge, your support, guidance, for believing in me, and helping me stay focused.

Thank you to my co-supervisor Henrik Toft Sørensen for introducing me to Danish registry data, and for welcoming me to stay at the Department of Clinical Epidemiology in Aarhus. Your generosity, epidemiological knowledge, and engagement in this project has meant a lot to me. Also, thank you to Hanne Kjeldahl Schlosser for keeping track and order, always with a smile.

In addition, I wish to thank my co-supervisor Sigrid Brækkan, and project team members Erzsébet Horvàth-Puhò and Kristina Laugesen for your true engagement in this project. You have been of invaluable support sharing your knowledge with me, and patiently explaining whatever challenge I have run into.

Thank you to all colleagues at the Thrombosis Research Center and at the Department of Clinical Epidemiology for creating great and stimulating work environments.

Finally, thank you to my family. Your support in life is unmeasurable. I would especially like to thank my three children who joined me for my research stay in Aarhus. Every day you help putting perspective into my life, and you always ensure to keep my mind busy when not at work.

Aarhus, May 2022

Summary

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and multifactorial disease,[1] and emerging knowledge suggests that its long-term complications negatively affect physical functioning and quality of life.[2] Socioeconomic status (SES) is known to affect the risk and prognosis of health and health behavioral outcomes,[3,4] Even though associations between VTE and physical health are well documented, research on the psychosocial risk factors for and outcomes of VTE is scarce. In this thesis, we aimed to study the association between SES and VTE (Study I). We further aimed to study the association between VTE and subsequent disability pension and to assess whether SES was associated with an increased risk of disability pension after VTE (Studies II and III). Finally, we aimed to assess the risk of depression after VTE (Study IV).

The present thesis compromises four scientific studies based on data collected from 1995 through 2016 from Danish national medical and administrative registries. The study populations included almost 125,000 individuals with VTE and a comparison cohort from the general population. In Study I, we applied a population-based case-control design and in Studies II-IV, we applied population-based cohort designs. In Study I, we assessed SES both as individual indicators and as a composite SES score in terms of education level, income level, and employment status. We found that low SES was a risk factor for VTE. We also found that the composite SES score performed better than individual SES indicators in assessing the VTE risk. In Study II, we observed that VTE patients had a 2 to 3-fold higher risk of subsequent disability pension compared to the general population. In Study III, we found that 45.6% of the disability pension incidence rate in individuals with low SES and VTE could be explained by interaction. In Study IV, we observed that VTE patients had a 1.9-fold increased risk of future depression compared to the general population.

Our findings provide an improved understanding of the psychosocial impact of VTE and they can form the basis for health recommendations and novel strategies to identify high-risk groups that would benefit from programs for prevention, follow-up, or treatment after a VTE.

Sammendrag på norsk

Venøs tromboembolisme (VTE), bestående av dyp venetrombose (DVT) og lungeemboli (PE), er en utbredt og multifaktoriell sykdom,[1] og ny kunnskap tyder på at langtidskomplikasjoner etter VTE negativt påvirker fysisk funksjon og livskvalitet.[2] Sosioøkonomisk status (SES) er kjent for å påvirke både risiko og prognose for helsemessige og helserelaterte utfall.[3,4] Selv om assosiasjoner mellom VTE og fysisk helse er godt dokumentert, finnes det lite forskning på psykososiale risikofaktorer og konsekvenser relatert til VTE. I denne avhandlingen ønsket vi å studere sammenhengen mellom SES og VTE (Studie I). Vi ville videre se på sammenhengen mellom VTE og påfølgende uføretrygd i befolkningen, samt å vurdere om SES var assosiert med økt risiko for uføretrygd etter VTE (Studier II og III). Avslutningsvis hadde som mål å vurdere risikoen for depresjon etter VTE (Studie IV).

Denne avhandlingen består av fire vitenskapelige studier basert på data samlet inn fra 1995 til 2016 fra danske nasjonale medisinske og administrative registre. Studiepopulasjonen inkluderte nesten 125 000 individer med VTE, i tillegg til en sammenligningskohorte fra den generelle befolkningen. I Studie I brukte vi et populasjonsbasert kasus-kontroll design, og i Studie II-IV brukte vi populasjonsbaserte kohortdesign. I studie I vurderte vi SES, definert som utdanningsnivå, inntekt og sysselsettingsstatus, både som individuelle indikatorer og som en sammensatt SES score. Vi fant at lav sosioøkonomisk status var en risikofaktor for VTE,. Videre fant vi at SES score modellen var bedre til å vurdere VTE risikoen sammenlignet med de individuelle indikatorene. I studie II fant vi at VTE var assosiert med en 2 til 3 ganger forhøyet risiko for påfølgende uføretrygd. I studie III fant vi at interaksjon stod for 45,6% av forekomsten av uføretrygd hos personer med lav SES og VTE. I studie IV fant vi at VTE var assosiert med en 1.9-ganger forhøyet risiko for fremtidig depresjon.

Våre funn kan bidra til en forbedret forståelse av psykososiale risikofaktorer og konsekvenser for VTE, og de kan danne grunnlag for helsemessige anbefalinger og nye strategier for identifisering av høyrisikogrupper for forebygging, oppfølging eller behandlingsprogrammer etter en VTE.

Resumé på dansk

Venøs tromboembolisme (VTE), bestående af dyb venetrombose (DVT) og lungeemboli (PE), er en udbredt og multifaktoriel sygdom,[1] og ny viden tyder på, at langvarige komplikationer efter VTE påvirker fysisk funktion og livskvalitet negativt.[2] Socioøkonomisk status (SES) er kendt for at påvirke både risiko og prognose for helbred og sundhedsrelaterede udfald.[3,4] Selvom sammenhængen mellem VTE og fysisk sundhed er veldokumenteret, er der ikke meget forskning i psykosociale risikofaktorer for og konsekvenser efter VTE. I denne afhandling ønskede vi at studere sammenhængen mellem SES og VTE (Studie I). Vi ville desuden se på sammenhængen mellem VTE og efterfølgende førtidspension samt vurdere, om SES var forbundet med en øget risiko for førtidspension efter VTE (Studierne II og III). Endelig havde vi som formål at vurdere risikoen for depression efter VTE (Studie IV).

Denne afhandling består af fire videnskabelige studier baseret på data indsamlet fra 1995 til og med 2016 fra danske landsdækkende medicinske og administrative registre. Studiepopulationen omfattede næsten 125.000 personer med VTE samt en sammenligningskohorte fra den generelle befolkning. I studie I brugte vi et populationsbaseret case-kontrol design, og i studierne II-IV brugte vi et populationsbaseret kohortedesign. I Studie I vurderede vi SES, defineret som uddannelsesniveau, indkomst og beskæftigelsesstatus, både som individuelle indikatorer og som en sammensat SES-score. Vi fandt, at lav sosioøkonomisk status var en risikofaktor for VTE. Desuden fandt vi, at SES-scoremodellen var bedre til at vurdere VTE-risiko sammenlignet med de enkelte indikatorer. I Studie II fandt vi, at VTE var forbundet med to til tre gange øget risiko for efterfølgende førtidspension sammenlignet med den generelle befolkning. I Studie III fandt vi at interaktion forårsagede 45,6% af forekomsten af førtidspension hos personer med lav SES og VTE. I Studie IV fandt vi, at VTE var forbundet med 1.9 gange øget risiko for fremtidig depression. Vores resultater kan bidrage til en forbedret forståelse af de psykosociale risikofaktorer for og konsekvenser af VTE, og de kan danne grundlag for sundhedsanbefalinger og nye strategier til at identificere højrisikogrupper, der kan have gavn af programmer til forebyggelse, opfølgning eller behandling efter en VTE.

List of Studies

The thesis is based on the following Studies:

I. **Socioeconomic status and the risk of incident venous thromboembolism**
Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan SK, Hansen JB, Sørensen HT
J Thromb Haemost. 2021 Dec;19(12):3051-3061. doi: 10.1111/jth.15523

II. **Risk of a permanent work-related disability pension after incident venous thromboembolism in Denmark: A population-based cohort study**
Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan SK, Hansen JB, Sørensen HT
PLoS Med. 2021 Aug 31;18(8): e1003770. doi: 10.1371/journal.pmed.1003770

III. **The interaction between venous thromboembolism and socioeconomic status on the risk of disability pension**
Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan SK, Hansen JB, Sørensen HT
Clin Epidemiol. 2022 Apr 14; 14:489-500. doi: 10.2147/CLEP.S361840.

IV. **Venous thromboembolism and risk of depression: A Danish population-based cohort study**
Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan SK, Hansen JB, Sørensen HT
Submitted

Abbreviations

ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CHD	Coronary heart disease
CI	Confidence Interval
CIF	Cumulative incidence function
COC	Combined oral contraceptives
COPD	Chronic obstructive pulmonary disease
CPR	Central Personal Registration
CRS	Civil Registration System
CTEPH	Chronic thromboembolic pulmonary hypertension
CVD	Cardiovascular Disease
DNPR	The Danish National Patient Registry
DPCRR	The Danish Psychiatric Central Research Registry
DVT	Deep vein thrombosis
FVL	Factor Five Leiden
GDP	Gross domestic product
GWAS	Genome-wide association studies
HR	Hazard Ratio
QoL	Quality of life
HRQoL	Health related quality of life
HRT	Postmenopausal hormone therapy
IC	Interaction contrast
ICD	International Classification of Disease
IDA	The Integrated Database for Labor Market Research
IR	Incidence Ratio
MI	Myocardial Infarction
OECD	Organization for Economic Co-operation and Development

OR	Odds Ratio
PE	Pulmonary embolism
Post-PE	Post-pulmonary embolism
PTS	Post-thrombotic syndrome
PTSD	Post-traumatic stress disorder
SAS	Statistical Analysis System
SES	Socioeconomic status
SNP	Single nucleotide polymorphism
VTE	Venous thromboembolism
WHO	World Health Organization

Introduction

VTE

Venous thromboembolism (VTE), encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is the third most common cardiovascular disease following coronary heart disease and stroke.[5] VTE is a major cause of human suffering and premature mortality, and it represents a significant public health concern in times where demographics are shifting towards an aging population.[6]

VTE is caused by a disturbance in the haemostatic system leading to thrombin generation and thrombus (clot) formation. The framework for understanding the pathophysiology of thrombus formation includes abnormalities in blood flow, changes in the blood vessel wall, and activation of blood clotting components, known collectively as Virchow's triad (Figure 1).[7] In DVT, a thrombus forms in the deep veins, most often in the lower extremities, with pain, swelling and erythema as the main symptoms.[8] In PE, the blood clot dislodges from its site of origin and travels to the pulmonary arteries where it ultimately obstructs the circulation and causes symptoms such as dyspnea, chest pain, hemoptysis, and in severe cases, syncope and sudden death.[5] PE was until recently seen as a complication of DVT, however, more recent studies have revealed that around 50% of PEs have an untraceable origin.[9] Alternative etiologies for PE include local thrombus formation in the lung vasculature as a result of local inflammatory conditions like pneumonia,[9,10] or embolization from a right-sided cardiac thrombus caused by atrial fibrillation.[9,11,12] DVT is known to account for two-thirds of all VTEs, while PE with or without a concurrent DVT accounts for one third.[5] However, more recent findings report a stable or even decreased incidence in DVT,[13,14] while the incidence in PE has increased, likely due to improved diagnostic tools and increased awareness of the condition.[14] VTE is treated with anticoagulants, efficiently preventing thrombus growth and embolization.[15,16] Even though anticoagulants reduce the ability of the blood to clot, they increase the risk of bleeding. Therefore, prevention of a recurrent VTE always needs to be balanced against the risk of major bleeding.[16,17]

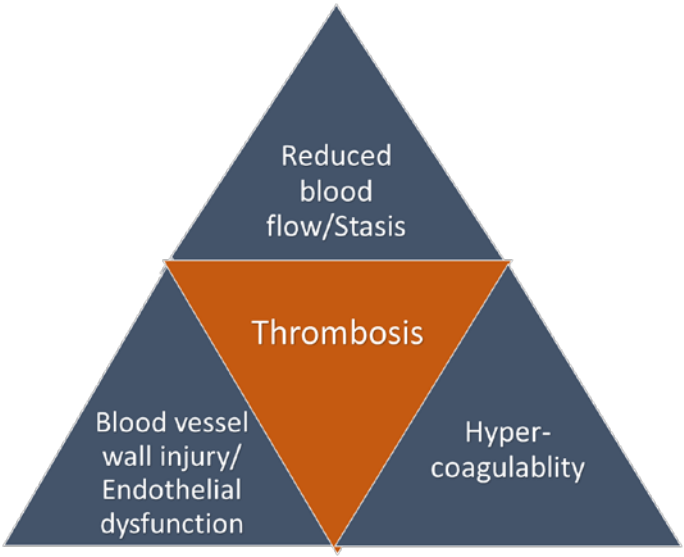


Figure 1. Illustration of Virchow's triad explaining the pathophysiology of VTE by the components changes in blood flow (stasis), changes in the composition of blood (hypercoagulability) and blood vessel wall injury.

Socioeconomic status

Socioeconomic status (SES) describes an individual's economic situation and social capital relative to others. SES in relation to health can be used to assess the access to the basic resources required to accomplish and sustain good health.[18] SES is a highly important factor that can help to explain differences in societal structures and social status over time, as well as health related social inequalities.[19] By assessing SES, the social distribution of a disease can be observed and monitored over time and across different geographical regions or social groups. Also, SES might indicate whether policy targets to diminish health inequalities have been reached.[20] Several terms, such as social class, socioeconomic position, or socioeconomic status are commonly used to describe and measure social relationships. Some argue that status, in contrast to position, does not sufficiently differentiate economic resources such as income, wealth or education, and social prestige. However, as there is no consensus on this distinction and both concepts continue to be used, we have chosen to apply the term socioeconomic status in this thesis, as it is a more established and commonly used term in the existing literature.

The SES of an individual is complex as it includes various elements such as income, wealth, education, occupation, neighborhood characteristics, welfare services, and social class.[21] Different socioeconomic indicators can impact health at different time-points, and impact

health at several levels and causal pathways. Socioeconomic indicators also interact with different social characteristics, like racial/ethnic groups or sex, to produce different health effects across groups.[21] Further, SES consists of several constructs such as the level of measurement (i.e., individual, family, and neighborhood) and the way of measurement (i.e., objectively or subjectively), it can be a cause or a consequence of something, and it may be measured at one time-point or by examining changes or variability over the life course. There is no single indicator of SES suitable for all study aims or that is applicable at all time-points and in all settings. Each indicator measures different, often related aspects of socioeconomic stratification which may be more or less important to different health outcomes and life-stages. The choice of SES measure(s) should ideally be chosen by consideration of the specific research question and the proposed mechanisms linking SES to the outcome. However, in practice, measures used is often driven by what is available or has been previously collected.[22]

Studies of the relationship between SES and health inequalities have a long scientific history and relationships between worse health and poverty associated adverse living environments were already observed during the decades of intense industrialization and extensive migration into urban areas of Europe.[23]Across several health outcomes, such as cancer, cardiovascular disease, respiratory disease, and mental health-related disorders,[24,25,26] persons with low SES are at greater risk for poorer health outcomes than individuals with high SES.[27] Reported effects of low SES are poor health, increased mortality and morbidity, worse health behaviour, and increased risk of long-term sick leave.[27-33] However, knowledge on the impact of SES on the long- term socioeconomic and psychological consequences after a VTE is limited.

The epidemiology of VTE

The annual incidence rate (IR) of VTE is 1-2 per 1,000 person-years in the general adult population, with an estimated incidence in the European Union of over 1.1 million events per year.[1,34,35] Despite increased awareness, better treatment, and improved prophylaxis, the VTE incidence has increased during the past decades, mainly due to increased diagnostic detection rates of PE.[13,14,35,36] An increased prevalence of VTE-related risk factors such as cancer, obesity, and an aging population will likely contribute to a further increase in VTE incidence in the coming years.[2,34,36,37] Even though VTE affects both men and women of all ages, it has

an exponential rise in incidence with age from one per 1,000 in adults under 50 years of age to more than eight per 1,000 in elderly over 80 years of age.[35,38] Evidence on the VTE incidence by sex is divergent. Some studies show a higher risk in women,[14,35] some show a higher risk in men,[38-40] while others report no difference.[41] Men are found to have a higher incidence than women in the older age groups, while women have a higher incidence than men during childbearing years.[5,35] However, the life-time risk of VTE has been shown to be slightly higher in women than in men.[42,43]

The estimated amount of VTE-related deaths in the EU exceeds 540,000 each year, and the one-year all-cause mortality rate after VTE is around 21-24%.[35,44,45] A history of VTE yields an 55% increased risk of mortality up to 30 years after the initial VTE, as compared to the general population.[46,47] Mortality rates attributed to PE are higher than for DVT with almost one quarter of all PEs presenting as sudden death.[35,45,48] Also, provoked VTE yields a higher mortality risk than unprovoked VTE, likely due to advanced age and more comorbid conditions in patients with provoked VTE.[44,45] Importantly, there is no consensus on how to define PE-related deaths.[49] The clinical signs and symptoms of PE are non-specific, and the non-forensic autopsy rates have decreased over the years so that PE-related deaths are rarely objectively confirmed by post-mortem examination, nor by imaging before death.[49] Consequently, it remains a challenge to distinguish between mortality associated with and caused by VTE. These variations in the way data are collected and how decisions about death events are made, may result in skewed risk estimations of study results, which will compromise the internal and external study validities.[50]

In addition to an increased mortality risk,[35,46,47,51] VTE patients are at high risk of serious complications of short and long durance such as recurrence,[52,53] the post-thrombotic syndrome (PTS),[54,55] and the post-pulmonary embolism (post-PE) syndrome.[56-60] Both the VTE and its complications have been shown to cause reduced mobility, reduced ability to work, reduced quality of life and increased mortality and morbidity in a large number of patients.[2,37,55,61]

Risk factors of VTE

A risk factor affects the incidence of a disease. The likelihood of disease occurring is higher in the presence of either genetic risk factors, acquired risk factors, or both. VTE is a multi-causal

disease associated with inherited/genetic and acquired risk factors, and in most cases, more than one risk factor must be present for a VTE to occur.[8] The thrombosis potential model as proposed by Professor Frits Rosendaal illustrates how this accumulation of risk factors can overwhelm the natural anticoagulant mechanisms, exceed the thrombosis threshold and result in thrombosis (Figure 2).[8] In this model, risk factors such as heredity and age, in addition to provoking factors, may change or increase over time and exceed a person's thrombosis threshold, and thereby lead to a VTE.[8] Therefore, the individual thrombosis risk will vary according to the presence of concurrent risk and provoking factors, the thrombosis-inducing properties of the factors, as well as the interaction between them.

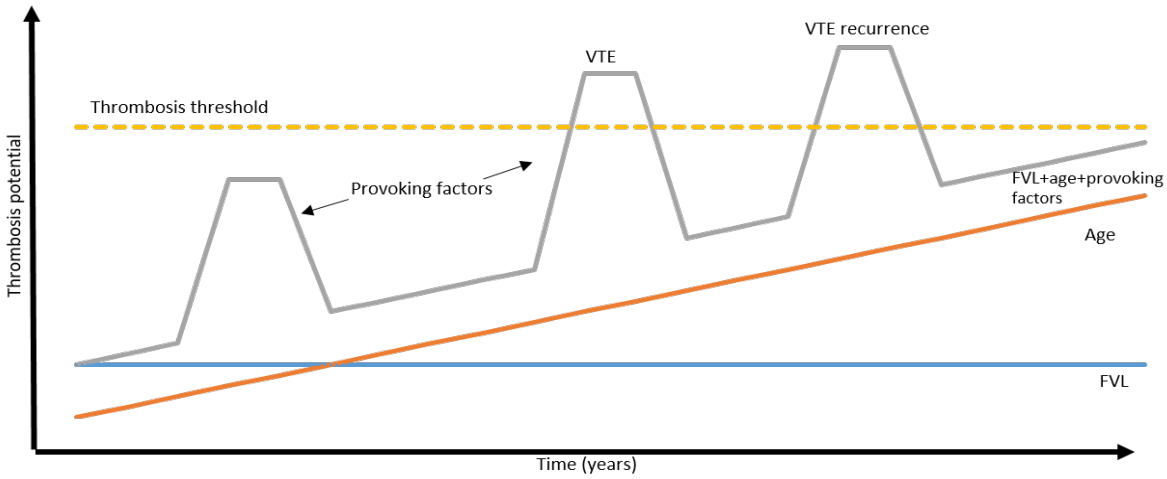


Figure 2. The thrombosis potential model. The blue line shows the impact of a genetic risk factor (e.g., factor V Leiden (FVL), and the orange line shows the impact of age. The grey line shows the impact of FVL and age combined with provoking factors. Adapted from Rosendaal, F, Venous thrombosis: a multicausal disease 1999.

Hereditary risk factors

VTE is a highly hereditary condition with family and twin studies showing that 50-60% of the VTE risk is attributable to genetic risk factors.[62-65] Genetic risk factors for VTE mainly promote thrombus formation either through loss-of-function or gain-of-function of anticoagulant proteins.[66] Loss-of-function mutations causes deficiency of either of the natural anticoagulants anti-thrombin, protein C and protein S. Gain-of-function mutations comprise mutations in genes encoding for factor V (Factor V Leiden or APC-resistance), prothrombin (rs20210A), non-O blood type, fibrinogen or Factor XI.[67] Gain-of-function mutations are relatively

prevalent and associated with a 1.3 to 3-fold increased risk of VTE.[62] Loss-of-function mutations are less common but associated with an 8 to 10-fold increased risk of VTE.[62,66]

During the recent decades, additional gene variants (single nucleotide polymorphisms (SNPs)) have been found to be modestly or weakly associated with VTE.[62] To improve the prediction of VTE, several recent studies have attempted to create genetic risk scores based on several VTE-associated SNPs.[62,68] In recent years, larger genome-wide association studies (GWAS) have used meta-analyses to reveal novel and previously unsuspected genetic associations that may uncover new biological pathways contributing to VTE and phenotypes with possible shared genetic determinants contributing to the disease, which may identify new targets for VTE treatment.[68-70]

Acquired risk factors

Acquired, or environmental, risk factors for VTE include age, obesity, cancer, hospitalization, surgery, trauma, acute medical conditions, immobilization, pregnancy, and use of drugs such as oral contraceptives.[71,72] A VTE caused by a known predisposing acquired risk factor is classified as provoked. When no acquired risk factor is identified, the VTE is classified as unprovoked. Approximately 60-75% of all VTEs in the general population are caused by established VTE-related risk factors, suggesting that 25-40% of all VTEs in the community are unprovoked.[13,73]A VTE can be provoked by a transient risk factor that resolves after having triggered the VTE, like recent surgery, or by a persistent risk factor with continued effect after the VTE, like cancer.[74] Transient risk factors are considered as major (i.e. major surgery), or minor (i.e. leg injury) dependent on the degree of which they increase the risk of the initial VTE and the risk of VTE recurrence.[75] The recurrence risk after 3 to 6 months of anticoagulant therapy is almost 50% lower in VTEs caused by transient provoking risk factor, compared to unprovoked VTE.[76] Transient provoking factors (i.e. major surgery or major trauma) have the lowest recurrence risk after anticoagulation cessation, while acute medical illness (i.e. heart failure) and unprovoked VTE have an intermediate recurrence risk.[74,77] VTEs provoked by major persistent provoking factors (i.e. cancer) have the highest recurrence risk after discontinuation of anticoagulation compared to VTE provoked by a major transient risk factor.[74] Therefore, a potential prolonged or indefinite oral anticoagulant therapy treatment is largely dependent on the classification of the VTE, even though the initial anticoagulation

treatment is the same for both unprovoked and provoked acute VTE.[75] Due to the high incidence, active cancer is considered the most significant persistent provoking factor for VTE.[74] Furthermore, 4-9% of patients with unprovoked VTE are diagnosed with cancer within a year after the VTE diagnosis.[74,78,79] Thus, there is an ongoing debate whether or not to screen patients with unprovoked VTE for cancer.[78,79] The clinical classification of VTE as provoked or unprovoked is challenged by the diverse recurrence risk within different subgroups of provoked and unprovoked VTE.[80-82] Therefore, more refined risk estimation within different subgroups is still warranted to tailor anticoagulation treatment.

Age is an important risk factor for VTE and it is estimated that 70-90% of VTEs can be ascribed to increased age.[83,84] Functional or degenerative changes in the vascular system, procoagulant alteration related to age in the haemostatic system, or general immobility or weakness are potential explanations for this increased risk in the elderly.[84,85] A higher burden of comorbid diseases could also explain some of the VTE risk. However, a Norwegian study found that cancer did not explain the increased risk of VTE with advanced age.

Cancer is considered acquired risk factors for VTE. Thrombosis is a major cause of morbidity and mortality in cancer patients, and a VTE can often be the first symptom of an occult malignancy in an otherwise healthy individual.[86,87]Around 20% of all VTEs are cancer-related and cancer patients have a 4 to 9-fold higher risk of developing VTE, with the highest risk during the first year after cancer diagnosis.[87,88] Also, studies have shown that around 10% of patients with unprovoked VTE were diagnosed with cancer within one year.[89] The VTE risk is dependent on patient characteristics, cancer type, cancer stage, chemotherapy treatment.[87,88,90] Hematological malignancies and cancers of the lung, the gastrointestinal tract and the brain, in addition to metastatic cancers, show the strongest association with VTE.[88,90] The mechanisms behind the association between cancer and VTE may be explained by tumour-derived pro-coagulant factors that induce thrombosis, or venous compression or vascular injury from local tumour invasion.[86,87] Additionally, individuals with cancer are often exposed to VTE-related risk factor like hospitalization and surgery that increase the risk of infections and immobilization.[86,87]

Obesity, defined as a body mass index (BMI) over 30 kg/m^2, is associated with a 2 to 3-fold increased risk of VTE[91] and Mendelian Randomization studies have suggested a causal relationship between VTE and BMI.[92-94] The relationship between obesity and VTE risk is also found to be dose-dependent,[91] with a one standard deviation increase in genetically elevated BMI yielding a 57% increased risk of VTE.[94] Weight gain further increases the VTE risk, particularly in those already obese.[95,96] BMI is the most commonly used anthropometric measure of obesity, but studies have shown that increased waist circumference might detect more subjects at risk with stronger risk estimates than other obesity measures.[97,98] Other measures, including body weight,[97] waist to height ratio,[97] total body fat mass,[98] and weight gain[95] have also been found to be associated with an increased VTE risk. Possible mechanisms associated with VTE and obesity include chronic low-grade inflammation, impaired venous return due to raised intra-abdominal pressure, and pro-coagulant and hypo-fibrinolytic changes in plasma.[91,99,100]

Hospital related VTE, defined by patients hospitalized, or undergoing surgery within 8 to 12 weeks preceding the VTE, contribute to up to 50% of VTE cases in the general population.[101,102] Notably, Hospital related VTE happens more shortly after hospital discharge, suggesting that the VTE initiated clinically silent during hospitalization.[103,104] The increased risk of hospital associated VTE might be mediated by immobilization, in-hospital procedures, and causes of hospitalization like acute disease, trauma/surgery and central venous catheters. Importantly, due to temporal evolution and variable health record documentation, hospital associated VTE might be challenging to identify. In spite of improved awareness of use medical prophylaxis the last decades, hospital-related VTE rates have not changed significantly, indicating that risk assessment in hospitals, as well as the duration of thromboprophylaxis, may still be improved.[103] *Hospitalization or residency in nursing homes* are important risk factor for VTE. Compared to community residents, hospitalized residents have >100-fold increased incidence of VTE.[73,105] *Major surgery* is associated with a 4 to 22-fold increased VTE risk, with major orthopedic surgery, neurosurgery, and major cancer surgery among the high-risk procedures.[106,107] With insufficient thromboprophylaxis, the absolute risk of VTE has been observed to be 50% increased in *major trauma* patients.[108] Other *acute medical conditions,* like

myocardial infarction (MI), heart failure, ischemic stroke, respiratory disease and infections, are additionally considered risk factors for VTE.[109]

Immobilization is a well-known risk factor for VTE and it accompanies many medical conditions such as acute medical illness, surgery, infection, or major trauma.[105,107,110] Most circumstances characterized by immobilization (e.g., long-haul travel and paralysis) are considered VTE risk factors, and patients with plaster casts, neurologic paralysis, or confinement to bed for at least two to three days have been found to have a 2-fold increased risk of VTE.[110-113] Venous stasis may explain the increased VTE risk related to immobilization and inactivity.

Regular *physical activity* is found to be associated with decreased VTE risk in a non-dose response manner.[114-121] Compared to moderate physical activity, inactivity and sedentary lifestyle have been associated with a 20-40% increased risk of VTE[119,120,122] and a 2-fold higher risk of PE.[123] However, the association between physical activity and VTE is debated, and the absence of definitions of physical activities and standardized assessment methods obscures the understanding of existing findings.[124] Some studies have shown that strenuous physical activity may be associated with an increased risk of VTE, especially in the elderly[116,125-127] while others suggest that physical activity does not influence the VTE risk in either direction.[123,127-130]

Pregnancy-related VTE is a leading cause of maternal morbidity and mortality, however the absolute VTE risk is low (approximately 1.2 per 1000 deliveries).[131] Pregnant women have been shown to have a 4 to 5-fold higher risk of VTE with the highest risk during the postpartum period.[132,133] The association between pregnancy and VTE might be caused by procoagulant changes of the hemostatic system initiated to reduce the risk of major bleeding during labor.[8,134]

Several *drugs* may cause an onset of prothrombotic states or activated pathways leading to thrombosis, most likely in combination with another triggering or concomitant factor.[135] Antipsychotics,[136] antidepressants,[137] glucocorticoids,[138,139] diuretics, oral corticosteroids, and anti-inflammatory drugs (NSAIDs) have all been associated with increased VTE risk.[136,140,141] However, the prevalence of thrombosis varies for the different drugs. Women using postmenopausal hormone therapy (HRT) have a 2 to 4-fold higher VTE risk compared to non-

users,[140] while users of combined oral contraceptives (COC) have a 3 to 4-fold higher VTE risk compared with non-users, dependent on the progestogen and the dose of ethinylestradiol in the COC.[142,143] The VTE risk is mostly increased during the first months of use of both HRT and COC.[143,144 140]

VTE and SES

Few studies have assessed the association between individual SES indicators and VTE and the results are ambiguous. A cohort study of 6,958 Swedish men aged 45-55 years with a follow-up of 28 years, reported that self-reported high socioeconomic occupational status measured at VTE/index date was associated with reduced PE -risk. The study reported no association with DVT.[145] A cohort study from the Copenhagen City Health study of 18,954 Danes >20 years of age, with 19.5 years as median follow-up of, reported that compared to low income, medium household income was associated with a lower risk of VTE. The study did not find any associations between VTE risk and education.[130] A Swedish cohort of adults >20 years of with a follow-up of 17 years reported a lower risk of VTE in with high-status occupations and high educational level assessed at index date. The study did not report any associations between VTE risk and income.[146] A cohort study of Swedes >25 years of age at inclusion, followed for 13 years, reported an increased VTE risk with single marital status, low household income, and low education measured at VTE/index date.[147] However, the analyses did not include adjustments for comorbidities.[147]

Existing literature indicates that different socioeconomic indicators play a role in the VTE risk, comparable to that for other cardiovascular diseases, however, the SES indicators found to be associated with VTE vary within and between studies. This could be due to differences the study populations (age and sex), study designs, time between SES and VTE assessments, and methods for monitoring SES indicators. Thus, there is a need to further assess the strength of the association between different SES indicators and VTE. The discrepancies in existing findings could also be attributed to inconsistent comorbidity adjustments. Low SES has previously been reported to be associated with VTE-related comorbidities such as cancer and cardiovascular diseases.[24,148-150] However, it remains to be discovered to what extent comorbid conditions might explain or mediate the reported associations between SES and VTE.

Complications of VTE

The risk of a *recurrent VTE* is highest the first 6 to 12 months after a VTE.[1] Approximately 7-13% of all VTE patients experience a recurrence within the first year and 30% within ten years.[44,46,52] The risk of recurrence is highest in VTEs provoked by persistent risk factors,[151] and men have a 2 to 4-fold higher recurrence rate than women.[1,52,53,152] As a recurrent VTE often presents at the same site as the first thrombus, it aggravates the clinically severe consequences of VTE and increases the risk of long-term complications.[44,46,54,55]

Around 25-50% of all DVT patients develop the *post thrombotic syndrome* (PTS) 1-2 years after the initial VTE.[54] PTS is a chronic complication of DVT caused by damaged venous valves, leading to venous hypertension, structural changes in the vessel wall, and impaired venous return.[153] PTS risk factors include obesity, advanced age, inadequate anticoagulation, proximal DVT, and varicose veins.[154] PTS is characterized by chronic pain, cramps, itching, and swelling of the affected limb with 5-10% of PTS patients suffering from severe open venous leg ulcers.[54,55] PTS symptoms usually worsen with standing and walking, thereby limiting daily activities and causing impaired quality of life (QoL) and reduced health-related quality of life (HRQoL).[54,55,155-159]

More recent studies investigating long-term complications of PE have reported that almost 50% of PE patients are affected by *post-PE syndrome*. Patients suffering from post-PE syndrome may experience functional limitations of various degrees after the initial PE,[56-60,160-162] with signs and symptoms that varies from persistent dyspnea to life-threating chronic thromboembolic pulmonary hypertension (CTEPH).[57-60] The post-PE syndrome is likely caused by changes in the pulmonary artery flow, pulmonary gas exchange, or unresolved thrombi and right ventricular dysfunction after acute PE.[56-60,161,162] Its risk-factors include male sex, young age, high BMI, and smoking.[163] Symptoms of CTEPH include increased pulmonary vascular resistance following fibrotic transformation of the non-resolved thrombus and pulmonary artery.[164] CTEPH risk factors include cancer, chronic inflammatory states, previous splenectomy, infected ventriculoarterial shunts, thyroid replacement therapy, indwelling venous catheters, and leads.[153] Even though CTEPH is rare, affecting only 0.5-4% of PE patients within two years after a PE diagnosis, it is a severe complication causing a high degree of suffering in VTE patients due to exertional dyspnea and cardiac impairment.[164,165]

VTE might lead to functional impairment and poor health.[59,158,166,167] The long-term effects on QoL and HRQoL after VTE are therefore severe, especially in PE patients where limited ability to do exercise, dyspnea, and reduced functional capacity persist for many years after the VTE.[167-170] In addition, long-term anticoagulant treatment is known to negatively impact lifestyle due to the increased risk of bleeding.[171] A meta-analysis assessing patient-reported HRQoL beyond one year after an episode of PE or DVT found that while DVT patients reported a generic and disease-specific QoL comparable to that of the general population, patients with PE reported poorer physical health when compared to population norms.[172] For patients who developed CTEPH or PTS, both generic and disease-specific QoL outcomes were substantially worse than population norms.[172]

VTE and disability pension

VTE is common among the working age population.[1,5] With an ageing workforce, more individuals will have health problems that might hinder their ability to retain an employment.[173,174] A VTE is therefore likely to impact not only morbidity, but also the ability to work, which often may persist for longer time periods or even become a permanent condition. Effective treatments may enable VTE patients to continue working afterwards,[1,5] but the risk of losing a substantial number of years in paid employment following a VTE remains high.[2,37] Even though VTE has been demonstrated to be an important contributor to lost disability-adjusted life-years worldwide,[175] studies on the work-related consequences for VTE patients are limited.

Findings from two European multi-centers show that around 30% of DVT and PE patients had not returned to work one year after diagnosis.[176,177] These numbers are in line with rates for return to work within 12 months for diseases such as stroke and myocardial infarction, but the studies did not adjust for comorbidities and follow-up stopped 12 months after the DVT/PE.[176,177] Further, differences in retirement age, sickness and disability benefits, and prevalence of early retirement in the participating countries were factors that, in addition to comorbid diseases, probably affected the work loss following both DVT and PE.[176] Also, it is not known if the patients returned to work after one year, or if they were permanently unable to work. Of the DVT patients returning to work after 12 months, 17.6% had reduced working hours, which might suggest that they still experienced limited work ability.[176]

A Norwegian population-based study found that compared to the general population, VTE patients had a 26% increased risk of subsequent disability pension, after adjustments for VTE-related comorbidities.[61] Further adjustments for self-reported health measured on average six years prior to the VTE, attenuated the risk to 17%.[61] In a subgroup analysis, only DVT was associated with disability and the authors argued that the low number of PE patients (n=15) versus DVT patients (n=38), combined with the fact that CTEPH and PTS are rare after PE, could explain the lack of association between PE and disability.[61]

Even though these studies point towards VTE as a risk factor for premature exit from the labor market, the findings are limited and inconsistent. To validate existing findings and to promote further research on lost working ability and disability after a VTE, larger nationwide cohort studies taking comorbidities into account are needed.

VTE and depression

Depression is a mental health condition with symptoms ranging in both severity and duration. Depression is characterized by loss of interest or pleasure in activities, poor concentration, feelings of hopelessness or low self-worth, disrupted sleep, changes in appetite or weight, and tiredness or having no energy. Over 300 million people worldwide suffer from depression with prevalence rates peaking in older adulthood (>7.5% of women and >5.5% of men aged 55-74 years), and depression accounted for 7.5% of all years lived with disability in 2015 as reported by the WHO.[178] Depression is a frequent complication in patients with chronic diseases and there is consistent evidence of individuals with cardiovascular diseases (CVD) having a 10-40% increased risk of depression compared to individuals without CVD.[179-186] Depression after a VTE may result in non-adherence to medication and treatment, functional impairment, disability, and increased risk of morbidity and mortality.[187] However, research on the psychological complications of VTE is scarce.

Numerous reviews and meta-analysis have assessed the prevalence of depression following CVD.[180-186] In a meta-analysis of 22 prospective studies (6,367 patients), post-MI depression yielded a 2 to 2.5-fold increased risk of impaired cardiovascular outcome. [188] In a review of 8 studies (10,785 patients) major depression was present in 19.8% of acute MI patients, of whom 31.1% had clinically significant depression.[182] Coronary heart disease (CHD) patients had an

estimated 15 to 18% prevalence of depression,[186] while the prevalence of depression after stroke was estimated to be 20-65%,[189] with one meta-analysis (20,293 patients) reporting a depression prevalence of 29% in 43 studies[190] and another (25,488 patients) reporting a prevalence of 31% in 61 prospective studies.[183]

There is evidence of depression and antidepressant use being associated with an increased risk of VTE.[137] The limited studies to date on mental health after VTE indicate that VTE is associated with symptoms of fatigue, psychological or post-traumatic stress, and poor health, particularly after a PE.[191-205] Nevertheless, these studies are limited by qualitative research with interviews or self-reported data measured in the months following a VTE diagnosis, small sample sizes, inclusion of selected patients, and limited control for confounding factors such as comorbidities, SES, and lifestyle factors. Consequently, confounding factors, causal order, and time between VTE and onset of depression remain unknown.

Aims of the thesis

The specific aims of the thesis were:

I. To study the association between educational level, income level, and employment status, assessed individually and in a composite score, and incident VTE in a population-based case-control study from the general Danish population of working age.

II. To assess the association between VTE and subsequent permanent disability pension, and to investigate if this association could be explained by comorbid conditions such as cancer and arterial cardiovascular disease, in a nationwide Danish population-based cohort of working age.

III. To assess the interaction between incident VTE and SES on the risk of subsequent disability pension in a Danish nationwide population-based cohort of working age.

IV. To explore the association between VTE and the risk of future depression in a Danish nationwide population-based cohort.

Methods

Setting and data sources

Similar to the other Nordic countries, Denmark has a government–funded, tax-supported welfare system for the entire Danish population, ensuring free and equal access to education and medical care for all residents.[31] The Danish Civil Registration System (CRS) assigns all Danish residents a unique 10-digit personal identifier (CPR number) upon birth or immigration, This number is used in all Danish registries enabling record linkage to up-to-date individual-level data across all Danish government-maintained nationwide registries, with almost complete long-term follow-up.[31] In this thesis, we collected data from the Danish longitudinal nationwide medical and administrative databases described below.

Administrative and medical databases

The CRS is a nationwide register containing personal information on Danish residents. The CRS records information on migration and vital status for the entire Danish population from 1968 onwards, with daily updates.[206] The CRS contains information on date of birth and death, sex, place of residence, civil status, migration, and emigration status.[206] We collected information on age and sex.

The Danish National Patient Registry (DNPR) provides nationwide longitudinal registration of detailed administrative and clinical data. The DNPR contains data on all hospital discharges from Danish hospitals, with recorded information on hospitalizations from 1977 onwards and outpatient clinic and emergency room contacts from 1995 onwards. For each patient contact, a primary and an optional secondary discharge diagnosis are registered according to the International Classification of Diseases (ICD) eight revision (ICD-8) from 1977 to 1993 and the tenth revision (ICD-10) from 1994 onwards.[207]

We used the DNPR to identify all inpatients and outpatients with a first-time primary or secondary diagnosis of DVT, PE, and depression. We also retrieved information on the following comorbidities: Obesity, cancer, coronary heart disease (including atrial fibrillation, MI, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases (besides anxiety or depression),

surgery and trauma, alcohol and drug-related disorders, dementia, and conditions in the Charlson Comorbidity Index (CCI) not listed above. Based on ICD codes, the CCI combines coexisting medical conditions with the aim of establishing a single continuous variable that merges relevant information on the confounding properties of all variables. Each comorbidity category contains an associated weight based on the adjusted risk of mortality or resource consumption. The sum of the weights yields a single comorbidity score.[208] With a higher score, the likelihood that the predicted outcome will result in mortality, or augmented use of resources, increases.[208]

Danish Psychiatric Central Research Register (DPCRR) includes admission and discharge dates and diagnoses of all psychiatric admissions and outpatient contacts at psychiatric hospitals in Denmark since 1969. From 1995 onwards, the DPCRR also includes information on outpatient contacts and emergency department visits. Diagnostic information is based on the clinical diagnosis assigned by the attending physician at the end of the hospitalization or outpatient contact.[209] We used the DPCRR to identify depression diagnoses, as well as diagnoses of comorbidities.

The Danish National Prescription Registry has recorded all dispensed prescriptions for reimbursed drugs at Danish community pharmacies since 1995. The registry contains data on drug names and types according to the Anatomical Therapeutical Chemical (ATC) classification system.[210] We used the registry to identify redeemed prescriptions of antidepressants.

The Integrated Database for Labor Market Research (IDA) contains information on income, employment status, workplace, and employers of the entire Danish population on a yearly basis since 1980.[211] We used the registry to retrieve information on disability pension, income, and employment status.

The Educational Attainment Register contains individual data on highest completed education of Danish residents from 1974 onwards. We used the registry to identify information on educational level.

Study designs and source population

In Study I, we conducted a population-based case-control study to investigate the association between SES and VTE risk. We used the DNPR to select 51,350 individuals 25-65 years of age that had a first-time primary or secondary discharge diagnosis of PE or DVT between January 1, 1995 and December 31, 2016. If a patient was diagnosed with PE and DVT at the same time, we classified the event as PE because of higher mortality rates in PE. We classified the VTE date as the first hospital admission/outpatient clinic visit date. VTEs registered only in emergency room departments were excluded because they often are working diagnoses that yield a high probability of clinical misclassification. Individuals <25 years of age were not included. The reason for this was that they would have a high probability of being under education and not have a stable income or employment. Individuals ≥65 years of age were not included because they would receive an old age pension instead of a work-related income due to retirement from work-life. Five controls from the general working age population (n= 256,750) was individually matched by year of birth, sex, and calendar year of VTE diagnosis, with replacement, using the CRS.The hospital admission date for the VTE patient was used as the index date for the matched controls. Controls could not have been hospitalized for VTE prior to their index date. As cases and controls were drawn from an established prospective cohort based on nationwide registries we able to include also fatal cases of VTE.

In Studies II-IV, we used a cohort design. The source population, as well as the identification and classification of VTE was the same as in Study I. Due to the work-related aspect of the outcomes of disability pension and SES, the study population in Studies I-III included individuals of working age. In Study II, we included individuals aged 25-66 years, and in Studies I and III we included individuals aged 25-65 years. The upper age limit varied slightly due to different definitions of the age of retirement from work. As the outcome of depression also is prevalent among the elderly, we included individuals aged 25-80 years in Study IV. We excluded individuals with a history of disability pension in Studies II and III and individuals with a diagnosis of depression or a redeemed prescription of antidepressants before the VTE in Study IV.

The study designs will be further discussed in the section on methodological considerations.

Exposure measurements

Socioeconomic status

In Studies I and III, SES was defined as an exposure variable, while it was a covariate in Studies II and IV. In Study I, SES was measured one and five years prior to the VTE/index date and defined both as the individual indicators educational level, annual income, and employment status and as a SES score combining the three indicators. In Studies II and III, SES was retrieved one year prior to the VTE/index date and measured as a SES score. In Study IV, SES was retrieved one year prior to the VTE/index date and measured as educational level and annual income.

Educational level (i.e., low, medium, high) was distributed in age-specific groups based on the educational distribution in each group. We applied different categorizations for high, medium, and low educational level for different age groups to account for the fact that low and high levels of education should be weighted differently for persons born in, e.g., 1940 versus 1970.

To take into account salary changes over calendar time and to prevent the impact of inflation, annual income was calculated for each index year based on the previous year in Study II (*e.g.*, income for 1999 was calculated based on the income of exposed and unexposed persons with a VTE/index date in 1998). In Studies I, III and IV we re-calculated annual income values using a gross domestic product (GDP) deflator downloaded from the World Banks homepage (www.worldbank.org). After recalculation or deflation, we calculated income in quartiles based on the VTE cases and controls in Study I and based on exposed/non–exposed individuals in Studies II-IV, and combined the two middle quartiles to get three income categories (*i.e.*, high, medium, and low).

We measured employment status as “employed,” “unemployed,” or “outside the workforce,” and characterized the employment status as low (unemployed in Studies II and III and unemployed or receiving disability pension in Study I), medium (outside the workforce), and high (employed). “Outside the workforce” included persons in an educational program, persons in early retirement, in addition to persons receiving other types of state benefits.

In Studies I-III, each of the indicators educational level, income, and employment status were divided into categories and assigned a score of high (score of 3), medium (score of 2), or low (score of 1). These scores were then combined into a composite SES score ranging from 3 to 9 with categories of high (scores of 8 and 9), medium (scores of 5 to 7), and low (scores of 3 and 4). (Figure 3).

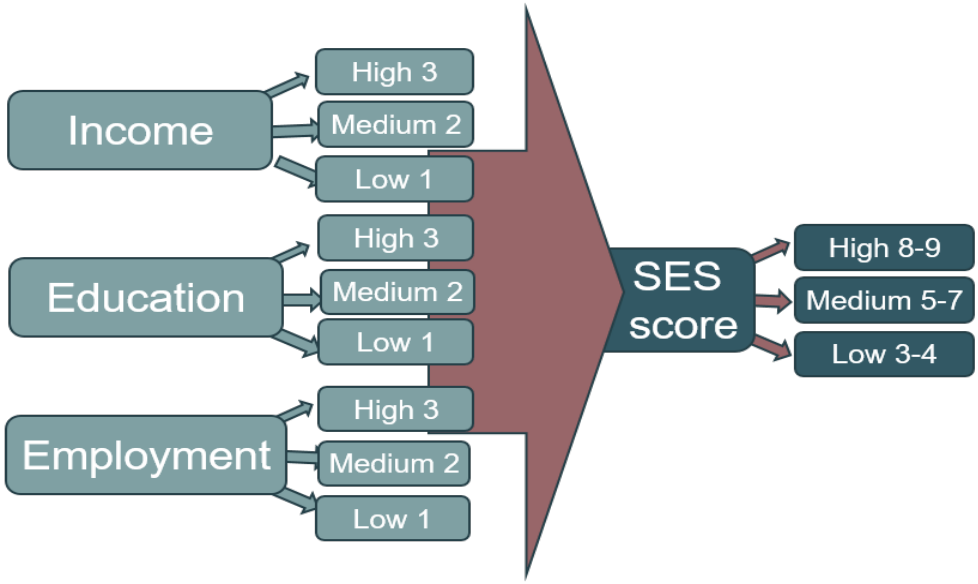


Figure 3. Illustration of the Socioeconomic status score

VTE

VTE was defined as an exposure in Studies II-IV, while it was the main outcome in Study I. We identified all inpatients and outpatients (25-65 years of age in Studies I and III, 25-66 years of age in Study II, and 25-80 years of age in Study IV) with a first primary or secondary diagnosis of DVT or PE. We classified VTE as either PE or DVT and categorized a simultaneous PE and DVT diagnosis as PE due to its higher mortality rate.[46] Provoked VTE was defined as a VTE with a preexisting cancer diagnosis before or on the index date or a fracture, trauma, surgery and/or a pregnancy within 90 days prior to VTE diagnosis. Unprovoked VTE was defined as a VTE without the presence of any of these factors.[151]

Outcome measurements

Disability pension

Disability pension was the main outcome in Studies II and III. We measured receipt of disability pension annually at the end of November and defined the disability pension date as January 1

of that year. Individuals living in Denmark for at least three years since their 15th birthday and holding a permanent residence are qualified for a disability pension until public retirement age.[212] To be entitled a disability pension, your ability to work must have been considerably and lastingly reduced to such a degree that you will never be able to provide for yourself through regular or flexible employment.[212]

Depression

The main outcome in Study IV was depression defined as any hospital diagnosis of depression, or a minimum of one redeemed prescription of an antidepressant. Depression diagnoses from all inpatient admissions, outpatient contacts, and visits to emergency care units at a Danish hospital between January 1, 1996 and December 31, 2016 were retrieved from the DNPR and the DCPRR. We excluded referral diagnoses and temporal diagnoses as they were not necessarily confirmed. Information on redeemed prescriptions for antidepressants were collected from the Danish Prescription Registry.

Covariates

To characterize the study population and to adjust for confounding, we retrieved information on covariates on the index date. We considered age and sex as confounders in all studies. Other confounders were comorbidities diagnosed prior to the VTE/index date. Comorbidities are concomitant diseases an individual might have other than the VTE, but that are not a consequence of the VTE.[213] They may lead to a delayed diagnosis, be confounders of the VTE status and course, and increase morbidity and mortality.[214] We included the following comorbidities: obesity, cancer, coronary heart disease (including atrial fibrillation, MI, and heart failure), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, mental diseases, surgery and trauma three months prior to the VTE/index date, alcohol and drug-related disorders, dementia, and CCI score excluding the listed comorbidities. In Study IV, alcohol and drug-related disorders and co-medication of glucocorticoids used ≤90 days prior to the VTE/index date were added as covariates.

Statistical analyses

Conditional logistic regression analysis (Study I)

Study I was a matched case-control study where we used conditional logistic regression models to compute odds ratios (ORs) with 95% confidence intervals (CIs) to measure the VTE incidence rate ratio. For each VTE case, we used incidence density sampling to select five controls from the general population that were matched birth-year, sex, and calendar year of VTE. Crude and adjusted OR for *a priori*-defined potential confounders in terms of age, sex, obesity, and comorbidities were computed according to individual SES indicators and a composite SES score. In the analyses of individual SES indicators, we also adjusted for SES indicators that could be confounders. Thus, in the analyses where education was as the exposure, we did not adjust for income or employment status. In analyses where employment was the exposure, we adjusted for education. In the analysis where income was the exposure, we adjusted for education and employment status).

We also performed age and sex-stratified analyses, subgroup analyses of DVT and PE, and analyses stratified by CCI score. Additionally, we performed sensitivity analyses measuring the SES five years prior to the VTE/index date. The potential nonlinearity in the associations was tested against a confounder-adjusted restricted cubic spline with a pre-specified list of five knots.

Cox proportional hazard regression analysis (Studies II-IV)

Studies II-IV were cohort studies. The outcomes disability pension (Studies II and III) and depression (Study IV) were assessed using Cox proportional hazard regression models comparing individuals with VTE with the general population. Crude and adjusted hazard ratios (HRs) with 95% CIs were computed in the overall cohorts and within strata of age and sex, PE, DVT, unprovoked and provoked VTE, and CCI score. In the multivariable analyses, we adjusted for age, sex, obesity and SES (in Studies II and IV). We also assessed the impact of comorbid conditions, such as cancer and arterial cardiovascular diseases by adjusting for the following comorbidities: cancer, coronary heart disease (including atrial fibrillation, MI, and heart failure), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, mental

diseases, surgery and trauma three months prior to the VTE/index date, alcohol and drug-related disorders, dementia, and CCI score excluding the listed comorbidities.

The proportional hazards assumption was evaluated using log-log plots and found to be not violated. To test the robustness of our estimates in Study IV, we performed several sensitivity analyses: We limited the analyses to include only a depression diagnosis either from the DNPR or the DPCRR; analyses with a follow-up restricted to 0-1 year and 0-10 years after the VTE/index date to detect any temporal effect of the timing of the depression diagnosis; and finally, we repeated the analysis excluding persons with alcohol and drug-related disorders or dementia, as depression can be difficult to assess in individuals with these conditions.

Cumulative incidence analysis (Studies II-IV)

In studies II-IV, mortality rates were likely to differ between those with and those without VTE. As a result, outcome rates could potentially be overestimated because of competing risk of death. Competing risk is an event (i.e., death) whose occurrence precludes the occurrence of the VTE.[213] A competing risk prevents the observation of an event of interest or alters the chance that this event might happen.[215] To overcome this problem, we calculated the cumulative incidence of disability pension (Studies II and III) and depression (Study IV), treating death as a competing risk. We estimated and visualized absolute risks according to VTE/no VTE, sex, and age groups by cumulative incidence functions treating death as a competing event, as proposed by Fine and Gray.[216]

Interaction analysis (Study III)

In Study III, interaction between SES and VTE on disability pension was assessed by interaction contrast (IC) (difference in IR differences.) IC shows the deficit, or excess disability pension IR below, or beyond the baseline IR among individuals with high SES and no VTE, the individual effect of SES on the disability pension IR, and the effect of VTE on the disability pension IR. Complete case analysis were perfomed and we computed IRs per 1,000 person-years with 95% CIs for disability pension using individuals with no VTE and high SES as the reference category. We divided the IC with the disability pension IR among individuals with low SES and VTE to find the attributable proportion of the disability pension IR that could be explained by interaction.

In all Studies, the statistical analyses were performed using the Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC).

Ethical considerations

According to Danish legislation, registry-based studies conducted in Denmark do not require approval from an ethics committee or patient information. The project was approved by the Danish Data Protection Agency, record number 2016-051-000001-811.

Main results

Socioeconomic status and risk of incident VTE (Study I)

Even though VTE is a major cause of morbidity and mortality and SES has been demonstrated to impact human health and health behavior, research on the relationship between SES and VTE is scarce. The aim of this study was therefore to investigate the association between SES and VTE. We identified 51,350 persons aged 25-65 years with incident VTE during 1995 through 2016 through Danish medical and administrative registries. For each case, five controls matched on age, sex, and index year were selected from the general Danish population by density sampling (n=256,750). We computed ORs with 95% CIs for VTE according to education, income, employment status, and a composite SES score using conditional logistic regression.

We found a lower OR of VTE among individuals with a high education (OR 0.74; 95% CI 0.71-0.77), a high income (OR 0.70; 95% CI 0.68-0.72), and a high employment status (OR 0.66; 95% CI 0.64-0.68), compared to individuals with low levels of the respective indicator, in analyses adjusted for age, sex, and comorbidities. Residual increments in ORs remained for education, income and employment status even after additional adjustments for the confounding SES indicators. (Figure 4).

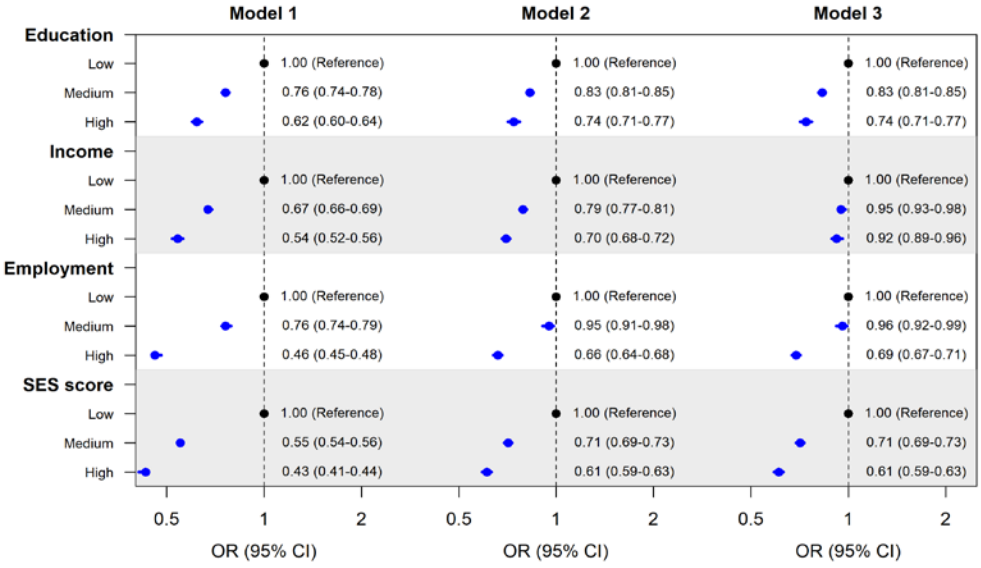


Figure 4. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for venous thromboembolism (VTE), according to education, income, employment status, and SES score.
Model 1: Crude model controlled for matching variables by study design.

Model 2: Adjusted for obesity, cancer, coronary heart disease (including atrial fibrillation and heart failure), diabetes, stroke, COPD, acute kidney failure, chronic kidney disease, mental diseases, surgery three months prior to 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.*
Figure from Jørgensen H, et al. Socioeconomic status and risk of incident venous thromboembolism. 2021. Appendix I.

The SES score was also associated with a lower OR for VTE. Compared to a low SES score, those a medium SES score (60% of the controls) yielded an OR of VTE of 0.71 (95% CI 0.69-0.73), while a high SES score (24% of the controls) yielded an OR for VTE of 0.61 (95% CI 0.59-0.63), compared to a low SES score (13% of the controls) after adjustments for potential confounders. (Figure 4). The ORs associated with high levels of the individual SES indicators, as well as high levels of the composite SES score, were lower in DVT compared to PE, and lower in men in the two youngest age groups (25-34 years and 35-44 years) and in women in the two oldest age groups (45-54 years and 55-65 years) when compared to low levels.

Cubic spline regression models showed that an annual income of over 600,000 DKK was protective against VTE. According to the OECD, the 2016 average income in Denmark was approximately 355,000 DKK. Further, an educational level above tertiary education yielded a reduced risk of VTE for the age group 25-44 years. A clear association between increased VTE risk and below average SES scores was also observed. In sensitivity analyses with SES indicators measured five years prior to the VTE, the risk estimates remained similar to that observed in the main analysis.

In conclusion, our findings suggest that low socioeconomic status is a risk factor for VTE.

Risk of a permanent work-related disability pension after incident VTE in Denmark: A population-based cohort study (Study II)

Long-term complications of VTE are known to hamper functional activities and impair QoL. However, it remains unclear whether a VTE increases the risk of permanent exclusion from the labor market. The aim of this study was to investigate the association between VTE and subsequent disability pension. We identified 43,769 individuals aged 25-66 years with incident VTE during 1995 through 2016 and an age, sex- and calendar-year matched comparison cohort (n= 218,845) from the general population from Danish medical and administrative registries.

We calculated Hazard ratios (HRs) with 95% CI for disability pension and stratified them by sex and age groups.

A disability pension was granted to 4,415 individuals with VTE and 9,237 comparison cohort members during a median overall follow-up time of 4.9 years. Individuals with VTE had a disability pension IR of 17.8 (95% CI: 17.3-18.3) compared to 6.2 (95% CI: 6.0-6.3) in the comparison cohort per 1,000 person-years at risk, yielding an absolute rate difference of 11.6 events. Individuals with VTE had a 3-fold (HR 3.0, 95% CI: 2.8-3.1) higher risk of receiving disability pension compared to the general population. The HRs attenuated (HR 2.3, 95% CI: 2.2-2.4) after adjustments for SES, obesity, and comorbidities such as cancer and cardiovascular diseases. Compared to the general population, HRs of disability pension was slightly lower in women than in men women (HR 2.1, 95% CI: 2.0-2.3 versus HR 2.5, 95% CI: 2.3-2.6) and in patients with PE than in those with DVT (HR 2.6, 95% CI: 2.4-2.8 versus HR 2.2, 95% CI: 2.0-2.3)

In conclusion, Individuals with VTE had an increased risk of disability pension compared to the general population even after adjusting for comorbidities.

The interaction between VTE and socioeconomic status on the risk of disability pension (Study III)

In Study II, we found that VTE was associated with increased risk of disability pension compared to the general population, however, it remains unknown how SES impacts the risk of disability pension after a VTE. Therefore, we aimed to assess whether incident VTE and SES interact to increase the risk of subsequent disability pension.

We used Danish medical and administrative databases to create a cohort of 41,781 individuals 25-65 years of age with incident VTE from 1995 through 2016 and a age, sex, and calendar year matched comparison cohort (n=208,905) from the general population. We computed IRs as the number of disability pensions per 1,000 person-years at risk. We calculated interaction on an additive scale was by IC between VTE and levels of SES. Absolute risks and HRs were also computed.

Disability pension was granted to 4,203 (10.1%) individuals with VTE and 8,637 (4.1%) comparison cohort members. The median follow-up was 4.4 years in the VTE cohort compared to 6.0 years in the comparison cohort. Among individuals with high SES, the IR of disability pension per 1,000 person-years at risk in the VTE cohort was 5.4 (95% CI: 4.8-6.1) compared to 1.6 (95% CI: 1.5-1.7) in the comparison cohort (IR difference of 3.8). In individuals with low SES, the IR of disability pension per 1,000 person-years at risk was 55.1 (95% CI: 52.1-58.1) in the VTE cohort compared to 26.1 (95% CI: 25.1-27.1) in the comparison cohort (IR difference of 24.5). An IC of 25.1 (95% CI: 21.9-28.4) in individuals with VTE and low SES, showed that 45.6% of the total disability pension IR was due to an interaction between VTE and SES. (Figure 5).

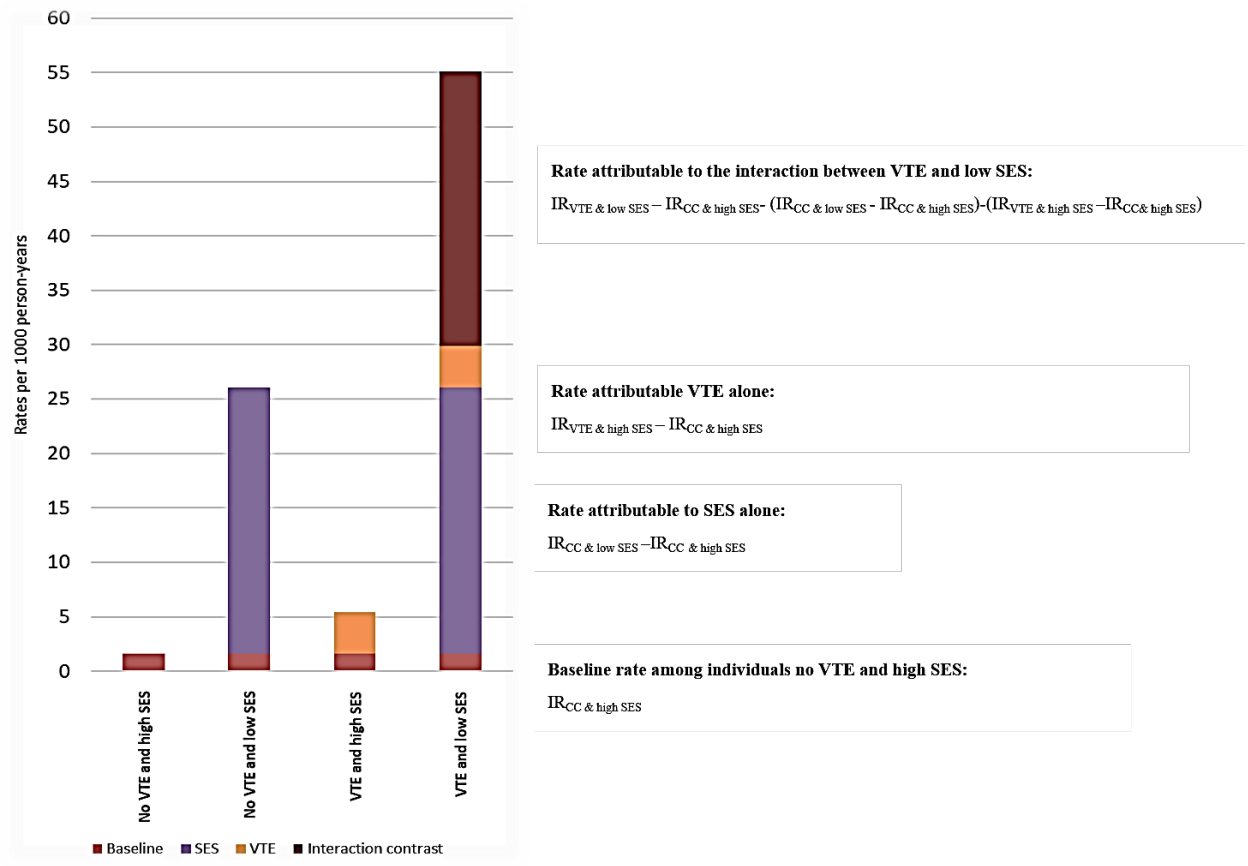


Figure 5. Incidence rates per 1,000 person-years at risk of disability pension according to combined categories of socioeconomic status score and venous thromboembolism indicating the proportion of the disability pension incidence attributable to socioeconomic status, venous thromboembolism, and their interaction. Figure from Jørgensen H, et al. The Interaction between Venous Thromboembolism and Socioeconomic Status on the Risk of Disability Pension. 2021. Appendix III.

The attributable proportion explained by interaction between DVT and low SES was 47.8% while it was 38.8% for PE and low SES. When stratifying on CCI score, the interaction for those with a CCI score of 0 agreed with the main analysis, while it was somewhat divergent for those with a CCI score of ≥1.

In competing risk by death analysis, the cumulative incidence of disability pension three years following the VTE was 18.7% (95% CI: 17.6-19.9%) in individuals with VTE and low SES. Six years following the VTE it was 25.6% (95% CI: 24.2-26.9%), and 12 years following the VTE it was 35.0% (95% CI: 33.3-36.8%). VTE and low SES was associated with an HR of 18.8 (, 95% CI: 17.0-20.8) of disability pension, compared to no VTE and high SES.

In conclusion, interaction between SES and VTE increased the risk of disability pension after VTE beyond their independent effects.

VTE and risk of depression: A Danish Population-Based Cohort Study (Study IV)

VTE as well as depression are prevalent causes of disability and disease burden worldwide, but evidence on psychological consequences of VTE is lacking. We aimed to explore the association between VTE and future depression. We used Danish administrative and health registries to establish a cohort of 64,596 individuals aged 25-80 years with incident VTE during 1996 through 2016 and a comparison cohort (n=2,322,999) randomly selected from the general population and individually matched on age, sex, and calendar year of VTE diagnosis. Depression was defined as any diagnosis of depression, or ≥1 prescription of an antidepressant. IRs and HRs with 95% CIs for depression were computed and adjusted for socioeconomic variables and comorbidities. Absolute risks were estimated and visualized by cumulative incidence functions treating death as a competing event.

Figure 6.1

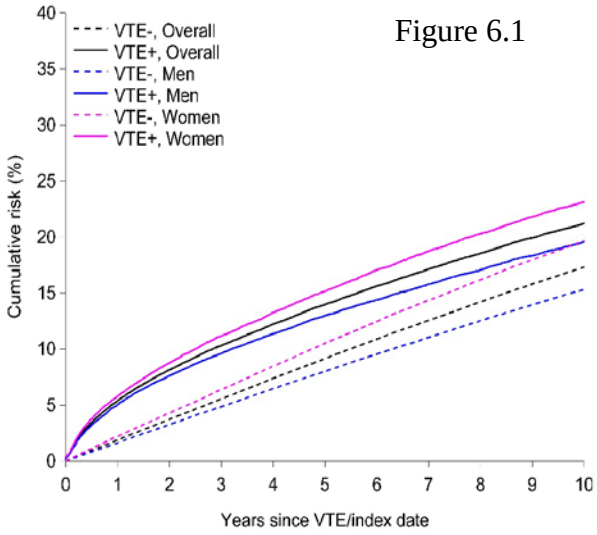


Figure 6.1 Cumulative incidence (%) of subsequent depression in persons with (VTE+) and without (VTE-) venous thromboembolism taking the competing risk of death into account. From Jørgensen H, et al. Venous Thromboembolism and risk of depression. Draft. Appendix IV.

Figure 6.2

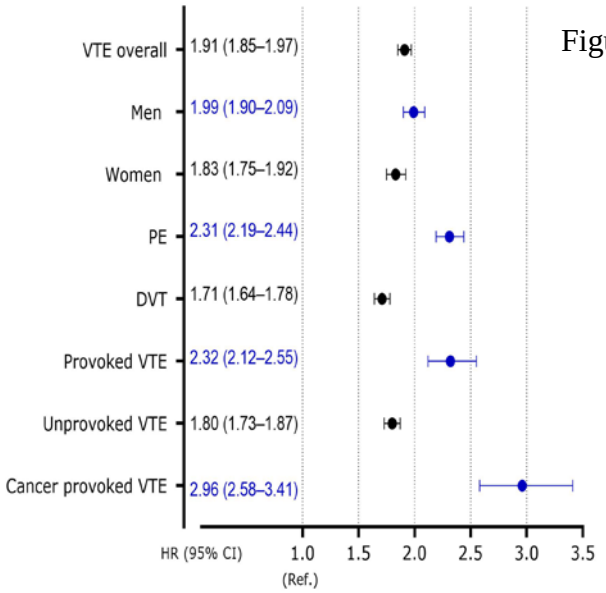


Figure 6.2 Forest plot of adjusted Hazard Ratios (HRs) of subsequent depression in persons with and without venous thromboembolism.
HRs adjusted for socioeconomic status (education and income), obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases (other than depression), alcohol and drug related disorders, dementia, surgery and trauma three months prior to the VTE/index date, Charlson Comorbidity Index score (CCI) excluding the comorbidities listed above, and co-medication. From Jørgensen H, et al. Venous Thromboembolism and risk of depression. Draft. Appendix IV.

After three years of follow up, we observed depression in 6,225 individuals after VTE and in 316,636 comparison cohort members (IRs = 44.4 and 19.4 per 1,000 person-years, respectively). Within three years after the VTE/index date, the absolute risk of depression in the VTE cohort was 10.3% (95% CI 10.1%-10.6%) while it was 5.6% (95% CI 5.5%-5.6%) in the comparison cohort, equivalent to 4.7 excess depression cases per 100 individuals with VTE (Figure 6.1) VTE was associated with a HR of 2.35 (95% CI 2.28-2.43) of depression, compared to the general population. After adjusting for SES and comorbidities such as cancer and cardiovascular diseases, the risk estimate attenuated to a HR of 1.91 (95% CI: 1.85-1.97) in individuals with VTE compared to the general population (Figure 6.2).

In conclusion, VTE was associated with an increased risk of depression compared to the general population irrespective of comorbidities.

Main conclusions

Socioeconomic status and risk of incident VTE (Study I)

We found that low socioeconomic status was a risk factor for VTE. The odds of having high levels of the composite SES score, as well as high levels of education, income and employment was 30-40% decreased in VTE patients compared to controls, even after adjustment for comorbid conditions. When we additionally adjusted for confounding SES indicators, we observed that each indicator had an independent effect on the odds of VTE. A high SES score was associated with a lower odds of VTE than high levels of the individual SES indicators.

Risk of a permanent work-related disability pension after incident VTE in Denmark: A population-based cohort study (Study II)

We observed that compared to the general population, individuals with VTE had a 2 to 3-fold increased risk of a subsequent disability pension. The association was strongest in patients with PE and among the youngest patients. The risk estimates remained increased after adjustments for comorbidities and competing risk by death, suggesting that the relationship could not be explained by the presence of VTE-related comorbidities, or by an increased mortality in individuals with VTE.

The interaction between VTE and socioeconomic status on the risk of disability pension (Study III)

We found that VTE and low SES were individually associated with an increased risk of disability pension, and that 45.6% of the disability pension IR due to VTE and low SES could be attributed to interaction. Men and women within all included age-groups, as well as and subtypes of VTE had interaction present.

VTE and risk of depression: A Danish Population-Based Cohort Study (Study IV)

We found that VTE was associated with a 1.9 fold increased risk of subsequent compared to the general population, even after adjustments for SES and comorbidities. The risk was particularly high in patients with PE and those with cancer-provoked VTE.

General discussion

Discussion of main results

Socioeconomic status and risk of incident VTE (Study I)

In our study, education, income, and employment status, measured one year prior to the outcome, were all associated with VTE. We also applied a composite SES score and found a lower OR for VTE by high values of the SES score compared to high levels of the individual indicators. Prior to the present thesis, associations were reported between VTE and stress,[145] low income,[130,147] low educational status,[130,146,147,217] low occupational class,[145,146,217] single status,[147] and neighborhood deprivation.[218,219] However, these existing findings were divergent. The indicator(s) found to be associated with VTE varied between studies, and the study populations and time from SES measurement to the VTE were divergent with a maximum follow-up of almost 29 years from SES assessment to VTE.[145]

There are several mechanisms through which SES can lead to an increased risk of VTE.[220] One comprises access to care and includes (i) approachability, meaning your capacity to identify healthcare services and the positive effects using healthcare services have on health; (ii) accommodation and availability, which is physical access to healthcare services; (iii) affordability, which is the financial ability to devote resources and time on healthcare; and (iv) acceptability, which is the socio-cultural aspects that form an individual's view on healthcare.[220] Another mechanism compromises health risk behaviours such as obesity,[147,221,222] physical inactivity,[119,223] and trauma/injury due to occupational risks,[146] where individuals with low SES might have less to gain from healthy behavior and less reason to focus on future possible gains, when making decisions about health behaviors.[220]

Education, income, and employment impact SES in different, but also overlapping, ways. Further, they are all indicators related to the labor market, where education often precedes and influences employment status, which in turn affects income. Education might be indicative of knowledge and skills, while employment might imply social skills and exposure to stress.[22,224] Income on the other hand, might mirror status and access to material resources and services.[22,225] Having lower levels of education or employments with fewer learning possibilities may lead to less understanding of the harms of unhealthy behavior and thereby

lower motivation to embrace healthy behaviors,[220] and psychosocial stress and subsequent increased disease risk might occur secondary to low income and unemployment.[4] A low level of education might also lead to less chances of being employed and reduced flexibility when it comes to occupational opportunities, which again will reduce possibilities to change employment if the current work setting is challenging. In addition, working life might be more tedious as more industrial occupations might include increased exposure to psychological risk and physical hazard through low income, job strain, sedentary or strenuous work.[4]

The optimal lag time between the SES measurement and disease outcomes, as well as the question about whether good health leads to high SES or vice versa,[226] remain subjects of debate. Work-related SES indicators change over time-course in modern Western societies. Life phases such as early adulthood and midlife, transition phases from student to employee or from employee to being retired from work might cause frequent changes in the SES, thus creating spurious associations if SES is measured long before an outcome. We investigated SES among working-age individuals (25-65 years) one and five years before to the VTE event. The relatively short time interval from SES assessment to VTE, combined with a large study population based on the general population and restricted to individuals of working age may explain why we found that all measured SES indicators were robustly associated with VTE risk, compared to other studies.

Biological mechanisms in the observed association between SES and VTE include a relationship between chronic psychosocial stressors, and coagulation and fibrinolysis variables.[145,221,227,228] Further, having a low level of circulating inflammatory and hemostatic markers, and high levels of activated fibrinolysis markers are demonstrated to be more associated with high socioeconomic staus.[227-229] However, existing findings are inconsistent and further evidence is needed to shed light on the possible biological pathways that may explain the associations between SES and VTE.

Socioeconomic status, VTE, and risk of a disability pension (Studies II and III)

In our nation-wide register-based cohort study, we found that individuals with VTE had a 2 to 3-fold higher risk of disability pension compared to the general population. The risk was highest among men and in the youngest age-groups, and PE was associated with an overall higher

relative risk than DVT. Prior to the present thesis, socioeconomic inequalities had been found to be associated with an increased risk of both VTE[130,145-147] and disability pension.[230-232] However, only a few studies have investigated the risk of disability-after VTE.[61,176,177] Previous research included two European multicenter studies reporting that around 30 % of all PE and DVT patients did not return to work within a year after their VTE event.[176,177] Also, a Norwegian cohort study found that VTE patients had a 26% increased risk of receiving a disability pension compared to the general population.[61]

Our observed increased risk of disability after DVT might be explained by the post-thrombotic syndrome (PTS). PTS affects 20-50% of individuals with DVT and leads to swelling, itching pain, cramps, and reduced mobility in the affected limb.[54] For PE, the increased risk might be due to the post-PE syndrome. The post-PE syndrome affects up to 50% of PE patients and ranges from persistent dyspnea to life-threating CTEPH.[57-60,161,166,169,172] The post-PE syndrome has been associated with low QoL and low HRQoL in individuals with PE, [59,166,169,172] especially in individuals with CTEPH,[161,172] and low self-rated QoL and HRQoL have been strongly related to later health consequences, such as sick leave.[233-235] Therefore, individuals with PE might suffer an equal, or higher, disability risk compared to individuals with DVT as a result of the frequency of the post-PE syndrome, and its impact on physical function and QoL.

We found that the interaction between low SES and VTE could account for 45.6% of the disability pension IR. Existing data on joint effects of VTE and SES on the risk of disability pension were lacking. However, two studies reported that there was a combined effect of arterial cardiovascular disease and occupational status on the risk of disability pension.[232,236] Having both cardiovascular disease and low occupational status was associated with a 4.5-fold increased risk of disability pension compared to having a high occupational class and no cardiovascular disease in a cohort of 44,516 survey respondents from the Finnish public sector.[236] A synergy index score of 1.55 indicated a greater than additive effect of the combination of low occupational class and cardiovascular disease.[236] Another Finnish registry-based study including 258,428 individuals of working age reported an IR of disability due to cardiovascular diseases of 3.3 per 1000 person-years in male manual workers aged 35-54 years and an IR of 2.4 in male manual workers aged 55-64 years.[232] The observed IRs were lower in women.[232]

Our findings might be explained by several factors. First, we measured SES in a composite SES score by combining the SES indicators education, income, and employment status. Several studies support the inclusion and measurement of multiple SES indicators as SES is considered innately multidimensional.[225,237] Compared to one individual indicator, a composite SES score can capture this broader aspect of SES and the temporal causation among the different SES indicators. We assessed SES one year prior to the event, thereby we reduced the likelihood of misclassifications and spurious associations due to long follow-up time, which could dilute the findings. The mechanisms by which SES might affect disability are multiple and include elements like access to healthcare, legislation, physical ability, lifestyle, employment options and tasks, as well as the psychosocial work-environment.[28,238] Low education and low income might lead to disability as a result of few working possibilities and little flexibility at work, and low educational levels have been associated with unfavorable working conditions through unfavorable psychosocial and physical work demands.[239,240] Further, low levels of education and income are known to yield fewer working possibilities and less flexibility at work, and factors such as work related stress, less control and decision autonomy are recognized to lead to mental and physical health complications and challenges staying employed.[174,240] As recurrences of VTE, the post-thrombotic syndrome, and the post PE-syndrome often lead to reduced physical functioning after a VTE,[53,159,241] it might be challenging to remain employed in typical blue-collar professions or employments with manual and tedious tasks. Employments requiring a high educational level and associated with a high income, on the other hand, might provide less stress and more flexibility at work, making it more manageable to retain employment despite reduced physical functioning.[174,240]

In agreement with previous studies, we found that women in the general population had an increased IR of disability pension compared to men, likely caused by differences in self-perceived health, the person's family situation, work factors, and educational level.[242-245] In the VTE cohort, however, the IR of disability pension was higher in men than in women, mainly driven by an increased risk in young men. Also, the interaction between low SES and VTE on disability pension was higher in men, and especially in young men. Our findings support previous data reporting socioeconomic factors as strong contributing factors to disability in the young population.[230,246,247] Previous studies also indicate that compared to women, men are

more likely to involve themselves in behaviours that yields increased risk of injury and disease.[248,249] Additionally, women have a lower risk of the post-thrombotic syndrome, the post-PE syndrome, and recurrence, compared to men, which could potentially explain the increased risk of disability pension in men with VTE.[53,163,250]

VTE and risk of depression: A Danish population-based cohort study (Study IV)

We observed an increased risk of subsequent depression in individuals with VTE compared to the general population, particularly after a PE or a cancer-provoked VTE. As far as we know, there are no previous population-based studies that have quantified the long-term risk of subsequent depression, taking comorbid conditions into account. Our findings are consistent with numerous reviews and meta-analyses on the risk of depression following CVD.[180-186] Existing self-report and interview studies on the psychological and psychosocial consequences of VTE reported long-term and chronic mental and emotional distress following a VTE diagnosis, much due to persistent fear of VTE recurrence.[191,200-202] The psychological distress after VTE was also present in young adults due to uncertainty of long-term health and fear of relapse.[194,195]

A VTE can lead to depression through multiple psychosocial mechanisms. Depression may be a psychological reaction to the consequences of a VTE, such as functional impairment, early exit from work-life, and lower QoL.[59,158,166,167,251] In addition, depression might occur secondary to the adverse effects of long-term anticoagulant treatment, which is known to negatively impact lifestyle due to the increased bleeding risk.[171] Further, depression might also be a result of functional deterioration due to pain, swelling, dyspnea, and reduced mobility, as well as complications such as recurrence,[52,53] the post-thrombotic syndrome[38,54,159,252] and the post-PE syndrome.[57,60,168]

We found that the risk of depression was increased in patients with PE compared to those with DVT. A PE is a traumatic, sudden, and fatal event and results from qualitative studies show that PE patients experience psychological distress after their diagnosis, similar to PTSD.[192,193,198] Existential anxiety, lost sense of identity, and negative self-perception were other reported consequences of PE.[192,193,199,204] PE patients report that the psychological distress after an event is amplified by persisting pain and dyspnea, loss of physical capability, and

changed lifestyle due to bleeding and recurrence risk. Delayed diagnosis and lack of expert information further aggravated these symptoms.[192,193,199,204] We also observed that the association between provoked VTE, and notably cancer-provoked VTE, and depression remained high, even after confounder adjustments. A VTE is a serious complication of cancer negatively affecting QoL and overall survival rates.[86,87] Therefore, factors such as immobilization, cancer treatment, hospitalization, extended anticoagulation treatment, or poor underlying health likely increase the risk of depression after VTE.[121,253-255]

Both VTE and depression risk have been associated with psychosocial factors, former depression, use of antidepressants,[137,256] SES,[255] and lifestyle factors.[121,257] In our study, we did not include individuals with a former diagnosis of depression or previous use of antidepressants. We also adjusted for SES and obesity. However, undiagnosed depression, or lifestyle factors prior to the VTE, which might influence the observed association, might still be present.

As VTE and depression share common risk factors, the biological pathways between them is likely bidirectional.[137,256] The course and the development of both VTE and depression are therefore probably triggered by multiple joint mechanistic pathways such as pro-coagulant activity, increased platelet activation, inflammatory processes, and endothelial dysfunction.[184,258-260] Stress caused by imbalance in the hemostatic system is reported as an underlying trigger that might lead to both VTE and depression.[197,201,260-262] Furthermore, there is emerging evidence of a relationship between depression and prothrombotic states and dysfunctions in the stress response system.[260] Despite the probability of behavioral and biological mechanisms linking VTE and depression, current research is inconsistent and broader evidence is required to elucidate the possible pathways that might cause depression after VTE.

Methodological considerations

Study design

In this thesis, we aimed to assess the risk and prognosis of VTE in relation to SES. Risk is the probability of a future VTE, where a risk factor (i.e., SES) is something that increases the chance of developing the future event in non-diseased individuals.[214] Prognosis, on the other

hand, refers to the risk of other health outcomes (i.e., depression or disability) in individuals that have experienced a VTE.[214]

We based this thesis on Danish nationwide population-based registries. A population-based registry is intended to include all people with a given trait, exposure, or event, within a geographic area and within a given time period.[263] The registries cover data collected prospectively over several decades and the recording of data of an exposure before knowing the outcome.[264] Population-based registry studies are therefore efficient in terms of both time and costs and make it possible to study occurrence and prognosis of disease, which could not be done in a clinical setting.[213,263] They also allow for a large study size, comprehensive population coverage, and less probability of differential misclassification.[263] However, registry-based data lack clinical information making it challenging to assess disease severity and progression. Therefore, the definitions or categories will be relatively broad. Further, as registry information is collected with a different purpose than answering a specific research question, registries might be incomplete and information on specific covariates might be lacking, introducing possible distortions of associations.[214,215]

We conducted one nested case-control study (Study I) and three cohort studies (Studies II-IV). A case-control study identifies the cases (i.e., VTE patients in Denmark) and controls known to be free of the outcome from a source population (i.e., Denmark). Looking back in time, one can identify which cases and controls had the exposure (i.e., low SES) by comparing the frequency of the exposure in the cases and the controls.[215] In a nested case-control study, cases and controls are selected from a predefined source population with known sample size. Controls are drawn among those in the cohort who have not developed the disease by the time of disease occurrence.[215] Each individual in the source population therefore has the same possibility to be randomly selected as a control, and an individual in the control-group is might be selected as a case at a later stage. When selecting controls one must therefore make sure that the exposure distribution in the control group is comparable to the exposure distribution in the source population. This way, the ratio of outcome frequency in the cases relative to that of the controls can be determined. Age and sex are common matching factors that often are applied in case-control studies to increase efficiency by ensuring similar numbers of cases and controls in confounder strata.[214] Importantly, matching does not control for confounding by the matching

factors, and control for confounding is usually required by applying either conditional logistic regression during the analysis.[265] Case-control studies are both efficient and fast to make as they do not require data on a large number of people nor do they require us to wait from measurement of exposure to an outcome occurs. However, they only produce estimates of relative risks and are prone to yield uncertainties in managing bias.[214]

In the cohort study, a defined group of individuals free of the outcome of interest are identified and followed until the outcome of interest (i.e., disability pension or depression), or another censoring event (i.e., migration, death, or end of study) occurs.[266] The exposure (i.e., VTE) is recorded at study entry, and the occurrence of the outcome is compared accordingly. In registry-based cohort studies, it is possible to obtain a large population size and multiple outcomes that may be associated with multiple exposures.[215] Other important strengths of the cohort design are the possibility to estimate both incidence and relative risks and several outcomes at the same time, in addition to a clear temporal sequence between exposure and outcome.[266]

However, registry-based cohorts might be inefficient for studying rare and latent outcomes as many more subjects than those who develop an event, must be enrolled.[214] They may also be susceptible to confounding due to limitations in data selection and quality, as methods of data collection are not controlled by the researcher and data required for the research may be lacking.[267]

Socioeconomic status

The relationship between SES and health is defined in two causal models: the social causation model where SES affects health, and the health selection model where differences in health lead to differences in SES.[268] Both models lead to health inequalities, and the relationship between them is reciprocal.[268] The complexity in SES leads to challenges when assessing SES associated with health outcomes as each SES indicator emphasizes a particular aspect of social stratification, which, in turn, may be relevant to different health outcomes and different stages of the life course.[22]

There are different ways of measuring SES and there is no established best practice on which SES indicators to use. When designing a study including SES, it is therefore up to the individual

researcher(s) to define which SES indicator(s) to include and how to measure them. Thus, it is of major importance that the design and interpretation of SES-related studies reflect the research question and the proposed mechanism linking SES to the outcome being investigated.[269]

The main limitations related to assessing SES are limited access to information on relevant indicators, imprecise indicators and difficulties in the collection of individual SES data. Further, challenges in assessing the dynamic nature of SES, the categorization of women, children, those retired and unemployed, in addition to lack of, or poor, associations between individual SES measures, as well as incorrect or ambiguous results, are other limitations in SES assesments.[20,270]

Socioeconomic indicators

The most common indicators used to capture SES in adult life are income, education, and occupation/employment. These SES indicators are usually split into three levels (low. Medium and high) to categorize a family or an individual. After categorizing a family or an individual, SES indicators can be assessed individually or jointly.

Education is often referred to as the most basic SES component as it is relatively easy to measure educational achievement in most individuals.[4] The level of education is important because of its influence on future occupational opportunities and earning potential.[27] Also, educational level is considered to create differences between people in terms of access to information and benefits from knowledge.[27] Advantages of measuring education include the fact that it can be used to assess individuals that are not in the workforce. Also, education is often completed prior to the onset of major health problems and therefore less vulnerable to the impact of reverse causation (poor health leading to low SES and not low SES leading to poor health) than other markers. Besides, education remains constant throughout adult life.[23] However, educational level does not necessarily capture the quality or the field of the education, which are important determinants of cognitive skills (and subsequent profession or income), and the level of education considered to be high or low might differ between older and younger populations.

Income is a useful indicator of SES since it can be measured as the flow of income over a time period. Income is sometimes employed as a more accurate measure of access to limited material resources or standard of living because it directly links to the material situations that may impact health, compared to for instance, occupation or education. However, income varies between those in the labor market and those under education or those retired from work due to old age, as these groups will have low or reduced income. Thus, using income as a SES indicator in these populations might mask the level of economic status. Therefore, level of income might be measured by adding components, such as the net income of all household members adjusting for the size of the household.[4,271] Income is fairly easy to capture through self-reported surveys. However, people might be tempted to "inflate" their earnings, thus creating bias. Income can also fluctuate from one year to another or even from one month till the next and it is not the same as wealth. Wealth describes resources often accumulated during life, or by heritage, while income refers to the amount of earnings by a person or a household.[272]

Employment can be measured both as occupational status (category of occupation) or as employment status (employed versus unemployed). While occupational status is measured to position an individual in the social hierarchy and indicates exposure to specific occupational risks,[273] employment status is measured based on the hypotheses that employment improves the health of individuals and that healthy people are more able to obtain and retain employment.[4] However, using employment alone to quantify SES excludes a large part of the population such as pensioners, children, students, and unemployed people. Additionally, although it can be a good indicator of an individual's education and income, income cannot be used to elucidate social standing, including the degree of work prestige, or health and benefits related to an employment.[274]

SES assessment

SES can be assessed through a compositional or a contextual approach. Where the compositional approach focuses on the socioeconomic and behavioral characteristics of individuals (i.e., educational level or income) and their associated health outcomes, the contextual approach focuses on social and economic characteristics that impacts all individuals in a specific social setting (i.e., neighborhood deprivation or attitudes and beliefs in a community).[18] Further, SES can be measured by one single indicator, by several indicators

measured separately, or by a composite measure where several indicators are combined to form an index or a score. A composite SES measure might create a single summary for reporting, greater reliability, improved representation of the full range of SES indicators, as well as an improved prediction of the disease outcome. However, only applying composite measures of individual-level SES indicators may make it difficult to reveal underlying mechanisms and to understand the pathways between SES and health.

In this thesis, we measured SES through a compositional approach, focusing on the socioeconomic and behavioral characteristics of individuals and their associated health outcomes. We measured SES through the three most established and common SES indicators educational level, employment status, and personal income. A SES indicator represent both unique dimensions of the specific SES indicator, such as education representing knowledge and skills (a), as well as general dimensions of SES, such as economic resources, social status and political power (b) (Figure 7).[275] To capture the complexity of influences and the temporal relation among indicators, we assessed the indicators both individually and in a composite SES score.

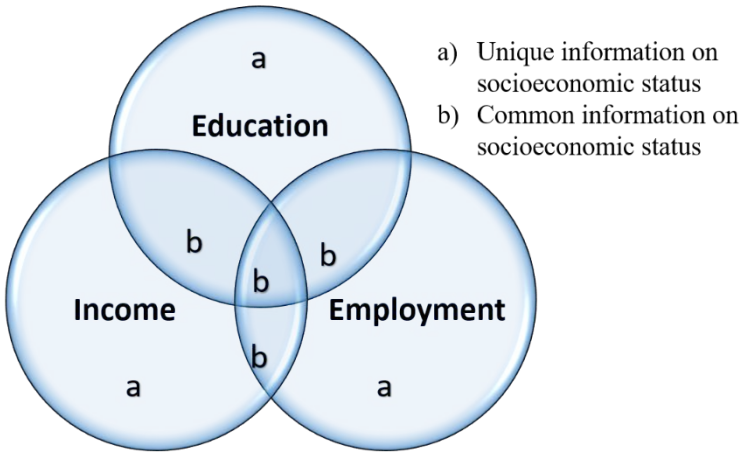


Figure 7. Common and unique representation of socioeconomic status by education, income, and employment.

Importantly, when assessing the effect of an individual indicator, the causal relationship between other indicators included must be considered. Education precedes both income and occupation and employment often precedes income. Mutually adjusting for indicators would therefore create comparison between different assumptions (total effect versus direct effect).[275]

In the analyses of the individual SES indicators in Study I, we therefore only adjusted for the SES indicators that could be confounders in the association between SES and VTE. Therefore, we made no adjustments for income or employment status in when education was the exposure, but we adjusted for education when employment was the exposure, and we adjusted for education and employment status, when income was as the exposure.

Bias in epidemiological studies

Epidemiological studies aim to present valid and precise estimates of the effect of an exposure on an outcome. However, all studies are prone to random errors, which affect the precision of the study, and to systematic errors, affecting the internal validity.[215] Internal validity is the degree of confidence that the causal relationship being tested is trustworthy in the specific setting/study it is tested in, and not influenced by other factors or variables. In contrast, external validity represent the degree of generalizability of findings to a more general population.

Quantitative bias analysis is an overall term for methods that allow us to estimate systematic errors, assess the magnitude and direction of biases, and quantify their uncertainties. Selection bias and information bias cannot be controlled for by statistical analysis. However, sensitivity analyses may be helpful in quantifying systematic errors for effect estimates. Confounding can be reduced by randomization, restriction, and matching in the design phase, and by standardization, stratification, and adjustment (using regression models) in the analysis phase. The risk of random errors can be reduced by conducting large studies with a high number of events, and by increasing the precision in measurements of exposure information.

Information bias

Information bias is the misclassification of collected information regarding an exposure or an outcome.[215] Misclassification is termed differential if associated with other study variables and non-differential of not associated with other study variables.[215] Differential misclassification may lead to an overestimation or underestimation of an association depending on the proportions of subjects misclassified, while a non-differential misclassification of dichotomous variables tends to weaken an association towards the null.[266] If the variable is polytomous, exposure groups may be biased towards one another, but the overall exposure-response relationship will usually be biased towards the null.[213]

SES defined as education, income and employment served as an exposure in Studies I and III and as a covariate in Studies II and IV. We classified income, education, and employment, as well as SES score, as low, medium, or high. A potential non-differential misclassification in the different categories of income, education, employment, and SES score would likely cause a bias of the risk estimates towards an equalization between the categories. However, data on education, employment status, and income were retrieved from registries of high validity with few missings.[276,277,278] Further, we re-calculated income values to correspond to yearly variation, thereby reducing the risk of non-differential misclassification of income levels. Of note, a potential misclassification of income was possible as income data were based on reports to the tax authorities and therefore did not include undeclared work or defective reports.

Income was categorized using percentiles to facilitate comparison across studies and to ease communication of the findings. However, by categorizing a continuous variable such as income, we assume that the association with the outcome is similar in all values of the variable. Further, we assume that the applied percentiles are representative for the income levels where biologically significant change would happen. We therefore explored the potential nonlinearity in the associations between VTE and income using a confounder-adjusted restricted cubic spline model in Study I. The same approach was used for education and SES score.

VTE was an exposure in Studies II-IV and an outcome in Study I. A first primary or secondary diagnosis of DVT or PE was extracted from the DNPR, a registry that is considered complete.[207] The probability that persons classified with VTE truly have VTE is high due to the high positive predictive values in the DNPR of 86% for DVT and 90% for PE.[279]

A correct classification in medical registries like the DNPR is dependent on several factors such as errors or variations in coding between persons performing the coding or in the clinical diagnoses on which the coding is based. Further, limitations in the specificity of codes or changes in diagnostic criteria, classification, methods, and reporting to the registries might also affect the classification.[280] Additionally, even if a register includes all patients diagnosed with a certain disease in the population, it might not capture all individuals with the disease in the population.

Diagnoses of VTE are not made by a general practitioner without referral to the hospital, therefore they likely capture all diagnosed individuals with VTE. Thus, potential missing information on individuals with VTE in the DNPR would be due to factors concerning the medical staff, and not the patient, and would therefore be non-differential and bias the association towards the null, provided that the misclassification of VTE was independent of the outcomes/exposures.

Disability Pension was defined as an outcome in Studies II and III. We based disability pension data on the Integrated Database for Labor Market Research. Although not validated, the database is considered to be of high quality.[276] Direct transition from work to disability pension is not common because the majority as most individuals go through a period of sick-leave and processes to recover work capacity prior to a disability pension. We did exclude individuals with a disability pension recorded in the same or the following calendar year of the VTE/index date, to make sure that the VTE was a cause, and not a result of a different condition causing disability pension,. Although this step increased the likelihood that VTE was the main cause of a disability pension among cases, disability pension might also be granted to individuals for other reasons than a VTE, which might have caused confounding. Further, disability will not always lead to a permanent exit from employment as it can differ in both severity and length. We might therefore have underrated the real disability incidence due to SES and VTE by applying disability pension as the outcome, without assessing episodes of sick leave, or similar. Such misclassification of disability due to under-detection has probably biased the association with VTE and SES towards the null.

Depression was defined as the outcome in Study IV. Diagnosis of depression was based on hospital inpatient or outpatient diagnoses from the DNPR and the DPCRR and antidepressant prescriptions from the Danish Prescription Registry. With an interview as reference, the positive predictive value in the DPCRR of a single depression episode is 83% for severe, 76% for moderate, and 65% for mild depression.[281] However, individuals might receive treatment for depression in the primary care setting, and Danish medical registries do not include complete recording of diagnoses from primary care. To compensate for this potential incomplete recording which would have caused a misclassification of depression, we obtained information on depression from redeemed prescriptions of antidepressants from the Danish

Prescription Registry. Even though this registry is complete[282] and antidepressants are not sold over the counter in Denmark, antidepressants may be prescribed for patients with other conditions than depression. These factors have likely caused some degree of misclassification of patients. The consequence of this misclassification is less predictable and depends on whether the underlying conditions for antidepressant use are associated with the outcome. It is worth noting that as opposed to other European countries, antidepressants are less frequently used for other indications than depression in Denmark.[283]

Selection bias

Selection bias may occur if there are systematic errors in the recruitment or retention of study participants affecting the association between exposure and outcome.[266]

The structure of the Danish tax supported universal healthcare system with virtually complete follow-up reduces concerns on critical selection bias.[31] Hover, as we used data from administrative registries, we had no influence on the methods used to collect the data. Further, even though our cohort might include all individuals diagnosed with VTE, it might not capture all persons with VTE. This may particularly be due to underdiagnoses in severely ill, or asymptomatic patients. As mentioned, VTE diagnoses likely capture all individuals diagnosed with VTE.

The risk of selection bias differs according to study design. Selection bias may occur in case-control studies if controls are not truly representative of the population that produced the cases. This might happen if the outcome affects participation or if the selection of participants is associated with the exposure. Selection bias can also occur if controls are chosen to match the cases by a factor that also is related to the exposure.[213]

Selection bias is less likely to occur in cohort studies as the selection process happens prior to the development of the outcome. Nevertheless, selection bias may occur in cohort studies if the participation rates or the rates for loss to follow-up are different with regards to exposure and health outcome status. Through to the linkage to Danish health and administrative registries the inclusion and follow-up in DNPR is complete. Therefore, the risk of selection bias in this thesis was minimal.

Selection bias might occur due to different mortality rates. In study I we drew the cases and controls from an established prospective cohort based on nationwide registries, and the study could be considered as a nested case-control study. In contrast to traditional case control design where cases needs to be alive in order to be included in the study, we were therefore able to include also fatal cases of VTE. Also as we measured odds ratios and not risk competing risk by death was not a major concern. It is likely that our rates might be slightly overestimated due to an increased prevalence of mortality in VTE cases compared to controls, but as we studied a young population (25-65 years of age) the mortality would generally be low.

In Studies II-IV we handled selection bias due to mortality by treating death as a competing event to the outcome. In classical survival analyses, individuals dying from outcomes other than the outcome of interest are usually treated as censored observations. For instance, as the mortality rates may differ between those with and those without VTE, participants lost to follow-up might differ from subjects that remain under investigation, leading to the outcome rates potentially being overestimated. In Studies II-IV, we addressed competing risk of death by assessing the cumulative incidence function (CIF) as proposed by Fine and Grey.[216] The Fine and Grey model use the sub-distribution hazard function, which represents the instantaneous rate of suffering from an event in patients that have not experienced any event, and those who have experienced death due to other events.[216] The CIF showed that VTE yielded an increased risk of a disability pension or depression in all age groups, even after competing risk by death was taken into account.

Confounding

Confounding is present when an observed relationship between an exposure and an outcome is due to the influence of another variable.[215] A confounder is not an intermediate in the causal pathway as it is related to both the exposure and the outcome and is unevenly distributed among the exposure groups. In a study, a confounder might reduce, increase, or change the direction of an association. Strategies to deal with confounding can be implemented during study design (randomization, matching, and restriction) or during analysis (stratification, adjustment, and standardization). However, lack of information on potential confounding variables or imprecise measurements of existing variables may lead to residual confounding in observational studies.

In this thesis, we addressed confounding by restriction, matching, stratification, and adjustment.

As we based all studies in this thesis on medical and administrative registries, we lacked information on risk factors that could confound or mediate the relationship between VTE and SES, such as the size or the severity of the VTE, the incidence of the post-PE syndrome, the post-thrombotic syndrome, or recurrence during follow-up. Nor did we have information on the quality and outcome of post-VTE care, individual health behavior or lifestyle factors (e.g., BMI, diet, smoking, and physical activity), or relevant SES indicators such as occupational category, household income, or length of employment. In Studies II and III, we did not have information on workplace aspects that also might be associated with disability pension. Even though we adjusted for comorbid diseases prior to the VTE, we did not have information on medical conditions occurring in the time between VTE diagnosis and the outcome. Therefore, medical conditions, such as cancer, which we considered as confounders before VTE, might also be unmeasured mediators happening after the VTE, but before the outcome, and thus affecting the association between VTE and disability or depression. Also, as the abovementioned factors were unevenly distributed among the exposure groups, confounding due to unmeasured factors cannot be completely ruled out.

Sufficient control for confounding by comorbidities requires high data quality and accurate measures of comorbidities. ICD-10 diagnosis registered in the DNRP for conditions included in the CCI have a positive predictive value greater than 90%, suggesting that ICD-10 codes in the DNPR are coded accurately and can be used to control for confounding by comorbidity as measured by the Charlson comorbidity index.[284]

The effect of SES on VTE and the driving mechanisms behind the association are complex and not necessarily clear. As a clear causal inference cannot be drawn to explain the effect, uncertainties regarding unmeasured factors that may influence SES and the association between SES and VTE exist. Further, it remains unclear whether socioeconomic indicators impact VTE at different times of the life-course, or if they are ever-present. We know that indicators such as income and employment are time-dependent. To reduce the risk of reverse causation and residual confounding, we therefore restricted our study population in Studies I-III to individuals of working age (25 to 65/66 years) as they would be able to provide information on all the SES

indicators education, income and employment. Additionally, we performed repeated SES measurements one and five years prior to the VTE/index date (Study I). In Study IV, the study population consisted of individuals aged 25 to 80 years. As a large proportion of this study population would be retired from work due to old age, we did not include employment status in this study.

Interaction

Epidemiological studies often focus on the causal effect of one exposure on an outcome. However, as most outcomes are not caused by a single exposure, but by a combination of multiple exposures, it is relevant to investigate whether the causal relation between an exposure and the outcome under study is different for different types or groups of individuals.[285] This relationship between two or more variables, where the values of one vary in some systematic way with the values of another, refers to the concept of interaction.[215] Whereas confounding is a bias that should be prevented, or removed from the data, interaction is a property of causal effect to be reported.[214] The main aim of assessing interaction is to provide insight into specific combinations of interventions that could be advantageous for a target population as a whole and to elucidate mechanisms of causal effects.[285,286] In public health, interaction can help target specific populations and resource allocation, as it shows whether the effect of a risk factor is larger in one subpopulation than in another.[286]

When dealing with interaction, one needs to be aware of the difference between effect modification which is the measurement of the causal effect of one exposure within strata of another exposure, and interaction which is the measurement of causal effects of two (or more) exposures together.[285] However, both effect modification and interaction are reflections of the reality and the complexity of multi-causality.

A synergistic interaction is when the joint effect of two or more exposures is higher than the effect expected by the amount of their separate effects. Effect modification, on the other hand, is when the effect of an exposure is investigated in different strata of another variable, but without investigating a combined effect.[287] A deviation from risk additivity is when there is a difference between the total number of cases that can be attributed to the combined effects of two risk factors and the total number of cases that could be attributed to each risk factor

individually. When the combined effect of risk factors are different from the sum of the individual factors, there is interaction on an additive scale. When the combined effect of risk factors are different from the product of the individual factors, there is interaction on an multiplicative scale.[288] Interaction on an additive scale can be computed by relative excess risk due to interaction, attributable proportion, or synergy index. These measures estimate the departure or deviance from additivity that occurs when the joint effect of the exposure variables is different from what one would expect from their independent effects on an outcome.[288]

In Study III, we measured biological interaction between VTE and SES on the risk of the risk of disability pension. K. Rothman argues that biological interaction should be quantified on an additive scale rather than a multiplicative scale.[215] Further, a deviation from risk additivity can imply that some subgroups would benefit more than others from the intervention in terms of absolute risk reduction.[289] As the additive scale considers absolute risks, it is more pertinent for public health and clinical decision making that the multiplicative scale.[286,288]

We assessed the presence of interaction by calculating the difference of risk differences, also known as the IC. IC is a measure of the attributable proportion due to interaction of risk factors and it is designed to measure risk estimates pointing in the same direction.[215] In Study III, we found presence of interaction as the 55.1-fold increased relative risk of disability pension due to the combined effect of VTE and low SES was much higher than what would be expected from summarizing the individual effects of the baseline risk from no VTE and high SES (IR 1.6), the effect of VTE (IR difference 3.8), and the effect of SES (IR difference 24.5).

Implications of the results and future perspectives

This thesis adds to the current understanding of the complexity of socioeconomic inequalities in individuals with VTE. We have shown that low SES increases the risk of VTE, that individuals with VTE, particularly those with low SES, are at increased risk of disability pension, and that VTE increases the risk of subsequent depression. We have also shown how VTE is related to a considerable economic burden to society through disability pension, and treatment of mental health challenges following a VTE.

The VTE-related direct and indirect costs in the EU are vast, ranging from 1.5 to 3.2 billion Euro annually,[290] and the 3-year attributable societal costs to a single VTE event are approximately 40,024 Euro, with 53% of these costs appearing in the first year.[291] The consequences of increased unemployment and welfare needs, lost productivity and reduced taxation revenue due to disability, are therefore enormous and extend far beyond the direct costs of treatment of both VTE and mental health disorders. Prevention of psychosocial complications after VTE will not only reduce the demand for health and welfare services, but also lead to increased productivity and participation in the labor market, and thereby greatly ease the economic and health care burden on society.

To reduce health disparities and psychosocial consequences of VTE, we need to develop targeted prevention and intervention strategies for vulnerable individuals. An improved understanding of the type and burden of psychosocial consequences in VTE is therefore crucial to address both physicians' and patients' need of adequate supportive and preventive measures to enhance recovery, return to work and health-related quality of life. By identifying and assessing psychosocial complications in VTE, we can increase the knowledge and improve awareness, as well as guide clinical decisions to facilitate targeted preventive actions in VTE patients with high risk of adverse mental health or disability.

When individuals with both VTE and psychosocial complications arrive in health care, they are usually treated for one, or the other, of their conditions, but not both. As a result, psychosocial complications might go unrecognized and untreated in their early stages, increasing the risk of disability or premature death after VTE. This thesis can inform new strategies for an integrated

treatment where physical- and psychosocial complications after a VTE are considered, managed, and monitored simultaneously through treatment methods that involve both cognitive behavioral therapy strategies, as well as approaches to support motivation and functional recovery.

SES is a significant predictor of social inequalities in health. The great diversity in SES assessment, however, creates inconsistency and challenges when validating SES. If SES was measured with more consistency across studies, it would allow for a better identification of the societal gaps in SES, an increased understanding of the implications of SES, and stronger evidence to change policy and health-care practice. In this thesis, we applied a SES composite score to assess SES. Although not validated, we believe that the score model is one step towards enabling a common and accurate way of identifying individuals at higher risk of a disease and with a greater societal disadvantage. SES impacts VTE through physical capacity, access to healthcare, legislation, lifestyle, labour market possibilities, work characteristics, cohabitation status, and regional differences. Thus, to improve our knowledge of socioeconomic disparities and psychosocial consequences related to VTE, further attention to these SES indicators and the pathways by which they influence VTE and adverse outcomes after VTE is needed.[27]

Disability pension after VTE has traditionally been associated with physical complications of VTE. However, the strong association we found between VTE and depression may suggest that psychosocial factors also has an impact on the disability risk after VTE. This speculation needs to be further explored. There is also a need for further investigations on to what extent psychosocial consequences and other mental health conditions have on VTE prognosis and vice versa.

References

1. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis* 2016; **41**(1): 3-14.

2. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol* 2014; **34**(11): 2363-71.

3. Marmot M, Wilkinson R. Social determinants of health: OUP Oxford; 2005.

4. Shavers VL. Measurement of socioeconomic status in health disparities research. *Journal of the National Medical Association* 2007; **99**(9): 1013-23.

5. White RH. The epidemiology of venous thromboembolism. *Circulation* 2003; **107**(23 Suppl 1): I4-8.

6. Stein PD, Hull RD, Kayali F, Ghali WA, Alshab AK, Olson RE. Venous thromboembolism according to age: the impact of an aging population. *Archives of internal medicine* 2004; **164**(20): 2260-5.

7. Virchow R. Thrombose und Embolie (1846-1856). Leipzig, Germany: Verlag von Johann Ambrosius Barth; 1910.

8. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999; **353**(9159): 1167-73.

9. van Langevelde K, Srámek A, Vincken PW, van Rooden JK, Rosendaal FR, Cannegieter SC. Finding the origin of pulmonary emboli with a total-body magnetic resonance direct thrombus imaging technique. *Haematologica* 2013; **98**(2): 309-15.

10. Van Gent JM, Zander AL, Olson EJ, et al. Pulmonary embolism without deep venous thrombosis: De novo or missed deep venous thrombosis? *The journal of trauma and acute care surgery* 2014; **76**(5): 1270-4.

11. Enga KF, Rye-Holmboe I, Hald EM, et al. Atrial fibrillation and future risk of venous thromboembolism:the Tromso study. *Journal of thrombosis and haemostasis : JTH* 2015; **13**(1): 10-6.

12. Sørensen HT, Horvath-Puho E, Lash TL, et al. Heart Disease May Be a Risk Factor for Pulmonary Embolism Without Peripheral Deep Venous Thrombosis. *Circulation* 2011; **124**(13): 1435-41.

13. Arshad N, Isaksen T, Hansen JB, Braekkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. *Eur J Epidemiol* 2017; **32**(4): 299-305.

14. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985-2009). *Am J Med* 2014; **127**(9): 829-39 e5.

15. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet (London, England)* 1960; **1**(7138): 1309-12.

16. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. *Jama* 2014; **311**(7): 717-28.

17. Barnes GD, Kanthi Y, Froehlich JB. Venous thromboembolism: Predicting recurrence and the need for extended anticoagulation. *Vascular medicine (London, England)* 2015; **20**(2): 143-52.

18. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. *Annals of the New York Academy of Sciences* 1999; **896**: 3-15.

19. Oakes MJ, Kaufman, J. Methods in Social Epidemiology. *Jossey-Bass* 2017.

20. Jeynes WH. The challenge of controlling for SES in social science and education research. *Educ Psychol Rev* 2002; **14**(2): 205-21.

21. Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic status in health research: one size does not fit all. *Jama* 2005; **294**(22): 2879-88.

22. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). *Journal of epidemiology and community health* 2006; **60**(1): 7-12.

23. Matthews KA, Gallo LC. Psychological perspectives on pathways linking socioeconomic status and physical health. *Annual review of psychology* 2011; **62**: 501-30.

24. de Mestral C, Stringhini S. Socioeconomic Status and Cardiovascular Disease: an Update. *Curr Cardiol Rep* 2017; **19**(11): 115.

25. Bashinskaya B, Nahed BV, Walcott BP, Coumans JV, Onuma OK. Socioeconomic status correlates with the prevalence of advanced coronary artery disease in the United States. *PLoS One* 2012; **7**(9): e46314.

26. Businelle MS, Mills BA, Chartier KG, Kendzor DE, Reingle JM, Shuval K. Do stressful events account for the link between socioeconomic status and mental health? *Journal of public health (Oxford, England)* 2014; **36**(2): 205-12.

27. Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. *Health Aff (Millwood)* 2002; **21**(2): 60-76.

28. Levesque JF, Harris MF, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. *Int J Equity Health* 2013; **12**: 18.

29. Campbell DJ, Ronksley PE, Manns BJ, et al. The association of income with health behavior change and disease monitoring among patients with chronic disease. *PLoS One* 2014; **9**(4): e94007.

30. Clark AM, DesMeules M, Luo W, Duncan AS, Wielgosz A. Socioeconomic status and cardiovascular disease: risks and implications for care. *Nat Rev Cardiol* 2009; **6**(11): 712-22.

31. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019; **11**: 563-91.

32. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. *Public health reports (Washington, DC : 1974)* 2014; **129 Suppl 2**(Suppl 2): 19-31.

33. Marmot M. Inequalities in health. *The New England journal of medicine* 2001; **345**(2): 134-6.

34. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007; **98**(4): 756-64.

35. Næss IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost* 2007; **5**(4): 692-9.

36. Münster AM, Rasmussen TB, Falstie-Jensen AM, et al. A changing landscape: Temporal trends in incidence and characteristics of patients hospitalized with venous thromboembolism 2006-2015. *Thromb Res* 2019; **176**: 46-53.

37. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. *Thromb Res* 2016; **137**: 3-10.

38. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998; **158**(6): 585-93.

39. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *The American journal of medicine* 2004; **117**(1): 19-25.

40. Severinsen MT, Johnsen SP, Tjønneland A, Overvad K, Dethlefsen C, Kristensen SR. Body height and sex-related differences in incidence of venous thromboembolism: A Danish follow-up study. *European journal of internal medicine* 2010; **21**(4): 268-72.

41. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Family history of myocardial infarction is an independent risk factor for venous thromboembolism: the Tromso study. *Journal of thrombosis and haemostasis : JTH* 2008; **6**(11): 1851-7.

42. Arnesen CAL, Veres K, Horváth-Puhó E, Hansen J-B, Sørensen HT, Brækkan SK. Estimated lifetime risk of venous thromboembolism in men and women in a Danish nationwide cohort: impact of competing risk of death. *European Journal of Epidemiology* 2021.

43. Bell EJ, Lutsey PL, Basu S, et al. Lifetime Risk of Venous Thromboembolism in Two Cohort Studies. *The American journal of medicine* 2016; **129**(3): 339.e19-.e3.39E26.

44. Arshad N, Bjori E, Hindberg K, Isaksen T, Hansen JB, Braekkan SK. Recurrence and mortality after first venous thromboembolism in a large population-based cohort. *J Thromb Haemost: JTH* 2017; **15**(2): 295-303.

45. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. *The American journal of medicine* 2013; **126**(9): 832.e13-21.

46. Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation* 2014; **130**(10): 829-36.

47. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999; **159**(5): 445-53.

48. Heit JA, Silverstein MD, Mohr DN, et al. Predictors of survival after deep vein thrombosis and pulmonary embolism: A population-based, cohort study. *Archives of internal medicine* 1999; **159**(5): 445-53.

49. Kraaijpoel N, Tritschler T, Guillo E, Girard P, Le Gal G. Definitions, adjudication, and reporting of pulmonary embolism-related death in clinical studies: A systematic review. *Journal of thrombosis and haemostasis : JTH* 2019; **17**(10): 1590-607.

50. Barco S, Valerio L, Gallo A, et al. Global reporting of pulmonary embolism–related deaths in the World Health Organization mortality database: Vital registration data from 123 countries. *Research and Practice in Thrombosis and Haemostasis* 2021; **5**(5): e12520.

51. Søgaard KK, Schmidt M, Pedersen L, Horváth-Puhó E, Sørensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation* 2014; **130**(10): 829-36.

52. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med* 2000; **160**(6): 761-8.

53. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. *The New England journal of medicine* 2004; **350**(25): 2558-63.

54. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med* 2008; **149**(10): 698-707.

55. Kachroo S, Boyd D, Bookhart BK, et al. Quality of life and economic costs associated with postthrombotic syndrome. *American Journal of Health-System Pharmacy* 2012; **69**(7): 567-72.

56. Laviolette L, Laveneziana P, Faculty ERSRS. Dyspnoea: a multidimensional and multidisciplinary approach. *Eur Respir J* 2014; **43**(6): 1750-62.

57. Pugliese SC, Kawut SM. The Post-Pulmonary Embolism Syndrome: Real or Ruse? *Ann Am Thorac Soc* 2019; **16**(7): 811-4.

58. Sista AK, Klok FA. Late outcomes of pulmonary embolism: The post-PE syndrome. *Thromb Res* 2018; **164**: 157-62.

59. Tavoly M, Wik HS, Sirnes PA, et al. The impact of post-pulmonary embolism syndrome and its possible determinants. *Thromb Res* 2018; **171**: 84-91.

60. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood Rev* 2014; **28**(6): 221-6.

61. Braekkan SK, Grosse SD, Okoroh EM, et al. Venous thromboembolism and subsequent permanent work-related disability. *Journal of thrombosis and haemostasis : JTH* 2016; **14**(10): 1978-87.

62. Morange PE, Suchon P, Tregouet DA. Genetics of Venous Thrombosis: update in 2015. *Thromb Haemost* 2015; **114**(5): 910-9.

63. Heit JA, Phelps MA, Ward SA, Slusser JP, Petterson TM, De Andrade M. Familial segregation of venous thromboembolism. *Journal of thrombosis and haemostasis : JTH* 2004; **2**(5): 731-6.

64. Larsen TB, Sorensen HT, Skytthe A, Johnsen SP, Vaupel JW, Christensen K. Major genetic susceptibility for venous thromboembolism in men: a study of Danish twins. *Epidemiology* 2003; **14**(3): 328-32.

65. Sorensen HT, Riis AH, Diaz LJ, Andersen EW, Baron JA, Andersen PK. Familial risk of venous thromboembolism: a nationwide cohort study. *Journal of thrombosis and haemostasis : JTH* 2011; **9**(2): 320-4.

66. Martinelli I, De Stefano V, Mannucci PM. Inherited risk factors for venous thromboembolism. *Nat Rev Cardiol* 2014; **11**(3): 140-56.

67. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. *The New England journal of medicine* 2001; **344**(16): 1222-31.

68. Trégouët DA, Morange PE. What is currently known about the genetics of venous thromboembolism at the dawn of next generation sequencing technologies. *Br J Haematol* 2018; **180**(3): 335-45.

69. Lindstrom S, Wang L, Smith EN, et al. Genomic and Transcriptomic Association Studies Identify 16 Novel Susceptibility Loci for Venous Thromboembolism. *Blood* 2019.

70. Klarin D, Busenkell E, Judy R, et al. Genome-wide association analysis of venous thromboembolism identifies new risk loci and genetic overlap with arterial vascular disease. *Nat Genet* 2019; **51**(11): 1574-9.

71. Rosendaal FR. Risk factors for venous thrombosis: prevalence, risk, and interaction. *Semin Hematol* 1997; **34**(3): 171-87.

72. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003; **107**(23 Suppl 1): I9-16.

73. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med* 2002; **162**(11): 1245-8.

74. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *Journal of thrombosis and haemostasis : JTH* 2016; **14**(7): 1480-3.

75. White RH. Identifying Risk Factors for Venous Thromboembolism. *Circulation* 2012; **125**(17): 2051-3.

76. White RH, Murin S, Wun T, Danielsen B. Recurrent venous thromboembolism after surgery-provoked versus unprovoked thromboembolism. *J Thromb Haemost* 2010; **8**(5): 987-97.

77. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med* 2010; **170**(19): 1710-6.

78. Carrier M, Lazo-Langner A, Shivakumar S, et al. Screening for Occult Cancer in Unprovoked Venous Thromboembolism. *The New England journal of medicine* 2015; **373**(8): 697-704.

79. van Es N, Le Gal G, Otten HM, et al. Screening for cancer in patients with unprovoked venous thromboembolism: protocol for a systematic review and individual patient data meta-analysis. *BMJ Open* 2017; **7**(6): e015562.

80. Spencer FA, Emery C, Joffe SW, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. *J Thromb Thrombolysis* 2009; **28**(4): 401-9.

81. Timp JF, Lijfering WM, Rosendaal FR, le Cessie S, Cannegieter SC. Risk prediction of recurrent venous thrombosis; where are we now and what can we add? *Journal of thrombosis and haemostasis : JTH* 2019; **17**(9): 1527-34.

82. Braekkan SK, Hansen JB. Substantial recurrence risk after venous thromboembolism provoked by minor risk factors. *Journal of thrombosis and haemostasis : JTH* 2018; **16**(9): 1671-3.

83. Heit JA, Ashrani A, Crusan DJ, McBane RD, Petterson TM, Bailey KR. Reasons for the persistent incidence of venous thromboembolism. *Thromb Haemost* 2017; **117**(2): 390-400.

84. Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. *Journal of thrombosis and haemostasis : JTH* 2010; **8**(10): 2105-12.

85. Wilkerson WR, Sane DC. Aging and thrombosis. *Semin Thromb Hemost* 2002; **28**(6): 555-68.

86. Costa J, Araújo A. Cancer-Related Venous Thromboembolism: From Pathogenesis to Risk Assessment. *Semin Thromb Hemost* 2021; **47**(6): 669-76.

87. Khorana AA, Mackman N, Falanga A, et al. Cancer-associated venous thromboembolism. *Nat Rev Dis Primers* 2022; **8**(1): 11.

88. Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood* 2021; **137**(14): 1959-69.

89. Carrier M, Le Gal G, Wells PS, Fergusson D, Ramsay T, Rodger MA. Systematic review: the Trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism? *Ann Intern Med* 2008; **149**(5): 323-33.

90. Cronin-Fenton DP, Sondergaard F, Pedersen LA, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. *Br J Cancer* 2010; **103**(7): 947-53.

91. Braekkan SK, Siegerink B, Lijfering WM, Hansen JB, Cannegieter SC, Rosendaal FR. Role of obesity in the etiology of deep vein thrombosis and pulmonary embolism: current epidemiological insights. *Seminars in thrombosis and hemostasis* 2013; **39**(5): 533-40.

92. Lindstrom S, Germain M, Crous-Bou M, et al. Assessing the causal relationship between obesity and venous thromboembolism through a Mendelian Randomization study. *Hum Genet* 2017; **136**(7): 897-902.

93. Klovaite J, Benn M, Nordestgaard BG. Obesity as a causal risk factor for deep venous thrombosis: a Mendelian randomization study. *J Intern Med* 2015; **277**(5): 573-84.

94. Klarin D, Emdin CA, Natarajan P, Conrad MF, Kathiresan S. Genetic Analysis of Venous Thromboembolism in UK Biobank Identifies the ZFPM2 Locus and Implicates Obesity as a Causal Risk Factor. *Circulation: Cardiovascular Genetics* 2017; **10**(2): e001643.

95. Horvei LD, Braekkan SK, Hansen JB. Weight Change and Risk of Venous Thromboembolism: The Tromso Study. *PloS one* 2016; **11**(12): e0168878.

96. Sundbøll J, Ängquist L, Adelborg K, et al. Changes in Childhood Body-Mass Index and Risk of Venous Thromboembolism in Adulthood. *Journal of the American Heart Association* 2019; **8**(6): e011407-e.

97. Horvei LD, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Obesity measures and risk of venous thromboembolism and myocardial infarction. *European journal of epidemiology* 2014; **29**(11): 821-30.

98. Severinsen MT, Kristensen SR, Johnsen SP, Dethlefsen C, Tjonneland A, Overvad K. Anthropometry, body fat, and venous thromboembolism: a Danish follow-up study. *Circulation* 2009; **120**(19): 1850-7.

99. Morange PE, Alessi MC. Thrombosis in central obesity and metabolic syndrome: mechanisms and epidemiology. *Thromb Haemost* 2013; **110**(4): 669-80.

100. Horvei LD, Grimnes G, Hindberg K, et al. C-reactive protein, obesity, and the risk of arterial and venous thrombosis. *J Thromb Haemost* 2016; **14**(8): 1561-71.

101. Bjori E, Arshad N, Johnsen HS, Hansen JB, Braekkan SK. Hospital-related first venous thromboembolism and risk of recurrence. *Journal of thrombosis and haemostasis : JTH* 2016; **14**(12): 2368-75.

102. Bjori E, Johnsen HS, Hansen JB, Braekkan SK. Hospitalization as a trigger for venous thromboembolism - Results from a population-based case-crossover study. *Thromb Res* 2019; **176**: 115-9.

103. Heit JA, Crusan DJ, Ashrani AA, Petterson TM, Bailey KR. Effect of a near-universal hospitalization-based prophylaxis regimen on annual number of venous thromboembolism events in the US. *Blood* 2017; **130**(2): 109-14.

104. Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. *Arch Intern Med* 2007; **167**(14): 1471-5.

105. Heit JA, Melton LJ, 3rd, Lohse CM, et al. Incidence of venous thromboembolism in hospitalized patients vs community residents. *Mayo Clinic proceedings* 2001; **76**(11): 1102-10.

106. Samama MM, Dahl OE, Quinlan DJ, Mismetti P, Rosencher N. Quantification of risk factors for venous thromboembolism: a preliminary study for the development of a risk assessment tool. *Haematologica* 2003; **88**(12): 1410-21.

107. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost* 2003; **90**(3): 446-55.

108. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**(6 Suppl): 381s-453s.

109. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**(2 Suppl): e195S-e226S.

110. Pottier P, Hardouin JB, Lejeune S, Jolliet P, Gillet B, Planchon B. Immobilization and the risk of venous thromboembolism. A meta-analysis on epidemiological studies. *Thromb Res* 2009; **124**(4): 468-76.

111. Beam DM, Courtney DM, Kabrhel C, Moore CL, Richman PB, Kline JA. Risk of thromboembolism varies, depending on category of immobility in outpatients. *Annals of emergency medicine* 2009; **54**(2): 147-52.

112. Ettema HB, Kollen BJ, Verheyen CC, Büller HR. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. *Journal of thrombosis and haemostasis : JTH* 2008; **6**(7): 1093-8.

113. Dennis M, Mordi N, Graham C, Sandercock P. The timing, extent, progression and regression of deep vein thrombosis in immobile stroke patients: observational data from the CLOTS multicenter randomized trials. *J Thromb Haemost* 2011; **9**(11): 2193-200.

114. Wattanakit K, Lutsey PL, Bell EJ, et al. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. *Thrombosis and haemostasis* 2012; **108**(3): 508-15.

115. Olson NC, Cushman M, Judd SE, et al. American Heart Association's Life's Simple 7 and Risk of Venous Thromboembolism: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Journal of the American Heart Association* 2015; **4**(3).

116. Armstrong ME, Green J, Reeves GK, Beral V, Cairns BJ. Frequent physical activity may not reduce vascular disease risk as much as moderate activity: large prospective study of women in the United Kingdom. *Circulation* 2015; **131**(8): 721-9.

117. van Stralen KJ, Le Cessie S, Rosendaal FR, Doggen CJ. Regular sports activities decrease the risk of venous thrombosis. *J Thromb Haemost* 2007; **5**(11): 2186-92.

118. Lindqvist PG, Epstein E, Olsson H. The relationship between lifestyle factors and venous thromboembolism among women: a report from the MISS study. *British journal of haematology* 2009; **144**(2): 234-40.

119. Evensen LH, Braekkan SK, Hansen JB. Regular Physical Activity and Risk of Venous Thromboembolism. *Seminars in thrombosis and hemostasis* 2018; **44**(8): 765-79.

120. Evensen LH, Isaksen T, Hindberg K, Braekkan SK, Hansen JB. Repeated assessments of physical activity and risk of incident venous thromboembolism. *J Thromb Haemost* 2018; **16**(11): 2208-17.

121. Kunutsor SK, Mäkikallio TH, Seidu S, et al. Physical activity and risk of venous thromboembolism: systematic review and meta-analysis of prospective cohort studies. *Eur J Epidemiol* 2020; **35**(5): 431-42.

122. Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Body height, mobility, and risk of first and recurrent venous thrombosis. *Journal of thrombosis and haemostasis : JTH* 2015; **13**(4): 548-54.

123. Kabrhel C, Varraso R, Goldhaber SZ, Rimm E, Camargo CA. Physical inactivity and idiopathic pulmonary embolism in women: prospective study. *BMJ* 2011; **343**: d3867.

124. Evensen LH, Isaksen T, Hindberg K, Brækkan SK, Hansen J-B. Repeated assessments of physical activity and risk of incident venous thromboembolism. *Journal of Thrombosis and Haemostasis* 2018; **16**(11): 2208-17.

125. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *Am J Epidemiol* 2005; **162**(10): 975-82.

126. van Stralen KJ, Doggen CJ, Lumley T, et al. The relationship between exercise and risk of venous thrombosis in elderly people. *Journal of the American Geriatrics Society* 2008; **56**(3): 517-22.

127. Borch KH, Hansen-Krone I, Braekkan SK, et al. Physical activity and risk of venous thromboembolism. The Tromso study. *Haematologica* 2010; **95**(12): 2088-94.

128. Lutsey PL, Virnig BA, Durham SB, et al. Correlates and consequences of venous thromboembolism: The Iowa Women's Health Study. *Am J Public Health* 2010; **100**(8): 1506-13.

129. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med* 2002; **162**(10): 1182-9.

130. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. *Circulation* 2010; **121**(17): 1896-903.

131. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv* 2018; **2**(22): 3198-225.

132. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *Journal of thrombosis and haemostasis : JTH* 2008; **6**(4): 632-7.

133. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ, 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005; **143**(10): 697-706.

134. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. *The New England journal of medicine* 1996; **335**(2): 108-14.

135. Ramot Y, Nyska A, Spectre G. Drug-Induced Thrombosis: An Update. *Drug Safety* 2013; **36**(8): 585-603.

136. Liu Y, Xu J, Fang K, et al. Current antipsychotic agent use and risk of venous thromboembolism and pulmonary embolism: a systematic review and meta-analysis of observational studies. *Therapeutic Advances in Psychopharmacology* 2021; **11**: 2045125320982720.

137. Kunutsor SK, Seidu S, Khunti K. Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence. *Annals of Medicine* 2018; **50**(6): 529-37.

138. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, et al. Use of Glucocorticoids and Risk of Venous Thromboembolism: A Nationwide Population-Based Case-Control Study. *Jama Intern Med* 2013; **173**(9): 743-52.

139. Orsi FA, Lijfering WM, Geersing G-J, et al. Glucocorticoid use and risk of first and recurrent venous thromboembolism: self-controlled case-series and cohort study. *British journal of haematology* 2021; **193**(6): 1194-202.

140. Huerta C, Johansson S, Wallander M-A, García Rodríguez LA. Risk Factors and Short-term Mortality of Venous Thromboembolism Diagnosed in the Primary Care Setting in the United Kingdom. *Archives of Internal Medicine* 2007; **167**(9): 935-43.

141. Girolami A, Cosi E, Tasinato V, Santarossa C, Ferrari S, Girolami B. Drug-Induced Thrombophilic or Prothrombotic States: An Underestimated Clinical Problem That Involves Both Legal and Illegal Compounds. *Clin Appl Thromb Hemost* 2017; **23**(7): 775-85.

142. Stegeman BH, de Bastos M, Rosendaal FR, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *Bmj* 2013; **347**: f5298.

143. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. *Jama* 2002; **288**(7): 872-81.

144. Sandset PM. Mechanisms of hormonal therapy related thrombosis. *Thromb Res* 2013; **131 Suppl 1**: S4-7.

145. Rosengren A, Freden M, Hansson PO, Wilhelmsen L, Wedel H, Eriksson H. Psychosocial factors and venous thromboembolism: a long-term follow-up study of Swedish men. *J Thromb Haemost* 2008; **6**(4): 558-64.

146. Zoller B, Li X, Sundquist J, Sundquist K. Socioeconomic and occupational risk factors for venous thromboembolism in Sweden: a nationwide epidemiological study. *Thromb Res* 2012; **129**(5): 577-82.

147. Isma N, Merlo J, Ohlsson H, Svensson PJ, Lindblad B, Gottsater A. Socioeconomic factors and concomitant diseases are related to the risk for venous thromboembolism during long time follow-up. *J Thromb Thrombolysis* 2013; **36**(1): 58-64.

148. Stringhini S, Carmeli C, Jokela M, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. *The Lancet* 2017; **389**(10075): 1229-37.

149. Schultz William M, Kelli Heval M, Lisko John C, et al. Socioeconomic Status and Cardiovascular Outcomes. *Circulation* 2018; **137**(20): 2166-78.

150. Addo J, Ayerbe L, Mohan KM, et al. Socioeconomic status and stroke: an updated review. *Stroke* 2012; **43**(4): 1186-91.

151. Kearon C, Ageno W, Cannegieter SC, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *Journal of thrombosis and haemostasis : JTH* 2016; **14**(7): 1480-3.

152. Roach RE, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. *Journal of thrombosis and haemostasis : JTH* 2014; **12**(10): 1593-600.

153. Winter MP, Schernthaner GH, Lang IM. Chronic complications of venous thromboembolism. *Journal of thrombosis and haemostasis : JTH* 2017; **15**(8): 1531-40.

154. Tick LW, Kramer MH, Rosendaal FR, Faber WR, Doggen CJ. Risk factors for post-thrombotic syndrome in patients with a first deep venous thrombosis. *Journal of thrombosis and haemostasis : JTH* 2008; **6**(12): 2075-81.

155. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; **125**(1): 1-7.

156. Baldwin MJ, Moore HM, Rudarakanchana N, Gohel M, Davies AH. Post-thrombotic syndrome: a clinical review. *Journal of thrombosis and haemostasis : JTH* 2013; **11**(5): 795-805.

157. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2014; **130**(18): 1636-61.

158. Utne KK, Tavoly M, Wik HS, et al. Health-related quality of life after deep vein thrombosis. *SpringerPlus* 2016; **5**(1): 1278.

159. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. *Arch Intern Med* 2002; **162**(10): 1144-8.

160. Stein PD, Beemath A, Matta F, et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. *The American journal of medicine* 2007; **120**(10): 871-9.

161. Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Huisman MV. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. *Respir Med* 2010; **104**(11): 1744-9.

162. Sanchez O, Caumont-Prim A, Riant E, et al. Pathophysiology of dyspnoea in acute pulmonary embolism: A cross-sectional evaluation. *Respirology* 2017; **22**(4): 771-7.

163. Kahn SR, Hirsch A, Beddaoui M, et al. "Post-Pulmonary Embolism Syndrome" after a First Episode of PE: Results of the E.L.O.P.E. Study. *Blood* 2015; **126**(23): 650-.

164. Lang I. Chronic thromboembolic pulmonary hypertension: a distinct disease entity. *Eur Respir Rev* 2015; **24**(136): 246-52.

165. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *The New England journal of medicine* 2004; **350**(22): 2257-64.

166. Ghanima W, Wik HS, Tavoly M, Enden T, Jelsness-Jorgensen LP. Late consequences of venous thromboembolism: Measuring quality of life after deep vein thrombosis and pulmonary embolism. *Thromb Res* 2018; **164**: 170-6.

167. Klok FA, van Kralingen KW, van Dijk AP, et al. Quality of life in long-term survivors of acute pulmonary embolism. *Chest* 2010; **138**(6): 1432-40.

168. Tavoly M, Utne KK, Jelsness-Jørgensen L-P, et al. Health-related quality of life after pulmonary embolism: a cross-sectional study. *BMJ Open* 2016; **6**(11): e013086.

169. Kahn SR, Akaberi A, Granton JT, et al. Quality of Life, Dyspnea, and Functional Exercise Capacity Following a First Episode of Pulmonary Embolism: Results of the ELOPE Cohort Study. *The American journal of medicine* 2017; **130**(8): 990.e9-.e21.

170. van Es J, den Exter PL, Kaptein AA, et al. Quality of life after pulmonary embolism as assessed with SF-36 and PEmb-QoL. *Thrombosis Research* 2013; **132**(5): 500-5.

171. Wells PS, Forgie MA, Rodger MA. Treatment of Venous Thromboembolism. *JAMA* 2014; **311**(7): 717-28.

172. Lubberts B, Paulino Pereira NR, Kabrhel C, Kuter DJ, DiGiovanni CW. What is the effect of venous thromboembolism and related complications on patient reported health-related quality of life? A meta-analysis. *Thromb Haemost* 2016; **116**(3): 417-31.

173. Burdorf A. ICF from a Population Health Perspective: The Impact of Chronic Disease on Work Participation and Its Consequences for Intervention and Treatment. Cham: Cham: Springer International Publishing; 2014. p. 43-53.

174. van Rijn RM, Robroek SJ, Brouwer S, Burdorf A. Influence of poor health on exit from paid employment: a systematic review. *Occupational and environmental medicine* 2014; **71**(4): 295-301.

175. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Semin Thromb Hemost* 2014; **40**(7): 724-35.

176. Chuang LH, van Hout B, Cohen AT, et al. Deep-vein thrombosis in Europe - Burden of illness in relationship to healthcare resource utilization and return to work. *Thromb Res* 2018; **170**: 165-74.

177. Willich SN, Chuang LH, van Hout B, et al. Pulmonary embolism in Europe - Burden of illness in relationship to healthcare resource utilization and return to work. *Thromb Res* 2018; **170**: 181-91.

178. Organization WH. Depression and Other Common Mental Disorders: Global Health Estimates. . In: Organization WH, editor. Print. Geneva: World Health Organization; 2017.

179. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *The Medical journal of Australia* 2009; **190**(S7): S54-60.

180. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *European Heart Journal* 2013; **35**(21): 1365-72.

181. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. *Am J Hypertens* 2015; **28**(11): 1295-302.

182. Thombs BD, Bass EB, Ford DE, et al. Prevalence of depression in survivors of acute myocardial infarction. *Journal of general internal medicine* 2006; **21**(1): 30-8.

183. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke* 2014; **9**(8): 1017-25.

184. Chauvet-Gélinier J-C, Trojak B, Vergès-Patois B, Cottin Y, Bonin B. Review on depression and coronary heart disease. *Arch Cardiovasc Dis* 2013; **106**(2): 103-10.

185. Easton K, Coventry P, Lovell K, Carter LA, Deaton C. Prevalence and Measurement of Anxiety in Samples of Patients With Heart Failure: Meta-analysis. *J Cardiovasc Nurs* 2016; **31**(4): 367-79.

186. Carney RM, Freedland KE. Depression and coronary heart disease. *Nature Reviews Cardiology* 2017; **14**(3): 145-55.

187. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues in clinical neuroscience* 2011; **13**(1): 7-23.

188. van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosomatic medicine* 2004; **66**(6): 814-22.

189. De Ryck A, Brouns R, Geurden M, Elseviers M, De Deyn PP, Engelborghs S. Risk factors for poststroke depression: identification of inconsistencies based on a systematic review. *Journal of geriatric psychiatry and neurology* 2014; **27**(3): 147-58.

190. Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. *The British journal of psychiatry : the journal of mental science* 2013; **202**(1): 14-21.

191. Lukas PS, Krummenacher R, Biasiutti FD, Begré S, Znoj H, Känel Rv. Association of fatigue and psychological distress with quality of life in patients with a previous venous thromboembolic event. *Thromb Haemost* 2009; **102 6**: 1219-26.

192. Noble S, Lewis R, Whithers J, Lewis S, Bennett P. Long-term psychological consequences of symptomatic pulmonary embolism: a qualitative study. *BMJ Open* 2014; **4**(4): e004561.

193. Tran A, Redley M, de Wit K. The psychological impact of pulmonary embolism: A mixed-methods study. *Res Pract Thromb Haemost* 2021; **5**(2): 301-7.

194. Højen AA, Dreyer PS, Lane DA, Larsen TB, Sørensen EE. Adolescents' and Young Adults' Lived Experiences Following Venous Thromboembolism: "It will always lie in wait". *Nurs Res* 2016; **65**(6): 455-64.

195. Fiandaca D, Bucciarelli P, Martinelli I, Tantardini F, Clemente C, Mannucci PM. Psychological impact of thrombosis in the young. *Internal and Emergency Medicine* 2006; **1**(2): 119.

196. Liu CP, Li XM, Chen HW, et al. Depression, anxiety and influencing factors in patients with acute pulmonary embolism. *Chin Med J (Engl)* 2011; **124**(16): 2438-42.

197. Hunter R, Lewis S, Noble S, Rance J, Bennett PD. "Post-thrombotic panic syndrome": A thematic analysis of the experience of venous thromboembolism. *Br J Health Psychol* 2017; **22**(1): 8-25.

198. Kirchberger I, Ruile S, Linseisen J, Haberl S, Meisinger C, Berghaus TM. The lived experience with pulmonary embolism: A qualitative study using focus groups. *Respir Med* 2020; **167**: 105978.

199. Rolving N, Brocki BC, Andreasen J. Coping with everyday life and physical activity in the aftermath of an acute pulmonary embolism: A qualitative study exploring patients' perceptions and coping strategies. *Thromb Res* 2019; **182**: 185-91.

200. Hunter R, Noble S, Lewis S, Bennett P. Long-term psychosocial impact of venous thromboembolism: a qualitative study in the community. *BMJ Open* 2019; **9**(2): e024805.

201. Bennett P, Patterson K, Noble S. Predicting post-traumatic stress and health anxiety following a venous thrombotic embolism. *J Health Psychol* 2014; **21**(5): 863-71.

202. Hunter R, Lewis S, Noble S, Rance J, Bennett PD. “Post-thrombotic panic syndrome”: A thematic analysis of the experience of venous thromboembolism. *British Journal of Health Psychology* 2017; **22**(1): 8-25.

203. Tran A, Redley M, de Wit K. The psychological impact of pulmonary embolism: A mixed-methods study. *Research and Practice in Thrombosis and Haemostasis* 2021; **5**(2): 301-7.

204. Kirchberger I, Ruile S, Linseisen J, Haberl S, Meisinger C, Berghaus TM. The lived experience with pulmonary embolism: A qualitative study using focus groups. *Respiratory Medicine* 2020; **167**: 105978.

205. Chuang L-H, Gumbs P, van Hout B, et al. Health-related quality of life and mortality in patients with pulmonary embolism: a prospective cohort study in seven European countries. *Quality of Life Research* 2019; **28**(8): 2111-24.

206. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *European Journal of Epidemiology* 2014; **29**(8): 541-9.

207. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; **7**: 449-90.

208. Schneeweiss S, Wang PS, Avorn J, Glynn RJ. Improved comorbidity adjustment for predicting mortality in Medicare populations. *Health Serv Res* 2003; **38**(4): 1103-20.

209. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scandinavian journal of public health* 2011; **39**(7 Suppl): 54-7.

210. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol* 2017; **46**(3): 798-f.

211. Timmermans B. The Danish Integrated Database for Labor Market Research: Towards Demystification for the English Speaking Audience. *DRUID, Copenhagen Business School, Department of Industrial Economics and Strategy/Aalborg University, Department of Business Studies, DRUID Working Papers* 2010.

212. Directorate-General for Employment SAaI, The European Comission. Your social security rights in Denmark. 2019.

213. Rothman KJLTLVTJHS. Modern epidemiology; 2021.

214. Fletcher GS. Clinical epidemiology : the essentials. 2021.

215. Rothman KJ. Epidemiology: an introduction: Oxford university press; 2012.

216. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**(446): 496-509.

217. Samkoff JS, Comstock GW. Epidemiology of pulmonary embolism: mortality in a general population. *Am J Epidemiol* 1981; **114**(4): 488-96.

218. Kort D, van Rein N, van der Meer FJM, et al. Relationship between neighborhood socioeconomic status and venous thromboembolism: results from a population-based study. *Journal of thrombosis and haemostasis : JTH* 2017; **15**(12): 2352-60.

219. Zoller B, Li X, Sundquist J, Sundquist K. Neighborhood deprivation and hospitalization for venous thromboembolism in Sweden. *J Thromb Thrombolysis* 2012; **34**(3): 374-82.

220. Pampel FC, Krueger PM, Denney JT. Socioeconomic Disparities in Health Behaviors. *Annual review of sociology* 2010; **36**: 349-70.

221. Havranek EP, Mujahid MS, Barr DA, et al. Social Determinants of Risk and Outcomes for Cardiovascular Disease. *Circulation* 2015; **132**(9): 873-98.

222. Sobal J, Stunkard AJ. Socioeconomic status and obesity: a review of the literature. *Psychological bulletin* 1989; **105**(2): 260-75.

223. Stalsberg R, Pedersen AV. Are Differences in Physical Activity across Socioeconomic Groups Associated with Choice of Physical Activity Variables to Report? *International journal of environmental research and public health* 2018; **15**(5).

224. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 2). *Journal of epidemiology and community health* 2006; **60**(2): 95-101.

225. Geyer S, Hemström Ö, Peter R, Vågerö D. Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. *J Epidemiol Community Health* 2006; **60**(9): 804-10.

226. Mackenbach JP. Health inequalities: Persistence and change in European welfare states. Oxford: Oxford University Press; 2019.

227. von Känel R, Mills PJ, Fainman C, Dimsdale JE. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease? *Psychosomatic medicine* 2001; **63**(4): 531-44.

228. Ramsay S, Lowe GDO, Whincup PH, Rumley A, Morris RW, Wannamethee SG. Relationships of inflammatory and haemostatic markers with social class: Results from a population-based study of older men. *Atherosclerosis* 2008; **197**(2): 654-61.

229. Kumari M, Marmot M, Brunner E. Social determinants of von willebrand factor: the Whitehall II study. *Arterioscler Thromb Vasc Biol* 2000; **20**(7): 1842-7.

230. Krokstad S, Johnsen R, Westin S. Social determinants of disability pension: a 10-year follow-up of 62 000 people in a Norwegian county population. *International Journal of Epidemiology* 2002; **31**(6): 1183-91.

231. Brun C, Boggild H, Eshoj P. [Socioeconomic risk indicators for disability pension within the Danish workforce. A registry-based cohort study of the period 1994-1998]. *Ugeskr Laeger* 2003; **165**(35): 3315-9.

232. Polvinen A, Laaksonen M, Gould R, Lahelma E, Martikainen P. The contribution of major diagnostic causes to socioeconomic differences in disability retirement. *Scandinavian Journal of Work, Environment and Health* 2014; **40**(4): 353-60.

233. Halford C, Wallman T, Welin L, et al. Effects of self-rated health on sick leave, disability pension, hospital admissions and mortality. A population-based longitudinal study of nearly 15,000 observations among Swedish women and men. *BMC public health* 2012; **12**: 1103.

234. Peterson U, Bergstrom G, Demerouti E, Gustavsson P, Asberg M, Nygren A. Burnout levels and self-rated health prospectively predict future long-term sickness absence: a study among female health professionals. *Journal of occupational and environmental medicine* 2011; **53**(7): 788-93.

235. Haukenes I, Farbu EH, Riise T, Tell GS. Physical health-related quality of life predicts disability pension due to musculoskeletal disorders: seven years follow-up of the Hordaland Health Study Cohort. *BMC public health* 2014; **14**(1): 167.

236. Virtanen M, Lallukka T, Ervasti J, et al. The joint contribution of cardiovascular disease and socioeconomic status to disability retirement: A register linkage study. *International Journal of Cardiology* 2017; **230**: 222-7.

237. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull* 2007; **81-82**: 21-37.

238. Leka S, Jain A, World Health O. Health impact of psychosocial hazards at work: an overview. Geneva: World Health Organization; 2010.

239. Robroek SJ, Rongen A, Arts CH, Otten FW, Burdorf A, Schuring M. Educational Inequalities in Exit from Paid Employment among Dutch Workers: The Influence of Health, Lifestyle and Work. *PLoS One* 2015; **10**(8): e0134867.

240. Bruusgaard D, Smeby L, Claussen B. Education and disability pension: A stronger association than previously found. *Scandinavian journal of public health* 2010; **38**(7): 686-90.

241. Stain M, Schönauer V, Minar E, et al. The post-thrombotic syndrome: risk factors and impact on the course of thrombotic disease. *Journal of Thrombosis and Haemostasis* 2005; **3**(12): 2671-6.

242. Haukenes I, Gjesdal S, Rortveit G, Riise T, Mæland JG. Women's higher likelihood of disability pension: the role of health, family and work. A 5–7 years follow-up of the Hordaland Health Study. *BMC public health* 2012; **12**(1): 720.

243. Ervasti J, Virtanen M, Lallukka T, et al. Permanent work disability before and after ischaemic heart disease or stroke event: a nationwide population-based cohort study in Sweden. *BMJ Open* 2017; **7**(9): e017910.

244. Osler M, Mårtensson S, Prescott E, Carlsen K. Impact of gender, co-morbidity and social factors on labour market affiliation after first admission for acute coronary syndrome. A cohort study of Danish patients 2001-2009. *PLoS One* 2014; **9**(1): e86758.

245. Karlsson N, Borg K, Carstensen J, Hensing G, Alexanderson K. Risk of disability pension in relation to gender and age in a Swedish county; a 12-year population based, prospective cohort study. *Work (Reading, Mass)* 2006; **27**(2): 173-9.

246. Haukenes I, Löve J, Hensing G, et al. Inequity in disability pension: an intersectional analysis of the co-constitution of gender, education and age. The Hordaland Health Study. *Critical Public Health* 2019; **29**(3): 302-13.

247. Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen J-B, Sørensen HT. Socioeconomic status and risk of incident venous thromboembolism. *Journal of Thrombosis and Haemostasis*; **n/a**(n/a).

248. Hoffmann R, Kröger H, Tarkiainen L, Martikainen P. Dimensions of Social Stratification and Their Relation to Mortality: A Comparison Across Gender and Life Course Periods in Finland. *Social Indicators Research* 2019; **145**(1): 349-65.

249. McDonough P, Williams DR, House JS, Duncan GJ. Gender and the socioeconomic gradient in mortality. *J Health Soc Behav* 1999; **40**(1): 17-31.

250. McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. *The Lancet* 2006; **368**(9533): 371-8.

251. Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen JB, Sørensen HT. Risk of a permanent work-related disability pension after incident venous thromboembolism in Denmark: A population-based cohort study. *PLoS Med* 2021; **18**(8): e1003770.

252. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. *J Thromb Thrombolysis* 2009; **28**(4): 465-76.

253. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *Jama* 2008; **300**(20): 2379-88.

254. Strine TW, Chapman DP, Kobau R, Balluz L. Associations of self-reported anxiety symptoms with health-related quality of life and health behaviors. *Soc Psychiatry Psychiatr Epidemiol* 2005; **40**(6): 432-8.

255. Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen J-B, Sørensen HT. Socioeconomic status and risk of incident venous thromboembolism. *Journal of Thrombosis and Haemostasis* 2021; **19**(12): 3051-61.

256. von Känel R, Margani A, Stauber S, et al. Depressive symptoms as a novel risk factor for recurrent venous thromboembolism: a longitudinal observational study in patients referred for thrombophilia investigation. *PLoS One* 2015; **10**(5): e0125858.

257. Evans CR, Hong C-P, Folsom AR, et al. Lifestyle Moderates Genetic Risk of Venous Thromboembolism. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2020; **40**(11): 2756-63.

258. Musselman DL, Tomer A, Manatunga AK, et al. Exaggerated platelet reactivity in major depression. *The American journal of psychiatry* 1996; **153**(10): 1313-7.

259. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological bulletin* 2014; **140**(3): 774-815.

260. Gold PW. The organization of the stress system and its dysregulation in depressive illness. *Molecular Psychiatry* 2015; **20**(1): 32-47.

261. Sandrini L, Ieraci A, Amadio P, Zarà M, Barbieri SS. Impact of Acute and Chronic Stress on Thrombosis in Healthy Individuals and Cardiovascular Disease Patients. *Int J Mol Sci* 2020; **21**(21).

262. Hammen CL. Stress and depression: old questions, new approaches. *Current Opinion in Psychology* 2015; **4**: 80-5.

263. Olsen J, Basso O, Sørensen HT. What is a population-based registry? *Scandinavian journal of public health* 1999; **27**(1): 78-.

264. Thygesen LC, Ersbøll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. *Eur J Epidemiol* 2014; **29**(8): 551-8.

265. Pearce N. Analysis of matched case-control studies. *BMJ* 2016; **352**: i969.

266. Szklo M, Nieto FJ. Epidemiology : beyond the basics. Burlington, Mass.: Jones & Bartlett Learning; 2014.

267. Sørensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. *Hepatology* 2006; **44**(5): 1075-82.

268. Hoffmann R, Kröger H, Geyer S. Social Causation Versus Health Selection in the Life Course: Does Their Relative Importance Differ by Dimension of SES? *Social Indicators Research* 2019; **141**(3): 1341-67.

269. Howe LD, Galobardes B, Matijasevich A, et al. Measuring socio-economic position for epidemiological studies in low- and middle-income countries: a methods of measurement in epidemiology paper. *Int J Epidemiol* 2012; **41**(3): 871-86.

270. Status CoS, Cynthia Hudley P, UC-Santa Barbara, Ramani Durvasula P, California State University, Los Angeles, et al. Examining the Complexities between

Health Disparities and Poverty. 2014.

271. Lynch J, Kaplan G. Socioeconomic position: Social epidemiology. New York: Oxford University Press; 2000.

272. Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic Status in Health ResearchOne Size Does Not Fit All. *JAMA* 2005; **294**(22): 2879-88.

273. Warren JR, Kuo HH. How to measure "what people do for a living" in research on the socioeconomic correlates of health. *Annals of epidemiology* 2003; **13**(5): 325-34.

274. Martikainen P, Valkonen T. Bias related to the exclusion of the economically inactive in studies on social class differences in mortality. *Int J Epidemiol* 1999; **28**(5): 899-904.

275. Green MJ, Popham F. Interpreting mutual adjustment for multiple indicators of socioeconomic position without committing mutual adjustment fallacies. *BMC public health* 2019; **19**(1): 10.

276. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scandinavian journal of public health* 2011; **39**(7 Suppl): 95-8.

277. Jensen VM, Rasmussen AW. Danish Education Registers. *Scandinavian journal of public health* 2011; **39**(7 Suppl): 91-4.

278. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scandinavian journal of public health* 2011; **39**(7 Suppl): 103-5.

279. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016; **6**(11): e012832.

280. Sørensen HT, Baron JA. Medical databases. *Teaching Epidemiology: A guide for teachers in epidemiology, public health and clinical medicine* 2015: 475.

281. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. *Clin Pract Epidemiol Ment Health* 2009; **5**: 4.

282. Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, Schmidt M, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012; **4**: 303-13.

283. Abbing-Karahagopian V, Huerta C, Souverein PC, et al. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. *European journal of clinical pharmacology* 2014; **70**(7): 849-57.

284. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC medical research methodology* 2011; **11**: 83.

285. Bours MJL. Tutorial: A nontechnical explanation of the counterfactual definition of effect modification and interaction. *Journal of Clinical Epidemiology* 2021; **134**: 113-24.

286. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *International Journal of Epidemiology* 2012; **41**(2): 514-20.

287. Corraini P, Olsen M, Pedersen L, Dekkers OM, Vandenbroucke JP. Effect modification, interaction and mediation: an overview of theoretical insights for clinical investigators. *Clinical epidemiology* 2017; **9**: 331-8.

288. Knol MJ, VanderWeele TJ, Groenwold RHH, Klungel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. *European Journal of Epidemiology* 2011; **26**(6): 433-8.

289. VanderWeele TJ, Knol MJ. A Tutorial on Interaction. *Epidemiologic Methods* 2014; **3**(1): 33-72.

290. Barco S, Woersching AL, Spyropoulos AC, Piovella F, Mahan CE. European Union-28: An annualised cost-of-illness model for venous thromboembolism. *Thromb Haemost* 2016; **115**(4): 800-8.

291. Gustafsson N, Poulsen PB, Stallknecht SE, Dybro L, Paaske Johnsen S. Societal costs of venous thromboembolism and subsequent major bleeding events: a national register-based study. *European Heart Journal - Quality of Care and Clinical Outcomes* 2019; **6**(2): 130-7.

Appendix 1

Received: 9 June 2021 | Accepted: 7 September 2021

DOI: 10.1111/jth.15523

ORIGINAL ARTICLE

Socioeconomic status and risk of incident venous thromboembolism

Helle Jørgensen[1,2,3] | Erzsébet Horváth-Puhó[2] | Kristina Laugesen[2] | Sigrid Brækkan[1,3] | John-Bjarne Hansen[1,3] | Henrik Toft Sørensen[2]

[1]Thrombosis Research Center (TREC), Department of Clinical Medicine, UiT, The Arctic University of Norway, Tromso, Norway

[2]Department of Clinical Epidemiology, Aarhus University Hospital and Aarhus University, Aarhus, Denmark

[3]Division of Internal Medicine, University Hospital of North Norway, Tromso, Norway

Correspondence
Helle Jørgensen, Thrombosis Research Center (TREC), Department of Clinical Medicine, UiT-The Arctic University of Norway, N-9037 Tromsø, Norway.
Email: helle.jorgensen@uit.no

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

Manuscript Handled by: Jean Connors

Final decision: Jean Connors, 07 September 2021

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

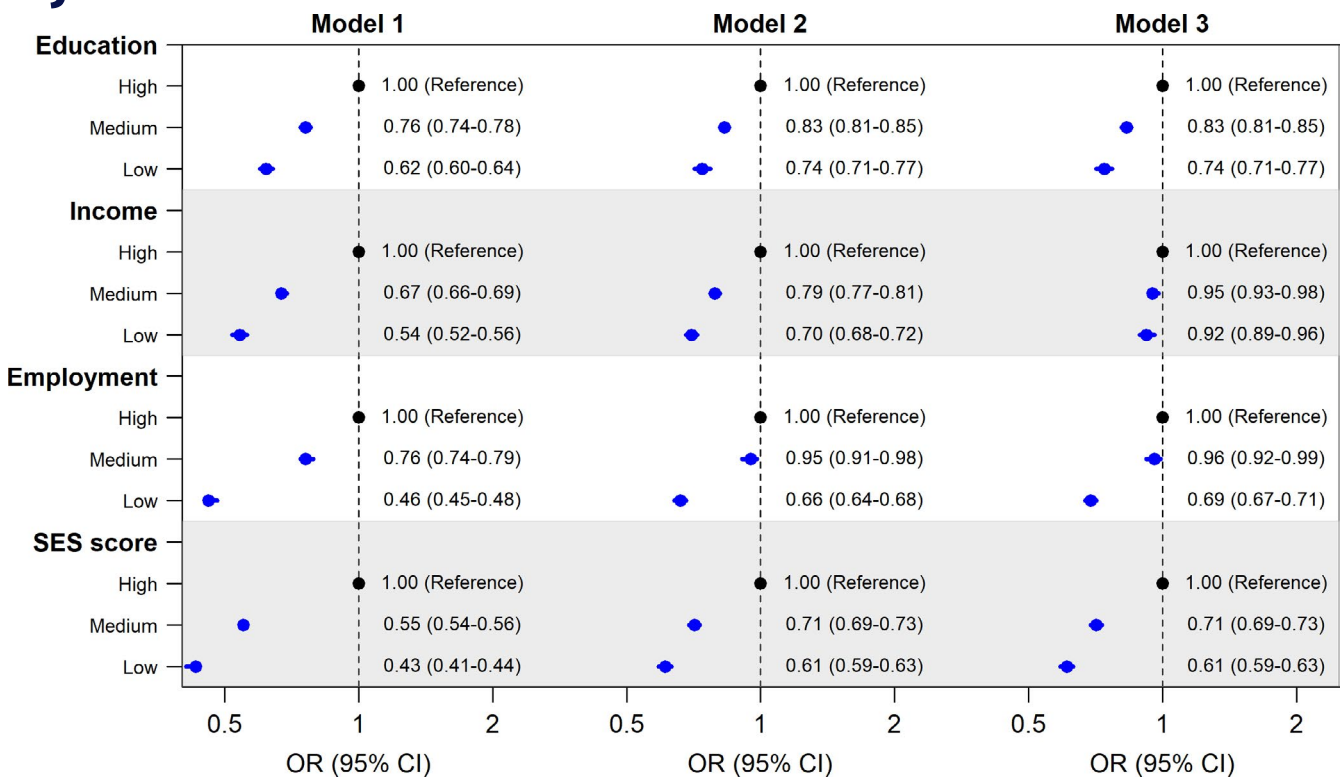


FIGURE 1 Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for venous thromboembolism (VTE), according to education, income, employment status, and SES score. Model 1: Crude model controlled for matching variables by study design. Model 2: Adjusted for obesity, cancer, coronary 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

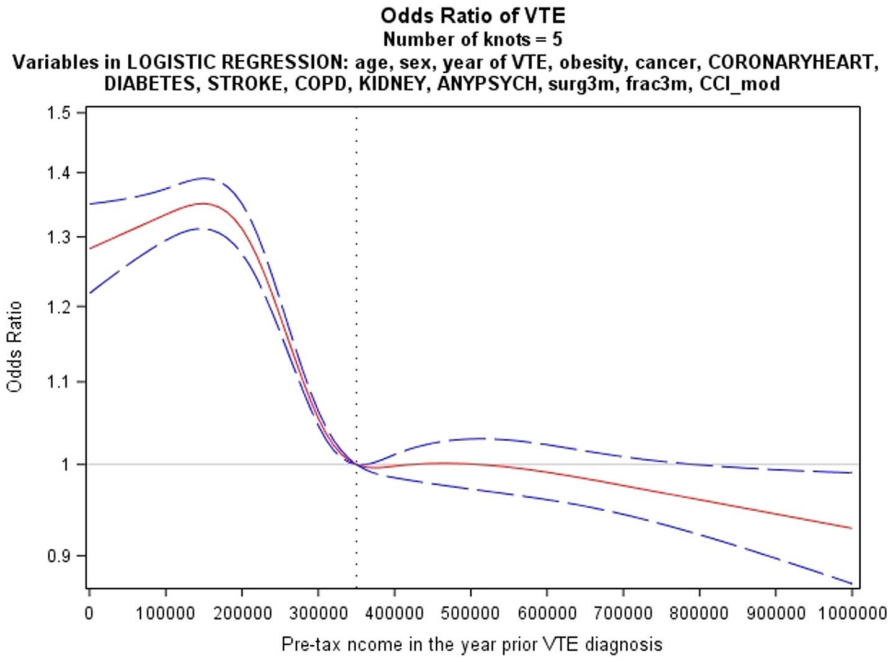


FIGURE 2 Restricted cubic spline models with adjusted odds ratios and 95% confidence intervals for venous thromboembolism (VTE), according to income

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]

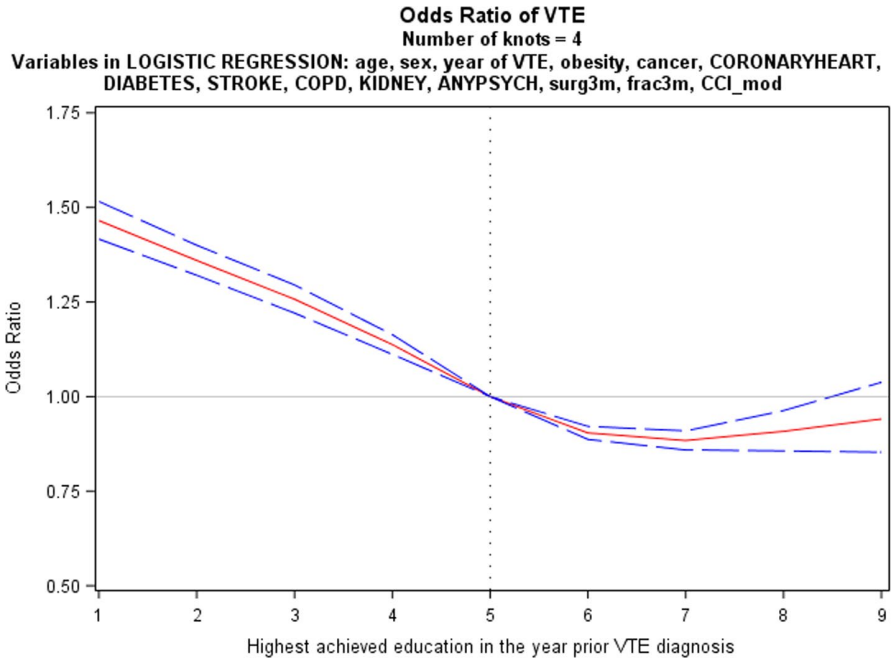


FIGURE 3 Restricted cubic spline models with adjusted odds ratios and 95% confidence intervals for venous thromboembolism (VTE), according to education

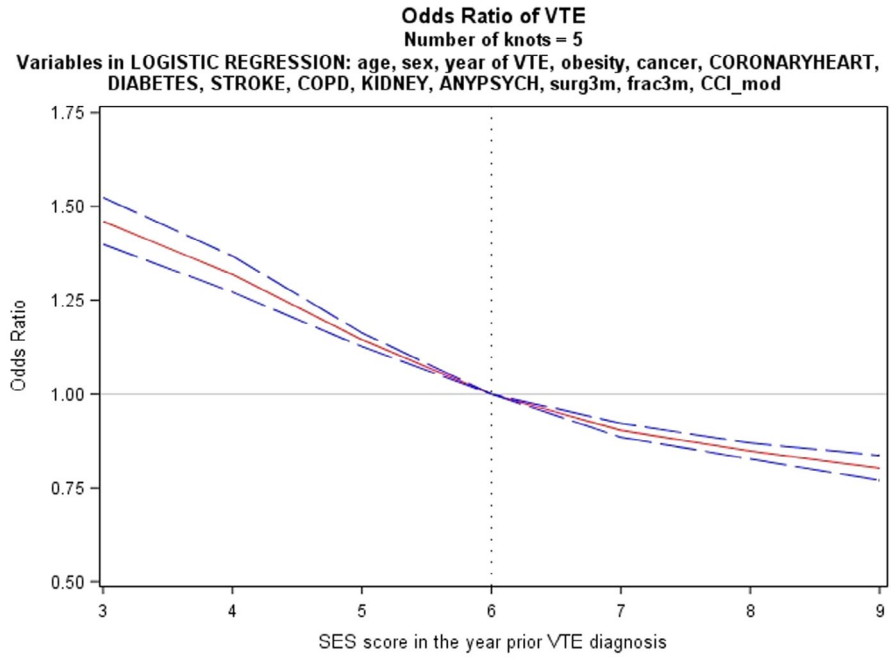


FIGURE 4 Restricted cubic spline models with adjusted odds ratios and 95% confidence intervals for venous thromboembolism (VTE), according to SES score

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.

ORCID

Helle Jørgensen https://orcid.org/0000-0003-2503-6694
Henrik Toft Sørensen https://orcid.org/0000-0003-4299-7040

REFERENCES

1. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I4-8.
2. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol*. 2014;34(11):2363-2371.
3. de Mestral C, Stringhini S. Socioeconomic status and cardiovascular disease: an update. *Curr Cardiol Rep*. 2017;19(11):115.
4. Addo J, Ayerbe L, Mohan KM, et al. Socioeconomic status and stroke: an updated review. *Stroke*. 2012;43(4):1186-1191.

5. Schultz William M, Kelli Heval M, Lisko John C, et al. Socioeconomic status and cardiovascular outcomes. *Circulation*. 2018;137(20):2166-2178.
6. Rosengren A, Freden M, Hansson PO, Wilhelmsen L, Wedel H, Eriksson H. Psychosocial factors and venous thromboembolism: a long-term follow-up study of Swedish men. *J Thromb Haemost*. 2008;6(4):558-564.
7. Isma N, Merlo J, Ohlsson H, Svensson PJ, Lindblad B, Gottsater A. Socioeconomic factors and concomitant diseases are related to the risk for venous thromboembolism during long time follow-up. *J Thromb Thrombolysis*. 2013;36(1):58-64.
8. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. *Circulation*. 2010;121(17):1896-1903.
9. Zoller B, Li X, Sundquist J, Sundquist K. Socioeconomic and occupational risk factors for venous thromboembolism in Sweden: a nationwide epidemiological study. *Thromb Res*. 2012;129(5):577-582.
10. Samkoff JS, Comstock GW. Epidemiology of pulmonary embolism: mortality in a general population. *Am J Epidemiol*. 1981;114(4):488-496.
11. Kort D, van Rein N, van der Meer FJM, et al. Relationship between neighborhood socioeconomic status and venous thromboembolism: results from a population-based study. *J Thromb Haemost*. 2017;15(12):2352-2360.
12. Zoller B, Li X, Sundquist J, Sundquist K. Neighborhood deprivation and hospitalization for venous thromboembolism in Sweden. *J Thromb Thrombolysis*. 2012;34(3):374-382.
13. Stringhini S, Carmeli C, Jokela M, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. *Lancet*. 2017;389(10075):1229-1237.
14. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591.
15. Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation*. 2014;130(10):829-836.
16. Adelborg K, Corraini P, Darvalics B, et al. Risk of thromboembolic and bleeding outcomes following hematological cancers: a Danish population-based cohort study. *J Thromb Haemost*. 2019;17(8):1305-1318.
17. Heide-Jorgensen U, Adelborg K, Kahlert J, Sorensen HT, Pedersen L. Sampling strategies for selecting general population comparison cohorts. *Clin Epidemiol*. 2018;10:1325-1337.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
19. Darin-Mattsson A, Fors S, Kåreholt I. Different indicators of socioeconomic status and their relative importance as determinants of health in old age. *Int J Equity Health*. 2017;16(1):173.
20. Geyer S, Hemström Ö, Peter R, Vågerö D. Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. *J Epidemiol Community Health*. 2006;60(9):804-810.
21. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. *Public Health Rep*. 2014;129:19-31.
22. Cirino PT, Chin CE, Sevcik RA, Wolf M, Lovett M, Morris RD. Measuring socioeconomic status: reliability and preliminary validity for different approaches. *Assessment*. 2002;9(2):145-155.
23. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull*. 2007;81–82:21-37.
24. Mackenbach JP. *Health inequalities: Persistence and change in European welfare states*. Oxford University Press; 2019:252.
25. Pampel FC, Krueger PM, Denney JT. Socioeconomic disparities in health behaviors. *Annu Rev Sociol*. 2010;36:349-370.
26. Shavers VL. Measurement of socioeconomic status in health disparities research. *J Natl Med Assoc*. 2007;99(9):1013-1023.
27. Levesque JF, Harris MF, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. *Int J Equity Health*. 2013;12:18.
28. Havranek EP, Mujahid MS, Barr DA, et al. Social determinants of risk and outcomes for cardiovascular disease. *Circulation*. 2015;132(9):873-898.
29. Sobal J, Stunkard AJ. Socioeconomic status and obesity: a review of the literature. *Psychol Bull*. 1989;105(2):260-275.
30. Stalsberg R, Pedersen AV. Are differences in physical activity across socioeconomic groups associated with choice of physical activity variables to report? *Int J Environ Res Public Health*. 2018;15(5):922.
31. Evensen LH, Braekkan SK, Hansen JB. Regular physical activity and risk of venous thromboembolism. *Semin Thromb Hemost*. 2018;44(8):765-779.
32. von Känel R, Mills PJ, Fainman C, Dimsdale JE. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease? *Psychosom Med*. 2001;63(4):531-544.
33. Ramsay S, Lowe GDO, Whincup PH, Rumley A, Morris RW, Wannamethee SG. Relationships of inflammatory and haemostatic markers with social class: results from a population-based study of older men. *Atherosclerosis*. 2008;197(2):654-661.
34. Kumari M, Marmot M, Brunner E. Social determinants of von Willebrand factor: the Whitehall II study. *Arterioscler Thromb Vasc Biol*. 2000;20(7):1842-1847.
35. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ open*. 2016;6(11):e012832.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen J-B, Sørensen HT. Socioeconomic status and risk of incident venous thromboembolism. *J Thromb Haemost*. 2021;00:1–11. https://doi.org/10.1111/jth.15523

Appendix 2

PLOS MEDICINE

RESEARCH ARTICLE

Risk of a permanent work-related disability pension after incident venous thromboembolism in Denmark: A population-based cohort study

Helle Jørgensen[1]*, Erzsébet Horváth-Puhó[2], Kristina Laugesen[2], Sigrid Brækkan[1,3], John-Bjarne Hansen[1,3], Henrik Toft Sørensen[2]

1 Thrombosis Research Center (TREC), Department of Clinical Medicine, UiT, The Arctic University of Norway, Tromsø, Norway, **2** Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, **3** Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

* helle.jorgensen@uit.no

Citation: Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen J-B, Sørensen HT (2021) Risk of a permanent work-related disability pension after incident venous thromboembolism in Denmark: A population-based cohort study. PLoS Med 18(8): e1003770. https://doi.org/10.1371/journal.pmed.1003770

Academic Editor: Jeremy D. Goldhaber-Fiebert, Stanford University, UNITED STATES

Received: February 9, 2021

Accepted: August 16, 2021

Published: August 31, 2021

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRS, Civil

Abstract

Background

Long-term complications of venous thromboembolism (VTE) hamper physical function and impair quality of life; still, it remains unclear whether VTE is associated with risk of permanent work-related disability. We aimed to assess the association between VTE and the risk of receiving a permanent work-related disability pension and to assess whether this association was explained by comorbidities such as cancer and arterial cardiovascular disease.

Methods and findings

A Danish nationwide population-based cohort study consisting of 43,769 individuals aged 25 to 66 years with incident VTE during 1995 to 2016 and 218,845 birth year-, sex-, and calendar year-matched individuals from the general population, among whom 45.9% (N = 120,540) were women, was established using Danish national registries. The cohorts were followed throughout 2016, with permanent work-related disability pension as the outcome. Hazard ratios (HRs) with 95% confidence intervals (CIs) for disability pension were computed and stratified by sex and age groups (25 to 34, 35 to 44, 45 to 54, and 55 to 66 years of age) and adjusted for comorbidities and socioeconomic variables.

Permanent work-related disability pensions were granted to 4,415 individuals with VTE and 9,237 comparison cohort members (incidence rates = 17.8 and 6.2 per 1,000 person-years, respectively). VTE was associated with a 3-fold (HR 3.0, 95% CI: 2.8 to 3.1) higher risk of receiving a disability pension. Adjustments for socioeconomic status and comorbidities such as cancer and cardiovascular diseases reduced the estimate (HR 2.3, 95% CI: 2.2 to 2.4). The risk of disability pension receipt was slightly higher in men than in women (HR 2.5, 95% CI: 2.3 to 2.6 versus HR 2.1, 95% CI: 2.0 to 2.3). As this study is based on medical and administrative registers, information on post-VTE care, individual health behavior, and workplace factors linked to disability pension in the general population are lacking.

Registration System; CTEPH, chronic thromboembolic pulmonary hypertension; DNPR, Danish National Patient Registry; DVT, deep vein thrombosis; HR, hazard ratio; HRQoL, health-related quality of life; IDA, Integrated Database for Labour Market Research; IR, incidence rate; PE, pulmonary embolism; post-PE syndrome, post-pulmonary embolism syndrome; PTS, post-thrombotic syndrome; QoL, quality of life; SES, socioeconomic status; VTE, venous thromboembolism.

Furthermore, as disability pension schemes vary, our results might not be directly generalizable to other countries or time periods.

Conclusions

In this study, incident VTE was associated with increased risk of subsequent permanent work-related disability, and this association was still observed after accounting for comorbidities such as cancer and cardiovascular diseases. Our results emphasize the social consequences of VTE and may help occupational and healthcare professionals to identify vulnerable individuals at risk of permanent exclusion from the labor market after a VTE event.

Author summary

Why was this study done?

- Long-term complications of venous thromboembolism (VTE) are known to hamper functional activities and impair quality of life.
- Existing research on the risk of permanent exclusion from the labor marked after a VTE is scarce.

What did the researchers do and find?

- In this large nationwide study of >250,000 individuals, we found that VTE is associated with a 3-fold (hazard ratio (HR) 3.0, 95% confidence interval (CI): 2.8 to 3.1) higher risk of permanent work-related disability compared to the general population.
- The association between VTE and disability pension was still observed (HR 2.3, 95% CI: 2.2 to 2.4) after adjustments for socioeconomic status and comorbidities such as cancer and cardiovascular diseases.

What do these findings mean?

- Patients suffering from a VTE are at risk of permanent exclusion from the labor market.
- Our findings emphasize the social consequences of VTE and can contribute to further improvement of protective strategies to diminish the burden of VTE on public health and healthcare systems.
- As disability pension schemes vary, our results might not be directly generalizable to other countries or time periods.
- Even though we have adjusted for multiple comorbidities and socioeconomic factors, residual confounding (e.g., due to individual health behavior or work place factors) cannot be completely ruled out.

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a prevalent multifactorial disease with an incidence rate (IR) of 1 to 2 per 1,000 person-years in adults [1,2]. Despite increased public awareness of the disease and availability of preventive measures, VTE incidence has increased during the past decades [3]. Severe complications such as increased mortality risk [4], recurrence [5,6], post-thrombotic syndrome (PTS) [7,8], and post-pulmonary embolism (post-PE) syndrome [9–13] may cause reduced mobility, lessened capacity for work, and a lowered quality of life (QoL) in a large proportion of individuals with VTE [7,8,14–17].

Although VTE has been documented as a leading cause of lost disability-adjusted life-years, existing research on work-related disability and socioeconomic consequences following a VTE is scarce [5,17]. Two European multicenter studies including 1,399 individuals with PE and 2,056 individuals with DVT found that 27.8% of those with PE and 29.5% of those with DVT had not returned to work 1 year after their VTE diagnosis [18,19]. However, these studies did not adjust for other comorbidities, and the follow-up time was limited to 12 months [18,19]. A Norwegian cohort study of 66,005 individuals, including 386 individuals with VTE, with 14 years of follow-up, reported a 37% increased risk of permanent work-related disability in individuals with VTE compared to the general population, with a higher risk in individuals with DVT than in individuals with PE [14]. Thus, VTE represents a major burden to public health and healthcare systems [16,17,20]. Further research on the work-related consequences of VTE is required to improve protective strategies that diminish the indirect costs and social burden of the disease. The aim of this nationwide population-based cohort study was to assess the risk of receiving a permanent work-related disability pension among patients with VTE compared to individuals from the general population without VTE, according to age, sex, and VTE subtypes. As VTE often occurs secondary to comorbidities such as cancer or cardiovascular disease (i.e., myocardial infarction and stroke) [2,21,22], we also investigated whether a potential association between VTE and receipt of a permanent disability pension was explained by comorbidities.

Methods

Design and setting

The prospective analysis plan for this study can be found in the supporting information (S1 Analysis plan). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (S1 Checklist).

We conducted this population-based cohort study using linked data from Danish administrative and medical databases. The Danish healthcare system is government funded, ensuring free and equal access to tax-supported healthcare for all legal residents [23]. Around 90% of Denmark's population is of Danish descent, defined as having at least 1 parent who was born in Denmark and has Danish citizenship. Upon birth or immigration, the Danish Civil Registration System (CRS) assigns a unique 10-digit personal identifier (CPR number) to all Danish residents. The CPR number allows accurate and complete individual-level linkage among all Danish registries, as well as tracking of study participants over time, allowing accurate censoring due to emigration or death [23].

VTE cohort

The Danish National Patient Registry (DNPR) contains data on all nonpsychiatric discharges from Danish hospitals since 1977 and on psychiatric inpatients, emergency department, and

outpatient specialty clinic contacts since 1995 [24]. DNPR data permit individual-level identification of patients' medical histories. Using ICD-10 codes, we searched the DNPR to identify all inpatients and outpatients with a primary or secondary diagnosis of DVT or PE in the period January 1, 1995 through December 31, 2016. The first hospital admission/outpatient visit date defined the VTE date. We excluded individuals already receiving a work-related disability pension and patients with a VTE diagnosis before 1994 (identified using ICD-8 codes). Patients aged <25 years and patients retired from work due to advanced age at study inclusion (>66 years) were also excluded, as they were unlikely to be eligible for the outcome. VTE registered solely in emergency room departments were excluded, as they frequently represent working diagnoses with high rates of clinical misclassification [25].

We classified VTE as either DVT or PE. If a patient had a simultaneous PE and DVT diagnosis, we used the PE diagnosis due to its higher mortality rate [4]. In addition, VTEs accompanied by a preexisting cancer diagnosis whenever before or on index date, in addition to fracture, trauma, surgery, and/or pregnancy within 90 days prior to VTE diagnosis, were classified as provoked VTE, while VTEs in the absence of these factors were classified as unprovoked VTE [26].

General population comparison cohort

We used the CRS to sample a population-based comparison cohort. For each VTE patient, up to 5 individuals from the general population were randomly matched on sex, year of birth, and calendar year, with replacement [27]. A VTE patient's hospital admission date was defined as the index date for the comparison cohort members. Individuals in the comparison cohort could not have been hospitalized for VTE or have received a permanent work-related disability pension prior to the index date. If a person from the comparison cohort subsequently experienced a VTE, he/she was censored and moved to the exposure cohort from that date onwards.

Outcome

We extracted information on receipt of a work-related disability pension from the Integrated Database for Labour Market Research (IDA) at Statistics Denmark. This database has covered the employment status, workplace, and employers of the entire Danish population yearly since 1980 [28]. Danish residents are entitled to a disability pension if their capacity for work is substantially and permanently reduced to such a degree that they will never be able to provide for themselves through regular or flexible work [29]. All persons who have permanent legal residence in Denmark and who have lived in Denmark for at least 3 years since their 15th birthday are eligible for a disability pension until public retirement age [29]. A 2013 legislative reform made granting of a disability pension to persons younger than age 40 years much stricter [29].

A direct transition from work to receipt of a disability pension rarely occurs, as most persons go through a period of sick leave and measures to improve their capacity for work before a disability pension is granted [30]. We therefore excluded individuals with VTE and comparison cohort members who had received a disability pension in the same or previous calendar year as their VTE/index date. This way we avoided potential bias and ensured that the VTE itself was the reason for disability, rather than a consequence of another condition. Receipt of a disability pension was ascertained annually at the end of November of a given calendar year, and we defined the disability pension date as January 1 of that year.

It is important to note that disability can vary in both length and severity and that it does not necessarily lead to a permanent exit from work life. Measuring permanent receipt of a disability pension as our study outcome might therefore underestimate the actual incidence of disability caused by VTE in the general population.

Cohort characteristics

We obtained information on comorbidities diagnosed prior to the VTE/index date using ICD-8 and ICD-10 codes from the DNPR for obesity, cancer, coronary heart disease (including atrial fibrillation), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, surgery 3 months prior to the VTE/index date, and diseases included in the Charlson Comorbidity Index [31]. All ICD codes used in the study are provided in S4 Table.

We measured socioeconomic status (SES) based on education, employment status, and income. Information on education was obtained from the Educational Attainment Register for the year prior to the VTE/index date. We divided the level of education (i.e., low, medium, and high) into age-specific groups based on the distribution of education in each group (S2 and S3 Tables). Income and employment status were extracted from the IDA. To avoid the impact of inflation and to account for salary changes over calendar time, we calculated yearly income quartiles for each index year based on the previous year (e.g., quartiles in 2001 were calculated based on the income of exposed and unexposed persons with an index date in 2000). The 2 middle quartiles were merged to yield 3 categories (i.e., low, medium, and high). Employment status was measured the year prior to VTE/index date and categorized as "employed, unemployed, and outside the workforce." The category "outside the workforce" included persons in an educational program, those in early retirement, and those receiving other types of public support. Employment status was categorized as low (i.e., unemployed), medium (i.e., outside the workforce), and high (i.e., employed).

Using the "low, medium, and high" categorical distributions described above, we created an SES index for education, income, and employment status ranging from 1 to 3 for each category. The total SES index score thus ranged from 3 to 9. Based on the distribution of the total index sum score, we divided the SES index into high (i.e., scores of 8 and 9), medium (i.e., scores of 5 to 7), and low (i.e., scores of 3 and 4) SES, with high SES serving as reference.

Statistical analysis

We followed all cohort members from their index date until January 1 the year the work-related disability pension was recorded, emigration from Denmark, date of death, age 66, or end of the study period (December 31, 2016), whichever came first. Persons who turned 66 years old, emigrated, or died during follow-up were censored on the date of the event. Crude IRs were calculated as number of events per 1,000 person-years at risk. We used stratified Cox proportional hazards regression models to compute unadjusted and adjusted hazard ratios (HRs) as a measure of work-related disability with 95% confidence intervals (CIs). The proportional hazards assumption was tested using log–log plots and found not violated. Additionally, we explored sensitivities around thresholds of different ages against a confounder-adjusted restricted cubic spline with a prespecified list of 5 knots with age = 30 as reference (S1 Fig) and performed age- and sex-stratified analyses (age groups: 25 to 34 years, 35 to 44 years 45 to 54 years, and 55 to 66 years at index date).

We adjusted the HRs for a priori-defined potential confounding, including comorbidities, using 3 different models stratified by age group and sex. Model 1 was unadjusted and controlled for matching variables by study design. Model 2 additionally included SES index and obesity; Model 3 included adjustment for SES index score, obesity, cancer, coronary heart disease (including atrial fibrillation), diabetes, stroke, COPD, acute kidney failure/chronic kidney disease, and surgery 3 months prior to the VTE/index date, and the Charlson Comorbidity Index score (excluding comorbidities already adjusted for). We also performed age- and sex-stratified subgroup analyses with PE, DVT, and unprovoked and provoked VTE as exposure variables.

As the mortality rates were likely to differ among those with and without VTE, the rates of disability pension could potentially be overestimated as a result of competing risk of death. In order to account for death as a competing event, cumulative incidence functions were estimated by the methods proposed by Fine and Gray [32] and visualized according to VTE/no VTE and age groups (age 25 to 34 years, 35 to 44 years, 45 to 54 years, and 55 to 66 years).

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

Ethics

According to Danish legislation, registry-based studies do not require informed consent and approval from an ethics committee. The study was approved by the Danish Data Protection Agency (record no.2016-051-000001).

Results

We identified 43,769 individuals with VTE and 218,845 matched individuals from the general population aged 25 to 66 years at inclusion, among whom 45.9% ($N = 120,540$) were women. Baseline characteristics for individuals with VTE and members of the comparison cohort are provided in Table 1. VTE was associated with a higher proportion of individuals with low or medium SES than the comparison cohort (62.1% versus 56.8%), and more comorbidity, such as surgery 3 months prior to VTE/index date (14.6% versus 2.5%), history of cancer (12.2% versus 3.2%), coronary heart disease (including atrial fibrillation) (6.7% versus 4.2%), COPD (5.8% versus 3.0%), obesity (6.1% versus 2.6%), and diabetes (5.5% versus 3.8%) (Table 1).

Permanent work-related disability pensions were granted to 13,652 persons (5.2%) during a median overall follow-up time of 4.9 years (Table 2). Among pension recipients, 4,415 were individuals with VTE (10.1% of all individuals with VTE) (Table 2). Individuals with VTE who subsequently received a disability pension were characterized by a higher proportion of women (48.4% versus 45.6%) and a higher proportion of individuals with DVT (69.4% versus 65.3%) than individuals with VTE without disability pension (S2 Table).

The IR of disability in individuals with VTE was 17.8 (95% CI: 17.3 to 18.3) compared to 6.2 (95% CI: 6.0 to 6.3) in the comparison cohort (Table 2). This corresponded to an absolute rate difference for work-related disability pension in individuals with and without incident VTE of 11.6 events per 1,000 person-years at risk. In the unadjusted model, incident VTE was associated with a 3-fold (HR 3.0, 95% CI: 2.8 to 3.1) increased risk of subsequently receiving a disability pension (Table 2). The risk estimate for receipt of a disability pension decreased to 2.7-fold (HR 2.7, 95% CI: 2.6 to 2.8) after adjusting for the SES index score and obesity. Further adjustment for comorbidities (Model 3) attenuated the risk estimate (HR 2.3, 95% CI: 2.2 to 2.4) (Table 2).

Although the IR of disability increased with age for both individuals with VTE and the general population comparison group, we found that the HR for subsequent receipt of a disability pension decreased with increasing age (Table 2). After adjusting for SES and comorbidities, the HR for receiving a disability pension among individuals with VTE decreased from 2.7 (95% CI: 2.4 to 3.1) in the youngest age group to HR 2.2 (95% CI: 2.0 to 2.4) in the oldest age group (Model 3). Of note, there was an increase in the absolute risk difference from 8.4 per 1,000 person-years in the youngest age group to 13.0 per 1,000 person-years in the oldest age group (Table 2).

The IR of disability in the general comparison cohort was higher overall for women (IR 6.7, 95% CI: 6.5 to 6.9) than for men (IR 5.6, 95% CI: 5.5 to 5.8). However, VTE was associated with a somewhat higher IR for disability in men than in women (IR 18.1, 95% CI: 17.3 to 18.8, versus IR 17.5, 95% CI: 16.8 to 18.3) (Table 3). VTE remained associated with a higher relative

Table 1. Baseline characteristics of persons with VTE and members of the general comparison cohort.

	VTE (*n* = 43,769)	Comparison cohort (*n* = 218,845)
Sex (% women)	20,090 (45.9)	100,450 (45.9)
PE	15,006 (34.3)	
DVT	28,763 (65.7)	
Unprovoked VTE	32,788 (74.9)	
Provoked VTE	10,981 (25.1)	
SES score		
Low	5,173 (11.8)	18,334 (8.4)
Medium	22,037 (50.3)	105,921 (48.4)
High	15,308 (35.0)	88,533 (40.5)
Missing	1,251 (2.9)	6,057 (2.8)
Comorbidities		
Cancer	5,347 (12.2)	7,108 (3.2)
Coronary heart disease	2,948 (6.7)	9,201 (4.2)
Diabetes	2,406 (5.5)	8,321 (3.8)
COPD	2,537 (5.8)	6,531 (3.0)
Obesity	2,675 (6.1)	5,693 (2.6)
Stroke	772 (1.8)	2,054 (0.9)
Moderate to severe renal disease	767 (1.8)	1,221 (0.6)
Surgery 3 months prior to VTE/index date	6,410 (14.6)	5,364 (2.5)
Pregnancy 3 months prior VTE/index date	667 (1.5)	1,029 (0.5)
Trauma/fracture 3 months prior to VTE/index date	1,904 (4.4)	1,299 (0.6)
CCI*		
CCI score: 0	38,488 (87.9)	206,732 (94.5)
CCI score: 1	4,346 (9.9)	10,660 (4.9)
CCI score: > = 2	935 (2.1)	1,453 (0.7)

*CCI: Modified Charlson Comorbidity Index excluding ICD codes used in the covariate definition.

Values are numbers, with percentages in brackets.

COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PE, pulmonary embolism; SES, socioeconomic status; VTE, venous thromboembolism.

https://doi.org/10.1371/journal.pmed.1003770.t001

risk of receiving a disability pension in men (HR 2.5, 95% CI: 2.3 to 2.6) than in women (HR 2.1, 95% CI: 2.0 to 2.3), even after adjusting for SES and comorbidities.

The sex-specific difference in relative risk was largest in the youngest age group. VTE was associated with a 3.2-fold higher risk of disability pension in men (HR 3.2, 95% CI: 2.5 to 4.0) and 2.5-fold higher risk in women (HR 2.5, 95% CI: 2.1 to 2.9) aged 25 to 34 years, compared to the general population (Table 3). The HR for receiving a disability pension in men decreased gradually with increasing age from 3.2 (95% CI 2.5 to 4.0) in the age group 25 to 34 years to 2.2 (95% CI: 2.0 to 2.5) in the age group 55 to 66 years. Only a modest decline in the HR among women with VTE was observed across age groups. The absolute rate difference in disability pension receipt among men remained relatively stable at 13 per 1,000 person-years, while the absolute rate difference in women increased from 6.4 per 1,000 person-years in the age group 25 to 34 years to 16.6 per 1,000 person-years in the age group 55 to 66 years.

PE was associated with a higher relative risk of receiving a disability pension than DVT (Table 4). PE was associated with a 2.6-fold (HR 2.6, 95% CI: 2.4 to 2.8) higher risk and DVT a 2.2-fold higher risk (HR 2.2, 95% CI: 2.0 to 2.3) of receiving a disability pension compared to persons without VTE, after adjusting for SES and comorbidities (Table 4). For PE, the overall

Table 2. IRs and HRs with 95% CIs by age for receipt of a work-related DP among persons with and without VTE.

	Comparison cohort			VTE					
	No DP	DP	IR (95% CI)	No DP	DP	IR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Overall	218,845	9,237	6.2 (6.0–6.3)	43,769	4,415	17.8 (17.3–18.3)	3.0 (2.8–3.1)	2.7 (2.6–2.8)	2.3 (2.2–2.4)
Age 25–34	27,072	825	3.1 (2.9–3.3)	5,393	550	11.5 (10.5–12.4)	3.9 (3.5–4.4)	3.0 (2.7–3.4)	2.7 (2.4–3.1)
Age 35–44	42,046	2,049	5.2 (5.0–5.4)	8,412	1,091	16.5 (15.5–17.5)	3.3 (3.0–3.5)	2.8 (2.5–3.0)	2.5 (2.2–2.7)
Age 45–54	59,765	3,610	7.4 (7.1–7.6)	11,962	1,623	20.6 (19.6–21.6)	2.7 (2.6–2.9)	2.6 (2.4–2.8)	2.1 (2.0–2.3)
Age 55–66	89,962	2,753	7.9 (7.6–8.2)	18,002	1,151	20.9 (19.7–22.1)	2.7 (2.5–2.9)	2.7 (2.5–2.9)	2.2 (2.0–2.4)

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

Model 2: adjusted for SES score (education, employment status, and income) and obesity.

Model 3: adjusted for SES score (education, employment status, and income), obesity, cancer, coronary heart disease (including atrial fibrillation), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, surgery 3 months prior to the VTE/index date, and Charlson Comorbidity Index score, excluding comorbidities already adjusted for.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DP, disability pension; HR, hazard ratio; IR, incidence rate; SES, socioeconomic status; VTE, venous thromboembolism.

https://doi.org/10.1371/journal.pmed.1003770.t002

risk of receiving a disability pension was similar in men (HR 2.7, 95% CI: 2.4 to 3.0) and in women (HR 2.6, 95% CI: 2.3 to 2.9), while DVT showed a higher risk estimate for receipt of a disability pension in men (HR 2.4, 95% CI: 2.2 to 2.6) than in women (HR 2.0, 95% CI: 1.8 to 2.1).

The overall risk of receiving a disability pension following a PE remained relatively stable across age groups, while the risk after a DVT decreased with advancing age (Table 5). VTE in men in the age group 25 to 34 years was associated with a 3.1-fold higher risk of subsequent receipt of disability pension after both PE (HR 3.1, 95% CI: 1.8 to 5.2) and DVT (HR 3.2, 95%

Table 3. IRs and HRs with 95% CIs by sex and age of receipt of a work-related DP for persons with and without VTE.

	Comparison cohort			VTE					
							Model 1	Model 2	Model 3
	No DP	DP	IR (95% CI)	No DP	DP	IR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
MEN									
Overall	118,395	4,335	5.6 (5.5–5.8)	23,679	2,279	18.1 (17.3–18.8)	3.2 (3.0–3.4)	2.9 (2.7–3.1)	2.5 (2.3–2.6)
Age 25–34	9,050	283	3.1 (2.7–3.4)	1,804	243	15.6 (13.6–17.5)	5.3 (4.4–6.3)	3.5 (2.8–4.4)	3.2 (2.5–4.0)
Age 35–44	19,618	885	4.7 (4.4–5.1)	3,923	551	18.0 (16.5–19.5)	4.0 (3.6–4.5)	3.2 (2.8–3.7)	2.9 (2.5–3.4)
Age 45–54	33,841	1,810	6.6 (6.3–6.9)	6,757	876	19.6 (18.3–20.9)	2.9 (2.6–3.1)	2.7 (2.5–3.0)	2.3 (2.0–2.5)
Age 55–66	55,886	1,357	6.3 (6.0–6.6)	11,195	609	17.2 (15.9–18.6)	2.8 (2.5–3.1)	2.8 (2.5–3.1)	2.2 (2.0–2.5)
WOMEN									
Overall	100,450	4,902	6.7 (6.5–6.9)	20,090	2,136	17.5 (16.8–18.3)	2.7 (2.6–2.9)	2.5 (2.3–2.6)	2.1 (2.0–2.3)
Age 25–34	18,022	542	3.1 (2.8–3.3)	3,589	307	9.5 (8.4–10.5)	3.2 (2.8–3.7)	2.7 (2.3–3.2)	2.5 (2.1–2.9)
Age 35–44	22,428	1,164	5.6 (5.3–6.0)	4,489	540	15.2 (13.9–16.5)	2.7 (2.5–3.1)	2.4 (2.1–2.7)	2.1 (1.9–2.4)
Age 45–54	25,924	1,800	8.3 (7.9–8.7)	5,205	747	21.9 (20.3–23.5)	2.6 (2.4–2.8)	2.4 (2.2–2.6)	2.0 (1.8–2.2)
Age 55–66	34,076	1,396	10.7 (10.1–11.2)	6,807	542	27.3 (25.0–29.6)	2.6 (2.4–2.9)	2.6 (2.3–2.9)	2.2 (1.9–2.4)

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

Model 2: adjusted for SES (education, employment status, and income) and obesity.

Model 3: adjusted for SES score (education, employment status, and income), obesity, cancer, coronary heart disease (including atrial fibrillation), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, surgery 3 months prior to the VTE/index date, and Charlson Comorbidity Index score, excluding comorbidities already adjusted for.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DP, disability pension; HR, hazard ratio; IR, incidence rate; SES, socioeconomic status; VTE, venous thromboembolism.

https://doi.org/10.1371/journal.pmed.1003770.t003

Table 4. Subgroup analysis by age with IRs and HRs with 95% CIs by age for receipt of a work-related DP for persons with and without VTE (PE vs. DVT).

		Comparison cohort			VTE		Model 1	Model 2	Model 3
	No DP	DP	IR (95% CI)	No DP	DP	IR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
PE									
Overall	75,030	2,836	6.3 (6.0–6.5)	15,006	1,351	19.5 (18.4–20.5)	3.2 (3.0–3.5)	3.1 (2.9–3.4)	2.6 (2.4–2.8)
Age 25–34	7,927	228	3.2 (2.8–3.6)	1,575	128	10.1 (8.4–11.9)	3.5 (2.8–4.3)	2.8 (2.2–3.6)	2.6 (2.0–3.4)
Age 35–44	12,514	560	5.2 (4.7–5.6)	2,515	275	15.4 (13.5–17.2)	3.0 (2.6–3.5)	2.9 (2.4–3.4)	2.6 (2.1–3.1)
Age 45–54	19,315	1,058	7.2 (6.8–7.6)	3,852	496	23.2 (21.1–25.2)	3.2 (2.8–3.5)	3.0 (2.7–3.5)	2.5 (2.2–2.9)
Age 55–66	35,274	990	7.9 (7.4–8.4)	7,064	452	25.9 (23.5–28.3)	3.4 (3.0–3.8)	3.5 (3.0–3.9)	2.8 (2.4–3.2)
DVT									
Overall	143,815	6,401	6.1 (6.0–6.3)	28,763	3,064	17.2 (16.5–17.8)	2.8 (2.7–3.0)	2.5 (2.4–2.6)	2.2 (2.0–2.3)
Age 25–34	19,145	597	3.0 (2.8–3.3)	3,818	422	11.9 (10.8–13.1)	4.1 (3.6–4.6)	3.1 (2.7–3.6)	2.8 (2.3–3.2)
Age 35–44	29,532	1,489	5.2 (5.0–5.5)	5,897	816	17.0 (15.8–18.1)	3.4 (3.1–3.7)	2.7 (2.4–3.0)	2.4 (2.1–2.7)
Age 45–54	40,450	2,552	7.4 (7.1–7.7)	8,110	1,127	19.6 (18.5–20.8)	2.6 (2.4–2.8)	2.4 (2.2–2.6)	2.0 (1.8–2.2)
Age 55–66	54,688	1,763	8.0 (7.6–8.3)	10,938	699	18.5 (17.2–19.9)	2.4 (2.2–2.6)	2.3 (2.1–2.5)	1.9 (1.7–2.1)

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

Model 2: adjusted for SES (education, employment status, and income) and obesity.

Model 3: adjusted for SES score (education, employment status, and income), obesity, cancer, coronary heart disease (including atrial fibrillation), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, surgery 3 months prior to the VTE/index date, and Charlson Comorbidity Index score, excluding comorbidities already adjusted for.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DP, disability pension; DVT, deep vein thrombosis; HR, hazard ratio; IR, incidence rate; PE, pulmonary embolism; SES, socioeconomic status; VTE, venous thromboembolism.

https://doi.org/10.1371/journal.pmed.1003770.t004

CI: 2.5 to 4.2), after adjustment for SES and comorbidities (Model 3). These risk estimates decreased to HR 2.8 for PE (95% CI: 2.3 to 3.4) and HR 1.9 for DVT (95% CI: 1.7 to 2.3) in the age group 55 to 66 years (Table 5). In women in the age group 25 to 34 years, PE was associated with a 2.4-fold (HR 2.4, 95% CI: 1.7 to 3.3) higher risk of subsequent receipt of a disability pension. The corresponding HR in women in the age group 55 to 66 years was 2.8 (95% CI: 2.3 to 3.4). The risk of receiving a disability pension in women with DVT decreased gradually, compared to women without VTE. The association decreased from 2.5-fold (HR 2.5, 95% CI: 2.0 to 3.0) in the age group 25 to 34 years to 1.9-fold (HR 1.9, 95% CI: 1.6 to 2.2) in the age group 55 to 66 years (Table 5).

The risk estimates for receipt of a disability pension were essentially similar for unprovoked (HR 2.3, 95% CI: 2.2 to 2.4) and provoked VTE (HR 2.4, 95% CI: 2.0 to 2.8) (Table 3). The association between provoked VTE and receipt of a disability pension gradually increased with age for women, while it decreased with age for men. The association between unprovoked VTE and receipt of a disability pension declined with age for both sexes (Table 6).

Cumulative incidence functions (Fig 1) showed an association between VTE and disability pension in all age groups, even after competing risk by death was taken into account. The cumulative incidence of a disability pension associated with VTE in the 2 middle age groups (age 45 to 54 and 35 to 44 years) was 11.8% (95% CI, 11.1% to 12.4%) and 9.2% (95% CI, 8.6% to 9.9%), respectively, after 5 years, when death was considered as a competing event.

Discussion

We found that VTE was associated with a 2- to 3-fold higher risk of subsequently receiving a permanent disability pension. The relative risk of disability pension receipt after VTE was highest among the youngest patients, and PE was associated with an overall higher relative risk

Table 5. Subgroup analysis by age and sex with IRs and HRs with 95% CIs of receipt of a work-related DP among persons with and without VTE (PE versus DVT).

	Comparison cohort		VTE		Model 1	Model 3
	No DP	DP	No DP	DP	HR (95% CI)	HR (95% CI)
PE						
PE Men overall	40,270	1,331	8,054	696	3.4 (3.1–3.7)	2.7 (2.4–3.0)
PE Men age 25–34	2,321	63	459	50	5.2 (3.5–7.9)	3.1 (1.8–5.2)
PE Men age 35–44	5,589	245	1,124	123	3.1 (2.4–3.9)	2.6 (1.9–3.4)
PE Men age 45–54	10,833	526	2,156	273	3.3 (2.8–3.8)	2.6 (2.1–3.1)
PE Men age 55–66	21,527	497	4,315	250	3.4 (2.9–4.0)	2.8 (2.3–3.4)
PE Women overall	34,760	1,505	6,952	655	3.1 (2.8–3.4)	2.6 (2.3–2.9)
PE Women age 25–34	5,606	165	1,116	78	2.8 (2.2–3.8)	2.4 (1.7–3.3)
PE Women age 35–44	6,925	315	1,391	152	3.0 (2.4–3.6)	2.5 (2.0–3.2)
PE Women age 45–54	8,482	532	1,696	223	3.0 (2.6–3.6)	2.5 (2.0–3.0)
PE Women age 55–66	13,747	493	2,749	202	2.3 (2.8–4.0)	2.8 (2.3–3.4)
DVT						
DVT Men overall	78,125	3,004	15,625	1,583	3.1 (3.0–3.4)	2.4 (2.2–2.6)
DVT Men age 25–34	6,729	220	1,345	193	5.3 (4.3–6.5)	3.2 (2.5–4.2)
DVT Men age 35–44	14,029	640	2,799	428	4.4 (3.9–5.0)	3.1 (2.6–3.6)
DVT Men age 45–54	23,008	1,284	4,601	603	2.7 (2.5–3.0)	2.2 (1.9–2.4)
DVT Men age 55–66	34,359	860	6,880	359	2.5 (2.2–2.8)	1.9 (1.7–2.3)
DVT Women overall	65,690	3,397	13,138	1,481	2.6 (2.4–2.7)	2.0 (1.8–2.1)
DVT Women age 25–34	12,416	377	2,473	229	3.4 (2.9–4.0)	2.5 (2.0–3.0)
DVT Women age 35–44	15,503	849	3,098	388	2.7 (2.4–3.0)	2.0 (1.7–2.3)
DVT Women age 45–54	17,442	1,268	3,509	524	2.4 (2.2–2.7)	1.8 (1.6–2.1)
DVT Women age 55–66	20,329	903	4,058	340	2.3 (2.0–2.7)	1.9 (1.6–2.2)

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

Model 3: adjusted for SES score (education, employment status, and income), obesity, cancer, coronary heart disease (including atrial fibrillation), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, surgery 3 months prior to the VTE/index date, and Charlson Comorbidity Index score, excluding comorbidities already adjusted for.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DP, disability pension; DVT, deep vein thrombosis; HR, hazard ratio; IR, incidence rate; PE, pulmonary embolism; SES, socioeconomic status; VTE, venous thromboembolism.

https://doi.org/10.1371/journal.pmed.1003770.t005

than DVT. Unlike the general population, VTE was associated with a higher risk of receiving a disability pension in men than in women. Although the association between VTE and disability pension receipt was attenuated by adjustments for comorbidities and competing risk of death, the association was still significantly increased, thus suggesting that the relationship was not explained by the presence diseases adjusted for, or by an increased mortality in individuals with VTE. The magnitude of our risk estimates for receipt of a disability pension after VTE was essentially similar to findings from a Finnish cohort study investigating the risk of work-related disability pension following cerebrovascular and heart diseases [33]. As incident VTE is a prevalent disease also at working ages, this has the potential to cause a substantial impact on the socioeconomic challenges of VTE in the society.

The association with disability pension was higher for PE than for DVT. In contrast to this higher risk in PE, the Norwegian study [14] reported a 53% increased risk of receiving a disability pension in DVT, while no association was found between PE and disability. In the 2 European studies, the proportion who returned to work after 1 year was marginally lower in individuals with DVT compared to individuals with PE [18,19]. The PTS, characterized by pain, swelling, and reduced mobility of the affected limb, occurs in 20% to 50% of individuals

Table 6. Subgroup analysis by age and sex with IRs and HRs with 95% CIs of receipt of a work-related DP among persons with and without VTE by provoked VTE vs. unprovoked VTE.

	Comparison cohort		VTE		Model 1	Model 3
	No DP	DP	No DP	DP	HR (95% CI)	HR (95% CI)
Unprovoked VTE						
Overall	163,940	7,044	32,788	3,354	2.8 (2.7–2.9)	2.3 (2.2–2.4)
Age 25–34	21,183	621	4,225	427	4.0 (3.5–4.6)	2.6 (2.2–3.0)
Age 35–44	33,800	1,617	6,756	890	3.3 (3.0–3.6)	2.5 (2.3–2.8)
Age 45–54	46,213	2,792	9,249	1,236	2.5 (2.4–2.7)	2.1 (2.0–2.3)
Age 55–66	62,744	2,014	12,558	801	2.4 (2.2–2.6)	2.2 (2.0–2.4)
Provoked VTE						
Overall	54,905	2,193	10,981	1,061	3.6 (3.3–3.9)	2.4 (2.0–2.8)
Age 25–34	5,889	204	1,168	123	3.5 (2.8–4.4)	3.0 (1.9–4.6)
Age 35–44	8,246	432	1,656	201	3.1 (2.6–3.7)	2.2 (1.5–3.2)
Age 45–54	13,552	818	2,713	387	3.6 (3.2–4.1)	2.2 (1.7–2.9)
Age 55–66	27,218	739	5,444	350	4.0 (3.5–4.6)	2.4 (1.9–3.2)

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

Model 3: adjusted for SES score (education, employment status, and income), obesity, cancer, coronary heart disease (including atrial fibrillation), diabetes, stroke, COPD, acute kidney failure and chronic kidney disease, surgery 3 months prior to the VTE/index date, and Charlson Comorbidity Index score, excluding comorbidities already adjusted for.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DP, disability pension; HR, hazard ratio; IR, incidence rate; SES, socioeconomic status; VTE, venous thromboembolism.

https://doi.org/10.1371/journal.pmed.1003770.t006

with DVT [7] and may explain the increased risk of work-related disability after DVT. More recent studies investigating long-term complications of PE have reported that the post-PE syndrome affects almost 50% of individuals with PE, with symptoms and signs ranging from persistent dyspnea to life-threating chronic thromboembolic pulmonary hypertension (CTEPH) [10–13,34–39]. The post-PE syndrome reduces QoL and health-related quality of life (HRQoL) in individuals with PE [12,34–38], and CTEPH in particular is associated with poor QoL and reduced exercise capacity [37,39]. Low self-rated QoL and HRQoL have been associated strongly with subsequent health outcomes, such as sick leave [40–42]. Thus, the frequency of the post-PE syndrome, and its impact on physical function and QoL, may explain why individuals with PE suffer an equal or higher risk of work-related disability compared to individuals with DVT.

Data from studies in countries with universal welfare schemes and high female work participation have consistently shown that women overall are at higher risk of sick leave and disability pension than men [43–46]. Self-perceived health, family situation, work factors, and educational level have been proposed to explain this sex difference [43–46]. In our general comparison cohort, we found that the IR for receipt of a disability pension among women was equal to, or higher, than that for men. In contrast, the overall risk of receiving a disability pension after VTE was higher in men than women, and this sex difference in risk was driven by a higher risk in the youngest men. A higher risk of recurrence, PTS, and the post-PE syndrome in men compared to women could potentially explain this observation [6,47,48].

Our study has several strengths and limitations. The study was conducted in a setting where educational and healthcare services are government funded and free of charge to all citizens, thus preventing selection and referral bias. We used a large population-based cohort, consisting of the entire Danish population, with a long follow-up time. A validation study of DNPR data reported positive predictive values of 86% for DVT and 90% for PE, suggesting a

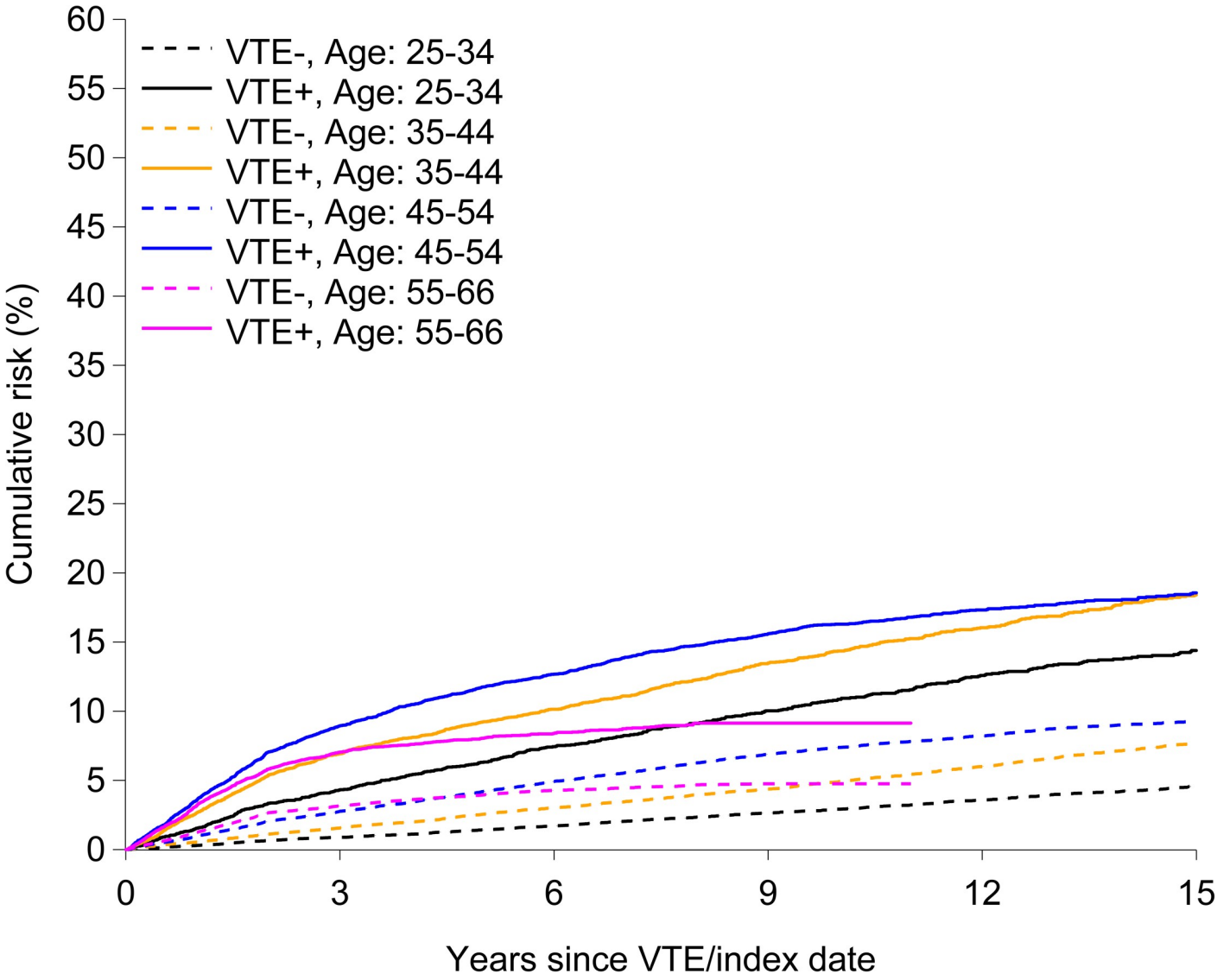


Fig 1. Cumulative incidence of persons with (VTE+) and without (VTE−) venous thromboembolism (VTE) receiving a work-related disability pension taking competing risk death into account.

https://doi.org/10.1371/journal.pmed.1003770.g001

low misclassification rate of VTE exposure [49]. Our outcome measure of work-related disability pension originated from highly accurate official registries. The large number of individuals with VTE allowed for analyses stratified on age and sex and a detailed interpretation of the association between VTE and disability. However, as disability schemes vary, our results might not be directly generalizable to other countries of time periods. We were only able to include information that was available in medical and administrative registers. We therefore lacked information on the quality and outcome of post-VTE care, individual health behavior, and workplace factors, which all are linked to receipt of a disability pension in the general population. Further, we had no information about the incidence of the post-PE syndrome, the PTS, or recurrence during follow-up in our individuals with VTE. Thus, even though we adjusted for multiple comorbidities and socioeconomic factors, residual confounding due to unmeasured factors cannot be completely ruled out.

As VTE is a prevalent disease also at working ages, our findings indicate that indirect costs due to loss of working ability may contribute substantially to the socioeconomic challenges of VTE in the society. The impact of the post-thrombotic and post-PE syndromes as mediators for permanent work-related disability is not well studied, and future research should focus on identifying determinants and risk factors for permanent loss of working ability in individuals with VTE.

In conclusion, VTE was associated with future risk of permanent work-related disability, and the association was still observed after accounting for comorbidities such as cancer and other cardiovascular diseases. Our results emphasize the social consequences of VTE and can help occupational and healthcare professionals to identify vulnerable individuals at risk of permanent exclusion from the labor market after a VTE event.

Supporting information

S1 STROBE Checklist. STROBE guideline.
(PDF)

S1 Analysis plan. Prospective analysis plan.
(PDF)

S1 Fig. Restricted cubic spline model with adjusted HRs and 95% CIs of receipt of a work-related disability pension according to age at VTE diagnosis. CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.
(TIF)

S1 Table. Baseline characteristics of persons with VTE and members of the general comparison cohort. VTE, venous thromboembolism.
(TIF)

S2 Table. Characteristics of patients with VTE with and without work-related disability pension. VTE, venous thromboembolism.
(TIF)

S3 Table. International Standard Classification of Education – 2011 English and Danish educational program names and corresponding levels of education.
(TIF)

S4 Table. Division of level of education (Danish levels) based on S3 Table.
(TIF)

S5 Table. ICD and ATC classification codes used to define exposure, provoking factors for VTE, covariables, and modified Charlson Comorbidity Index. ATC, Anatomical Therapeutic Chemical Classification; ICD, International Classification of Diseases; VTE, venous thromboembolism.
(TIF)

Author Contributions

Conceptualization: Helle Jørgensen, Sigrid Brækkan, John-Bjarne Hansen, Henrik Toft Sørensen.

Data curation: Erzsébet Horváth-Puhó, Kristina Laugesen, Henrik Toft Sørensen.

Formal analysis: Helle Jørgensen, Sigrid Brækkan, John-Bjarne Hansen.

Investigation: Helle Jørgensen, Erzsébet Horváth-Puhó.

Methodology: Helle Jørgensen, Erzsébet Horváth-Puhó, Sigrid Brækkan, John-Bjarne Hansen, Henrik Toft Sørensen.

Project administration: Helle Jørgensen.

Supervision: Sigrid Brækkan, John-Bjarne Hansen, Henrik Toft Sørensen.

Validation: Erzsébet Horváth-Puhó.

Writing – original draft: Helle Jørgensen.

Writing – review & editing: Helle Jørgensen, Erzsébet Horváth-Puhó, Kristina Laugesen, Sigrid Brækkan, John-Bjarne Hansen, Henrik Toft Sørensen.

References

1. White RH. The epidemiology of venous thromboembolism. Circulation. 2003; 107(23 Suppl 1):I4–8.
2. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016; 41(1):3–14. https://doi.org/10.1007/s11239-015-1311-6 PMID: 26780736
3. Arshad N, Isaksen T, Hansen JB, Braekkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. Eur J Epidemiol. 2017; 32(4):299–305. https://doi.org/10.1007/s10654-017-0238-y PMID: 28314981
4. Søgaard KK, Schmidt M, Pedersen L, Horváth-Puhó E, Sørensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. Circulation. 2014; 130(10):829–36. https://doi.org/10.1161/CIRCULATIONAHA.114.009107 PMID: 24970783
5. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000; 160(6):761–8. https://doi.org/10.1001/archinte.160.6.761 PMID: 10737275
6. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. N Engl J Med. 2004; 350(25):2558–63. https://doi.org/10.1056/NEJMoa032959 PMID: 15201412
7. Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. Ann Intern Med. 2008; 149(10):698–707. https://doi.org/10.7326/0003-4819-149-10-200811180-00004 PMID: 19017588
8. Kachroo S, Boyd D, Bookhart BK, LaMori J, Schein JR, Rosenberg DJ, et al. Quality of life and economic costs associated with postthrombotic syndrome. Am J Health Syst Pharm. 2012; 69(7):567–72. https://doi.org/10.2146/ajhp110241 PMID: 22441786
9. Laviolette L, Laveneziana P, Faculty ERSRS. Dyspnoea: a multidimensional and multidisciplinary approach. Eur Respir J. 2014; 43(6):1750–62. https://doi.org/10.1183/09031936.00092613 PMID: 24525437
10. Pugliese SC, Kawut SM. The Post-Pulmonary Embolism Syndrome: Real or Ruse? Ann Am Thorac Soc. 2019; 16(7):811–4. https://doi.org/10.1513/AnnalsATS.201901-061PS PMID: 30974063
11. Sista AK, Klok FA. Late outcomes of pulmonary embolism: The post-PE syndrome. Thromb Res. 2018; 164:157–62. https://doi.org/10.1016/j.thromres.2017.06.017 PMID: 28641836
12. Tavoly M, Wik HS, Sirnes PA, Jelsness-Jorgensen LP, Ghanima JP, Klok FA, et al. The impact of post-pulmonary embolism syndrome and its possible determinants. Thromb Res. 2018; 171:84–91. https://doi.org/10.1016/j.thromres.2018.09.048 PMID: 30267974
13. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev. 2014; 28(6):221–6. https://doi.org/10.1016/j.blre.2014.07.003 PMID: 25168205
14. Braekkan SK, Grosse SD, Okoroh EM, Tsai J, Cannegieter SC, Naess IA, et al. Venous thromboembolism and subsequent permanent work-related disability. J Thromb Haemost. 2016; 14(10):1978–87. https://doi.org/10.1111/jth.13411 PMID: 27411161
15. Kahn SR, Shbaklo H, Lamping DL, Holcroft CA, Shrier I, Miron MJ, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. J Thromb Haemost. 2008; 6(7):1105–12. https://doi.org/10.1111/j.1538-7836.2008.03002.x PMID: 18466316

16. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol. 2014; 34(11):2363–71. https://doi.org/10.1161/ATVBAHA.114.304488 PMID: 25304324

17. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res. 2016; 137:3–10. https://doi.org/10.1016/j.thromres.2015.11.033 PMID: 26654719

18. Willich SN, Chuang LH, van Hout B, Gumbs P, Jimenez D, Kroep S, et al. Pulmonary embolism in Europe—Burden of illness in relationship to healthcare resource utilization and return to work. Thromb Res. 2018; 170:181–91. https://doi.org/10.1016/j.thromres.2018.02.009 PMID: 30199784

19. Chuang LH, van Hout B, Cohen AT, Gumbs PD, Kroep S, Bauersachs R, et al. Deep-vein thrombosis in Europe—Burden of illness in relationship to healthcare resource utilization and return to work. Thromb Res. 2018; 170:165–74. https://doi.org/10.1016/j.thromres.2018.08.001 PMID: 30196194

20. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007; 98(4):756–64. PMID: 17938798

21. Cushman M. Epidemiology and risk factors for venous thrombosis. Semin Hematol. 2007; 44(2):62–9. https://doi.org/10.1053/j.seminhematol.2007.02.004 PMID: 17433897

22. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003; 107(23 Suppl 1):I9–16.

23. Schmidt M, Schmidt SAJ, Adelborg K, Sundboll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol. 2019; 11:563–91. https://doi.org/10.2147/CLEP.S179083 PMID: 31372058

24. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015; 7:449–90. https://doi.org/10.2147/CLEP.S91125 PMID: 26604824

25. Adelborg K, Corraini P, Darvalics B, Frederiksen H, Ording A, Horváth-Puhó E, et al. Risk of thromboembolic and bleeding outcomes following hematological cancers: A Danish population-based cohort study. J Thromb Haemost. 2019; 17(8):1305–18. https://doi.org/10.1111/jth.14475 PMID: 31054195

26. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost. 2016; 14(7):1480–3. https://doi.org/10.1111/jth.13336 PMID: 27428935

27. Heide-Jorgensen U, Adelborg K, Kahlert J, Sorensen HT, Pedersen L. Sampling strategies for selecting general population comparison cohorts. Clin Epidemiol. 2018; 10:1325–37. https://doi.org/10.2147/CLEP.S164456 PMID: 30310326

28. Timmermans B. The Danish Integrated Database for Labor Market Research: Towards Demystification for the English Speaking Audience. DRUID, Copenhagen Business School, Department of Industrial Economics and Strategy/Aalborg University, Department of Business Studies, DRUID Working Papers. 2010.

29. Directorate-General for Employment SAaI, The European Comission. Your social security rights in Denmark. [cited April 2021]. Available from: https://ec.europa.eu/social/main.jsp?catId = 1107&langId = en2020.

30. Pedersen J, Bjorner JB, Burr H, Christensen KB. Transitions between sickness absence, work, unemployment, and disability in Denmark 2004–2008. Scand J Work Environ Health. 2012; 38(6):516–26. https://doi.org/10.5271/sjweh.3293 PMID: 22441355

31. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987; 40(5):373–83. https://doi.org/10.1016/0021-9681(87)90171-8 PMID: 3558716

32. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999; 94(446):496–509.

33. Ervasti J, Kivimäki M, Pentti J, Salo P, Oksanen T, Vahtera J, et al. Health- and work-related predictors of work disability among employees with a cardiometabolic disease—A cohort study. J Psychosom Res. 2016; 82:41–7. https://doi.org/10.1016/j.jpsychores.2016.01.010 PMID: 26944398

34. Klok FA, Tijmensen JE, Haeck ML, van Kralingen KW, Huisman MV. Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: results of a questionnaire. Eur J Intern Med. 2008; 19(8):625–9. https://doi.org/10.1016/j.ejim.2008.02.006 PMID: 19046730

35. Kahn SR, Akaberi A, Granton JT, Anderson DR, Wells PS, Rodger MA, et al. Quality of Life, Dyspnea, and Functional Exercise Capacity Following a First Episode of Pulmonary Embolism: Results of the ELOPE Cohort Study. Am J Med. 2017; 130(8):990.e9–.e21.

36. Ghanima W, Wik HS, Tavoly M, Enden T, Jelsness-Jorgensen LP. Late consequences of venous thromboembolism: Measuring quality of life after deep vein thrombosis and pulmonary embolism. Thromb Res. 2018; 164:170–6. https://doi.org/10.1016/j.thromres.2017.07.025 PMID: 28760416

37. Lubberts B, Paulino Pereira NR, Kabrhel C, Kuter DJ, DiGiovanni CW. What is the effect of venous thromboembolism and related complications on patient reported health-related quality of life? A meta-analysis Thromb Haemost. 2016; 116(3):417–31. https://doi.org/10.1160/TH16-02-0152 PMID: 27362694

38. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating Quality of Life in Acute Venous Thrombosis. JAMA Intern Med. 2013; 173(12):1067–72. https://doi.org/10.1001/jamainternmed.2013.563 PMID: 23689427

39. Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Huisman MV. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med. 2010; 104 (11):1744–9. https://doi.org/10.1016/j.rmed.2010.06.006 PMID: 20599368

40. Halford C, Wallman T, Welin L, Rosengren A, Bardel A, Johansson S, et al. Effects of self-rated health on sick leave, disability pension, hospital admissions and mortality. A population-based longitudinal study of nearly 15,000 observations among Swedish women and men. BMC Public Health. 2012; 12:1103. https://doi.org/10.1186/1471-2458-12-1103 PMID: 23259777

41. Peterson U, Bergstrom G, Demerouti E, Gustavsson P, Asberg M, Nygren A. Burnout levels and self-rated health prospectively predict future long-term sickness absence: a study among female health professionals. J Occup Environ Med. 2011; 53(7):788–93. https://doi.org/10.1097/JOM.0b013e318222b1dc PMID: 21691218

42. Haukenes I, Farbu EH, Riise T, Tell GS. Physical health-related quality of life predicts disability pension due to musculoskeletal disorders: seven years follow-up of the Hordaland Health Study Cohort. BMC Public Health. 2014; 14(1):167. https://doi.org/10.1186/1471-2458-14-167 PMID: 24528674

43. Haukenes I, Gjesdal S, Rortveit G, Riise T, Mæland JG. Women's higher likelihood of disability pension: the role of health, family and work. A 5–7 years follow-up of the Hordaland Health Study. BMC Public Health. 2012; 12(1):720.

44. Ervasti J, Virtanen M, Lallukka T, Friberg E, Mittendorfer-Rutz E, Lundström E, et al. Permanent work disability before and after ischaemic heart disease or stroke event: a nationwide population-based cohort study in Sweden. BMJ Open. 2017; 7(9):e017910. https://doi.org/10.1136/bmjopen-2017-017910 PMID: 28965101

45. Osler M, Mårtensson S, Prescott E, Carlsen K. Impact of gender, co-morbidity and social factors on labour market affiliation after first admission for acute coronary syndrome. A cohort study of Danish patients 2001–2009. PLoS ONE. 2014; 9(1):e86758. https://doi.org/10.1371/journal.pone.0086758 PMID: 24497976

46. Karlsson N, Borg K, Carstensen J, Hensing G, Alexanderson K. Risk of disability pension in relation to gender and age in a Swedish county; a 12-year population based, prospective cohort study. Work. 2006; 27(2):173–9. PMID: 16971764

47. McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. Lancet. 2006; 368(9533):371–8. https://doi.org/10.1016/S0140-6736(06)69110-1 PMID: 16876665

48. Kahn SR, Hirsch A, Beddaoui M, Akaberi A, Anderson D, Wells PS, et al. "Post-Pulmonary Embolism Syndrome" after a First Episode of PE: Results of the E.L.O.P.E. Study . Blood. 2015; 126(23):650–.

49. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open. 2016; 6(11):e012832. https://doi.org/10.1136/bmjopen-2016-012832 PMID: 27864249

Appendix 3

Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

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

Helle Jørgensen[1–3], Erzsébet Horváth-Puhó[2], Kristina Laugesen[2], Sigrid K Braekkan[1,3], John-Bjarne Hansen[1,3], Henrik Toft Sørensen[2]

[1]Thrombosis Research Center (TREC), Department of Clinical Medicine, UiT, The Arctic University of Norway, Tromsø, Norway; [2]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University Hospital and Aarhus University, Aarhus, Denmark; [3]Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

Correspondence: Helle Jørgensen, Email helle.jorgensen@uit.no

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.

Received: 14 February 2022
Accepted: 5 April 2022
Published: 14 April 2022

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

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.

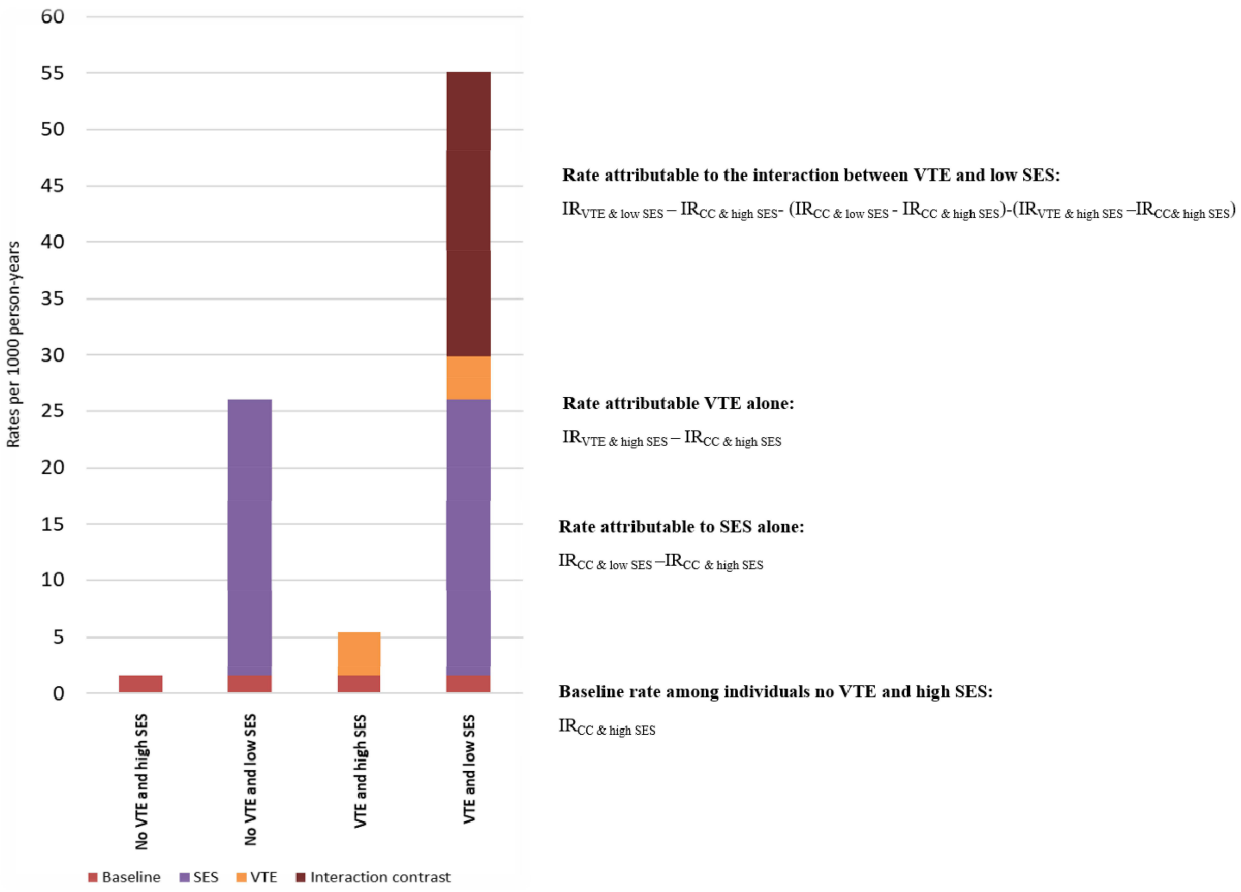


Figure 1 Proportion of the total disability pension incidence rate attributable to venous thromboembolism, low socioeconomic status, and their interaction.
Abbreviations: SES, socioeconomic status; VTE, venous thromboembolism; IR, incidence rate.

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.

https://doi.org/10.2147/CLEP.S361840 DovePress

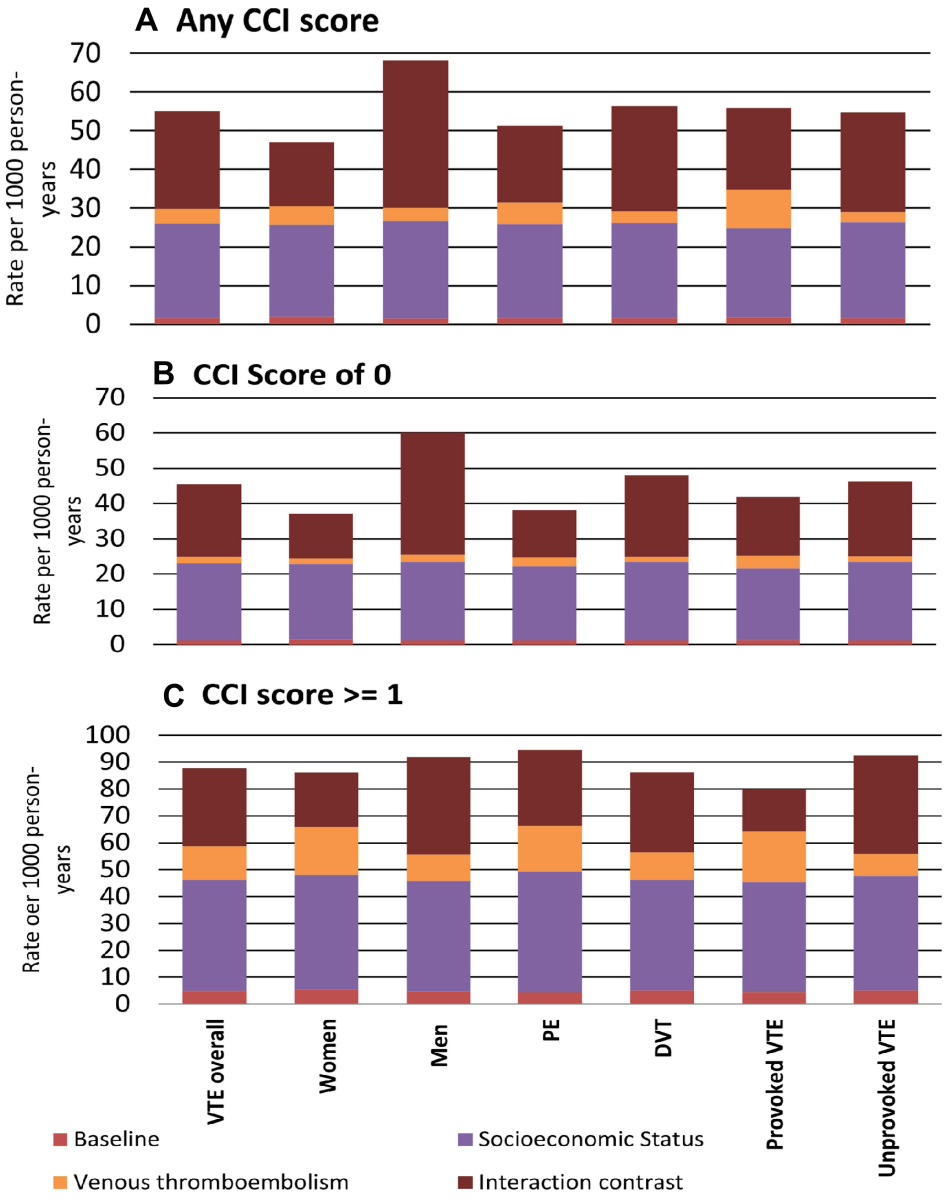


Figure 2 Proportion of the total disability pension rate attributable to venous thromboembolism, low socioeconomic status and their interaction in relation to men, women, pulmonary embolism, deep vein thrombosis, provoked and unprovoked venous thromboembolism in (**A**) main analysis, (**B**) analysis 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

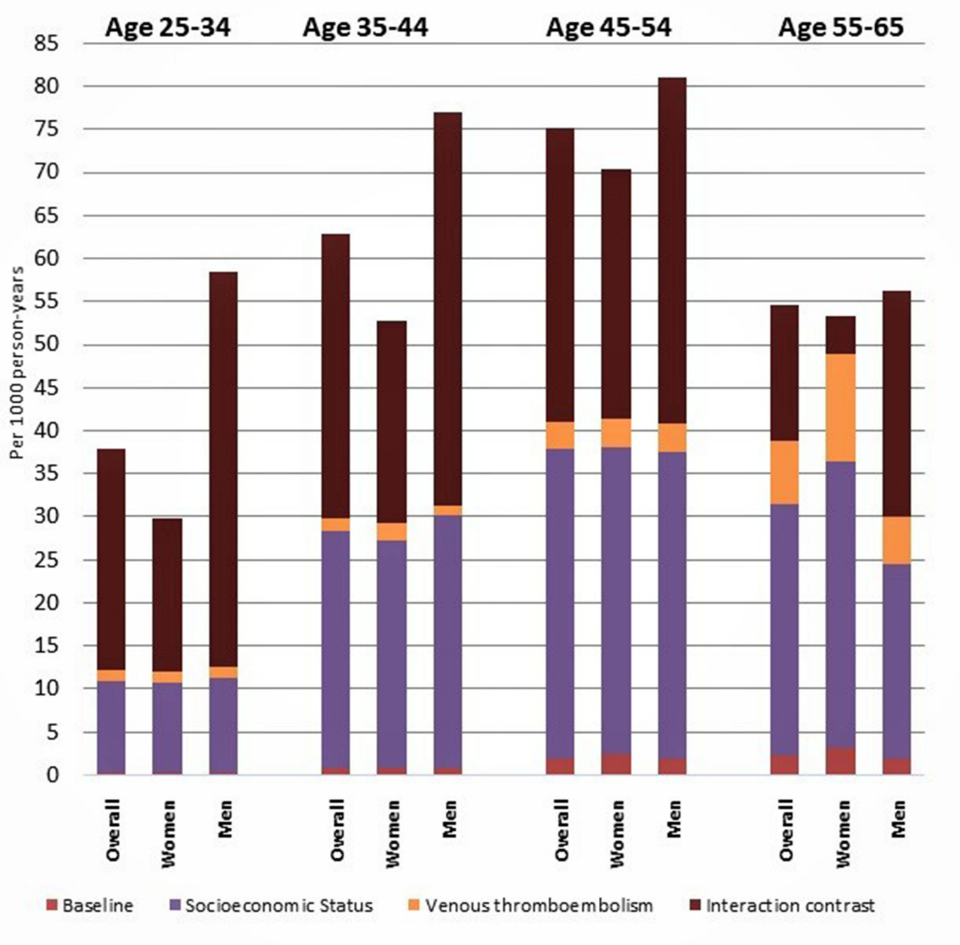


Figure 3 Proportion of the total disability pension incidence rate attributable to venous thromboembolism, low socioeconomic status, and their interaction by age and sex.

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 cardiovascular 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.

References

1. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol*. 2014;34(11):2363–2371. doi:10.1161/ATVBAHA.114.304488
2. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I4–8. doi:10.1161/01.CIR.0000078468.11849.66
3. van Rijn RM, Robroek SJ, Brouwer S, Burdorf A. Influence of poor health on exit from paid employment: a systematic review. *Occup Environ Med*. 2014;71(4):295–301. doi:10.1080/09581596.2018.1469730
4. Braekkan SK, Grosse SD, Okoroh EM, et al. Venous thromboembolism and subsequent permanent work-related disability. *J Thromb Haemost*. 2016;14(10):1978–1987. doi:10.1111/jth.13411
5. Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen JB, Sørensen HT. Risk of a permanent work-related disability pension after incident venous thromboembolism in Denmark: a population-based cohort study. *PLoS Med*. 2021;18(8):e1003770. doi:10.1371/journal.pmed.1003770
6. Zoller B, Li X, Sundquist J, Sundquist K. Socioeconomic and occupational risk factors for venous thromboembolism in Sweden: a nationwide epidemiological study. *Thromb Res*. 2012;129(5):577–582. doi:10.1016/j.thromres.2011.07.050
7. Isma N, Merlo J, Ohlsson H, Svensson PJ, Lindblad B, Gottsater A. Socioeconomic factors and concomitant diseases are related to the risk for venous thromboembolism during long time follow-up. *J Thromb Thrombolysis*. 2013;36(1):58–64. doi:10.1007/s11239-012-0858-8
8. Rosengren A, Freden M, Hansson PO, Wilhelmsen L, Wedel H, Eriksson H. Psychosocial factors and venous thromboembolism: a long-term follow-up study of Swedish men. *J Thromb Haemost*. 2008;6(4):558–564. doi:10.1111/j.1538-7836.2007.02857.x
9. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. *Circulation*. 2010;121(17):1896–1903. doi:10.1161/CIRCULATIONAHA.109.921460
10. Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen J-B, Sørensen HT. Socioeconomic status and risk of incident venous thromboembolism. *J Thromb Haemost*. 2021;19(12):3051–3061. doi:10.1111/jth.15523
11. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563–591. doi:10.2147/CLEP.S179083
12. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6(11):e012832. doi:10.1136/bmjopen-2016-012832
13. Adelborg K, Corraini P, Darvalics B, et al. Risk of thromboembolic and bleeding outcomes following hematological cancers: a Danish population-based cohort study. *J Thromb Haemost*. 2019;17(8):1305–1318. doi:10.1111/jth.14475
14. Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation*. 2014;130(10):829–836. doi:10.1161/CIRCULATIONAHA.114.009107
15. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost*. 2016;14(7):1480–1483. doi:10.1111/jth.13336
16. Heide-Jorgensen U, Adelborg K, Kahlert J, Sorensen HT, Pedersen L. Sampling strategies for selecting general population comparison cohorts. *Clin Epidemiol*. 2018;10:1325–1337. doi:10.2147/CLEP.S164456
17. Directorate-General for Employment SAaI, The European Comission. Your social security rights in Denmark; 2019.
18. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11(1):83. doi:10.1186/1471-2288-11-83
19. Schmidt M, Horváth-Puhó E, Ording AG, Bøtker HE, Lash TL, Sørensen HT. The interaction effect of cardiac and non-cardiac comorbidity on myocardial infarction mortality: a nationwide cohort study. *Int J Cardiol*. 2020;308:1–8. doi:10.1016/j.ijcard.2020.01.059
20. Bonnesen K, Schmidt M, Horváth-Puhó E, Sørensen HT. The interaction effect between comorbidity burden and venous thromboembolism on mortality: a nationwide cohort study. *Thromb Haemost*. 2021. doi:10.1055/a-1527-6215
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496–509. doi:10.1080/01621459.1999.10474144
22. Krokstad S, Johnsen R, Westin S. Social determinants of disability pension: a 10-year follow-up of 62 000 people in a Norwegian county population. *Int J Epidemiol*. 2002;31(6):1183–1191. doi:10.1093/ije/31.6.1183
23. Brun C, Boggild H, Eshoj P. [Socioeconomic risk indicators for disability pension within the Danish workforce. A registry-based cohort study of the period 1994–1998]. *Ugeskr Laeger*. 2003;165(35):3315–3319. Danish.
24. Polvinen A, Laaksonen M, Gould R, Lahelma E, Martikainen P. The contribution of major diagnostic causes to socioeconomic differences in disability retirement. *Scand J Work Environ Health*. 2014;40(4):353–360. doi:10.5271/sjweh.3411
25. Virtanen M, Lallukka T, Ervasti J, et al. The joint contribution of cardiovascular disease and socioeconomic status to disability retirement: a register linkage study. *Int J Cardiol*. 2017;230:222–227. doi:10.1016/j.ijcard.2016.12.166
26. Geyer S, Hemström Ö, Peter R, Vågerö D. Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. *J Epidemiol Community Health*. 2006;60(9):804–810. doi:10.1136/jech.2005.041319

27. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull*. 2007;81–82(1):21–37. doi:10.1093/bmb/ldm001
28. Leka S, Jain A, World Health O. *Health Impact of Psychosocial Hazards at Work: An Overview*. Geneva: World Health Organization; 2010.
29. Levesque JF, Harris MF, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. *Int J Equity Health*. 2013;12(1):18. doi:10.1186/1475-9276-12-18
30. Bruusgaard D, Smeby L, Claussen B. Education and disability pension: a stronger association than previously found. *Scand J Public Health*. 2010;38(7):686–690. doi:10.1177/1403494810378916
31. Robroek SJ, Rongen A, Arts CH, Otten FW, Burdorf A, Schuring M. Educational Inequalities in Exit from paid employment among Dutch workers: the influence of health, lifestyle and work. *PLoS One*. 2015;10(8):e0134867. doi:10.1371/journal.pone.0134867
32. Stain M, Schönauer V, Minar E, et al. The post-thrombotic syndrome: risk factors and impact on the course of thrombotic disease. *J Thromb Haemost*. 2005;3(12):2671–2676. doi:10.1111/j.1538-7836.2005.01648.x
33. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med*. 2004;350(25):2558–2563. doi:10.1056/NEJMoa032959
34. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. *Arch Intern Med*. 2002;162(10):1144–1148. doi:10.1001/archinte.162.10.1144
35. Haukenes I, Löve J, Hensing G, et al. Inequity in disability pension: an intersectional analysis of the co-constitution of gender, education and age. The Hordaland Health Study. *Crit Public Health*. 2019;29(3):302–313.
36. McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. *Lancet*. 2006;368(9533):371–378. doi:10.1016/S0140-6736(06)69110-1
37. Hoffmann R, Kröger H, Tarkiainen L, Martikainen P. Dimensions of Social Stratification and their relation to mortality: a comparison across gender and life course periods in Finland. *Soc Indic Res*. 2019;145(1):349–365. doi:10.1007/s11205-019-02078-z
38. McDonough P, Williams DR, House JS, Duncan GJ. Gender and the socioeconomic gradient in mortality. *J Health Soc Behav*. 1999;40(1):17–31. doi:10.2307/2676376

Appendix 4

Venous thromboembolism and risk of depression: A population-based cohort study

Helle Jørgensen[1,2,3], Erzsébet Horváth-Puhó[2], Kristina Laugesen[2], Sigrid Brækkan[1,3], John-Bjarne Hansen[1,3], Henrik Toft Sørensen[2]

[1]Thrombosis Research Center (TREC), Department of Clinical Medicine, UiT, The Arctic University of Norway, Norway

[2]Department of Clinical Epidemiology, Aarhus University Hospital and Aarhus University, Denmark

[3]Division of Internal Medicine, University Hospital of North Norway, Norway

Correspondence: Helle Jørgensen, Thrombosis Research Center (TREC), Department of Clinical Medicine, UiT-The Arctic University of Norway, N-9037 Tromsø, Norway Email: helle.jorgensen@uit.no

Running head title: Venous thromboembolism and risk of depression

Key points:

- The psychological consequences of VTE have not been investigated in depth
- We assessed the risk of depression within three years of follow-up after incident VTE in a large cohort from the general population of Denmark.
- The risk of depression remained increased after adjustment for comorbidities such as cancer and cardiovascular diseases.
- Our findings could inform new strategies for identifying high-risk groups for screening, prevention, and treatment of depression after VTE.

Key words: venous thromboembolism, depression, antidepressants, deep vein thrombosis, pulmonary embolism, post-thrombotic syndrome, post-PE syndrome, mental health, burden of illness, healthcare resource utilization, cohort study

Abstract

Background: The psychological consequences of acute venous thromboembolism (VTE) have not been investigated in depth. We aimed to examine the association between VTE and the risk of future depression.

Methods and findings: Using Danish nationwide registries, we established a population-based cohort of 64,596 individuals with incident VTE during 1996-2016 and a comparison cohort (n=322,999) selected randomly from the general population and individually matched by birth year, sex, and calendar-year of VTE. Depression was defined as any hospital diagnosis of depression or ≥1 prescription for antidepressants. We estimated absolute risks using cumulative incidence functions treating death as a competing event. Incidence rates (IR) were computed as the number of depressive episodes per 1,000 person-years and hazard ratios (HR) with 95% confidence intervals (CIs) as estimates of the risk conferred by VTE, using the comparison cohort as reference.

Depression was observed in 6,225 individuals after VTE and in 16,363 comparison cohort members (IRs 44.4 and 19.4 per 1,000 person-years, respectively) within three years of follow-up. Three years after the VTE, the absolute risk of depression was 10.3% (95% CI 10.1%-10.6%) in the VTE cohort and 5.6% (95% CI 5.5%-5.6%) in the comparison cohort, corresponding to 4.7 excess depression cases per 100 individuals with VTE. VTE was associated with a 2.35-fold (95% CI 2.28-2.43) increased depression risk compared to the comparison cohort. The risk estimate decreased after adjustments for socioeconomic status and comorbidities (HR 1.91, 95% CI: 1.85-1.97).

Conclusions: VTE was associated with an increased risk of depression after adjustment for comorbidities such as cancer and cardiovascular diseases.

Introduction

Both venous thromboembolism (VTE) and depression are prevalent causes of disease burden and mortality worldwide.[1-3] VTE, encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is the second-most common contributor to disability-adjusted life-years in high-income countries,[1] and depression is ranked as one of the major causes of years lived with disability. Physical complications of VTE such as recurrence,[4] the post-thrombotic syndrome,[5] and the post-PE syndrome[6] have been shown to worsen functional impairment and quality of life after a VTE event.[7,8] Depression is a frequent complication of chronic diseases,[9] and there is strong evidence of a 10-40% increased risk of depression in individuals with cardiovascular disease (CVD), compared to individuals without CVD.[10-13] However, evidence on the psychological consequences of VTE is scarce.

Existing studies on mental health after VTE indicate that it is associated with symptoms of psychological distress and post-traumatic stress disorder (PTSD), particularly after PE.[14-28] However, the generalizability of available study results are limited by small sample sizes, inclusion of selected patients, use of qualitative methods with self-reported data collected in the months following a VTE diagnosis, and limited control of confounding factors such as comorbidities, socioeconomic status (SES), and lifestyle. Consequently, the incidence of depression following VTE, confounding factors, and time between onset of the two conditions is not well understood.

Depression after VTE may result in non-adherence to prescribed medication and treatment, functional impairment, disability, and increased risk of morbidity and mortality.[29] An improved understanding of the psychological consequences of the condition is required so adequate supportive and preventive measures can be initiated post-VTE to enhance mental health and treatment adherence. To address the knowledge gap concerning the psychological complications of VTE, we assessed the risk of depression after incident VTE according to sex, age, and VTE subtypes in a nationwide cohort of individuals with VTE.

Methods

Design and setting

In Denmark, a government-funded tax-supported welfare system ensures free and equal access to education and medical care.[30] Upon birth or immigration, a unique identifier (CPR number) is assigned to each Danish resident. The CPR number enables linkage to individual-level data across all Danish registries.[30]

This nationwide population-based cohort study linked prospectively collected data from January 1, 1996 through December 31, 2016 from six Danish longitudinal nationwide medical and administrative population-based registers. Demographic information and data on vital status were extracted from the Danish Civil Registration System (CRS). Information on diagnoses of VTE, depression, and comorbidities were obtained from the Danish National Patient Registry (DNPR) and the Danish Psychiatric Central Research Register (DPCRR).[30,31] Data on redeemed prescriptions for an antidepressant were obtained from the Danish National Prescription Registry.[32] Data on income was obtained from the Integrated Database for Labor Market Research (IDA), and The Educational Attainment Register provided data on education.[30]

VTE cohort

We used the *International Classification of Diseases, tenth revision* (ICD-10) codes in the DNPR to identify all hospital inpatients and outpatients aged 25 to 80 years of age with a first lifetime primary or secondary diagnosis of DVT or PE between from January 1, 1996 through December 31, 2016. The accuracy of VTE diagnoses in the DNPR has been validated previously, yielding positive predictive values of 86% for DVT and 90% for PE.[33]

VTE was classified as either PE or DVT. Simultaneous PE and DVT diagnoses were classified as PE due to its higher mortality rate.[34] VTE with a preexisting cancer diagnosis either before or on the VTE/index date, or trauma, surgery and/or a pregnancy within 90 days prior to the VTE diagnosis, was classified as provoked VTE. VTE without the presence of any of these factors was classified as unprovoked VTE.[35]

We excluded individuals with a hospital history of depression (identified using ICD-8 codes), or a redeemed prescription for an antidepressant before the VTE. We also excluded VTEs registered only in emergency room departments, as they often represent working diagnoses with high rates of clinical misclassification.[36]

General population comparison cohort

For each individual with VTE, we used the CRS to match up to five individuals from the general population by sex, year of birth, and calendar year of the VTE diagnosis, with replacement. The index date for the comparison cohort members was defined as the VTE diagnosis date for the corresponding individual with VTE. Comparison cohort members could not have been diagnosed with VTE, depression, or have a redeemed prescription for an antidepressant prior to the index date. Comparison cohort members who subsequently experienced a VTE were censored and moved to the VTE exposure cohort as of the date of their diagnosis.

Depression

We defined depression as any hospital inpatient or outpatient clinic diagnosis of depression as defined in Supplementary Table 1, or a minimum of one redeemed prescription for an antidepressant. We used the DNPR and DPCRR to identify depression diagnoses from all inpatient admissions to, and outpatient contacts with, Danish hospitals from January 1, 1996 through December 31, 2016. We excluded referral diagnoses and working diagnoses since these are not necessarily confirmed. Using interview responses as reference, the positive predictive value in the DPCRR of a single episode of depression has been found to be 83% for severe, 76% for moderate, and 65% for mild depression.[37] Many patients receive treatment for depression in the primary care setting, but the Danish medical registries do not cover complete recording of diagnoses from general practice. To compensate for this, we obtained information on redeemed prescriptions for an antidepressant.

Covariates

Using ICD-8 and ICD-10 codes from the DNPR, we collected information on comorbidities diagnosed prior to the VTE/index date. These included obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental

health disorders other than depression, surgery and trauma three months prior to the VTE/index date, alcohol-, and drug-related disorders, and dementia. We calculated a modified Charlson Comorbidity Index scores (CCIs) excluding the listed comorbidities. As glucocorticoids are associated with both VTE and depression,[38,39] we also collected information on glucocorticoids used as a co-medication ≤90 days prior to the VTE/index date (Supplementary Table 1).

We defined SES as educational level and annual income provided by the Educational Attainment Register and the Integrated Database for Labor Market Research for the year prior to the VTE/index date. Educational level was divided into categories (*I.e.*, high, medium, and low) in age-specific groups based on the distribution of education in each group (Supplementary Tables 2 and 3). Annual income was deflated using gross domestic product deflators downloaded from the World Bank homepage (www.worldbank.org) and calculated in quartiles based on income values for the study population. The two middle quartiles were merged to obtain three income categories (*i.e.*, high, medium, and low).

Statistical analysis

The study cohorts were followed from the VTE/index date until the date of a depression diagnosis or a redeemed prescription for an antidepressant, emigration from Denmark, death, or end of follow-up (December 31, 2016), whichever came first. Unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using Cox proportional hazards regression models, comparing individuals with VTE patients with members of the general population cohort. Analyses were conducted in the cohorts overall and within strata of sex and age groups (25-34 years, 35-44 years, 45-54 years, 55-64 years, and 65-80 years on the inclusion date). Sex and age-stratified subgroup analyses were also conducted, using PE, DVT, unprovoked VTE and, provoked VTE as exposure variables. In the multivariable regression analyses, we adjusted for age, sex, obesity, SES, and comorbidities. The proportional hazards assumption was evaluated using log-log plots and was found not to be violated. Overall and sex-specific absolute risks of depression in individuals with and individuals without VTE were estimated and visualized using cumulative incidence function plots treating death as a competing event, as proposed by Fine and Gray.[40] To further address potential confounding

by other comorbidities, Cox regression analyses were stratified by CCI score [0 (*i.e.*, no comorbidities prior to the VTE/index date) *vs*. ≥1].

To test the robustness of our estimates, we performed several sensitivity analyses. First, to detect any temporal effect of the timing of the depression diagnosis, we performed analyses with follow-up restricted to 0-1 year and 0-10 years after the VTE/index date. Second, as antidepressants can be used for both depression and other conditions such as anxiety, it is hard to separate the conditions through medication use. We therefore performed analyses limited to depression diagnoses from the DNPR or the DPCRR as the outcome. Finally, as depression can be difficult to assess in individuals with alcohol and drug-related disorders or dementia, we repeated the analysis excluding individuals with these conditions.

All analyses were performed using SAS (Statistical Analysis System) version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics of the study participants are displayed in Table 1. A total of 64,596 individuals aged 25-80 years were included in the VTE cohort and 322,999 individuals were included in the comparison cohort (Table 1). After three years, 6,225 (9.6%) individuals in the VTE cohort developed depression compared to 16,363 (5.1%) in the general population cohort (Table 2).

In the VTE cohort, the proportion of individuals with low SES was higher, and the proportion with high SES was lower, compared to the general population cohort (Table 1). Comorbidities, such as surgery/trauma within three months prior to the VTE/index date, a history of cancer, use of glucocorticoids, coronary heart disease (including atrial fibrillation), COPD and obesity, occurred as expected more frequently in the VTE cohort than in the comparison cohort (Table 1).

The three-year absolute risk of depression, taking the competing risk of death into account, was 10.3% (95% CI 10.1%-10.6%) in the VTE cohort and 5.6% (95% CI 5.5%-5.6%) in the comparison cohort, corresponding to 4.7 excess cases of depression per 100 individuals with VTE (Figure 1, upper panel). VTE was associated with a 2.35-fold (95% CI 2.28-2.43)

increased risk of subsequent depression compared to the general population cohort, after adjusting for age and sex (Table 2). Adjustments for SES and obesity had a minor effect on the risk estimate (HR 2.29, 95% CI 2.22-2.36), while further adjustment for comorbidities reduced the HR to 1.91 (95% CI 1.85-1.97) (Figure 2, Table 2).

The risk estimates for PE, DVT, provoked VTE, and unprovoked VTE showed similar trends as in the main analysis (Figures 1 and 2, Table 2). The three-year absolute risk of depression was 10.8% (95% CI 10.4%-11.2%) for PE, 10.1% (95% CI 9.8%-10.4%) for DVT, 13.4% (95% CI 12.9%-13.9%) for provoked VTE, and 9.1% (95% CI 8.8%-9.4%) for unprovoked VTE (Figure 1, lower panel). After multivariable adjustment, the HR for depression following PE was 2.31 (95% CI 2.19-2.44), while the HR for depression following DVT was 1.71 (95% CI 1.64-1.78) (Figure 2, Table 2). The corresponding HRs were 2.32 (95% CI 2.12-2.55) for provoked VTE and 1.80 (95% CI: 1.73-1.87) for unprovoked VTE, while the HR for VTE provoked by cancer was 2.96 (95% CI 2.58-3.41), and that for VTE not provoked by cancer was 1.78 (95% CI: 1.71-1.85) (Figure 2, Table 2).

In the VTE cohort, the three-year absolute risk of depression was higher in women (11.2%, 95% CI 10.8%-11.5%) than in men (9.6%, 95% CI 9.3%-9.9%) (Figure 1, upper panel). However, after adjustment for SES, obesity, and comorbidities, the relative risk estimates for depression were slightly higher in men (HR 1.99, 95% CI 1.90-2.09) than in women (HR 1.83 95% CI 1.75-1.92) (Figure 2, Table 3).

The absolute risk of depression in the general population cohort increased over time. (Figure 1, upper panel). The association between depression and VTE displayed a temporal pattern, with a particularly strong association during the first three years after VTE diagnosis. In the multivariable adjusted analysis, the HR of depression in the VTE cohort, compared to the general comparison cohort, was 2.57 (95% CI: 2.45-2.70) when follow-up was restricted to 0-1 years, and 1.53 (95% CI: 1.49-1.57) when follow-up was restricted to 0-10 years, (Supplementary Table 5).

In a sensitivity analysis in which individuals were stratified on CCI score, the risk estimates for depression were somewhat increased for those with scores ≥1 compared to a score of 0 (Supplementary Table 7). The results of the sensitivity analysis using only depression diagnoses

registered in the DNPR and DPCRR, and the sensitivity analysis excluding individuals with alcohol or drug-related disorder or dementia were in line with the results of the main analysis (Supplementary Tables 8 and 9). However, the HRs for depression in patients with PE, provoked VTE, and cancer-provoked VTE increased when individuals with a redeemed prescription for an antidepressant were excluded from the analysis (Supplementary Table 8).

Discussion

In this population-based cohort study, we found that individuals diagnosed with VTE were at increased risk of subsequent depression compared to the general population, particularly after a PE or a cancer-provoked VTE. The risk estimates were moderately attenuated after adjusting for SES and comorbidities.

Our findings extend previous research. Existing self-report and interview studies on the psychological and psychosocial consequences of VTE have documented mental and emotional distress following a VTE diagnosis.[14,23-25] This was also the case for young adults, for whom a VTE might lead to uncertainty about long-term health and fear of relapse.[17,18] Psychological distress after VTE was found to be long-term and chronic, due to persistent fear of VTE recurrence.[15,17,23,24] Qualitative studies of mental health after PE have pointed consistently towards a long-term increase in symptoms of anxiety, depression, or PTSD.[15,19,22-24,26,28] Major challenges reported by patients included delayed diagnosis, distress regarding recurrent PE and comorbid conditions, lack of expert information, and poor follow-up by the health care system.[15,16,22,27]

To our knowledge, this is the first population-based study to quantify the long-term risk of subsequent depression in individuals who suffer a VTE, compared to the general population and taking comorbid conditions at the VTE/index date into account. Our findings are consistent with numerous reviews and meta-analyses on the risk of depression following CVD.[10-13] A review of eight studies (encompassing 10,785 patients) reported that depression occurred in 19.8% of acute myocardial infarction patients, among whom almost a third had clinically significant depression,[12] while Coronary heart disease patients had an estimated 15-18% prevalence of depression.[11] One meta-analysis of 43 studies with a total of 20,293 patients

reported a depression prevalence after stroke of 29%,[13] while another meta-analysis of 61 prospective studies (25,488 patients) found a prevalence of 31%.[10]

There may be multiple psychosocial mechanisms through which VTE can lead to depression. VTE is an acute life-threatening event demonstrated to cause functional impairment, early exit from work life, and lower quality of life.[7,8,41] In addition, long-term anticoagulant treatment is known to negatively affect lifestyle due to the increased risk of bleeding.[42] Depression therefore may be a psychological reaction to the consequences of a VTE diagnosis or occur secondarily as an adverse effects of VTE treatment. Further, as indicated by qualitative studies on mental health after VTE, functional deterioration including pain, swelling, dyspnea, and reduced mobility, as well as with complications such as recurrence,[4] post-thrombotic syndrome,[5] and post-PE syndrome[6] may lead to depression.

We observed an increased risk of depression in PE patients. PE is sudden, life-threatening, and traumatic. Several qualitative studies indicate that PE patients experience psychological distress, suggestive of PTSD, following their diagnosis.[15,16,21] Thus, experiencing a PE can lead to existential anxiety, a lost sense of identity, and negative self-perception.[15,16,22,27] Persisting dyspnea, pain, loss of physical fitness, and need for lifestyle changes due to bleeding and recurrence risk, in addition to delayed diagnosis and lack of expert information, also might increase psychological distress after PE.[15,16,22,27]

We also found that the association between provoked VTE, especially cancer-provoked VTE, and depression remained elevated compared to unprovoked VTE, even after adjustment for potential confounders. A VTE is a serious complication of cancer and negatively affect quality of life and overall survival rates.[43] Other provoking factors, such as emotional distress and insecurity, poor underlying health, hospitalization, immobilization, cancer treatment, and prolonged anticoagulation treatment all could contribute to depression in cancer patients after VTE.[44,45]

Psychosocial factors, previous depression, antidepressant use, SES and lifestyle factors have been associated with increased risk of both VTE and depression.[45-48] Although we did not include individuals with a previous diagnosis of depression or former use of antidepressants, and adjusted for SES and obesity, we cannot completely rule out that latent but undiagnosed

depression or lifestyle factors operating prior to the VTE might influence the observed association.

The pathways between depression and VTE are likely bidirectional as they share common risk factors.[46] The development and course of both depression and VTE might be triggered by several common mechanistic pathways, such as increased platelet activation, pro-coagulant activity, endothelial dysfunction, and inflammatory processes.[49,50] There is also growing evidence relating depression and prothrombotic states to dysfunctions in the stress response system.[50] Stress has been proposed as an underlying trigger leading to both depression and VTE due to imbalances in the hemostatic system.[20,24,50,51] Despite the plausibility of both behavioral and biological mechanisms, existing findings are inconsistent. Further evidence is needed to shed light on possible pathways leading to depression after VTE.

Our study has both strengths and limitations. It was conducted in a setting in which educational and health care services are government-funded and provided free-of-charge to residents, thereby preventing selection and referral biases. Our outcome measure of depression was based on psychiatric diagnoses and prescriptions for antidepressant from highly accurate health registries. Although the Danish Prescription Registry is complete[52] and antidepressants are not sold over the counter in Denmark, they may be prescribed for a range of conditions. We therefore performed sensitivity analyses that included only individuals with a hospital diagnosis of depression, but the results were similar. As we could only include information available in medical and administrative registers, we lacked information on the quality and outcome of post-VTE care and individual health behaviors, as well as information about recurrence, the post-thrombotic syndrome, or the post-PE syndrome during follow-up. Although we adjusted for lifestyle factors, SES and multiple comorbidities, residual confounding due to unmeasured factors also cannot be completely ruled out.

In summary, this study showed that VTE is associated with increased risk of depression, especially after PE and provoked VTE. The improved understanding of post-VTE depression provided by our findings could inform new strategies for identifying high-risk groups for screening, prevention, and treatment of depression after VTE.

Authors contributions

H. Jørgensen, E. Horváth-Puhó, K. Laugesen, S.K. Brækkan, J-B Hansen, and H.T Sørensen contributed to the planning and design of the study and to the verification, analysis and interpretation of the data. E. Horváth-Puhó, K. Laugesen and H.T Sørensen verified the underlying data. H. Jørgensen drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version before submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All persons named in the acknowledgments section have provided the corresponding author with permission to be named in the manuscript.

Ethics

The study was approved by the Danish Data Protection Agency, record number 2016-051-000001-811. According to Danish legislation, approval from an ethics committee or informed consent from the patients is not required for registry-based studies conducted in Denmark

Role of funding source

This work was supported by Karen Elise Jensen's Foundation. The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or decision to submit it for publication.

Conflict of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any company for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. The authors have no disclosures.

References

1. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol. 2014;34(11):2363-71.
2. Søgaard KK, Schmidt M, Pedersen L, Horváth-Puhó E, Sørensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. Circulation. 2014;130(10):829-36.
3. Organization WH. Depression and Other Common Mental Disorders: Global Health Estimates. . In: Organization WH, editor. Print. Geneva: World Health Organization; 2017.
4. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. N Engl J Med. 2004;350(25):2558-63.
5. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. J Thromb Thrombolysis. 2009;28(4):465-76.
6. Pugliese SC, Kawut SM. The Post-Pulmonary Embolism Syndrome: Real or Ruse? Ann Am Thorac Soc. 2019;16(7):811-4.
7. Ghanima W, Wik HS, Tavoly M, Enden T, Jelsness-Jorgensen LP. Late consequences of venous thromboembolism: Measuring quality of life after deep vein thrombosis and pulmonary embolism. Thromb Res. 2018;164:170-6.
8. Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Kaptein AA, et al. Quality of life in long-term survivors of acute pulmonary embolism. Chest. 2010;138(6):1432-40.
9. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. Med J Aust. 2009;190(S7):S54-60.
10. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int J Stroke. 2014;9(8):1017-25.
11. Carney RM, Freedland KE. Depression and coronary heart disease. Nature Reviews Cardiology. 2017;14(3):145-55.
12. Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, et al. Prevalence of depression in survivors of acute myocardial infarction. Journal of general internal medicine. 2006;21(1):30-8.
13. Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. The British journal of psychiatry : the journal of mental science. 2013;202(1):14-21.
14. Lukas PS, Krummenacher R, Biasiutti FD, Begré S, Znoj H, Känel Rv. Association of fatigue and psychological distress with quality of life in patients with a previous venous thromboembolic event. Thromb Haemost. 2009;102 6:1219-26.
15. Noble S, Lewis R, Whithers J, Lewis S, Bennett P. Long-term psychological consequences of symptomatic pulmonary embolism: a qualitative study. BMJ Open. 2014;4(4):e004561.
16. Tran A, Redley M, de Wit K. The psychological impact of pulmonary embolism: A mixed-methods study. Res Pract Thromb Haemost. 2021;5(2):301-7.

17. Højen AA, Dreyer PS, Lane DA, Larsen TB, Sørensen EE. Adolescents' and Young Adults' Lived Experiences Following Venous Thromboembolism: "It will always lie in wait". Nurs Res. 2016;65(6):455-64.
18. Fiandaca D, Bucciarelli P, Martinelli I, Tantardini F, Clemente C, Mannucci PM. Psychological impact of thrombosis in the young. Internal and Emergency Medicine. 2006;1(2):119.
19. Liu CP, Li XM, Chen HW, Cui JY, Niu LL, He YB, et al. Depression, anxiety and influencing factors in patients with acute pulmonary embolism. Chin Med J (Engl). 2011;124(16):2438-42.
20. Hunter R, Lewis S, Noble S, Rance J, Bennett PD. "Post-thrombotic panic syndrome": A thematic analysis of the experience of venous thromboembolism. Br J Health Psychol. 2017;22(1):8-25.
21. Kirchberger I, Ruile S, Linseisen J, Haberl S, Meisinger C, Berghaus TM. The lived experience with pulmonary embolism: A qualitative study using focus groups. Respir Med. 2020;167:105978.
22. Rolving N, Brocki BC, Andreasen J. Coping with everyday life and physical activity in the aftermath of an acute pulmonary embolism: A qualitative study exploring patients' perceptions and coping strategies. Thromb Res. 2019;182:185-91.
23. Hunter R, Noble S, Lewis S, Bennett P. Long-term psychosocial impact of venous thromboembolism: a qualitative study in the community. BMJ Open. 2019;9(2):e024805.
24. Bennett P, Patterson K, Noble S. Predicting post-traumatic stress and health anxiety following a venous thrombotic embolism. J Health Psychol. 2014;21(5):863-71.
25. Hunter R, Lewis S, Noble S, Rance J, Bennett PD. “Post-thrombotic panic syndrome”: A thematic analysis of the experience of venous thromboembolism. British Journal of Health Psychology. 2017;22(1):8-25.
26. Tran A, Redley M, de Wit K. The psychological impact of pulmonary embolism: A mixed-methods study. Research and Practice in Thrombosis and Haemostasis. 2021;5(2):301-7.
27. Kirchberger I, Ruile S, Linseisen J, Haberl S, Meisinger C, Berghaus TM. The lived experience with pulmonary embolism: A qualitative study using focus groups. Respiratory Medicine. 2020;167:105978.
28. Chuang L-H, Gumbs P, van Hout B, Agnelli G, Kroep S, Monreal M, et al. Health-related quality of life and mortality in patients with pulmonary embolism: a prospective cohort study in seven European countries. Quality of Life Research. 2019;28(8):2111-24.
29. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues Clin Neurosci. 2011;13(1):7-23.
30. Schmidt M, Schmidt SAJ, Adelborg K, Sundboll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol. 2019;11:563-91.
31. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health. 2011;39(7 Suppl):54-7.
32. Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. Danish medical bulletin. 1997;44(4):445-8.
33. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open. 2016;6(11):e012832.

34. Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. Circulation. 2014;130(10):829-36.
35. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost. 2016;14(7):1480-3.
36. Adelborg K, Corraini P, Darvalics B, Frederiksen H, Ording A, Horváth-Puhó E, et al. Risk of thromboembolic and bleeding outcomes following hematological cancers: A Danish population-based cohort study. J Thromb Haemost. 2019;17(8):1305-18.
37. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. Clin Pract Epidemiol Ment Health. 2009;5:4.
38. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, Cannegieter SC, Jørgensen JOL, Ehrenstein V, et al. Use of Glucocorticoids and Risk of Venous Thromboembolism: A Nationwide Population-Based Case-Control Study. Jama Intern Med. 2013;173(9):743-52.
39. Steckler T, Holsboer F, Reul JM. Glucocorticoids and depression. Baillieres Best Pract Res Clin Endocrinol Metab. 1999;13(4):597-614.
40. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496-509.
41. Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen JB, Sørensen HT. Risk of a permanent work-related disability pension after incident venous thromboembolism in Denmark: A population-based cohort study. PLoS Med. 2021;18(8):e1003770.
42. Wells PS, Forgie MA, Rodger MA. Treatment of Venous Thromboembolism. JAMA. 2014;311(7):717-28.
43. Khorana AA, Mackman N, Falanga A, Pabinger I, Noble S, Ageno W, et al. Cancer-associated venous thromboembolism. Nat Rev Dis Primers. 2022;8(1):11.
44. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. Jama. 2008;300(20):2379-88.
45. Kunutsor SK, Mäkikallio TH, Seidu S, de Araújo CGS, Dey RS, Blom AW, et al. Physical activity and risk of venous thromboembolism: systematic review and meta-analysis of prospective cohort studies. Eur J Epidemiol. 2020;35(5):431-42.
46. Kunutsor SK, Seidu S, Khunti K. Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence. Annals of Medicine. 2018;50(6):529-37.
47. Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen J-B, Sørensen HT. Socioeconomic status and risk of incident venous thromboembolism. Journal of Thrombosis and Haemostasis. 2021;19(12):3051-61.
48. Evans CR, Hong C-P, Folsom AR, Heckbert SR, Smith NL, Wiggins K, et al. Lifestyle Moderates Genetic Risk of Venous Thromboembolism. Arteriosclerosis, Thrombosis, and Vascular Biology. 2020;40(11):2756-63.
49. Musselman DL, Tomer A, Manatunga AK, Knight BT, Porter MR, Kasey S, et al. Exaggerated platelet reactivity in major depression. The American journal of psychiatry. 1996;153(10):1313-7.
50. Gold PW. The organization of the stress system and its dysregulation in depressive illness. Molecular Psychiatry. 2015;20(1):32-47.

51. Sandrini L, Ieraci A, Amadio P, Zarà M, Barbieri SS. Impact of Acute and Chronic Stress on Thrombosis in Healthy Individuals and Cardiovascular Disease Patients. Int J Mol Sci. 2020;21(21).
52. Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, Schmidt M, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. Clin Epidemiol. 2012;4:303-13.

Table 1. Baseline characteristics of persons with venous thromboembolism and members of the general population comparison cohort, Denmark, 1996-2016.

	VTE cohort (*n*=64 596)	General Population Comparison Cohort (*n*= 322 999)
Sex (% women)	29 222 (45.2)	146 157 (45.2)
Age-group		
25-34 years	4 388 (6.8)	22 007 (6.8)
35-44 years	6 828 (10.6)	34 200 (10.6)
45-54 years	10 164 (15.7)	50 744 (15.7)
55-64 years	14 439 (22.4)	72 010 (22.3)
65-80 years	28 777 (44.5)	144 038 (44.6)
Pulmonary embolism	25 299 (39.2)	
Deep vein thrombosis	39 297 (60.8)	
Provoked VTE	18 562 (28.7)	
VTE provoked by cancer	11 237 (17.4)	
Unprovoked VTE	46 034 (71.3)	
Education		
Low	26 001 (40.3)	117 201 (36.3)
Medium	28 676 (44.4)	147 871 (45.8)
High	7 333 (11.4)	45 540 (14.1)
Missing	2 586 (4.0)	12 387 (3.8)
Income		
Low	17 055 (26.4)	77 335 (23.9)
Middle	17 396 (26.9)	79 011 (24.5)
Medium high	15 661 (24.2)	81 975 (25.4)
High	14 409 (22.3)	84 217 (26.1)
Missing	75 (0.1)	461 (0.1)
Comorbidities		
*High-risk cancer prior to VTE/index date	4 028 (6.2)	3 162 (1.0)
*Low-risk cancer prior to VTE/index date	6 991 (10.8)	17 996 (5.6)
Coronary heart disease	9 116 (14.1)	32 331 (10.0)
Diabetes	5 332 (8.3)	20 303 (6.3)
Chronic obstructive pulmonary disease	5 700 (8.8)	14 263 (4.4)
Obesity	3 601 (5.6)	7 680 (2.4)
Stroke	2 090 (3.2)	7 344 (2.3)
Moderate to severe renal disease	1 665 (2.6)	3 105 (1.0)
Surgery 3 months prior to VTE/index date	9 530 (14.8)	9 347 (2.9)
Trauma/fracture 3 months prior to VTE/index date	2 419 (3.7)	2 038 (0.6)
Other mental health conditions	1 805 (2.8)	5 212 (1.6)
Alcohol and drug-related disorders	2 586 (4.0)	5 866 (1.8)
Dementia	404 (0.6)	1 181 (0.4)
Glucocorticoid use (within 90 days)	5 326 (8.2)	6 192 (1.9)
Modified Charlson Comorbidity Index (CCI) score		
**CCI score: 0	53 970 (83.6)	291 936 (90.4)
**CCI score: 1	8 592 (13.3)	26 734 (8.3)
** CCI score: ≥2	2 034 (3.1)	4 329 (1.3)

Abbreviation: VTE, venous thromboembolism *Categorized according to 5-year mortality as high-risk cancer (>70% mortality) and low-risk cancer (≤70% mortality). **Charlson Comorbidity Index score excluding *International Classification of Disease* codes used in the covariate definition. Values are numbers, with percentages in brackets.

Table 2. Incidence rates and hazard ratios with 95% confidence intervals of subsequent depression among persons with and persons without venous thromboembolism.

	General Population Comparison Cohort			VTE Cohort					
VTE	**At risk**	**Events**	**IR (95% CI)**	**At risk**	**Events**	**IR (95% CI)**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**
Overall	322 999	16 363	19.42 (19.12-19.71)	64 596	6 225	44.43 (43.32-45.53)	2.35 (2.28–2.43)	2.29 (2.22–2.36)	1.91 (1.85–1.97)
Men	176 842	7 795	16.98 (16.60-17.35)	35 374	3 167	41.16 (39.73-42.59)	2.50 (2.40–2.61)	2.43 (2.33–2.54)	1.99 (1.90–2.09)
Women	146 157	8 568	22.33 (21.86-22.81)	29 222	3 058	48.41 (46.69-50.12)	2.22 (2.13–2.32)	2.16 (2.07–2.25)	1.83 (1.75–1.92)
PE	126 412	6 252	19.54 (19.05-20.02)	25 299	2 501	53.03 (50.95-55.11)	2.84 (2.71–2.99)	2.79 (2.66–2.94)	2.31 (2.19–2.44)
DVT	196 316	10 101	19.35 (18.97-19.73)	39 297	3 724	40.06 (38.77-41.35)	2.11 (2.03–2.19)	2.04 (1.96–2.12)	1.71 (1.64–1.78)
Provoked VTE	92 742	4 709	19.77 (19.21-20.34)	18 562	2 331	71.64 (68.73-74.55)	3.77 (3.57–3.98)	3.68 (3.49–3.89)	2.32 (2.12–2.55)
Unprovoked VTE	229 986	11 644	19.28 (18.93-19.63)	46 034	3 894	36.20 (35.06-37.33)	1.92 (1.85–1.99)	1.87 (1.80–1.94)	1.80 (1.73–1.87)
Cancer-provoked VTE	56 177	2 829	19.99 (19.25-20.73)	11 237	1 504	97.46 (92.54-102.39)	5.10 (4.74–5.49)	5.02 (4.66–5.40)	2.96 (2.58–3.41)
Cancer-unprovoked VTE	266 551	13 524	19.31 (18.98-19.63)	53 359	4 721	37.86 (36.78-38.94)	2.01 (1.94–2.08)	1.95 (1.88–2.02)	1.78 (1.71–1.85)

Abbreviations: IR, incidence rate; HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; PY, Person years; PE, pulmonary embolism; DVT, deep vein thrombosis.
Model 1: Unadjusted model controlled for matching variables by study design.
Model 2: Adjusted for socioeconomic status (education and income) and obesity.
Model 3: Adjusted for socioeconomic status (education and income), obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases (other than depression), alcohol and drug-related disorders, dementia, surgery, and trauma three months prior to the VTE/index date, Charlson Comorbidity Index score (CCI) excluding the comorbidities listed above, and co-medication.

Table 3. Incidence rates and hazard ratios with 95% confidence intervals for subsequent depression among persons with and persons without venous thromboembolism, stratified by age and sex.

General Population Comparison Cohort		VTE Cohort			
	IR (95% CI)	IR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
VTE by age					
25-34 years	16.48 (15.46-17.51)	32.63 (29.31-35.94)	1.96 (1.73–2.21)	1.89 (1.67–2.13)	1.62 (1.42–1.86)
35-44 years	17.17 (16.33-18.01)	37.95 (35.04-40.87)	2.22 (2.02–2.44)	2.02 (1.84–2.23)	1.67 (1.50–1.86)
45-54 years	16.60 (15.91-17.28)	38.88 (36.39-41.37)	2.39 (2.20–2.58)	2.24 (2.06–2.42)	1.86 (1.70–2.03)
55-64 years	14.57 (14.03-15.12)	40.41 (38.20-42.61)	2.81 (2.62–3.01)	2.73 (2.54–2.93)	2.18 (2.02–2.35)
65-80 years	24.10 (23.59-24.60)	53.57 (51.64-55.49)	2.27 (2.17–2.37)	2.25 (2.15–2.35)	1.89 (1.81–1.99)
VTE Men by age					
25-34 years	12.33 (10.84-13.82)	36.07 (30.16-41.99)	2.94 (2.39–3.63)	2.75 (2.22–3.41)	2.21 (1.72–2.83)
35-44 years	14.46 (13.36-15.55)	33.51 (29.60-37.41)	2.35 (2.04–2.71)	2.07 (1.78–2.39)	1.62 (1.37–1.92)
45-54 years	14.14 (13.31-14.98)	33.95 (30.92-36.98)	2.47 (2.21–2.76)	2.30 (2.05–2.57)	1.84 (1.62–2.08)
55-64 years	13.18 (12.53-13.82)	35.43 (32.85-38.00)	2.70 (2.46–2.96)	2.63 (2.40–2.89)	2.09 (1.88–2.31)
65-80 years	21.63 (20.97-22.28)	51.35 (48.78-53.92)	2.41 (2.27–2.57)	2.39 (2.25–2.55)	2.00 (1.87–2.14)
VTE Women by age					
25-34 years	18.77 (17.40-20.13)	30.79 (26.80-34.78)	1.62 (1.39–1.88)	1.57 (1.35–1.83)	1.42 (1.21–1.67)
35-44 years	19.81 (18.54-21.08)	42.25 (37.94-46.56)	2.13 (1.89–2.41)	1.98 (1.74–2.24)	1.69 (1.47–1.94)
45-54 years	19.97 (18.81-21.13)	45.97 (41.74-50.20)	2.31 (2.06–2.58)	2.18 (1.94–2.44)	1.89 (1.67–2.14)
55-64 years	16.95 (16.00-17.91)	49.30 (45.23-53.36)	2.97 (2.67–3.30)	2.88 (2.58–3.20)	2.36 (2.09–2.65)
65-80 years	26.90 (26.12-27.68)	56.14 (53.24-59.04)	2.14 (2.01–2.28)	2.11 (1.98–2.24)	1.79 (1.67–1.92)

Abbreviations: IR, incidence rate; HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; PY, person years; PE, pulmonary embolism; DVT, deep vein thrombosis.
Model 1: Unadjusted model controlled for matching variables by study design.
Model 2: Adjusted for socioeconomic status (education and income) and obesity.
Model 3: Adjusted for socioeconomic status (education and income), obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases (other than depression), alcohol and drug related disorders, dementia, surgery and trauma three months prior to the VTE/index date, Charlson Comorbidity Index score (CCI) excluding the comorbidities listed above, and co-medication.

Figure 1. Cumulative incidence (%) of subsequent depression in persons with (VTE+) and persons without (VTE-) venous thromboembolism taking the competing risk of death into account, overall and according to sex (1.1) and according to VTE subtypes (1.2).

Figure 1.1

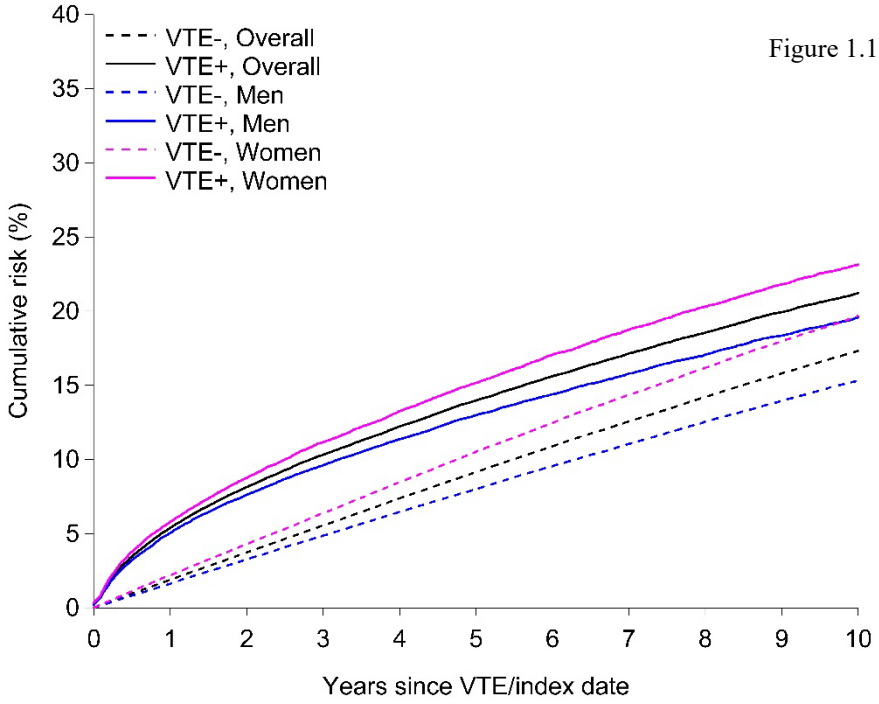
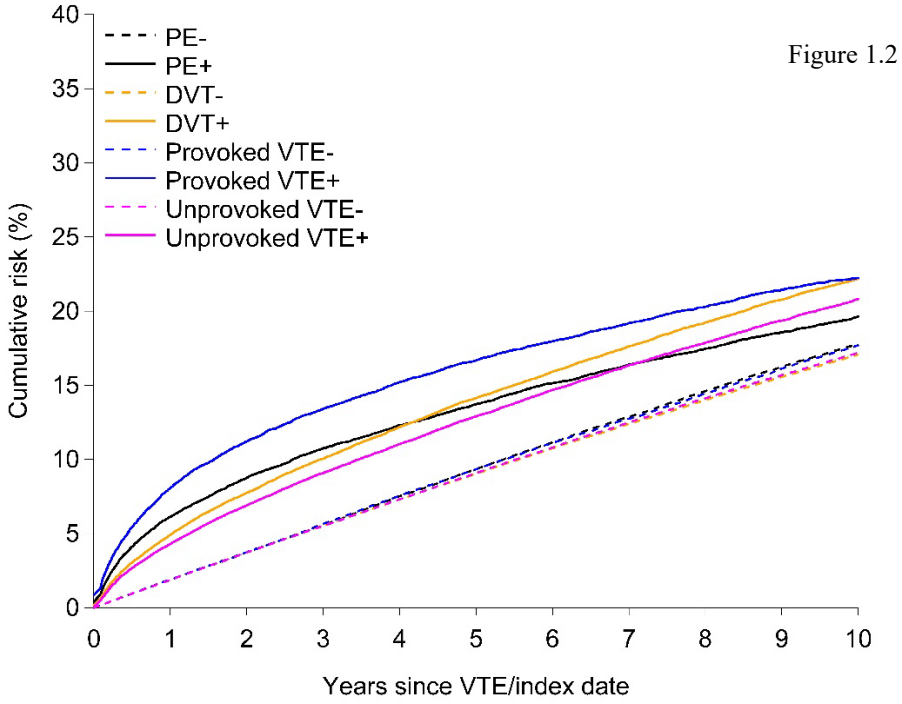
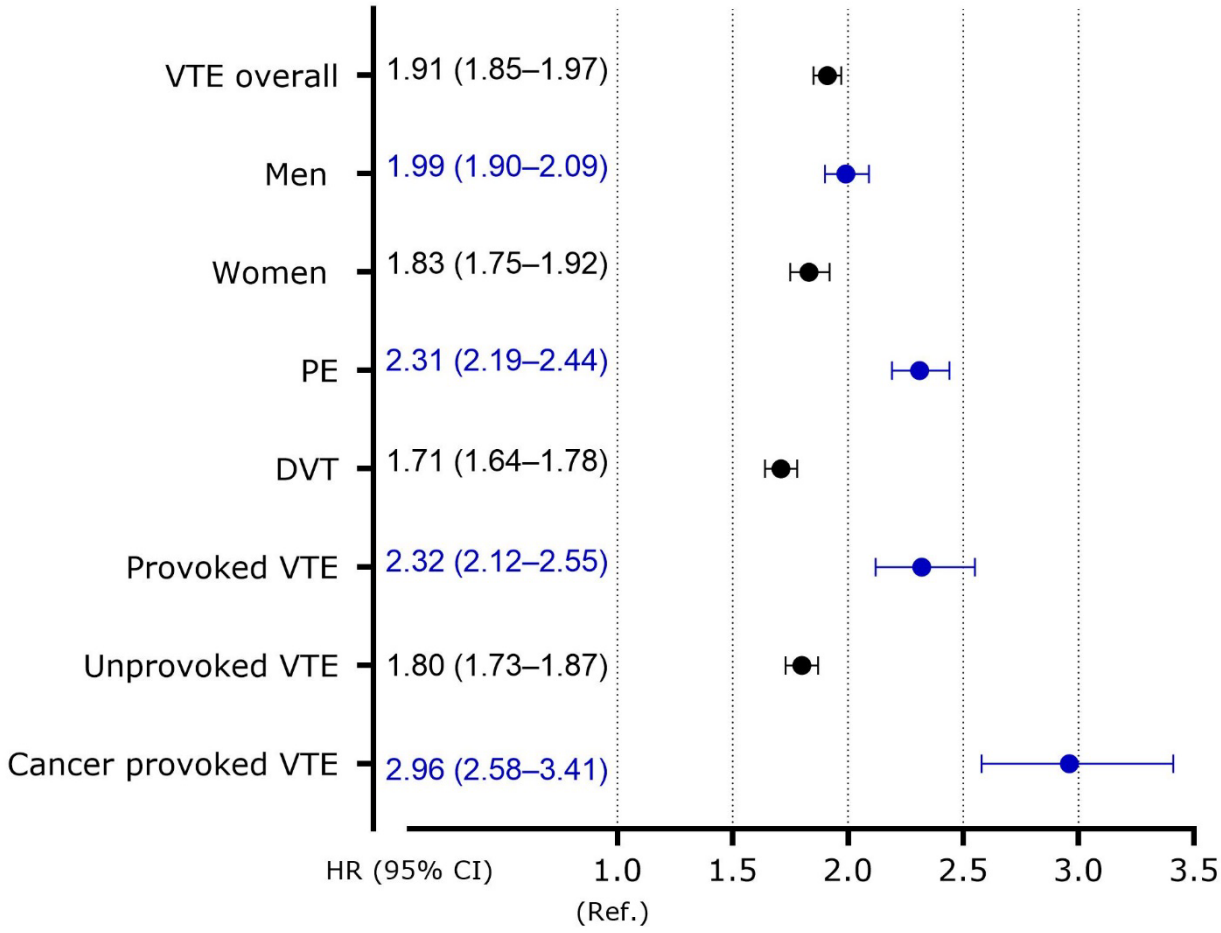


Figure 1.2



Abbreviations: VTE, venous thromboembolism

Figure 2. Forest plot of subsequent depression in persons with and persons without venous thromboembolism according to sex and venous thrombosis subtypes.



Supplementary Table 1. *International Classification of Disease*s and Anatomical Therapeutic Chemical Classification codes used to define exposure, provoking factors for VTE, covariables, and conditions included in the Modified Charlson Comorbidity Index.

Variables	ICD-8 codes	ICD-10 codes	ATC codes
Exposure			
Pulmonary embolism	45099	I26	
Deep venous thrombosis	45100	I801; I802; I803	
Outcome diagnosis			
Depression	296.09; 296.29; 296.99; 298.09; 298.19; 300.49; 300.19; 790.2	F32-F33	
Outcome prescriptions			
Antidepressants	N/A	N/A	N06A
Provoking factors for venous thromboembolism			
Fracture/trauma	800-929; 950-959	S00-T14	
Surgery	00000-99960	KA-KQ; KX; KY	
Pregnancy	630-680	O00-O99	
High-risk cancer	148; 150; 151; 153.9;155; 156; 157; 162; 171; 196; 197; 198; 205.0; 205.9; 206.0; 207	C13; C15; C16; C22-C26; C33; C34; C45; C77-79; C95; C920; C923-C929	
Low-risk cancer	140-209 (except 172; 148; 150; 151; 153.9;155; 156; 157; 162; 171; 196; 197; 198; 205.0; 205.9; 206.0; 207)	C00- C97 (except C13; C15; C16; C22-C26; C33; C34; C44; C45; C77-79; C95; C920; C923-C929)	
Covariables			
Coronary heart disease (including myocardial infarction, atrial fibrillation, and heart failure)	41009; 41099; 41109; 41199; 41209; 41299; 41309; 41399; 41409; 41499; 42793; 42794; 42709, 42710; 42711; 42719; 42899; 78249	I20-I25; I48; I500-I503; I508; I509; I110; I130; I132; I420; I426-I429	
Diabetes mellitus type I or II	249; 250	E10; E11; E14	A10
Chronic obstructive pulmonary disease	490–493	J40-J49	
Obesity	277.99	E65-E68	
Stroke (hemorrhagic or ischemic)	430; 431; 432; 433; 434; 435; 437.0; 437.1	I60; I61; I62; I63; I65; I66; I67.2; I67.8	
Acute kidney failure and chronic kidney disease	403; 404; 580-584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17- N19; Q61	
Mental health disorders	290; 292-302 (except 296.09; 296.29; 296.99; 298.09; 298.19; 300.49; 300.19); 305-315	F04-F09, F20-F31, F34-F92, F94-99	
Alcohol- and drug-related disorders	291; 29430; 29438; 29439; 303-304; 98009	F10-F16; F18-F19	
Alzheimer's disease	290.10, 290.09	F00, G30	
Vascular dementia	293.09, 293.19	F01	
Other dementia	094.19, 290.11-290.19, 292.09	F02-F03, F10.73, F11.73, F12.73, F13.73, F14.73, F15.73, F16.73, F18.73, F19.73, B22.0A, G31	
Co-medication			
Glucocorticoids			H02AB
Modified Charlson Comorbidity Index			
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	
Cerebrovascular disease	430-438	I60-I69; G45; G46	

Chronic pulmonary disease	515-518	J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0;
Hemiplegia	344	G81; G82
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
AIDS	079.83	B21-B24

Supplementary Table 2. International Standard Classification of Education-2011 English and Danish educational program names and corresponding levels of education.

ISCED-2011 level	ISCED-2011 Program Name (English)	Danish Level	Danish program name (Danish)
0	Early childhood education	0	Førskole," Vuggestuer, Børnehaver"
1	Primary education	10	"Grundskole"
2	Lower secondary education	10	"Grundskole"
3	Upper secondary education		
	General upper secondary education	20	"Almengymnasiale uddannelser (stx, hf)"
	General upper secondary education	25	"Erhvervsgymnasiale uddannelser (hhx, htx)"
	Vocational education and training	35	"Erhvervsfaglige praktik og hovedforløb (eud)"
4	Post-secondary non-tertiary education	-	No corresponding Danish level exists
5	Short-cycle tertiary education	40	"Korte videregående uddannelser (Erhvervsakademi)"
6	Bachelor's degree or equivalent level		
	Bachelor's degree, but not necessarily from a university	50	"Mellemlange videregående uddannelser
	Bachelor's degree from a university	60	"Bachelor"
7	Master's degree or equivalent level	65	"Lange videregående uddannelser"
8	Doctoral degree or equivalent level	70	"Forskeruddannelser"

Translation from Danish levels to the International Standard Classification of Education are based on the work of the European Commission/EACEA/Eurydice, 2015:" The *Structure of the European Education Systems 2015/16: Schematic Diagrams."* Eurydice Facts and Figures. Luxembourg: Publications Office of the European Union.

Supplementary Table 3. Division of level of education (Danish levels) based on Supplementary Table 2.

Overall educational Level	Levels for those with baseline age 25-34	Levels for those with baseline age 35-44	Levels for those with baseline age 45-54	Levels for those with baseline age 55-64	Levels for those with baseline age 65-80
Low	1, 10, 20, 25	1, 10, 20, 25	1, 10, 20, 25	1 and 10	1 and 10
Medium	35, 40, 50	35, 40, 50	35, 40, 50	20, 25, 35, 40	20, 25, 35, 40
High	60, 65, 70	60, 65, 70	60, 65, 70	50, 60, 65, 70	50, 60, 65, 70

We divided overall educational level into low, medium, or high based on the distribution of Danish educational levels in Supplementary Table 2. By using a different categorization for different age groups, we could account for the need to weight low and high education differently for persons born in different generations, *e.g.*, 1940 versus 1970.

Supplementary Table 4. Baseline characteristics (year of VTE diagnosis/index year) of persons with venous thromboembolism and members of the general population comparison cohort.

	VTE Cohort (*n*=64 596)	**General Population Comparison Cohort (*n*=322 999)**
Year of VTE diagnoses		
1996-1999	10 435 (16.2)	52 190 (16.2)
2000-2004	13 864 (21.5)	69 322 (21.5)
2005-2009	15 632 (24.2)	78 149 (24.2)
2010-2016	24 665 (38.2)	123 338 (38.2)

Values are numbers, with percentages in brackets. Abbreviation: VTE, venous thromboembolism

Supplementary Table 5. Sensitivity analysis on incidence rates and hazard ratios with 95% confidence intervals of subsequent depression among persons with and persons without provoked and unprovoked venous thromboembolism, stratified by years of follow-up.

	General Population Comparison Cohort			VTE Cohort					
VTE	**At risk**	**Events**	**IR (95% CI)**	**At risk**	**Events**	**IR (95% CI)**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**
0-1 years of follow-up									
Overall	322 999	5 899	19.10 (18.61-19.59)	64 596	3 398	62.65 (60.55-64.76)	3.35 (3.21–3.50)	3.27 (3.13–3.42)	2.57 (2.45–2.70)
Men	176 842	2 782	16.47 (15.86-17.09)	35 374	1 742	58.39 (55.65-61.14)	3.62 (3.40–3.85)	3.53 (3.32–3.76)	2.70 (2.52–2.89)
Women	146 157	3 117	22.28 (21.49-23.06)	29 222	1 656	67.86 (64.59-71.13)	3.11 (2.92–3.31)	3.04 (2.85–3.23)	2.45 (2.29–2.63)
PE	126 412	2 277	19.00 (18.22-19.78)	25 299	1 507	78.88 (74.90-82.86)	4.33 (4.04–4.64)	4.28 (3.99–4.59)	3.33 (3.09–3.60)
DVT	196 316	3 617	19.17 (18.54-19.79)	39 297	1 891	53.83 (51.40-56.26)	2.84 (2.68–3.01)	2.75 (2.60–2.91)	2.18 (2.05–2.32)
Provoked VTE	92 742	1 708	19.36 (18.44-20.27)	18 562	1 462	107.17 (101.67-112.66)	5.69 (5.27–6.13)	5.59 (5.18–6.03)	2.90 (2.55–3.31)
Unprovoked VTE	229 986	4 186	19.00 (18.42-19.58)	46 034	1 936	47.69 (45.57-49.82)	2.56 (2.42–2.70)	2.49 (2.35–2.63)	2.42 (2.28–2.56)
Cancer-provoked VTE	56 177	1 008	18.97 (17.80-20.14)	11 237	1 047	145.56 (136.74-154.37)	7.93 (7.19–8.75)	7.82 (7.09–8.64)	4.25 (3.46–5.21)
Cancer-unprovoked VTE	266 551	4 886	19.13 (18.59-19.67)	53 359	2 351	49.98 (47.96-52.00)	2.66 (2.53–2.80)	2.59 (2.47–2.73)	2.34 (2.21–2.47)
0-10 years of follow-up									
Overall	322 999	40 351	20.29 (20.10-20.49)	64 596	10 757	34.48 (33.83-35.13)	1.78 (1.74–1.83)	1.74 (1.70–1.78)	1.53 (1.49–1.57)
Men	176 842	19 204	17.91 (17.66-18.17)	35 374	5 393	31.73 (30.88-32.57)	1.87 (1.81–1.93)	1.82 (1.76–1.88)	1.58 (1.53–1.64)
Women	146 157	21 147	23.08 (22.77-23.39)	29 222	5 364	37.78 (36.77-38.79)	1.71 (1.65–1.76)	1.66 (1.61–1.71)	1.48 (1.43–1.53)
PE	126 412	15 020	20.99 (20.65-21.32)	25 299	3 797	38.74 (37.51-39.97)	1.99 (1.92–2.07)	1.96 (1.89–2.04)	1.71 (1.64–1.79)
DVT	196 316	25 295	19.91 (19.66-20.15)	39 297	6 960	32.53 (31.77-33.30)	1.69 (1.64–1.73)	1.63 (1.59–1.68)	1.44 (1.40–1.49)
Provoked VTE	92 742	11 255	20.83 (20.44-21.21)	18 562	3 349	50.48 (48.77-52.18)	2.60 (2.49–2.71)	2.54 (2.43–2.65)	1.83 (1.71–1.97)
Unprovoked VTE	229 986	29 060	20.10 (19.86-20.33)	46 034	7 408	30.16 (29.47-30.85)	1.56 (1.52–1.60)	1.52 (1.48–1.56)	1.46 (1.42–1.50)
Cancer-provoked VTE	56 177	6 545	21.45 (20.93-21.96)	11 237	1 897	70.55 (67.38-73.73)	3.62 (3.40–3.84)	3.58 (3.37–3.81)	2.37 (2.13–2.64)
Non-cancer-provoked VTE	266 551	33 770	20.09 (19.87-20.30)	53 359	8 860	31.08 (30.43-31.73)	1.61 (1.57–1.65)	1.56 (1.52–1.60)	1.44 (1.41–1.48)

Abbreviations: IR, incidence rate; HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; PY, Person years; PE, pulmonary embolism; DVT, deep vein thrombosis.

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

Model 2: Adjusted for socioeconomic status (education and income) and obesity.

Model 3: Adjusted for socioeconomic status (education and income), obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases (other than depression), alcohol and drug related disorders, dementia, surgery and trauma three months prior to the VTE/index date, Charlson Comorbidity Index score (CCI) excluding the comorbidities listed above, and co-medication.

Supplementary Table 6. Incidence rates and hazard ratios with 95% confidence intervals for subsequent depression among persons with and persons without venous thromboembolism, stratified by venous thrombosis subtype, age, and sex.

	General Population Comparison Cohort	VTE Cohort			
	IR (95% CI)	IR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
PE					
25-34 years	16.45 (14.47-18.43)	38.66 (31.59-45.73)	2.33 (1.87–2.92)	2.25 (1.79–2.83)	2.22 (1.74–2.84)
35-44 years	16.32 (14.79-17.86)	37.91 (32.37-43.45)	2.38 (1.99–2.85)	2.24 (1.86–2.70)	1.79 (1.45–2.20)
45-54 years	16.64 (15.39-17.89)	49.15 (43.80-54.51)	3.00 (2.61–3.46)	2.89 (2.51–3.33)	2.46 (2.11–2.88)
55-65 years	13.82 (12.95-14.69)	49.98 (45.69-54.28)	3.70 (3.30–4.16)	3.63 (3.23–4.08)	2.80 (2.46–3.19)
66-80 years	23.51 (22.77-24.25)	60.69 (57.47-63.92)	2.69 (2.52–2.88)	2.66 (2.49–2.85)	2.22 (2.07–2.39)
Men	16.92 (16.30-17.54)	50.71 (47.92-53.51)	3.15 (2.93–3.38)	3.10 (2.88–3.33)	2.51 (2.32–2.71)
Women	22.47 (21.72-23.23)	55.65 (52.54-58.75)	2.59 (2.41–2.77)	2.53 (2.36–2.72)	2.14 (1.98–2.30)
DVT					
25-34 years	16.55 (15.33-17.76)	30.50 (26.77-34.22)	1.83 (1.58–2.11)	1.75 (1.51–2.03)	1.42 (1.21–1.68)
35-44 years	17.51 (16.50-18.51)	37.97 (34.54-41.39)	2.17 (1.94–2.42)	1.95 (1.75–2.19)	1.64 (1.45–1.86)
45-54 years	16.58 (15.76-17.40)	35.01 (32.23-37.78)	2.15 (1.95–2.37)	1.99 (1.80–2.19)	1.64 (1.47–1.83)
55-65 years	15.01 (14.32-15.70)	35.78 (33.25-38.30)	2.42 (2.21–2.64)	2.33 (2.13–2.55)	1.90 (1.73–2.10)
66-80 years	24.59 (23.90-25.28)	48.73 (46.36-51.11)	2.00 (1.89–2.12)	1.98 (1.87–2.10)	1.69 (1.59–1.80)
Men	17.02 (16.54-17.49)	36.57 (34.92-38.21)	2.20 (2.08–2.32)	2.13 (2.01–2.25)	1.75 (1.65–1.86)
Women	22.26 (21.66-22.87)	44.49 (42.45-46.53)	2.02 (1.92–2.14)	1.96 (1.85–2.07)	1.68 (1.58–1.78)
Provoked VTE					
25-34 years	16.75 (14.52-18.99)	40.14 (32.16-48.13)	2.35 (1.84–2.99)	2.29 (1.78–2.94)	1.56 (0.97–2.51)
35-44 years	16.73 (14.86-18.61)	62.62 (53.69-71.54)	3.76 (3.10–4.55)	3.40 (2.79–4.14)	1.99 (1.29–3.08)
45-54 years	17.46 (15.96-18.95)	64.01 (56.54-71.48)	3.77 (3.22–4.41)	3.62 (3.09–4.26)	2.05 (1.46–2.87)
55-65 years	14.19 (13.18-15.20)	77.06 (70.58-83.53)	5.53 (4.88–6.26)	5.37 (4.73–6.10)	3.27 (2.57–4.15)
66-80 years	23.54 (22.68-24.40)	77.95 (73.57-82.33)	3.43 (3.19–3.70)	3.40 (3.15–3.66)	2.20 (1.96–2.47)
Men	17.61 (16.86-18.35)	70.93 (66.86-75.01)	4.24 (3.92–4.59)	4.15 (3.83–4.50)	2.49 (2.16–2.86)
Women	22.02 (21.17-22.87)	72.36 (68.20-76.51)	3.39 (3.15–3.66)	3.31 (3.06–3.57)	2.20 (1.94–2.49)
Unprovoked VTE					
25-34 years	16.46 (15.29-17.62)	30.60 (26.99-34.22)	1.85 (1.61–2.13)	1.78 (1.54–2.05)	1.64 (1.41–1.91)
35-44 years	17.27 (16.33-18.22)	32.70 (29.72-35.67)	1.90 (1.71–2.12)	1.74 (1.56–1.94)	1.64 (1.46–1.85)
45-54 years	16.35 (15.58-17.13)	33.25 (30.70-35.80)	2.06 (1.88–2.26)	1.92 (1.74–2.10)	1.85 (1.68–2.04)
55-65 years	14.73 (14.08-15.37)	30.00 (27.85-32.15)	2.07 (1.90–2.25)	2.01 (1.84–2.19)	1.94 (1.77–2.13)
66-80 years	24.38 (23.76-25.01)	44.01 (41.95-46.07)	1.84 (1.74–1.94)	1.82 (1.72–1.92)	1.79 (1.68–1.89)
Men	16.75 (16.32-17.19)	33.07 (31.62-34.52)	2.02 (1.92–2.13)	1.96 (1.86–2.06)	1.91 (1.80–2.02)
Women	22.49 (21.92-23.06)	40.21 (38.40-42.02)	1.83 (1.73–1.93)	1.78 (1.68–1.87)	1.71 (1.61–1.80)

Abbreviations: IR, incidence rate; HR, hazard ratio; CI, confidence intervals; VTE, venous thromboembolism; PY, person-years; PE, pulmonary embolism; DVT, deep vein thrombosis
Model 1: Unadjusted model controlled for matching variables by study design.
Model 2: Adjusted for socioeconomic status (education and income) and obesity.
Model 3: Adjusted for socioeconomic status (education and income), obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases (other than depression), alcohol and drug-related disorders, dementia, surgery and trauma three months prior to the VTE/index date, Charlson Comorbidity Index score (CCI) excluding the comorbidities listed above, and co-medication.

Supplementary Table 7. Subgroup analysis by age and sex with incidence rates and hazard ratios (with 95% confidence intervals) of subsequent depression among persons with and persons without venous thromboembolism, stratified on Charlson Comorbidity Index score (0 and ≥1).

	General Population Comparison Cohort	VTE Cohort			
VTE	IR (95% CI)	IR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
CCI = 0					
Overall	16.36 (16.05-16.67)	31.29 (30.16-32.43)	1.94 (1.87–2.03)	1.90 (1.83–1.98)	1.78 (1.71–1.86)
Men	13.69 (13.31-14.08)	27.50 (26.06-28.93)	2.03 (1.92–2.16)	1.99 (1.87–2.11)	1.85 (1.74–1.97)
Women	19.45 (18.96-19.95)	35.94 (34.12-37.76)	1.87 (1.76–1.97)	1.83 (1.73–1.93)	1.72 (1.62–1.82)
PE	16.29 (15.78-16.80)	36.15 (33.96-38.34)	2.25 (2.11–2.41)	2.23 (2.08–2.39)	2.16 (2.01–2.32)
DVT	16.40 (16.01-16.79)	29.11 (27.79-30.43)	1.80 (1.71–1.90)	1.76 (1.67–1.85)	1.62 (1.53–1.70)
Provoked VTE	16.48 (15.88-17.07)	42.17 (38.61-45.73)	2.65 (2.41–2.91)	2.57 (2.34–2.82)	2.69 (2.27–3.19)
Unprovoked VTE	16.32 (15.95-16.68)	29.56 (28.37-30.75)	1.83 (1.75–1.92)	1.80 (1.71–1.88)	1.75 (1.67–1.83)
CCI = ≥1					
Overall	30.18 (29.39-30.97)	70.39 (67.99-72.78)	2.35 (2.25–2.46)	2.33 (2.23–2.43)	2.10 (2.01–2.20)
Men	27.86 (26.85-28.86)	68.34 (65.15-71.53)	2.49 (2.34–2.64)	2.46 (2.32–2.62)	2.20 (2.06–2.34)
Women	33.27 (32.01-34.54)	72.86 (69.24-76.48)	2.22 (2.08–2.36)	2.18 (2.05–2.33)	2.00 (1.87–2.14)
PE	29.46 (28.26-30.65)	79.78 (75.68-83.88)	2.74 (2.57–2.93)	2.72 (2.54–2.90)	2.42 (2.26–2.60)
DVT	30.71 (29.67-31.76)	64.44 (61.51-67.37)	2.11 (1.99–2.24)	2.08 (1.97–2.21)	1.90 (1.79–2.01)
Provoked VTE	29.93 (28.53-31.34)	90.71 (86.51-94.90)	2.93 (2.74–3.13)	2.92 (2.73–3.12)	2.75 (2.55–2.97)
Unprovoked VTE	30.29 (29.34-31.25)	55.69 (52.89-58.49)	1.89 (1.78–2.00)	1.84 (1.74–1.96)	1.82 (1.71–1.93)

Abbreviations: IR, incidence rate; HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; PY, person-years; PE, pulmonary embolism; DVT, deep vein thrombosis
Model 1: Unadjusted model controlled for matching variables by study design.
Model 2: Adjusted for socioeconomic status (education and income) and obesity.
Model 3: Adjusted for socioeconomic status (education and income), obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases (other than depression), alcohol and drug-related disorders, dementia, surgery and trauma three months prior to the VTE/index date, Charlson Comorbidity Index score (CCI) excluding the comorbidities listed above, and comedication.

Supplementary Table 8. Sensitivity analysis with incidence rates and hazard ratios (with 95% confidence intervals) of depression defined diagnosis in the Danish National Patient Registry or the Danish Psychiatric Central Research Register among persons with and persons without venous thromboembolism.

	General Population Comparison Cohort			VTE Cohort					
	At risk	Dep	IR (95% CI)	At risk	Dep	IR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Overall	322 999	1 238	1.43 (1.35-1.51)	64 596	583	3.95 (3.63-4.27)	2.84 (2.57–3.15)	2.77 (2.50–3.07)	2.32 (2.08–2.60)
Men	176 842	615	1.31 (1.21-1.42)	35 374	318	3.94 (3.51-4.38)	3.10 (2.69–3.57)	3.02 (2.62–3.48)	2.54 (2.17–2.97)
Women	146 157	623	1.58 (1.45-1.70)	29 222	265	3.95 (3.47-4.43)	2.59 (2.23–3.00)	2.51 (2.16–2.92)	2.10 (1.78–2.47)
PE	126 412	511	1.56 (1.42-1.69)	25 299	285	5.69 (5.03-6.35)	3.72 (3.19–4.34)	3.67 (3.13–4.29)	2.95 (2.48–3.50)
DVT	196 316	725	1.36 (1.26-1.45)	39 297	298	3.05 (2.71-3.40)	2.32 (2.02–2.67)	2.26 (1.96–2.60)	1.96 (1.68–2.28)
Provoked VTE	92 742	399	1.64 (1.48-1.80)	18 562	218	6.26 (5.43-7.09)	3.95 (3.30–4.72)	3.91 (3.26–4.69)	2.62 (1.93–3.54)
Unprovoked VTE	229 986	837	1.35 (1.26-1.44)	46 034	365	3.23 (2.90-3.57)	2.44 (2.15–2.76)	2.36 (2.07–2.68)	2.25 (1.96–2.58)
Cancer-provoked VTE	56 177	250	1.73 (1.51-1.94)	11 237	149	8.99 (7.55-10.44)	5.00 (3.97–6.29)	5.02 (3.97–6.36)	2.94 (1.91–4.55)
Cancer-unprovoked VTE	266 551	986	1.37 (1.29-1.46)	53 359	434	3.31 (3.00-3.62)	2.48 (2.21–2.78)	2.40 (2.13–2.70)	2.22 (1.96–2.52)

Abbreviations: IR, incidence rate; HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; PY, Person-years; PE, pulmonary embolism; DVT, deep vein thrombosis; DNPR, Danish National Patient Registry; DPCRR, Danish Psychiatric Central Research Register
Model 1: Unadjusted model controlled for matching variables by study design.
Model 2: Adjusted for socioeconomic status (education and income) and obesity.
Model 3: Adjusted for socioeconomic status (education and income), obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases (other than depression), alcohol and drug-related disorders, dementia, surgery and trauma three months prior to the VTE/index date, Charlson Comorbidity Index score (CCI) excluding the comorbidities listed above, and co-medication.

Supplementary Table 9. Subgroup analysis with incidence rates and hazard ratios (with 95% confidence intervals) of subsequent depression among persons with and persons without venous thromboembolism excluding individuals with alcohol- or drug-related disorders, or a dementia diagnosis.

	General Population Comparison Cohort	VTE Cohort			
VTE	**IR (95% CI)**	**IR (95% CI)**	**Model 1** **HR (95% CI)**	**Model 2** **HR (95% CI)**	**Model 3** **HR (95% CI)**
Overall	18.86 (18.56-19.15)	43.15 (42.04-44.26)	2.35 (2.28–2.43)	2.30 (2.23–2.37)	1.94 (1.87–2.00)
Men	16.29 (15.91-16.66)	39.52 (38.07-40.96)	2.50 (2.39–2.62)	2.45 (2.34–2.56)	2.03 (1.93–2.14)
Women	21.89 (21.42-22.36)	47.43 (45.71-49.15)	2.23 (2.13–2.33)	2.17 (2.07–2.27)	1.85 (1.77–1.94)
PE	19.09 (18.61-19.58)	52.17 (50.07-54.26)	2.86 (2.71–3.00)	2.81 (2.66–2.95)	2.32 (2.19–2.45)
DVT	18.72 (18.35-19.09)	38.50 (37.21-39.79)	2.10 (2.01–2.18)	2.04 (1.96–2.13)	1.74 (1.67–1.82)
Provoked VTE	19.16 (18.60-19.72)	70.98 (68.03-73.93)	3.86 (3.65–4.08)	3.77 (3.56–3.99)	2.34 (2.13–2.57)
Unprovoked VTE	18.74 (18.39-19.09)	34.69 (33.55-35.82)	1.89 (1.82–1.97)	1.85 (1.78–1.92)	1.82 (1.75–1.90)

Abbreviations: IR, incidence rate; HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; PY, Person-years; PE, pulmonary embolism; DVT, deep vein thrombosis
Model 1: Unadjusted model controlled for matching variables by study design.
Model 2: Adjusted for socioeconomic status (education and income) and obesity.
Model 3: Adjusted for socioeconomic status (education and income), obesity, cancer, coronary heart disease (including atrial fibrillation, myocardial infarction, and heart failure), diabetes, stroke, chronic obstructive pulmonary disease (COPD), acute kidney failure and chronic kidney disease, mental diseases (other than depression), surgery and trauma three months prior to the VTE/index date, Charlson Comorbidity Index score (CCI) excluding the comorbidities listed above, and co-medication.