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

Helle Jørgensen *, †, ‡, Erzsébet Horváth-Puhó†, Kristina Laugesen†, Sigrid Brækkan *,‡,John-Bjarne Hansen *,‡, Henrik Toft Sørensen†

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

† Department of Clinical Epidemiology, Aarhus University Hospital and Aarhus University, Denmark

‡ 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, Hansine Hansens vei 18, N-9019 Tromsø, Norway. Email: helle.jorgensen@uit.no

**Running head title**: Venous thromboembolism and risk of depression

**Essentials:**

- The psychological consequences of VTE have not been investigated in depth
- We assessed the risk of depression after VTE in a large Danish cohort from the general population
- The depression risk remained increased even after adjusting for SES and comorbidities
- Our findings will guide future research to further identify and manage depression after VTE

# 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 subsequent depression.

**Methods:** 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. Participants were followed-up for three years, and depression was defined as any hospital diagnosis of depression or ≥1 prescription for antidepressants. Incidence rates (IR) were computed as the number of events 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. We estimated absolute risks using cumulative incidence functions treating death as a competing event.

**Results:** 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). 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 association was attenuated 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.



**Key words:**, antidepressants, deep vein thrombosis, depression, pulmonary embolism, venous thromboembolism.

# 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 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 ranked as one of the major causes of years lived with disability.[9] It is a frequent complication of chronic diseases,[10] and there is strong evidence of a 10-40% increased risk of depression in individuals with cardiovascular disease (CVD), compared to individuals without CVD.[11-14] However, evidence on the psychological consequences of VTE is scarce.

Existing studies on mental health after VTE indicate that VTE is associated with symptoms of psychological distress and post-traumatic stress disorder (PTSD), particularly after PE.[15-29] However, the studies 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.[30] An improved understanding of the psychological consequences of the condition is therefore 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.[31] Upon birth or immigration, a unique identifier assigned to each Danish residents enables linkage to individual-level data across all Danish registries.[31]

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).[31, 32] Data on redeemed prescriptions for an antidepressant were obtained from the Danish National Prescription Registry.[33] Data on income was obtained from the Integrated Database for Labor Market Research, and The Educational Attainment Register provided data on education.[31]

## 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,[34] and negative predictive values of 99.5% for DVT and 100% for PE.[35]

VTE was classified as either PE or DVT. Simultaneous PE and DVT diagnoses were classified as PE due to its higher mortality rate.[36] 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.[37]

We excluded individuals with a hospital history of depression (identified using ICD-8 codes through 1993 and ICD-10 codes from 1994 onwards), 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.[38]

## 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.[39] 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 codes through 1993 and ICD-10 codes from 1994 onwards 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. 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 for up to three years from the VTE/index date until the date of a depression diagnosis or a redeemed prescription for an antidepressant, emigration from Denmark, death, end of follow-up (three years after inclusion date), or date of study end (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 assess 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 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). In the VTE cohort, the proportion of individuals with low SES was higher, and the proportion of individuals 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).

After three years, 6,225 individuals in the VTE cohort developed depression (IRs 44.4 per 1,000 person-years) compared to 16,363 in the general population cohort (IRs 19.4 per 1,000 person-years) (Table 2). The 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 attenuated 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 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 1.80 (95% CI: 1.73-1.87) for unprovoked VTE , and 2.32 (95% CI 2.12-2.55) for provoked VTE. HRs for VTE provoked by cancer was 2.96 (95% CI 2.58-3.41), and for VTE provoked by other factor than cancer was 1.70 (95% CI: 1.38-2.10) (Figure 2, Table 2).

In the VTE cohort, the 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 association between depression and VTE displayed a temporal pattern, with a particularly strong association during the first years after VTE diagnosis. In analysis adjusted for SES, obesity and comorbidities, 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 (Supplementary Table 5).

In the 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.[15, 24-26] This was also the case for young adults, for whom a VTE might lead to uncertainty about long-term health and fear of relapse.[18, 19] Psychological distress after VTE was found to be long-term and chronic, due to persistent fear of VTE recurrence.[16, 18, 24, 25] Qualitative studies of mental health after PE have pointed consistently towards a long-term increase in symptoms of anxiety, depression, or PTSD.[16, 20, 23-25, 27, 29] 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.[16, 17, 23, 28]

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.[11-14] 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,[13] while Coronary heart disease patients had an estimated 15-18% prevalence of depression.[12] One meta-analysis of 43 studies with a total of 20,293 patients reported a depression prevalence after stroke of 29%,[14] while another meta-analysis of 61 prospective studies (25,488 patients) found a prevalence of 31%.[11]

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 event. Several qualitative studies indicate that PE patients experience psychological distress, suggestive of PTSD, following their diagnosis.[16, 17, 22] Thus, experiencing a PE can lead to existential anxiety, a lost sense of identity, and negative self-perception.[16, 17, 23, 28] 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, might additionally increase the psychological distress after PE.[16, 17, 23, 28]

We found that the association between cancer-provoked VTE and depression was particularly high, even after adjustment for potential confounders. A VTE is a serious complication of cancer which negatively affect quality of life and overall survival rates.[43] In addition, other factors, such as emotional distress and insecurity, poor underlying health, hospitalization, immobilization, cancer treatment, and prolonged anticoagulant treatment could all 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.[21, 25, 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. The cohort includes individuals with a VTE between 1996-2016. Direct oral anticoagulants (DOACs) for treatment of VTE were introduced during the last years of the study period, and thus, the majority of the VTE patients (>80%) were treated with vitamin K antagonists (VKA). Even though studies in other patient groups (i.e., atrial fibrillation) have shown little impact of VKA treatment on quality of life,[53, 54] a potential effect of treatment regimen on depression in VTE patients cannot be completely ruled out. Future studies, including more VTE patients treated with DOACs, are needed to differentiate to what extent depression after VTE is attributed to the VTE event itself or mediated by the treatment regimen." 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.

## 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.

## 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.

# 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. The New England journal of medicine. 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. Organization TWH. Transforming mental health for all. 2022.
10. 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.
11. 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.
12. Carney RM, Freedland KE. Depression and coronary heart disease. Nature Reviews Cardiology. 2017;14(3):145-55.
13. 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.
14. 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.
15. 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.
16. 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.

17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues in clinical neuroscience. 2011;13(1):7-23.
31. 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.
32. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scandinavian journal of public health. 2011;39(7 Suppl):54-7.
33. Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. Danish medical bulletin. 1997;44(4):445-8.

34. 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.
35. Galsklint J, Kold S, Kristensen SR, Severinsen MT, Gade IL. Validation of Postsurgical Venous Thromboembolism Diagnoses of Patients Undergoing Lower Limb Orthopedic Surgery in the Danish National Patient Registry. Clin Epidemiol. 2022;14:191-9.
36. 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.
37. 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. Journal of thrombosis and haemostasis : JTH. 2016;14(7):1480-3.
38. 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. Journal of Thrombosis and Haemostasis. 2019;17(8):1305-18.
39. 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.
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.
53. van Miert JHA, Kooistra HAM, Veeger N, Westerterp A, Piersma-Wichers M, Meijer K. Quality of life after switching from well-controlled vitamin K antagonist to direct oral anticoagulant: Little to GAInN. Thromb Res. 2020;190:69-75.
54. Kooistra HA, Piersma-Wichers M, Kluin-Nelemans HC, Veeger NJ, Meijer K. Impact of Vitamin K Antagonists on Quality of Life in a Prospective Cohort of 807 Atrial Fibrillation Patients. Circ Cardiovasc Qual Outcomes. 2016;9(4):388-94.

**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 per 1000 person-years 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) |
| 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) |
| 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) |
| *VTE provoked by cancer* | *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)* |
| *VTE provoked by factor other than cancer* | *36 565* | *1 880* | *19.46 (18.58-20.34)* | *7 325* | *827* | *48.34 (45.05-51.64)* | *2.56 (2.35–2.78)* | *2.46 (2.26–2.68)* | *1.70 (1.38–2.10)* |

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 per 1000 person-years 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 legends

**Figure 1.** Cumulative incidence (%) of subsequent depression in persons with venous thromboembolism (VTE) (VTE+) and those without VTE (VTE−) while taking the competing risk of death into account, overall according to (A) sex and (B) VTE subtypes. Provoked VTE was defined as VTE with a pre-existing cancer diagnosis either before or on the VTE or index date, or trauma, surgery, and/or pregnancy within 90 days prior to the VTE diagnosis. Unprovoked VTE was defined as VTE without the presence of any of the abovementioned factors. PE,

Figure A

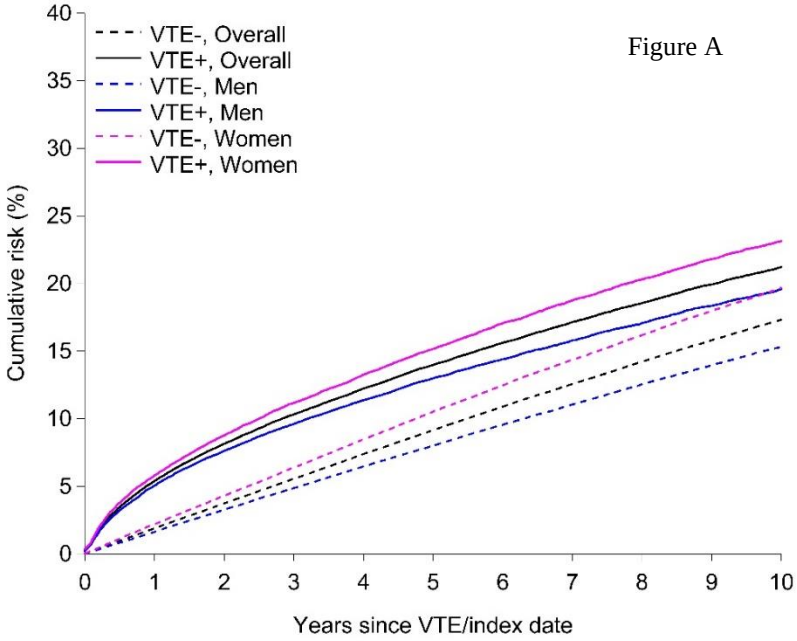



Figure B

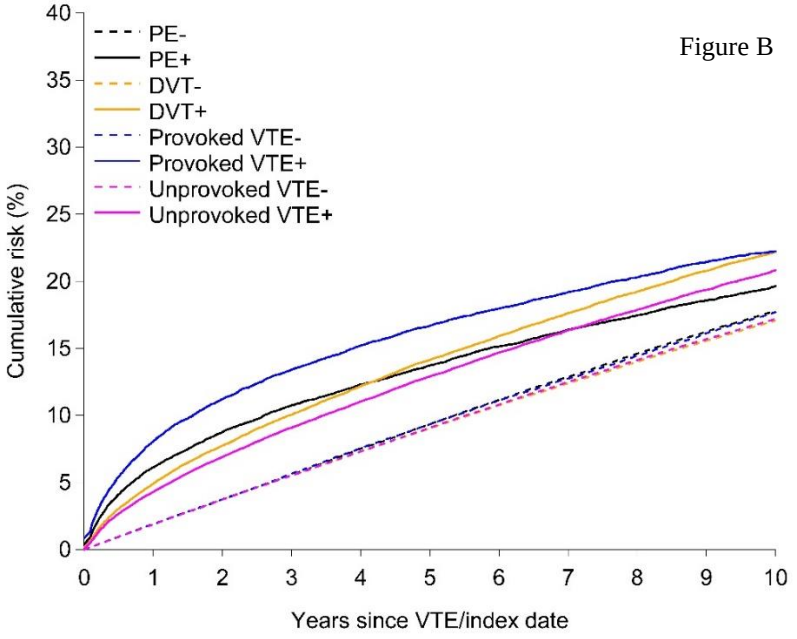
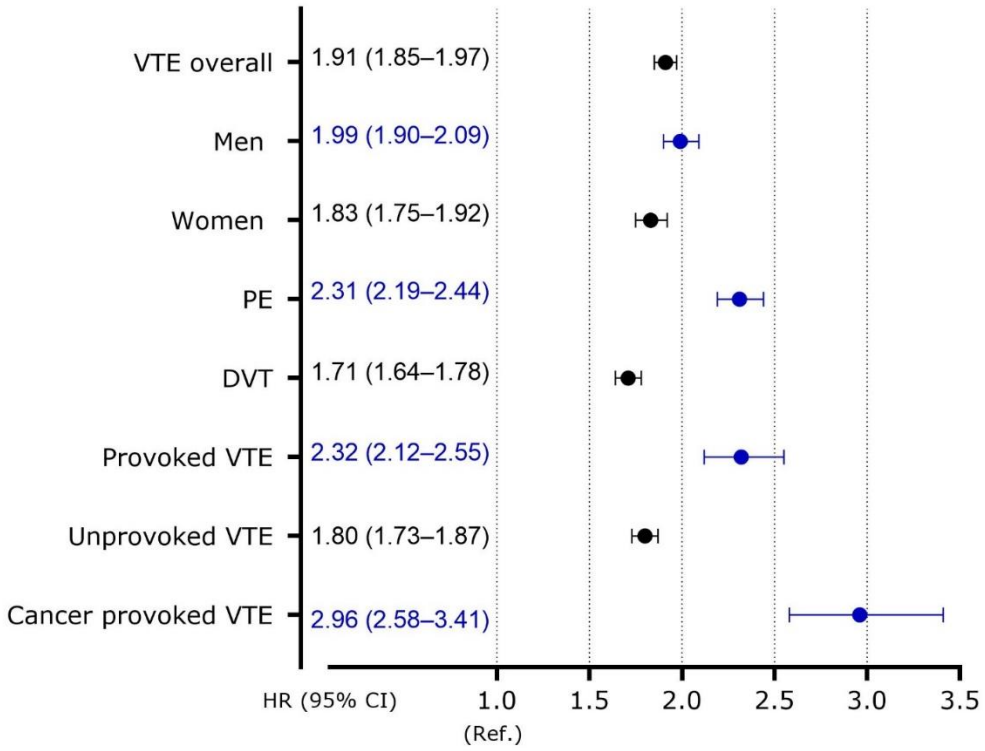


**Figure 2.** Forest plot of adjusted hazard ratios with 98% CIs of subsequent depression in patients with venous thromboembolism (VTE) and those without VTE according to sex and VTE subtypes.




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.

Abbreviations: HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis.