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Abstract

Introduction The mental health prognosis following a venous thromboembolism in youth has not been investigated comprehensively. Using psychotropic drug purchase as a proxy for mental health status, we investigated this issue in a large cohort of young incident venous thromboembolism patients.

Methods Using Danish nationwide administrative registries from the period 1997-2010, we identified 4,132 patients aged 13-33 years with a first-time venous thromboembolism diagnosis and no history of psychotropic drug usage. We sampled comparison cohort of random general population controls, matched individually in a 1:5 ratio based on sex and birth year. Participants were followed in prescription purchase registries for their first psychotropic drug purchase.

Results Among young venous thromboembolism case cases, the 1-year risk of psychotropic drug purchase was 7.1% (95% confidence interval [CI] 6.3, 7.9) and the 5-year risk 22.1% (95% CI 20.7, 23.5). This was substantially higher than among population controls, with 1- and 5-year risk differences relative to the controls of 4.7% (95% CI 3.9, 5.5), and 10.8% (95% CI 9.4, 12.3), respectively. Adjustment for the effects of recent pregnancy or somatic provocations attenuated risk differences to 4.1% (95% CI 3.5, 5.1) after 1 year and 9.6% (95% CI 8.3, 11.2) after 5 years.

Conclusions A venous thromboembolism diagnosis in youth is associated with a poorer mental health prognosis: one in five patients are prescribed psychotropic medication within the first 5 year after diagnosis.

Key words: Adolescent: Anxiety Disorders: Depression: Psychotropic Drugs: Venous Thromboembolism: Young Adults

Abbreviations CI=confidence interval; QOL= quality of life

Introduction

Chronic medical illness in youth can lead to emotional and behavioural problems and is a risk factor for poor mental health, including psychiatric disorders [1]. Venous thromboembolism, a common and potentially life-threatening disease encompassing deep venous thrombosis and pulmonary embolism, has received limited attention in this setting, perhaps because of its lower incidence in the younger populations (1-2 per 10.000 person years) [2,3]. Nonetheless, recent evidence suggests that the incidence of venous thromboembolism in adolescents and young adults is increasing [3,4]. It has been argued that venous thromboembolism should generally be considered a chronic illness, owing to its long-term somatic consequences which include post thrombotic syndrome, chronic pulmonary hypertension, and a risk of recurrent venous thromboembolism [5,6]. These long-term consequences have also been reported in young populations [7,8], but it is unclear whether venous thromboembolism in a young population should be considered a chronic illness in terms of its association with mental health. One study reported young venous thromboembolism patients to have lower self-esteem, and higher impairment in social activities as well as in familial functioning [9]. Other research on this issue pertains to elderly populations, in which venous thromboembolism has been found to be associated with poorer mental quality of life [10,11]. One study [12] examined anxiety and depression following venous thromboembolism, reporting elevated levels of anxiety and depression symptoms in the first 1-4 weeks following the event. In patients with chronic cardiovascular disease, anxiety is reported to persist in 20-25 % of patients following an acute cardiac event [13], and especially younger cardiac patients experience impaired mental health [14].

The purpose of the present study was to use epidemiological methods to describe the mental health prognosis following a venous thromboembolism diagnosis in youth. To quantify mental health status, we used psychotropic drug purchase derived from prescription purchase registries as a proxy measure. We hypothesized that young patients with venous thromboembolism would have a higher risk of psychotropic drug purchase compared to population controls.

Methods

Study design

We used the unique civil registration number assigned to all Danish residents to link data from four nationwide registries [15]: (i) Danish Civil Registration System recording gender, date of birth, death, and emigration of all Danish residents [16]; (ii) The Danish National Patient Register which

contains detailed information on more than 99% of all somatic hospital admissions [17]; (iii) The Danish National Prescription Registry which contains ATC codes and package sizes for all prescription purchases in Denmark since 1995 [18]; (iv) The Danish Medical Birth Registry which has registered all births in Denmark since 1973 [19].

In the registries, we identified all incident cases of venous thromboembolism among 13-33 year old Danish residents in the period January 1, 1997, to March 1, 2010. A diagnosis of venous thromboembolism was classified according to the Danish version of the International Classification of Diseases (ICD) 8th and 10th revision (ICD-8, ICD-10), presented in the supplementary Table 1. The index date was defined as the date of a venous thromboembolism diagnosis. Using a risk-set sampling approach, we randomly sampled from the full Danish population five venous thromboembolism-free population controls per case, matching on sex and birth year. The index date of each control was set to the index date of their corresponding case.

Transient risk factors for venous thromboembolism of potential importance to mental health prognosis were also ascertained. We defined 'recent provocation' as any of the following: a diagnosis of cancer (ICD-10, neoplasm's C00-D48) or autoimmune disease (ICD-10 rheumatoid arthritis M05-M07, inflammatory bowel disease K50-K51) within 1 year of index date; trauma requiring hospital admission within 3 months of index date; surgery requiring one or more days of hospital admission within the last 3 months of index date. In the Danish Medical Birth Registry, we identified 'recent pregnancy' as childbirth at up to 8 weeks before and up to 42 weeks after the index date. Cases with an ICD-8 or ICD-10 code indicating pregnancy-related venous thromboembolism (see Supplementary Table 1) were also classified as 'recent pregnancy'.

In the Danish National Prescription Registry, we identified prescription purchases using the Anatomical Therapeutic Chemical Classification System (ATC) in the period 1 January 1995 to 31 December 2011 for the following psychotropic drug purchase: antipsychotics (ATC codes: N05A); anxiolytics (ATC codes: N05B); sedatives (ATC codes: N05CD, N05CF, R06AD); and antidepressives (ATC codes: N06A) (supplementary table 2).

The final case and control cohorts were defined by excluding both cases and corresponding controls for all cases who had purchased psychotropic drugs within 2 years of the index date; and remaining controls with a history of a psychotropic drug purchase within 2 years of the index date.

Statistical analysis

Descriptive data were presented as counts and percentages. Time to first psychotropic drug purchase was measured from the index date. Subjects were right-censored at the time of death, emigration, or 31 December 2011, whichever came first. The cumulative risk of purchase of any psychotropic drug according to case status as a function of time was quantified using a Kaplan-Meier plot. We used pseudo-value regression [20] on a risk difference scale to assess the association between the case status and the risk of a psychotropic drug purchase event within 1 year, respectively 5 years. The pseudo-value regression technique reduces to regression on the event status indicator when there is no censoring and accounts for censored observations before 1 year, respectively 5 years. To ensure that risk differences were assessed between comparable venous thromboembolism cases and population controls, we also considered multivariate regression of pseudovalues, adjusting for the effect of ‘recent pregnancy’ (binary) and ‘recent provocation’ (binary). We repeated regression analyses after stratifying analyses on sex, venous thromboembolism type (pulmonary embolism or deep vein thrombosis), and calendar period (index date 1997-2002 or 2003-2010). We also carried out analyses for each psychotropic drug endpoint (antipsychotics; anxiolytics; sedatives; antidepressives) separately. Stata/MP version 12.1 was used for statistical analysis.

Results

Study population characteristics

We identified a total of 5,027 patients aged 13-33 years with an incident venous thromboembolism diagnosis. After exclusion of cases who died on the day of diagnosis ($n = 14$) and cases who had a psychotropic drug prescription purchases within 2 years before the index date ($n = 881$), 4,132 cases constituted the venous thromboembolism cohort. Of these 20.6% ($n = 852$) were pulmonary embolisms. Among the population controls, 1,368 had purchased psychotropic drugs within 2 years of the index date and were excluded, leaving 19,292 subjects in the control cohort. Baseline characteristics are shown in Table 1.

In the venous thromboembolism cohort, almost 75% were women and the median age was 25 years. Older age groups were more strongly represented, with the 28-33 year-old group 5 times larger than the 13-18 year-old group. The number of women with a recent pregnancy was 7% higher in the venous thromboembolism cohort compared to the control cohort; also, the proportion of patients who had experienced a recent provocation was 10-fold higher in the venous thromboembolism cohort compared to the control cohort.

Venous thromboembolism and psychotropic drug purchase

The Kaplan-Meier estimates of cumulative risk showed a substantially higher overall risk of any psychotropic drug purchases in the venous thromboembolism cohort compared to the control cohort (Figure 1). The absolute risks and risk differences of psychotropic drug purchases according to venous thromboembolism status are presented in Table 2. In the venous thromboembolism cohort, the 1-year risk of psychotropic drug purchase was 7.1% (95% confidence interval (CI): 6.3, 7.9) and the 5-year risk 22.1% (95% CI: 20.7, 23.5), corresponding to 1- and 5-year risk differences relative to the control cohort of 4.7% (95% CI: 3.9,5.5), and 10.8% (95% CI: 9.4,12.3), respectively. Risk differences for the venous thromboembolism cohort relative to the control cohort as a function of time is presented in Figure 2. The higher risk of psychotropic drug purchase in the venous thromboembolism cohort persisted when adjusting for the effect of recent pregnancy or recent provocation, (1-year risk difference 4.1% (95% CI: 3.5,5.1), 5 year risk difference 9.6% (95% CI: 8.3,11.2).

In the analyses stratified by various baseline characteristics, a substantial risk differences between venous thromboembolism cases and controls persisted across age strata (age \leq 25 years and age $>$ 25 years) and period of index date (1997-2002 and 2003-2010, respectively), as well as among both female and males (table 2). Of note, the 5-year risk difference was higher for males compared to females. Also, the 1-year risk difference was increased among PE patients compared to DVT patients.

We found no marked difference in the distribution of the psychotropic drug classes purchased in the venous thromboembolism cohort and the control cohort. Antidepressants were the most frequently purchased drug (53% of all purchases) followed by anxiolytics (20%), sedatives (22%), and finally antipsychotics (5%). To investigate the robustness of our findings when more specific endpoints

were used, we defined four different composite endpoints given purchase within each of the drug classes, antipsychotics, anxiolytics, sedatives, antidepressives. Repeating the main analyses for these endpoints did not change the overall findings (Supplementary table 3-6).

Discussion

In this large-scale registry-based study, we found that young patients diagnosed with venous thromboembolism in Denmark during the period 1997-2011 had a substantially higher risk of psychotropic drug use compared to age- and sex-matched population controls. The increased risk persisted after adjustment for known risk factors of venous thromboembolism, including cancer, trauma, surgery, inflammatory bowel disease, rheumatoid arthritis and pregnancy.

Our finding of an association between a venous thromboembolism diagnosis and long-term increased risk of psychotropic drug purchase is in line with observations in young chronically ill patients where psychiatric symptoms develop and persist over time, and result in a higher adjusted lifetime prevalence of psychiatric disorders [1]. Whether the present association derives from the same attributes is unclear. However, it has been argued that venous thromboembolism has the characteristics of a chronic illness, owing to the high risk of recurrence (10-year risk of 30%) and the potential for long-term somatic consequences; including post thrombotic syndrome, pulmonary hypertension, and the need for lifelong medicinal treatment [5,6].

We emphasize that our findings are strictly associational and do not imply that venous thromboembolism is a direct cause of decreased mental health. For example, although we adjusted for transient risk factors, it cannot be ruled out that the same inciting event (e.g. immobility) caused both the VTE and triggered mood disorder; or that the incident VTE may have necessitated more access to care, thereby leading to revealing of a previously undiagnosed psychiatric illness. However, the acute, life-threatening nature of venous thromboembolism is also a viable explanation of the increased risk of psychotropic drug purchase. Acute life-threatening medical events have been reported to negatively impact mental health of children and adolescents [20]. We observed similarly increased risks when comparing both patients with deep venous thrombosis and the more serious condition of pulmonary embolism to population controls. This is in line with the findings of Lukas and colleagues, who found no difference in mental health-related quality of life (QOL) among patients with deep venous thrombosis and pulmonary embolism [21]. Indeed, our finding is

consistent with the assertion that, when it comes to determining vulnerability to psychiatric disorders in young patients, the retrospective appraisal by the patient of how threatening the disease is plays a more prominent role than the actual life threat [1].

Socioeconomic factors were unavailable in the present study, but low socioeconomic position is generally associated with higher psychiatric morbidity, and has previously been associated with low-QOL scores in patients with pregnancy-related deep venous thrombosis [22]. Our findings encourage further exploration of these and other risk factors for mental health problems following venous thromboembolism in youth.

Limitations

The main strength of our study was the large number of venous thromboembolism patients included and the minimal loss to follow-up. The use of nationwide administrative registry data allowed a large-scale population-based design with complete long-term follow-up on psychotropic drug purchases, as well as death and migration. The use of administrative registries also entails some limitations. For example, misclassification of both venous thromboembolism diagnosis and baseline comorbidities cannot be ruled out. Validation studies in Denmark have found a positive predictive value of venous thromboembolism diagnosis of 75%, both in general [23] and in age specific analysis of adolescents [24]. In addition, the reliance on prescription purchase registries to define comedication at baseline has some limitations, since patients may not take their prescription medications. Another limitation relates to the use of psychotropic drug purchase as a proxy for mental health. Venous thromboembolism patients may be more likely to receive a psychotropic drug prescription simply because of frequent contact with the health care system. Lastly, the present study is insufficient to establish a causal link between venous thromboembolism and decreased mental health. Further research is needed to explore the nature and etiological reasons of the association.

Conclusions

Venous thromboembolism among adolescents and young adults has the characteristics of a chronic illness in relation to mental health: within the first 5 year after diagnosis, one in five young venous thromboembolism patients will experience mental health issues requiring psychotropic medication.

A long-term follow-up by the primary care physician or an outpatient clinic, with a focus on mental health, may be necessary in this young age group.

Contributors

All authors designed the study; AA Højen, A. Gorst-Rasmussen and T.B. Larsen obtained and analyzed the data; and all authors interpreted the data. A.A. Højen, A. Gorst-Rasmussen, G.Y.H. Lip, D.A. Lane, L.H. Rasmussen, E.E. Sørensen and T.B. Larsen drafted the manuscript, and all authors critically revised it.

Disclosure Statement

The study was supported by the Obel Family Foundation. The sponsor had no role in the study design, in the collection, analysis, and interpretation of the data, in the writing of this report, or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Associate professor Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim. Associate professor Larsen and Professor Rasmussen have been on the speaker bureaus for Bayer, BMS/Pfizer, Roche Diagnostics and Boehringer Ingelheim. Professor Lip has served as a consultant for Bayer Healthcare, Astellas, Merck, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and as a speaker for Bayer Healthcare, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo and Sanofi-Aventis. Dr. Lane has received investigator-initiated educational grants from Bayer Healthcare and Boehringer Ingelheim and served as speaker for Boehringer Ingelheim, and BMS/Pfizer. She is also a steering committee member of a Phase IV apixaban study (AEGEAN) and is a panellist on the 9th edition of the American College of Chest Physicians guidelines on antithrombotic therapy in atrial fibrillation. Other authors – none declared.

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Table 1. Baseline characteristics for the venous thromboembolism cohort and the control cohort

Variable	Case cohort	Control cohort ₁
Females, n (%)	2,905 (70.3)	13,472 (69.8)
Recent pregnancy ₂	725 (17.5)	2,237 (11.6)
Age at index date		
13-18	313 (7.6)	1,539 (8.0)
18-23	861 (20.8)	4,140 (21.5)
23-38	1,251 (30.3)	5,801 (30.1)
28-33	1,707 (41.3)	7,812 (40.5)
Period of index date		
1997-2002	1,672 (40.5)	7,906 (41.1)
2003-2010	2,460 (59.5)	11,386 (59.0)
Recent provocation ₃	684 (16.5)	311 (1.6)
Cancer	68 (1.7)	18 (0.1)
Surgery	548 (13.3)	251(1.3)
Trauma	172 (4.2)	26 (0.1)
Inflammatory bowel disease	55(1.3)	26(0.13)
Rheumatoid arthritis	9(0.2)	6(0.03)

1 Population controls matched on sex and birth year.

2 Childbirth at up to 8 weeks before and up to 42 weeks after the index date or cases with ICD-8 or ICD-10 code indicating pregnancy-related VTE.

3 Diagnosis of cancer, rheumatoid arthritis, inflammatory bowel disease within 1 year of index date; trauma requiring hospital admission within 3 months of index date; surgery requiring one or more days of hospital admission within the last 3 months of index date.

Table 2: Risks and risk differences of any psychotropic drug purchase for venous thromboembolism cases and controls.

	Risk of psychotropic drug purchase (per cent)		Risk difference: cases vs. controls (95% CI)	Adjusted risk difference ₃ : cases vs. controls (95% CI)
	Cases ₁	Controls ₂		
Within 1 year after index date				
All	7.1	2.4	4.7 (3.9,5.5)	4.1 (3.3,4.9)
Male	7.1	1.9	5.2 (3.7,6.7)	4.7 (3.2,6.3)
Female	7.1	2.6	4.5 (3.5,5.5)	3.9 (2.9,4.9)
Age ≤ 25 years	6.4	1.9	4.5 (3.2,5.7)	3.7 (2.4,5.0)
Age > 25 years	7.6	2.7	4.9 (3.8,5.9)	4.4 (3.3,5.5)
Index date 1997-2002	6.8	2.3	4.5 (3.2,5.7)	3.9 (2.7,5.2)
Index date 2003-2010	7.4	2.5	4.9 (3.8,5.9)	4.2 (3.1,5.3)
Deep venous thrombosis	6.8	2.3	4.5 (3.6,5.4)	4.0 (3.1,5.0)
Pulmonary embolism	8.5	2.8	5.7 (3.7,7.6)	5.2 (3.3,7.2)
Within 5 years after index date				
All	22.1	11.3	10.8 (9.4,12.3)	9.6 (8.1,11.1)
Male	22.2	8.5	13.7 (11.1,16.3)	11.7 (9.0,14.3)
Female	22.1	12.5	9.6 (7.8,11.3)	8.7 (6.9,10.5)
Age ≤ 25 years	21.2	10.2	11.0 (8.7,13.2)	9.7 (7.4,12.1)
Age > 25 years	22.7	12.0	10.7 (8.8,12.6)	9.6 (7.7,11.5)
Index date 1997-2002	20.6	11.4	9.1 (6.8,11.5)	7.7 (5.3,10.1)
Index date 2003-2010	23.1	11.2	12.0 (10.1,13.8)	10.9 (9.0,12.8)
Deep venous thrombosis	21.9	11.1	10.8 (9.2,12.5)	9.8(8.2,11.5)
Pulmonary embolism	22.9	12.2	10.7 (7.5,13.9)	9.4 (6.1,12.7)

1 First time incident VTE cases among 13-33 year old Danish residents.

2 Population controls matched on sex and birth year.

3 Adjusted for diagnosis of cancer, rheumatoid arthritis, inflammatory bowel disease within 1 year of index date; trauma requiring hospital admission within 3 months of index date; surgery requiring one or more days of hospital admission within the last 3 months of index date and childbirth at up to 8 weeks before and up to 42 weeks after the index date.

Figure legends

Figure 1. Kaplan-Meier estimates of the risk of any psychotropic drug purchase as a function of time, according to venous thromboembolism case status

Figure 2. Risk differences of any psychotropic drug purchase for venous thromboembolism-cases vs. population controls as a function of time

ACCEPTED MANUSCRIPT

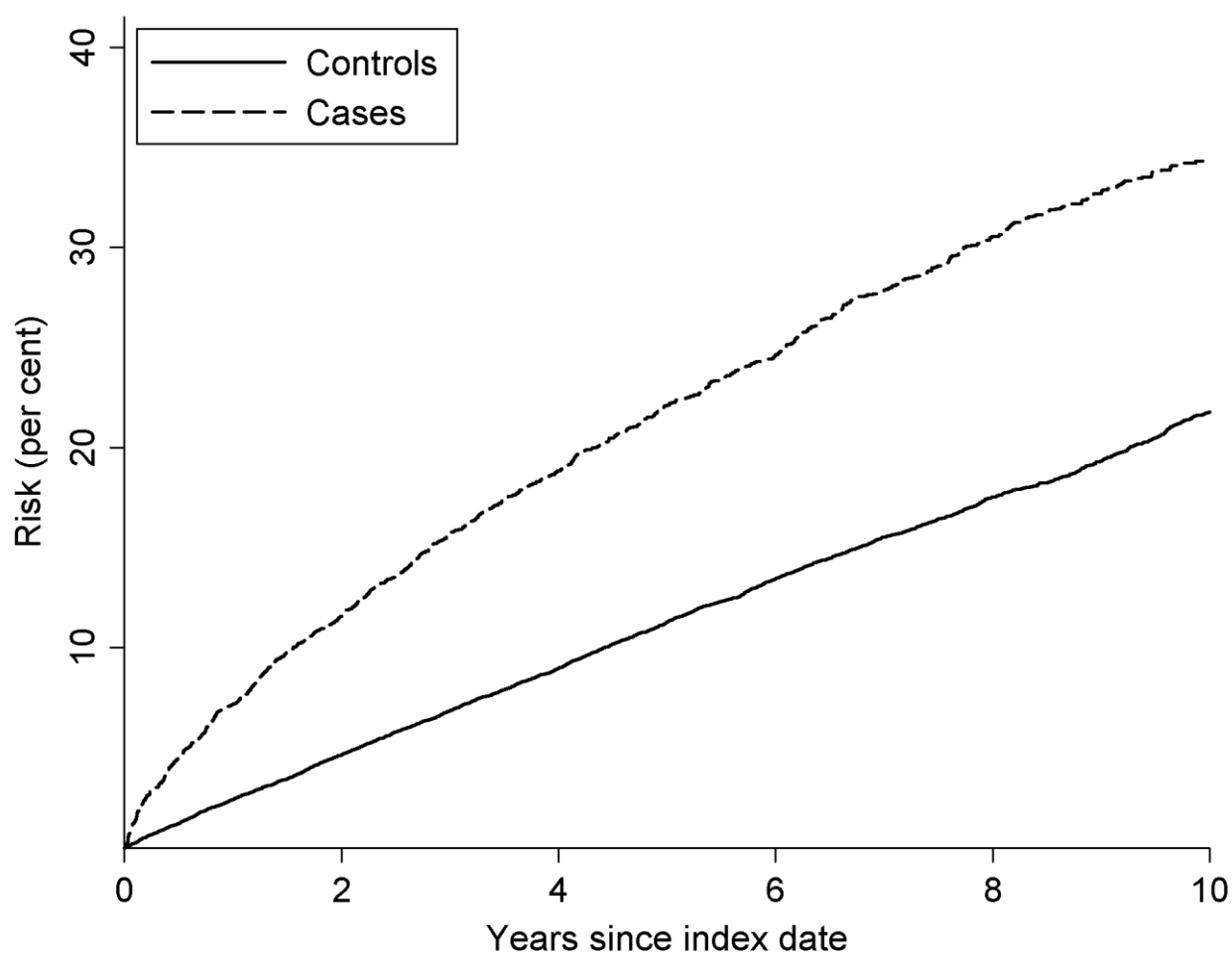


Figure 1

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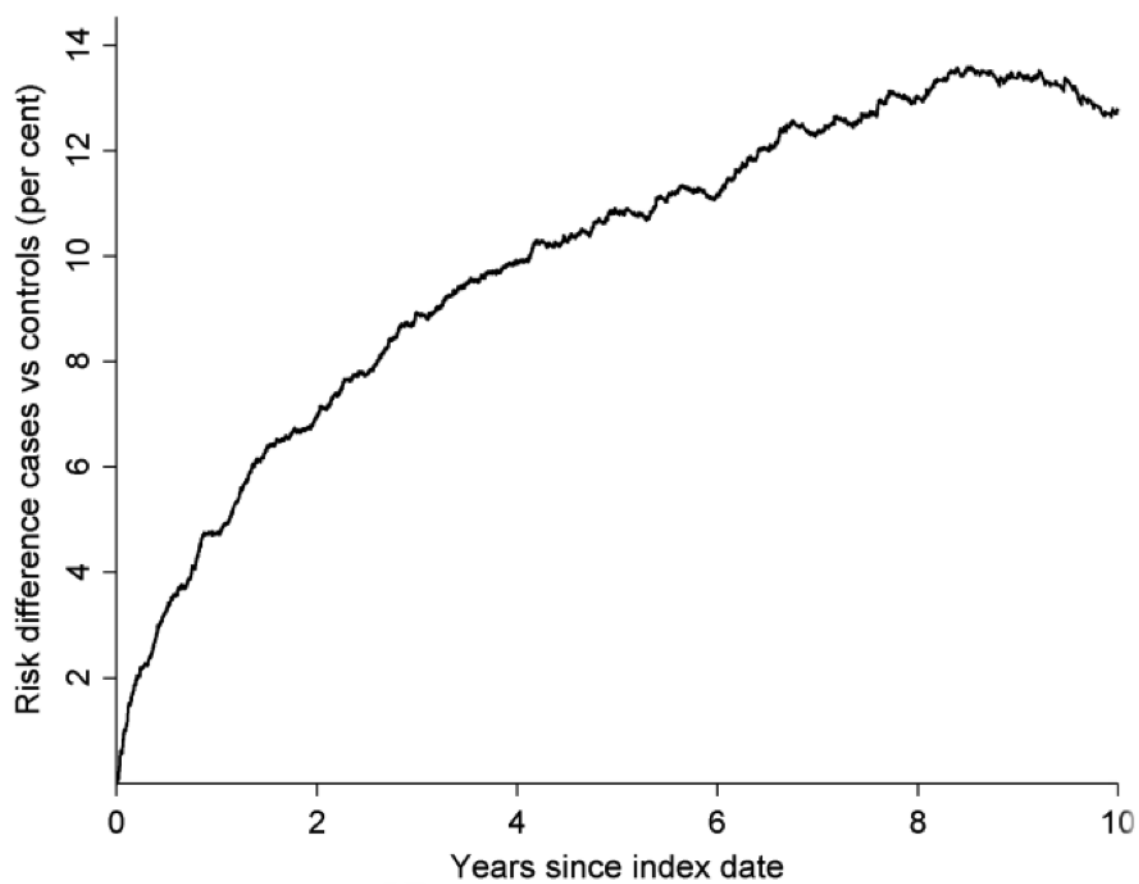


Figure 2

HIGHLIGHTS

- * VTE in the young is associated with a poor mental health prognosis
- * 1 in 5 patients purchase psychotropic drugs within 5 years after VTE diagnosis
- * Among similarly aged peers, only 1 in 10 purchase psychotropics in the same period
- * Young VTE patients may need long-term followup with a focus on mental health

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