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Psychotropic drug use following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study

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Title

Psychotropic drug use following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study

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Running title: Comparison of young VTE and diabetes patients' psychotropic drug use

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Summery

Objectives: Critical and chronic illness in youth such as diabetes can lead to impaired mental well-being. Despite the potentially traumatic and life-threatening nature of venous thromboembolism (VTE), the long-term mental wellbeing of adolescents and young adults with VTE is unclear. We compared the long-term mental wellbeing of adolescents and young adults with VTE versus adolescents and young adults with insulin-dependent diabetes mellitus (IDDM) using psychotropic drug purchase as proxy for mental health.

Design: Nationwide registry-based cohort study.

Setting: Denmark 1997-2015

Participants: All patients aged 13-33 years with an incident diagnosis of VTE (n=5,409) or IDDM (n=6,609)

Exposure: First time primary hospital diagnosis of VTE or IDDM.

Primary and secondary outcome measures: Adjusted absolute risk and risk difference at 1 and 5 years follow-up for first psychotropic drug purchase comparing patients with VTE and patients with IDDM.

Results: The absolute risk of psychotropic drug use among VTE patients was 6.2% after 1 year and 19.7% at 5 years of follow-up. The risk of psychotropic drug purchase was significantly higher among VTE patients compared to IDDM patients. At 1 year follow-up, the risk difference was 2.7% (95 % confidence interval (CI): 1.8%-3.6%), and at 5-years, 3.8% (95% CI: 2.2%-5.5%). The findings remained robust when adjusting for the effect of sex and risk factors for VTE and in analyses stratified by sex, age group, VTE provoking factors, and type of VTE.

Conclusion: One-fifth of adolescents and young adults with incident VTE had claimed a prescription for a psychotropic drug within 5 years, and the influence on long-term mental wellbeing following VTE was at least as great as seen in adolescents and young adults with IDDM.

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Keywords: Adolescents; Diabetes; Embolism and Thrombosis; Psychology; Venous Thromboembolism; Young Adult

Strengths and limitations of the study

- The study included all patients aged 13-33 years with a first-time hospital diagnosis of venous thromboembolism or insulin-dependent diabetes mellitus in Denmark in 1997-2015
- The study had complete long-term follow-up on psychotropic drug purchase
- The study lacked data regarding socioeconomic position, which has been associated with increased mental health problems in these patient groups.
- Finally, the data did not contain information on psychotropic drug compliance. However, it is inferred that a prescription for a psychotropic drug would be an indication of impaired mental health

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Introduction

Chronic illness such as diabetes mellitus in adolescence and young adulthood can have detrimental impact on well-being and psychological functioning [1,2]. Venous thromboembolism (VTE), which include deep venous thrombosis (DVT) and pulmonary embolism (PE), is not traditionally considered a chronic illness. Adolescents and young adults with VTE are not subject to the same level of disruption of everyday life as imposed by the complex daily dietary and medication regimens in patients with insulin-dependent diabetes (IDDM). Nonetheless, 25-50% of patients with DVT live with chronic complications in terms of post-thrombotic syndrome, and 0.4-4.0% of patients with PE develop chronic thromboembolic pulmonary hypertension [3]. Additionally, adolescents and young adults with VTE have to manage anticoagulant treatment and live with the perpetual risk of recurrent VTE, which may reach an incidence rate of 6.7 per 100 persons years among patients younger than 30 years [4]. Decreased quality of life and psychological impairment have been reported in younger VTE patients [5,6]. Thus, similar to young chronically ill patients with diabetes mellitus, the psychological well-being of adolescents and young adults with VTE could be impaired in long-term.

In the present nationwide cohort study, we compared the long-term mental well-being of adolescents and young adults with VTE to young patients with IDDM. To assess mental health status, we used information about psychotropic drug purchase derived from a Danish registry as a proxy for mental well-being. We hypothesized that adolescents and young adults with VTE would have a similar risk of psychotropic drug purchase as chronically ill adolescents and young adults with IDDM.

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Methods

Registry Data sources

We used three nationwide Danish registries in this study [7]; 1)The Danish National Patient Register, which contains detailed information on 99% of all somatic hospital admissions since 1977 along with diagnoses, coded according to the International Classification of Diseases (ICD) [8]; 2) The Danish National Prescription Registry, which contains data on redeemed prescriptions in Denmark since 1995, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System [9]; and 3) The Danish Civil Registration System, which holds information on gender, date of birth, death, and emigration of all Danish residents [10]. Data were linked using a unique civil registration number assigned to all Danish residents at birth or immigration and used in all Danish national registries.

In accordance with Danish law, no ethical approval is required for non-biomedical registry studies. The study was approved by the Danish Data Protection Agency (File No. 2012-41-0633).

Study population

We identified all patients aged 13-33 years with a first-time diagnosis of VTE or IDDM in the period January 1, 1997, to December 31, 2015 Patients with VTE were identified by a first-time primary hospital diagnosis of DVT or PE. VTE occurring in the absence of a diagnosis of major surgery, fracture, or trauma within 90 days before the VTE diagnosis or a diagnosis of cancer within one year prior to the VTE diagnosis were classified as unprovoked. Patients with IDDM were identified by a first-time hospital diagnosis of diabetes mellitus and a prescription claim for insulin within 30 days after diagnosis and no insulin prescription before 30 days prior to date of diagnosis. We excluded patients who died on the day of diagnosis. To identify new-onset impaired mental wellbeing, we further excluded patients with prior psychiatric diagnosis (depression, anxiety, bi-polar disorder, schizophrenia, and addiction) and patients who had purchased

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psychotropic drugs (antidepressants, anxiolytics, sedatives, antipsychotics) within 2 years before the date of VTE or IDDM diagnosis. Anticoagulant treatment among patients with VTE was identified by prescriptions for oral anticoagulants (OAC). Supplementary table 1 provides information on codes used in the study.

Outcome

The primary endpoint was a composite endpoint of psychotropic drug purchase, as a proxy for impaired mental wellbeing, recorded in the Danish National Prescription Registry following the index date. The secondary outcome was the specific types of psychotropic drugs: antipsychotics, anxiolytics, sedatives, and antidepressants.

Statistical Analysis

Descriptive characteristics of the study population at date of diagnosis of VTE or IDDM were presented using means and standard deviations for continuous measures and counts and percentages for categorical measures. Time to first psychotropic drug purchase was measured from date of diagnosis of VTE or IDDM. Patients were censored at the time of death, emigration, or end of study (December 31, 2015), whichever came first. Absolute risk of psychotropic drug purchase was calculated using the Kaplan-Meier estimator. We then used pseudo-value regression on a risk difference scale to assess the association between diagnosis type (VTE or IDDM) and the risk of a psychotropic drug purchase within 1 and 5 years. The pseudo-value regression technique reduces to simple regression on the event status indicator when there is no censoring and accounts for censored observations before 1 and 5 years, respectively [11]. To ensure that risk differences were assessed between comparable VTE and IDDM patients, we also conducted multivariate regression of pseudovalues, adjusting for the effect of sex (binary) and 'recent provocation' (binary). We repeated the analysis with stratification according to sex, age (13-25 or 26-33 years) VTE type (DVT or PE), and VTE-status (provoked or unprovoked). Finally, to assess the impact of extended

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anticoagulant treatment on mental wellbeing, we performed a supplementary analysis in which we stratified VTE patients according use of OAC at 1 year following the index date. Extended OAC usages was defined by a OAC purchase within 60 days before the 1 year land mark. We restricted this analysis to IDDM and VTE patients with no psychotropic drug purchase during the first year. Stata/MP version 13 was used for the statistical analysis (Stata Corporation, College Station, TX).

Results

We identified 6,683 patients with VTE and 7,616 patients with IDDM. After exclusion of patients who died on the day of diagnosis and patients with prior psychiatric diagnoses or a psychotropic drug purchase within 2 years prior to the diagnosis, the study population comprised 5,409 VTE patients, of which 78.2% had DVT and 21.8% had PE, and 6,609 IDDM patients (Figure 1). Patients with VTE patients were slightly older compared with patients with IDDM (mean age 25.7 years vs. 23.7 years), and a substantially higher proportion were females (68.3% vs. 38.1%) (Table 1). Approximately one-fifth of patients with VTE had an underlying recorded risk factor, such as trauma (11.9%) or major surgery (12.5%). In comparison, only 4.0% of patients with IDDM had a diagnosis of trauma, and 2.4% had major surgery (Table 1).

The absolute risk of psychotropic drug use among patients with VTE was 6.2% at 1 year of follow-up and 19.7% after 5 years of follow-up. The cumulative incidence curve revealed a significantly higher use of psychotropic drugs among patients with VTE compared with patients with IDDM (Figure 2). At 1 year follow-up, the risk difference was 2.7% (95 % confidence interval (CI): 1.8%-3.6%). Extending follow-up to 5 years did not materially change this conclusion; the 5-year risk-difference was 3.8% (95% CI: 2.2%-5.5%) (Table 2). The finding of a higher psychotropic drug use among patients with VTE compared with IDDM remained robust when adjusting for the effect

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of sex and risk factors for VTE (1-year risk difference 2.0%, 95% CI: 1.1-2.9); 5 year risk difference 2.0%, 95% CI: 0.3-3.6), and in analysis stratified by sex, age group, presence of provoking factors, and type of VTE (Table 2), with the exception of females in whom the long-term risk of psychotropic drugs were similar among IDDM and VTE patients (approximately 20%) (Table 2).

Antidepressants were the most frequently purchased drug class in both patient groups (VTE: 48%, IDDM: 58%) followed by sedatives (VTE: 24%, IDDM: 20%), anxiolytics (VTE: 19%, IDDM: 13%), antipsychotics (VTE: 5%, IDDM: 6%), and combined prescription of more than one drug class (VTE: 3% IDDM 3%). The absolute risk and risk difference comparing VTE patients and IDDM patients stratified by psychotropic drug class did not materially change the overall conclusions (data not shown).

At 1 year after diagnosis, 5062 (93%) of the VTE patients and 6360 (96%) of patients with IDDM had not claimed a prescription for a psychotropic drug. Among VTE patients without psychotropics, 781 (15%) had claimed a prescription for an oral anticoagulant drug within 60 days before the 1 year landmark. Compared with patients with IDDM, the risk of psychotropic drug use was not significantly increased among VTE patients with extended anticoagulant usage (5-year risk difference of 0.1%, (95 % CI: -2.6 – 2.8), whereas VTE patients without extended anticoagulant treatment had a higher risk (5-year risk difference of 2.5%, 95 % CI: 0.9 - 4.1) (Table 3).

Discussion

To our knowledge, this is the first study to compare the mental health of adolescents and young adults with VTE to that of patients with IDDM. Our nationwide cohort study revealed that the mental wellbeing of adolescents and young adults with VTE was impaired to the same extent as

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patients with IDDM. In fact, the impact of VTE on mental wellbeing appeared to be even worse than that of IDDM, as evidenced by a significantly higher risk of psychotropic drug use, which persisted over time and was evident across strata of age and type of VTE.

Our finding that one fifth of adolescents and young adults with VTE claim a prescription for a psychotropic drug within 5 years is of major concern. This finding extend results from previous studies, indicating that the psychological impact of VTE does not diminish over time [6,12,13]. This suggests that VTE could be considered a chronic illness [14,15]. The effect on mental health could have important clinical implications. For example, symptoms of depression and anxiety among patients treated with OAC have been associated with increased mortality and have been shown to impair several aspects of anticoagulant treatment [16]. Thus, our findings underscore the need for the healthcare community to emphasize and allocate resources to improve the mental wellbeing of adolescents and young adults with VTE. There is a need for further studies to prevent or at least to minimize psychological distress from VTE.

In accordance with prior observations of mental quality of life following VTE [17–19], we found no difference in psychotropic drug use among men and women with VTE. This lack of gender-related differences in mental well-being following VTE is at odds with studies from the general population, where women usually have higher levels of depression and lower quality of life [20]. In line with prior studies indicating no difference in quality of life according to OAC treatment status [21], use of extended anticoagulation was not associated with worse mental health. On the contrary, our findings suggest that patients without long-term OAC have slightly higher levels of psychological distress.

Study limitations

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Misclassification of VTE and IDDM diagnoses cannot be ruled out. Danish validation studies have previously found a positive predictive value of the VTE diagnosis of 88% [22], and ascertainment of diabetes mellitus by purchase of insulin in combination with a primary hospital discharge diagnosis has been shown to have a positive predictive value of 95%-97% [23,24]. We defined impaired mental wellbeing by prescription purchase of psychotropic drugs but do not know whether the patients actually took the medication. However, in the present study, we infer that a prescription for a psychotropic drug would be an indication of impaired mental health. We were unable to investigate the impact of socioeconomic factors. Low socioeconomic position has been associated with increased mental health problems, e.g., higher depression rates among young patients with IDDM [25] and low health related quality of life in young women with pregnancy-related DVT [26].

The major strengths of this study are the large sample size and complete coverage in the Danish hospital discharge and prescription purchase registries, which enabled a complete long-term follow-up on psychotropic drug purchases.

Conclusion

This nationwide cohort study showed a long-term negative impact on the mental well-being of adolescents and young adult patients following a first-time VTE diagnosis, which was even greater than the impact on mental health following a first diagnosis of IDDM. Our findings have important clinical implications and indicate that long-term focus on the mental well-being may be particularly pertinent in young VTE patients.

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Disclosures

Dr Lane has received investigator-initiated educational grants from Bayer Healthcare, Boehringer-Ingelheim and Bristol-Myers Squibb, served on speaker bureaus for Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer and is a consultant for Bristol-Myers Squibb and Boehringer-Ingelheim. Professor Goldhaber has received research support from BiO2 Medical, Boehringer-Ingelheim, BMS, BTG EKOS, Daiichi, National Heart Lung and Blood Institute of the National Institutes of Health, Janssen, Thrombosis Research Institute and served as a consultant for Bayer, Boehringer-Ingelheim, BMS, Daiichi, Janssen, Novartis, Portola, Zafgen. Associate Professor Larsen has been an investigator for Janssen Scientific Affairs and Boehringer-Ingelheim, and served on speaker bureaus for AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, Roche Diagnostics, Siemens Diagnostics and Takeda. Other authors – none declared

Contributors

All authors designed the study; A.A. Højen, L. Melgaard M. Søgaard and T.B. Larsen obtained and analyzed the data; and all authors interpreted the data. A.A. Højen drafted the manuscript, and L. Melgaard, M. Søgaard, D.A. Lane, S.Z. Goldhaber, E.E. Sørensen and T.B. Larsen critically revised it.

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Figure legends

Figure 1. Flowchart of patients included in the final study population

Figure 2. Kaplan-Meier estimates of the risk of any psychotropic drug purchase as a function of time

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Table 1: Study population characteristics

Variable	VTE	IDDM
N	5,409	6,609
Mean (SD) age, years	25.7 (5.3)	23.7 (6.5)
Age group, n (%)		
13-25 years	2,439 (45.1)	3,627 (54.9)
26-33 years	2,970 (54.1)	2,982 (45.1)
Females, n (%)	3,695 (68.3)	2,516 (38.1)
Risk factor for VTE, yes, n (%)	1,232 (22.8)	449 (6.8)
Trauma	645 (11.9)	267 (4.0)
Surgery	678 (12.5)	156 (2.4)
Cancer	68 (1.3)	16 (0.2)
Inflammatory bowel disease	55 (1.0)	26 (0.7)
Rheumatoid arthritis	8 (0.1)	5 (0.1)
DVT, n (%)	4,230 (78.2)	-
PE, n (%)	1,179 (21.8)	-

DVT: deep venous thrombosis, IDDM: insulin-dependent diabetes mellitus PE: pulmonary embolism, SD: standard deviation, VTE: venous thromboembolism

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Table 2. Risk of psychotropic drug purchase following a diagnosis of venous thromboembolism or insulin dependent diabetes mellitus in youth or adolescence

Characteristic	1 year follow-up				5 year follow-up			
	Psychotropic drug purchase (%)		Unadjusted risk difference	Adjusted risk difference	Psychotropic drug purchase (%)		Unadjusted risk difference	Adjusted risk difference
	VTE	IDDM	VTE vs. IDDM (95% CI)	VTE vs. IDDM (95% CI)	VTE	IDDM	VTE vs. IDDM (95% CI)	VTE vs. IDDM (95% CI)
Overall	6.7	3.9	2.9 (2.0-3.7)	2.0 (1.1-2.9)	20.3	15.8	4.5 (2.9 - 5.9)	2.0 (0.3-3.6)
Male	6.4	3.1	3.3 (2.0 - 4.6)	2.8 (1.5-4.2)	18.9	12.9	6.1 (3.8 - 8.4)	5.4 (2.9-7.8)
Female	6.9	5.2	1.7 (0.5 - 2.9)	1.4 (0.2 - 2.6)	20.9	20.5	-0.3 (-2.6 - 2.0)	-0.1 (-3.0-1.6)
Age 13-25 years	6.1	2.9	3.1 (2.0-4.2)	2.3 (1.1-3.5)	18.3	13.9	4.5 (2.5-6.6)	1.6 (-0.1-3.8)
Age 26-33 years	7.3	4.9	2.3 (1.1-3.5)	1.5 (0.1-5.8)	21.8	18.1	3.7 (1.4-5.9)	1.4 (-1.0-3.9)
Provoked VTE	6.6	3.9	2.8 (1.8-3.7)	2.1 (0.8-4.0)	19.9	15.8	4.1 (2.5-8.7)	2.1 (0.1-6.4)
Unprovoked VTE	7.1	3.9	3.3 (1.7-4.9)	2.6 (1.0-4.3)	21.5	15.8	5.7 (2.9-6.5)	3.5 (0.1-5.3)
DVT	6.6	3.9	2.7 (1.8-3.6)	1.9 (0.9-2.9)	20.1	15.8	4.3 (2.6-5.9)	1.8 (0.1-3.6)
PE	7.3	3.9	3.4 (1.8-5.0)	2.1 (0.5-3.8)	21.1	15.8	5.1 (2.5-7.7)	1.2 (-0.2-4.0)

CI: confidence interval, IDDM: insulin-dependent diabetes mellitus, VTE: venous thromboembolism

[a]Adjusted for sex, trauma, surgery, cancer, IBD, RA

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Table 3. Risk of psychotropic drug purchase in patients with venous thromboembolism and insulin-dependent diabetes mellitus 5 years following diagnosis, stratified by use of anticoagulant treatment among patients with VTE 1 year after diagnosis..

Characteristic	365 day-5 years after diagnosis[a]			
	Psychotropic drug purchase (%)		Unadjusted risk difference	Adjusted risk difference
	VTE	IDDM	VTE vs. IDDM (95% CI)	VTE vs. IDDM (95% CI)
Overall	14.6	12.4	2.1 (0.5- 3.2)	1.6 (0.1-3.0)
Anticoagulated	13.0	12.4	0.1 (-2.6 – 2.8)	0.1 (-2.6-2.4)
Not anticoagulated	15.0	12.4	2.5 (0.9 - 4.1)	2.1 (0.5-3.7)

CI: confidence interval, IDDM: insulin-dependent diabetes mellitus, VTE: venous thromboembolism

Number of participants contributing data (VTE: anticoagulated 781, non-anticoagulated 4,281; IDDM 6360)

[a] Index date 365 days after diagnosis

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Supplementary table 1: ICD-10 and ATC codes used in the study

ICD-10 Codes and ATC Codes		
	ICD 10 Codes	**ATC Codes**
Deep Venous Thrombosis	I801 I802 I803 I808 I809 I819 I636 I676 I822 I823 I829	
Pulmonary Embolism	I26	
Insulin depended diabetes mellitus	E100, E101, E109, E110, E111, E119	A10
Psychotropic drugs Antidepressants Antipsychotics Anxiolytics Sedatives		 N06A N05A N05B N05CD, N05CF, R06AD
Psychiatric diagnosis Schizofrenia Bi-polar Depression Anxiety Addiction	 F20 F30, F31 F322, F323, F332 F333 F40, F41, F93 F10-F19	
Risk factors for VTE Cancer[a] Inflammatory bowel disease[a] Rheumatoid arthritis[a] Major surgery[b] Trauma[b]	 C K50, K51 M05, M06 Procedure codes: A, B, F, G, H, J, K, L,M,N,P S, T0, T10, T11, T12, T13, T14	
Provoked VTE Major surgery[b] Trauma[b] Oral anticoagulant drugs Warfarin Phenprocoumon Dabigatran Rivaroxaban Apixaban	 Procedure codes: A, B, F, G, H, J, K, L,M,N,P S, T0, T10, T11, T12, T13, T14	 B01AA03 B01AA04 B01AE07 B01AF01 B01AF02

[a] *Within 1 year before diagnosis*
[b] *Within 90 days before diagnosis*
[c] *Within 8 weeks before and 42 weeks after diagnosis (data from the Danish Medical Birth Registry)*

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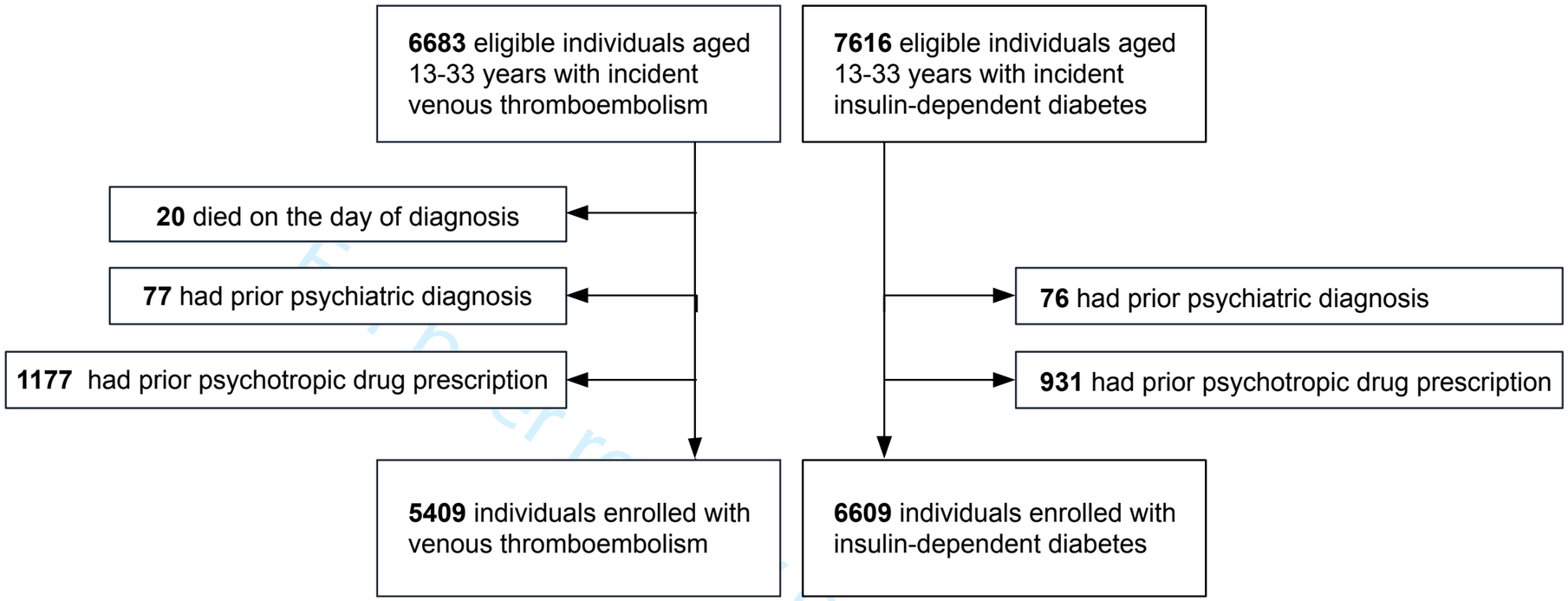

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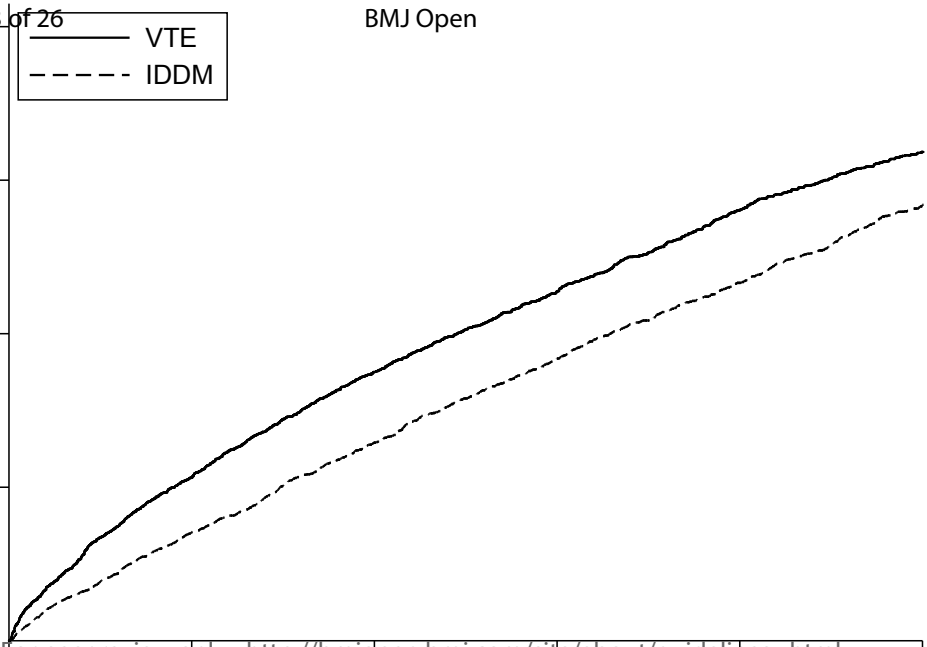

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STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study Design	4	Present key elements of study design early in the paper	1, 2, 4, 5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	5-6
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7

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Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study Size	10	Explain how the study size was arrived at	6-7
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	6
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, Flowchart
		(b) Give reasons for non-participation at each stage	Flowchart
		(c) Consider use of a flow diagram	Flowchart
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

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Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	tabel 2
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key Results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Psychotropic drug use following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Nursing
Keywords:	Adolescents, Diabetes, Thromboembolism < CARDIOLOGY, Psychology, Young Adult

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Title

Psychotropic drug use following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study

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Running title: Comparison of young VTE and diabetes patients' psychotropic drug use

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Summery

Objectives: Critical and chronic illness in youth such as diabetes can lead to impaired mental health. Despite the potentially traumatic and life-threatening nature of venous thromboembolism (VTE), the long-term mental health of adolescents and young adults with VTE is unclear. We compared the long-term mental health of adolescents and young adults with VTE versus adolescents and young adults with insulin-dependent diabetes mellitus (IDDM) using psychotropic drug purchase as proxy for mental health.

Design: Nationwide registry-based cohort study.

Setting: Denmark 1997-2015

Participants: All patients aged 13-33 years with an incident diagnosis of VTE (n=5,172) or IDDM (n=6,609)

Exposure: First time primary hospital diagnosis of VTE or IDDM.

Primary and secondary outcome measures: Adjusted absolute risk and risk difference at 1 and 5 years follow-up for first psychotropic drug purchase comparing patients with VTE and patients with IDDM.

Results: The absolute risk of psychotropic drug use among VTE patients was 6.4% after 1 year and 19.9% at 5 years of follow-up. The risk of psychotropic drug purchase was comparable and slightly higher among patients with VTE than patients with IDDM. , At 1 year follow-up, the risk difference was 2.6% (95 % confidence interval (CI): 1.7%-3.4%), and at 5-years, 4.1% (95% CI: 2.6%-5.6%). The findings remained robust when adjusting for the effect of sex and risk factors for VTE and in analyses stratified by sex, age group, VTE provoking factors, and type of VTE.

Conclusion: One-fifth of adolescents and young adults with incident VTE had claimed a prescription for a psychotropic drug within 5 years, a risk comparable to that of young patients with IDDM.

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Keywords: Adolescents; Diabetes; Embolism and Thrombosis; Psychology; Venous Thromboembolism; Young Adult

Strengths and limitations of the study

- The study included all patients aged 13-33 years with a first-time hospital diagnosis of venous thromboembolism or insulin-dependent diabetes mellitus in Denmark in 1997-2015
- The study had complete long-term follow-up on psychotropic drug purchase
- The study lacked data regarding socioeconomic position, which has been associated with increased mental health problems in these patient groups.
- Finally, the data did not contain information on psychotropic drug compliance. However, it is inferred that a prescription for a psychotropic drug would be an indication of impaired mental health

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Introduction

The incidence of VTE increases with age, and is lowest among the young [1]. However, adolescents and young adults may be particularly vulnerable to psychological distress, as they are in a phase of life in which they are creating identities and making decisions regarding their educational path, career, and family [2]. This phase often continues into the early thirties. Chronic illness such as diabetes mellitus in adolescence and young adulthood have been associated with co-morbid mental health problems, with documented negative effect on disease management and prognosis [3–5]. Venous thromboembolism (VTE), which include deep venous thrombosis (DVT) and pulmonary embolism (PE), is not traditionally considered a chronic illness. Adolescents and young adults with VTE are not subject to the same level of disruption of everyday life as imposed by the complex daily dietary and medication regimens in patients with insulin-dependent diabetes (IDDM). Nonetheless, 25-50% of patients with DVT live with chronic complications in terms of post-thrombotic syndrome, and 0.4-4.0% of patients with PE develop chronic thromboembolic pulmonary hypertension [6]. Additionally, adolescents and young adults with VTE have to manage anticoagulant treatment and live with the perpetual risk of recurrent VTE, which may reach an incidence rate of 6.7 per 100 persons years among patients younger than 30 years [1].

Decreased quality of life and psychological impairment have been reported in younger VTE patients [7,8]. Similar to IDDM patients, symptoms of anxiety and depression among VTE patients have been associated with poor disease management and mortality [9,10]. Thus, similar to young chronically ill patients with IDDM, the mental health of adolescents and young adults with VTE could be impaired in long-term We hypothesized that adolescents and young adults with VTE would have a similar risk of psychotropic drug purchase as chronically ill adolescents and young adults with IDDM. In the present nationwide cohort study, we therefore compared the long-term

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mental health of adolescents and young adults with VTE to young patients with IDDM. To assess mental health status, we used information about psychotropic drug purchase derived from a Danish registry as a proxy for mental health.

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Methods

Registry Data sources

We used three nationwide Danish registries in this study [11]; 1)The Danish National Patient Register, which contains detailed information on 99% of all somatic hospital admissions since 1977 along with diagnoses, coded according to the International Classification of Diseases (ICD) [12]; 2) The Danish National Prescription Registry, which contains data on redeemed prescriptions in Denmark since 1995, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System [13]; and 3) The Danish Civil Registration System, which holds information on gender, date of birth, death, and emigration of all Danish residents [14]. Data were linked using a unique civil registration number assigned to all Danish residents at birth or immigration and used in all Danish national registries.

In accordance with Danish law, no ethical approval is required for non-biomedical registry studies. The study was approved by the Danish Data Protection Agency (File No. 2012-41-0633).

Study population

We identified all patients aged 13-33 years with a first-time diagnosis of VTE or IDDM in the period January 1, 1997, to December 31, 2015. Patients with VTE were identified by a first-time primary hospital diagnosis of DVT or PE. If a patient had a diagnosis of both DVT and PE, preference was given to PE. Risk factors for VTE included major surgery, fracture, or trauma within 90 days before the VTE diagnosis or a diagnosis of cancer, inflammatory bowel disease or rheumatoid arthritis within one year prior to the VTE diagnosis. Patients with IDDM were identified by a first-time hospital diagnosis of diabetes mellitus and a prescription claim for insulin within 30 days after diagnosis and no insulin prescription before 30 days prior to date of diagnosis. The index date was defined as the date of the VTE diagnosis or IDDM diagnosis, respectively. We excluded patients who had not been residents in Denmark for at least 2 years before the date of

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VTE or IDDM in order to ensure sufficient lookback time for diagnoses and medications, as well as patients who died on the day of diagnosis. To identify new-onset impaired mental health, we further excluded patients with prior psychiatric diagnosis (depression, anxiety, bi-polar disorder, schizophrenia, and addiction) and patients who had purchased psychotropic drugs (antidepressants, anxiolytics, sedatives, antipsychotics) within 2 years before the date of VTE or IDDM diagnosis. Further, we excluded patients with gestational diabetes mellitus and pregnancy-related VTE because of the distinct clinical course of pregnancy-related VTE and gestational diabetes, as well the risk of postpartum depression. Supplementary table 1 provides information on codes used in the study.

Outcome

The primary endpoint was a composite endpoint of psychotropic drug purchase, as a proxy for impaired mental health, recorded in the Danish National Prescription Registry following the index date. The secondary outcome was the specific types of psychotropic drugs: antipsychotics, anxiolytics, sedatives, and antidepressants.

Statistical Analysis

Descriptive characteristics of the study population at date of diagnosis of VTE or IDDM were presented using means and standard deviations for continuous measures and counts and percentages for categorical measures. Time to first psychotropic drug purchase was measured from date of diagnosis of VTE or IDDM. Patients were censored at the time of death, emigration, or end of study (December 31, 2015), whichever came first. Absolute risk of psychotropic drug purchase was calculated using the Kaplan-Meier estimator. We then used pseudo-value regression approach with identity link function on a risk difference scale to assess the association between diagnosis type (VTE or IDDM) and the risk of a psychotropic drug purchase within 1 and 5 years. The pseudo-value regression technique reduces to simple regression on the event status indicator when there is

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no censoring and accounts for censored observations before 1 and 5 years, respectively [15]. To ensure that risk differences were assessed between comparable VTE and IDDM patients, we also conducted multivariate regression of pseudovalues, adjusting for the effect of sex (binary) and 'recent provocation' (binary). We repeated the analysis with stratification according to sex, age (13-25 or 26-33 years) VTE type (DVT or PE), and VTE-status (provoked or unprovoked).

Stata/MP version 13 was used for the statistical analysis (Stata Corporation, College Station, TX).

Patient and public involvement

Patients and public were not directly involved in the development of the research question and outcome measures or design of this nationwide cohort study.

Results

We identified 6,408 patients with VTE and 7,616 patients with IDDM. After exclusion of patients who died on the day of diagnosis and patients with prior psychiatric diagnoses or a psychotropic drug purchase within 2 years prior to the diagnosis, the study population comprised 5,172 VTE patients, of which 77.2% had DVT and 22.8% had PE, and 6,609 IDDM patients (Figure 1). Patients with VTE were slightly older compared with patients with IDDM (mean age 25.7 years vs. 23.7 years), and a substantially higher proportion were females (68.1% vs. 38.1%) (Table 1). Approximately one-fifth of patients with VTE had an underlying recorded risk factor, such as trauma (12.2%) or major surgery (12.7%). In comparison, only 4.0% of patients with IDDM had a diagnosis of trauma, and 2.4% had major surgery (Table 1).

The absolute risk of psychotropic drug use among patients with VTE was 6.4% at 1 year of follow-up and 19.9% after 5 years of follow-up. The cumulative incidence curve revealed a higher risk of psychotropic drugs among patients with VTE compared with patients with IDDM (Figure 2). At 1 year follow-up, the risk difference was 2.6% (95 % confidence interval (CI): 1.7%-3.4%).

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Extending follow-up to 5 years did not materially change this conclusion; the 5-year risk-difference was 4.1% (95% CI: 2.6%-5.6%) (Table 2). The finding of a higher psychotropic drug use among patients with VTE compared with IDDM was slightly attenuated when adjusting for the effect of sex and risk factors for VTE (1-year risk difference 1.7%, 95% CI: 0.8-2.6); 5 year risk difference 1.8%, 95% CI: 0.2-3.5), and in analysis stratified by sex, age group, presence of provoking factors, and type of VTE (Table 2), with the exception of females in whom the long-term risk of psychotropic drugs were similar among IDDM and VTE patients (approximately 20%) (Table 2).

Antidepressants were the most frequently purchased drug class in both patient groups (VTE: 48%, IDDM: 58%) followed by sedatives (VTE: 24%, IDDM: 20%), anxiolytics (VTE: 19%, IDDM: 13%), antipsychotics (VTE: 5%, IDDM: 6%), and combined prescription of more than one drug class (VTE: 3% IDDM 3%). The absolute risk and risk difference comparing VTE patients and IDDM patients stratified by psychotropic drug class did not materially change the overall conclusions (data not shown).

Discussion

To our knowledge, this is the first study to compare the mental health of adolescents and young adults with VTE to that of patients receiving a diagnosis of a chronic disease such as IDDM. Our nationwide cohort study revealed that the long-term mental health of adolescents and young adults with VTE was comparable to that of IDDM patients as evidenced by a slightly higher risk of psychotropic drug use among the VTE patients, which persisted over time and was evident across strata of age and type of VTE.

Our findings extend the results from previous studies, indicating that mental health impairment does not diminish over time among VTE patients [8,16,17]. Compared to IDDM patients among whom

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long-term co-morbid mental health problems are well documented [3,5], we noted a slightly higher psychotropic use among patients with VTE. Indeed, our study revealed that one fifth of adolescents and young adults with VTE claim a prescription for a psychotropic drug within 5 years. This is of major concern, as it is well established that impaired mental health has an effect on outcome as well as disease management in medically ill patients [18]. Accordingly, symptoms of depression and anxiety among VTE patients have been associated with both increased mortality and poor disease management [9,10]. Thus, impaired mental health possibly plays an important role for disease management and long-term prognosis in a considerable number of young VTE patients as the proportion with impaired mental health was comparable to that of patients with IDDM. These findings indicate a need for further studies to prevent, or at least, to minimize psychological distress in patients with VTE.

At odds with studies from the general population, where higher levels of depression and lower quality of life are found in women than men [19], we found no difference in psychotropic drug use among men and women with VTE. This lack of gender-related differences in mental health following VTE is in accordance with prior observations of mental quality of life following VTE [20–22]

Study limitations

Misclassification of VTE and IDDM diagnoses cannot be ruled out. Danish validation studies have previously found a positive predictive value of the VTE diagnosis of 88% to 90% [23,24], and ascertainment of diabetes mellitus by purchase of insulin in combination with a primary hospital discharge diagnosis has been shown to have a positive predictive value of 95%-97% [25,26]. We defined impaired mental health by prescription purchase of psychotropic drugs but do not know whether the patients actually took the medication. However, in the present study, we infer that a

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prescription for a psychotropic drug would be an indication of impaired mental health. We were unable to investigate the impact of socioeconomic factors. Low socioeconomic position has been associated with increased mental health problems, e.g., higher depression rates among young patients with IDDM [27] and low health related quality of life in young women with pregnancy-related DVT [28].

The major strengths of this study are the large sample size and complete coverage in the Danish hospital discharge and prescription purchase registries, which enabled a complete long-term follow-up on psychotropic drug purchases.

Conclusion

This nationwide cohort study showed that one-fifth of adolescents and young adults with incident VTE had claimed a prescription for a psychotropic drug within 5 years, indicating an impact on mental health comparable to that of young patients with IDDM.

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Disclosures

Dr Lane has received investigator-initiated educational grants from Boehringer- Ingelheim and Bristol-Myers Squibb, served on speaker bureaus for Boehringer-Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer and has consulted for Bristol-Myers Squibb, Bayer, Boehringer-Ingelheim and Daiichi-Sankyo. Professor Goldhaber has received research support from BiO2 Medical, Boehringer-Ingelheim, BMS, BTG EKOS, Daiichi, National Heart Lung and Blood Institute of the National Institutes of Health, Janssen, Thrombosis Research Institute and served as a consultant for Bayer, Boehringer-Ingelheim, BMS, Daiichi, Janssen, Novartis, Portola, Zafgen. Associate Professor Larsen has been an investigator for Janssen Scientific Affairs and Boehringer-Ingelheim, and served on speaker bureaus for AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, Roche Diagnostics, Siemens Diagnostics and Takeda. Other authors – none declared.

Contributors

All authors designed the study; A.A. Højen, L. Melgaard M. Søgaard and T.B. Larsen obtained and analyzed the data; and all authors interpreted the data. A.A. Højen drafted the manuscript, and L. Melgaard, M. Søgaard, D.A. Lane, S.Z. Goldhaber, E.E. Sørensen and T.B. Larsen critically revised it.

Data Sharing Statement

No additional data are available

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Figure legends

Figure 1. Flowchart of patients included in the final study population

Figure 2. Kaplan-Meier estimates of the risk of any psychotropic drug purchase as a function of time

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Table 1: Study population characteristics

Variable	VTE	IDDM
N	5,172	6,609
Mean (SD) age, years	25.7 (5.2)	23.7 (6.5)
Age group, n (%)		
13-25 years	2,299 (44.5)	3,627 (54.9)
26-33 years	2,873 (55.5)	2,982 (45.1)
Females, n (%)	3,523 (68.1)	2,516 (38.1)
Risk factor for VTE, yes, n (%)	1,193 (23.1)	449 (6.8)
Trauma	633 (12.2)	267 (4.0)
Surgery	655 (12.7)	156 (2.4)
Cancer	64 (1.2)	16 (0.2)
Inflammatory bowel disease	51 (1.0)	26 (0.7)
Rheumatoid arthritis	8 (0.1)	5 (0.1)
DVT, n (%)	3,993 (77.2)	-
PE, n (%)	1,179 (22.8)	-

DVT: deep venous thrombosis, IDDM: insulin-dependent diabetes mellitus PE: pulmonary embolism, SD: standard deviation, VTE: venous thromboembolism

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Table 2. Risk of psychotropic drug purchase following a diagnosis of venous thromboembolism or insulin dependent diabetes mellitus in youth or adolescence

Characteristic	1 year follow-up				5 year follow-up			
	Psychotropic drug purchase (%)		Unadjusted risk difference	Adjusted risk difference[a]	Psychotropic drug purchase (%)		Unadjusted risk difference	Adjusted risk difference[a]
	VTE	IDDM	VTE vs. IDDM (95% CI)	VTE vs. IDDM (95% CI)	VTE	IDDM	VTE vs. IDDM (95% CI)	VTE vs. IDDM (95% CI)
Overall	6.4	3.9	2.6 (1.7-3.4)	1.7 (0.8-2.6)	19.9	15.8	4.1 (2.6-5.6)	1.8 (0.2-3.5)
Male	6.2	3.1	3.2 (1.9-4.5)	2.7 (1.3-4.1)	18.7	12.9	5.9 (3.5-8.2)	5.1 (2.7-7.5)
Female	6.5	5.2	1.3 (0.2-2.5)	1.0 (0.1 - 2.2)	20.5	20.5	-0.1 (-2.3-2.1)	-1.1(-3.4-1.2)
Age 13-25 years	5.8	2.9	2.9 (1.8-4.0)	2.0 (1.0-3.3)	18.0	13.9	4.1 (2.1-6.2)	1.2 (-0.1-3.5)
Age 26-33 years	6.9	4.9	1.9 (0.7-3.5)	1.1 (0.1-3.4)	21.4	18.1	3.3 (1.0-5.6)	1.1 (-1.4-3.5)
Provoked VTE	6.3	3.9	2.4 (1.5-3.3)	2.4 (0.8-4.0)	19.5	15.8	3.7 (2.0-8.2)	1.8 (0.1-6.2)
Unprovoked VTE	7.0	3.9	3.1 (1.5-4.7)	1.8 (0.8-4.2)	21.4	15.8	5.5 (2.8-7.5)	3.4 (0.1-5.2)
DVT	6.1	3.9	2.3 (1.4-3.2)	1.5 (0.5-2.5)	19.6	15.8	3.8 (2.2-5.5)	1.3 (0.1-3.2)
PE	7.3	3.9	3.4 (1.8-5.0)	2.1 (0.5-3.8)	21.1	15.8	5.1 (2.5-7.7)	1.2 (-0.2-4.0)

CI: confidence interval, IDDM: insulin-dependent diabetes mellitus, VTE: venous thromboembolism

[a]Adjusted for sex, trauma, surgery, cancer, IBD, RA

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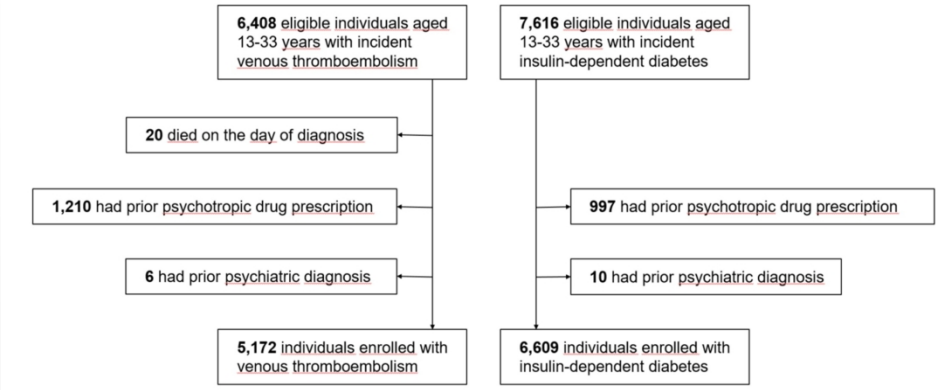

Figure 1. Flowchart of patients included in the final study population

199x149mm (300 x 300 DPI)

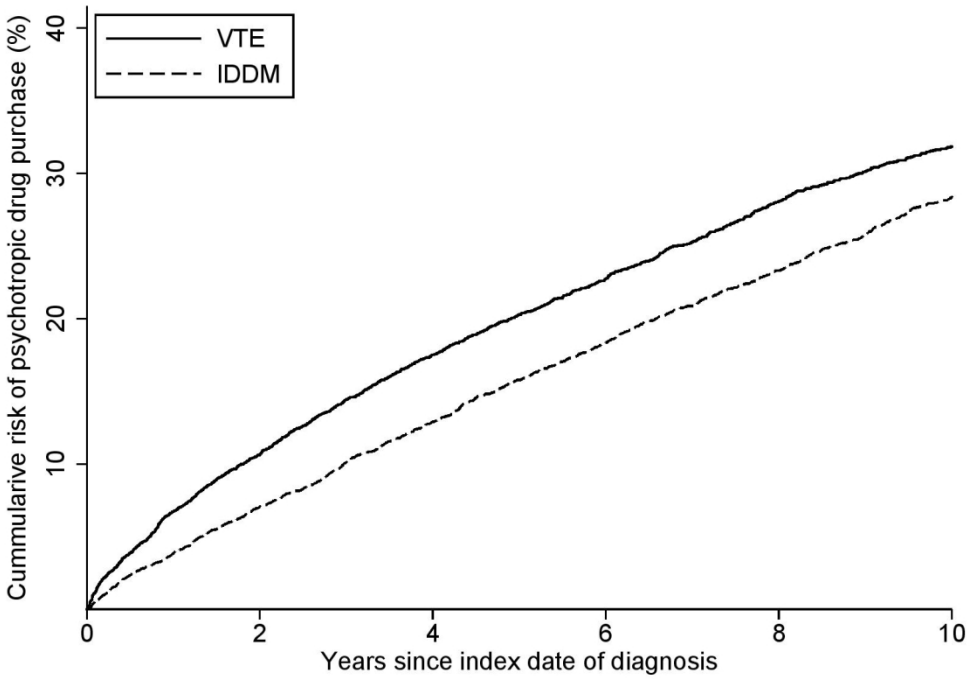

Figure 2. Kaplan-Meier estimates of the risk of any psychotropic drug purchase as a function of time

139x101mm (300 x 300 DPI)

Supplementary table 1: ICD-10, ATC and procedure codes used in the study

ICD-10, ATC and procedure codes			
	ICD 10 Codes	**ATC Codes**	**Procedure Codes**
Deep Venous Thrombosis	I801 I802 I803 I808 I809 I822 I823 I829		
Pulmonary Embolism	I26		
Insulin depended diabetes mellitus	E100, E101, E109, E110, E111, E119	A10	
Psychotropic drugs Antidepressants Antipsychotics Anxiolytics Sedatives		 N06A N05A N05B N05CD, N05CF, R06AD	
Psychiatric diagnosis Schizophrenia Bi-polar Depression Anxiety Addiction	 F20 F30, F31 F322, F323, F332 F333 F40, F41, F93 F10-F19		
Risk factors for VTE Cancer[a] Inflammatory bowel disease[a] Rheumatoid arthritis[a] Major surgery[b] Trauma[b]	 C K50, K51 M05, M06 S, T0, T10, T11, T12, T13, T14		 A, B, F, G, H, J, K, L,M,N,P

[a]*Within 1 year before diagnosis*
[b]*Within 90 days before diagnosis*

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STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study Design	4	Present key elements of study design early in the paper	1, 2, 4, 5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	5-6
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7

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Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study Size	10	Explain how the study size was arrived at	6-7
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	6
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, Flowchart
		(b) Give reasons for non-participation at each stage	Flowchart
		(c) Consider use of a flow diagram	Flowchart
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

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Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	tabel 2
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key Results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Psychotropic drug use following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study

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Title

Psychotropic drug use following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study

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Running title: Comparison of young VTE and diabetes patients' psychotropic drug use

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Abstract

Objectives: Critical and chronic illness in youth such as diabetes can lead to impaired mental health. Despite the potentially traumatic and life-threatening nature of venous thromboembolism (VTE), the long-term mental health of adolescents and young adults with VTE is unclear. We compared the long-term mental health of adolescents and young adults with VTE versus adolescents and young adults with insulin-dependent diabetes mellitus (IDDM) using psychotropic drug purchase as proxy for mental health.

Design: Nationwide registry-based cohort study.

Setting: Denmark 1997-2015

Participants: All patients aged 13-33 years with an incident diagnosis of VTE (n=5,065) or IDDM (n=6,609)

Exposure: First time primary hospital diagnosis of VTE or IDDM.

Primary and secondary outcome measures: Adjusted absolute risk and risk difference at 1 and 5 years follow-up for first psychotropic drug purchase comparing patients with VTE and patients with IDDM.

Results: The absolute risk of psychotropic drug use among VTE patients was 6.2% after 1 year and 19.3% at 5 years of follow-up. The risk of psychotropic drug purchase was comparable and slightly higher among patients with VTE than patients with IDDM. At 1 year follow-up, the risk difference was 2.6% (95 % confidence interval (CI): 1.3%-3.9%), and at 5-years, 4.6% (95% CI: 2.3%-6.9%). The findings of comparable risk of psychotropic drug use remained robust when adjusting for the effect of sex and risk factors for VTE and in analyses stratified by sex, age group, VTE provoking factors, and type of VTE.

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Conclusion: One-fifth of adolescents and young adults with incident VTE had claimed a prescription for a psychotropic drug within 5 years, a risk comparable to that of young patients with IDDM.

Keywords: Adolescents; Diabetes; Embolism and Thrombosis; Psychology; Venous Thromboembolism; Young Adult

Strengths and limitations of the study

- The study included all patients aged 13-33 years with a first-time hospital diagnosis of venous thromboembolism or insulin-dependent diabetes mellitus in Denmark in 1997-2015
- The study had complete long-term follow-up on psychotropic drug purchase
- The study lacked data regarding socioeconomic position, which has been associated with increased mental health problems in these patient groups.
- Finally, the data did not contain information on psychotropic drug compliance. However, it is inferred that a prescription for a psychotropic drug would be an indication of impaired mental health

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Introduction

Mental co-morbidity is well established as a prevalent problem in young patients with insulin-dependent diabetes (IDDM), with documented negative effect on disease management and prognosis [1–3]. Venous thromboembolism (VTE), which include deep venous thrombosis (DVT) and pulmonary embolism (PE), is not traditionally considered a chronic illness. However, 25-50% of patients with DVT live with chronic complications in terms of post-thrombotic syndrome, and 0.4-4.0% of patients with PE develop chronic thromboembolic pulmonary hypertension [4]. Additionally, adolescents and young adults with VTE have to manage anticoagulant treatment and live with the perpetual risk of recurrent VTE, which may reach an incidence rate of 6.7 per 100 persons years among patients younger than 30 years [5]. Thus, from a transition theory perspective, adolescent and young adults with VTE are likely to be similar to IDDM patients in experiencing multiple and simultaneous transitions, making them particularly vulnerable to psychosocial distress [6]. In addition to the health-illness transition of VTE, the young patients will face the developmental transition of adolescence and young adulthood marked by intimacy, generativity, and career consolidation, which today often continues into the early thirties[7].

Younger patients with VTE have been shown to have a decreased quality of life and psychological impairment compared with the general population of same age [8,9].
Similar to IDDM patients, symptoms of anxiety and depression among VTE patients have been associated with poor disease management and mortality [10,11]. Thus, similar to young chronically ill patients with IDDM, the mental health of adolescents and young adults with VTE could be impaired in long-term.

We hypothesized that adolescents and young adults with VTE would have a similar risk of psychotropic drug purchase as chronically ill adolescents and young adults with IDDM. In the

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present nationwide cohort study, we therefore compared the long-term mental health of adolescents and young adults with VTE to young patients with IDDM. To assess mental health status, we used information about psychotropic drug purchase derived from a Danish registry as a proxy for mental health

Methods

Registry Data sources

We used three nationwide Danish registries in this study [12]: 1)The Danish National Patient Register, which contains detailed information on 99% of all somatic hospital admissions since 1977 along with diagnoses, coded according to the International Classification of Diseases (ICD) and surgical procedures coded according to the Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures[13]; 2) The Danish National Prescription Registry, which contains data on redeemed prescriptions in Denmark since 1995, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System [14]; and 3) The Danish Civil Registration System, which holds information on gender, date of birth, death, and emigration of all Danish residents [15]. Data were linked using a unique civil registration number assigned to all Danish residents at birth or immigration and used in all Danish national registries.

In accordance with Danish law, no ethical approval is required for non-biomedical registry studies. The study was approved by the Danish Data Protection Agency (File No. 2012-41-0633).

Study population

We identified all patients aged 13-33 years with a first-time diagnosis of VTE or IDDM in the period January 1, 1997, to December 31, 2015. Patients with VTE were identified by a first-time primary hospital diagnosis of DVT or PE. If a patient had a diagnosis of both DVT and PE, preference was given to PE. Risk factors for VTE included major surgery, fracture, or trauma

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within 90 days before the VTE diagnosis or a diagnosis of cancer, inflammatory bowel disease or rheumatoid arthritis within one year prior to the VTE diagnosis. Patients with IDDM were identified by a first-time hospital diagnosis of diabetes mellitus and a prescription claim for insulin within 30 days after diagnosis and no insulin prescription before 30 days prior to date of diagnosis. The index date for IDDM patients was defined as the date of first insulin prescription purchase after the diabetes diagnosis. The index date for VTE patients was based on day of VTE diagnosis and randomly shifted according to the distribution of time between diabetes diagnosis and insulin prescription purchase in the IDDM cohort. We excluded patients who had not been residents in Denmark for at least 2 years before the date of VTE or IDDM in order to ensure sufficient lookback time for diagnoses and medications, as well as patients who died on the day of diagnosis. To identify new-onset impaired mental health, we further excluded patients with prior psychiatric diagnosis (depression, anxiety, bi-polar disorder, schizophrenia, and addiction) and patients who had purchased psychotropic drugs (antidepressants, anxiolytics, sedatives, antipsychotics) within 2 years before the date of VTE or IDDM diagnosis. Further, we excluded patients with gestational diabetes mellitus and pregnancy-related VTE because of the distinct clinical course of pregnancy-related VTE and gestational diabetes, as well the risk of postpartum depression. Supplementary table 1 provides information on codes used in the study.

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Outcome

The primary endpoint was a composite endpoint of psychotropic drug purchase, as a proxy for impaired mental health, recorded in the Danish National Prescription Registry following the index date. The secondary outcome was the specific types of psychotropic drugs: antipsychotics, anxiolytics, sedatives, and antidepressants.

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Statistical Analysis

Descriptive characteristics of the study population at date of diagnosis of VTE or IDDM were presented using means and standard deviations for continuous measures and counts and percentages for categorical measures. Time to first psychotropic drug purchase was measured from date of diagnosis of VTE or IDDM. Patients were censored at the time of death, emigration, or end of study (December 31, 2015), whichever came first. Cumulative incidence functions (by means of the Aalen-Johansen estimator), assuming death as competing risks, were used to depict risk of psychotropic drug purchase within 10 years. We used pseudo-value regression approach with identity link function on a risk difference scale to assess the association between diagnosis type (VTE or IDDM) and the risk of a psychotropic drug purchase within 1 and 5 years taking into account the competing risk of death. The pseudo-value regression technique reduces to simple regression on the event status indicator when there is no censoring and accounts for censored observations before 1 and 5 years, respectively [16]. To assess to which extent the observed association could be explained by sex, age or recent provocation, we also conducted multivariate regression of pseudovalues, adjusting for the effect of sex (binary), age (continuous), and 'recent provocation' (binary). We repeated the analysis with stratification according to sex, age (13-25 or 26-33 years) VTE type (DVT or PE), and VTE-status (provoked or unprovoked).

Stata/MP version 13 was used for the statistical analysis (Stata Corporation, College Station, TX).

Patient and public involvement

Patients and public were not directly involved in the development of the research question and outcome measures or design of this nationwide cohort study.

Results

We identified 6,297 patients with VTE and 7,616 patients with IDDM. After exclusion of patients who died on the day of diagnosis and patients with prior psychiatric diagnoses or a psychotropic

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drug purchase within 2 years prior to the diagnosis, the study population comprised 5,172 VTE patients, of which 76.6% had DVT and 23.4% had PE, and 6,609 IDDM patients (Figure 1). Patients with VTE were slightly older compared with patients with IDDM (mean age 25.7 years vs. 23.7 years), and a substantially higher proportion were females (68.5% vs. 38.1%) (Table 1). Approximately one-fifth of patients with VTE had an underlying recorded risk factor, such as trauma (12.2%) or major surgery (12.9%). In comparison, only 4.0% of patients with IDDM had a diagnosis of trauma, and 2.4% had major surgery (Table 1).

The absolute risk of psychotropic drug use among patients with VTE was 6.2% at 1 year of follow-up and 19.3% after 5 years of follow-up. The cumulative incidence curve revealed a higher risk of psychotropic drugs among patients with VTE compared with patients with IDDM (Figure 2). At 1 year follow-up, the risk difference was 2.6% (95 % confidence interval (CI): 1.3%-3.9%). Extending follow-up to 5 years did not materially change this conclusion; the 5-year risk-difference was 4.6% (95% CI: 2.3%-6.9%) (Table 2). The finding of a higher psychotropic drug use among patients with VTE compared with IDDM was attenuated when adjusting for the effect of sex and risk factors for VTE (1-year risk difference 1.9%, 95% CI: 0.1-3.3); 5 year risk difference 1.9%, 95% CI: 0.5-3.3). In the analysis stratified by sex, age, presence of provoking factors (Table 2), we found similar risks among the VTE and IDDM patients with the exception of males in whom the long-term risk of psychotropic drugs were higher among the VTE patients (Table 2).

Antidepressants were the most frequently purchased drug class in both patient groups (VTE: 48%, IDDM: 58%) followed by sedatives (VTE: 24%, IDDM: 20%), anxiolytics (VTE: 19%, IDDM: 13%), antipsychotics (VTE: 5%, IDDM: 6%), and combined prescription of more than one drug class (VTE: 3% IDDM 3%). The absolute risk and risk difference comparing VTE patients and

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IDDM patients stratified by psychotropic drug class did not materially change the overall conclusions (data not shown).

Discussion

To our knowledge, this is the first study to compare the mental health of adolescents and young adults with VTE to that of patients receiving a diagnosis of a chronic disease such as IDDM. Our nationwide cohort study revealed that the long-term mental health of adolescents and young adults with VTE was comparable to that of IDDM patients as evidenced by a slightly higher risk of psychotropic drug use among the VTE patients, which persisted over time and was evident across strata of age and type of VTE.

Our findings extend the results from previous studies, indicating that mental health impairment does not diminish over time among VTE patients [9,17,18]. Compared to IDDM patients among whom long-term co-morbid mental health problems are well documented [1,3], we noted comparable psychotropic use among patients with VTE. Indeed, our study revealed that one fifth of adolescents and young adults with VTE claim a prescription for a psychotropic drug within 5 years. This is of major concern, as it is well established that impaired mental health has an effect on outcome as well as disease management in medically ill patients [19]. Accordingly, symptoms of depression and anxiety among VTE patients have been associated with both increased mortality and poor disease management [10,11]. Thus, impaired mental health possibly plays an important role for disease management and long-term prognosis in a considerable number of young VTE patients as the proportion with impaired mental health was comparable to that of patients with IDDM. These findings indicate a need for further studies to prevent, or at least, to minimize psychological distress in patients with VTE.

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At odds with studies from the general population, where higher levels of depression and lower quality of life are found in women than men [20], we found no difference in psychotropic drug use among men and women with VTE. This lack of gender-related differences in mental health following VTE is in accordance with prior observations of mental quality of life following VTE [21–23], and subject to further investigation.

Study limitations

Misclassification of VTE and IDDM diagnoses cannot be ruled out. Danish validation studies have previously found a positive predictive value of the VTE diagnosis of 88% to 90% [24,25], and ascertainment of diabetes mellitus by purchase of insulin in combination with a primary hospital discharge diagnosis has been shown to have a positive predictive value of 95%-97% [26,27]. We defined impaired mental health by prescription purchase of psychotropic drugs but do not know whether the patients actually took the medication. However, in the present study, we infer that a prescription for a psychotropic drug would be an indication of impaired mental health. We did not assess the duration of psychotropic drug use and other diseases occurring during follow-up, which may have been associated with the need for psychotropic therapy. We also lacked data on socioeconomic factors. Low socioeconomic position has been associated with increased mental health problems, e.g., higher depression rates among young patients with IDDM [28] and low health related quality of life in young women with pregnancy-related DVT [29]. Given these limitations, it is important to emphasize that based on this observational study we cannot infer a causal interpretation of the observed association between VTE and impaired mental health.

The major strengths of this study are the large sample size and complete coverage in the Danish hospital discharge and prescription purchase registries including all in- and outpatients with VTE or IDDM, which enabled a complete long-term follow-up on psychotropic drug purchases.

Conclusion

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This nationwide cohort study showed that one-fifth of adolescents and young adults with incident VTE had claimed a prescription for a psychotropic drug within 5 years, indicating an impact on mental health comparable to that of young patients with IDDM.

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Competing interests

Dr Lane has received investigator-initiated educational grants from Boehringer- Ingelheim and Bristol-Myers Squibb, served on speaker bureaus for Boehringer-Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer and has consulted for Bristol-Myers Squibb, Bayer, Boehringer-Ingelheim and Daiichi-Sankyo. Professor Goldhaber has received research support from BiO2 Medical, Boehringer-Ingelheim, BMS, BTG EKOS, Daiichi, National Heart Lung and Blood Institute of the National Institutes of Health, Janssen, Thrombosis Research Institute and served as a consultant for Bayer, Boehringer-Ingelheim, BMS, Daiichi, Janssen, Novartis, Portola, Zafgen. Associate Professor Larsen has been an investigator for Janssen Scientific Affairs and Boehringer-Ingelheim, and served on speaker bureaus for AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, Roche Diagnostics, Siemens Diagnostics and Takeda. Other authors – none declared.

Contributorship Statement

All authors designed the study; A.A. Højen, L. Melgaard M. Søgaard and T.B. Larsen obtained and analyzed the data; and all authors interpreted the data. A.A. Højen drafted the manuscript, and L. Melgaard, M. Søgaard, D.A. Lane, S.Z. Goldhaber, E.E. Sørensen and T.B. Larsen critically revised it.

Data Sharing Statement

No additional data are available.

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Figure legends

Figure 1. Flowchart of patients included in the final study population

Figure 2. Cumulative incidence of psychotropic drug purchase in patients with venous thromboembolism and patients with insulin-dependent diabetes mellitus

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Table 1: Study population characteristics

Variable	VTE	IDDM
N	5,065	6,609
Mean age (SD)	25.7 (5.2)	23.7 (6.5)
Age group, n (%)		
13-25 years	2,258 (44.6)	3,627 (54.9)
26-33 years	2,807 (54.4)	2,982 (45.1)
Females, n (%)	3,470 (68.5)	2,516 (38.1)
Risk factor for VTE, yes, n (%)	1,179 (23.3)	449 (6.8)
Trauma	618 (12.2)	267 (4.0)
Surgery	652 (12.9)	156 (2.4)
Cancer	64 (1.3)	16 (0.2)
Inflammatory bowel disease	49 (1.0)	26 (0.7)
Rheumatoid arthritis	8 (0.1)	5 (0.1)
DVT, n (%)	3,881 (76.6)	-
PE, n (%)	1,184 (23.4)	-

DVT: deep venous thrombosis, IDDM: insulin-dependent diabetes mellitus PE: pulmonary embolism, SD: standard deviation, VTE: venous thromboembolism

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Table 2. Risk of psychotropic drug purchase following a diagnosis of venous thromboembolism or insulin dependent diabetes mellitus in youth or adolescence

Characteristic	1 year follow-up				5 year follow-up			
	Psychotropic drug purchase (%)		Unadjusted risk difference	Adjusted risk difference[a]	Psychotropic drug purchase (%)		Unadjusted risk difference	Adjusted risk difference[a]
	VTE	IDDM	VTE vs. IDDM (95% CI)	VTE vs. IDDM (95% CI)	VTE	IDDM	VTE vs. IDDM (95% CI)	VTE vs. IDDM (95% CI)
Overall	6.2	3.6	2.6 (1.3-3.9)	1.9 (0.1-3.3)	19.3	14.7	4.6 (2.3-6.9)	1.9 (0.5-3.3)
Male	6.9	2.9	4.1 (1.8-6.4)	3.0 (0.7-5.4)	18.5	11.9	6.6 (2.7-10.4)	3.0 (0.7-5.4)
Female	5.9	4.9	1.0 (-0.1-2.7)	0.3 (-1.5-2.1)	19.7	19.5	0.2 (-2.9-3.4)	0.3 (-0.2-2.1)
Age 13-25 years	6.1	2.7	3.4 (1.5-5.2)	1.7 (0.1-3.7)	17.9	12.9	5.1 (1.9-8.3)	1.7 (-0.4-3.7)
Age 26-33 years	6.4	4.8	1.5 (-0.3-3.4)	0.7 (-0.1-2.8)	20.4	17.1	3.4 (0.1-6.8)	0.7 (-0.0-2.8)
Provoked VTE	6.3	3.6	2.4 (-0.2-5.0)	1.1 (-0.2-3.9)	18.8	14.7	4.1 (-0.7-8.9)	1.1 (-0.6-3.9)
Unprovoked VTE	6.0	3.6	2.7 (1.2-4.1)	1.5 (-0.1-3.0)	19.5	14.7	4.2 (1.6-6.8)	1.5 (-0.1-3.0)
DVT	6.1	3.6	2.6 (1.2-4.1)	1.2 (-0.1-2.7)	18.9	14.7	4.1 (1.2-4.1)	1.2 (-0.1-2.7)
PE	6.3	3.6	2.4(0.1-5.0)	1.0 (-0.2-3.6)	20.8	14.7	6.1 (1.7-10.6)	0.9 (-0.7-3.6)

CI: confidence interval, IDDM: insulin-dependent diabetes mellitus, VTE: venous thromboembolism

[a]Adjusted for sexage, recent provocation (trauma, surgery, cancer, IBD, RA)except when stratifying variable

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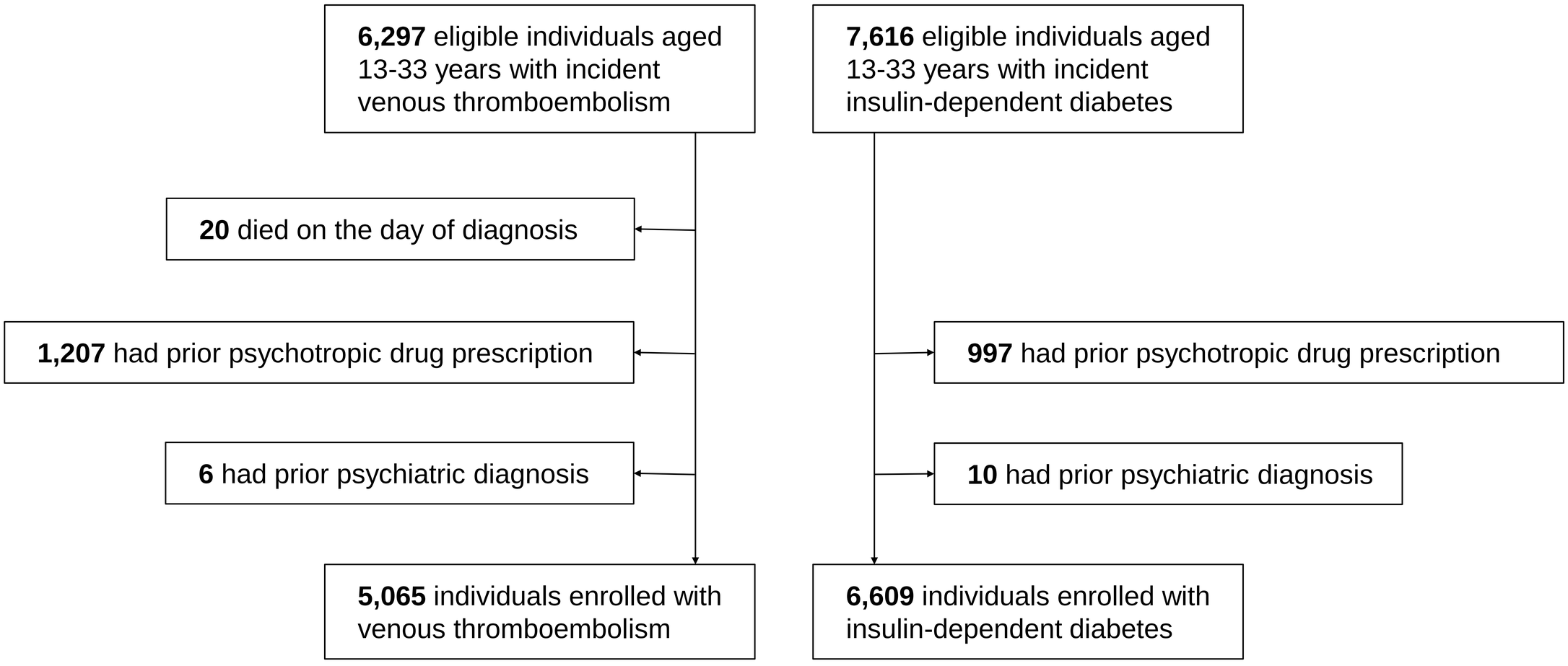
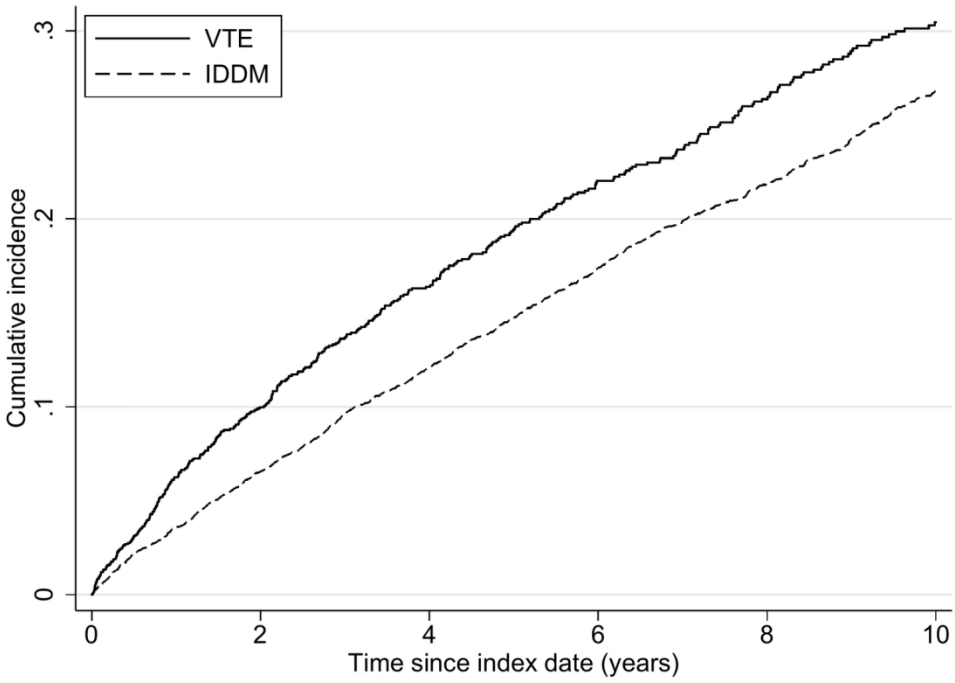

6,297 eligible individuals aged 13-33 years with incident venous thromboembolism
20 died on the day of diagnosis
1,207 had prior psychotropic drug prescription
6 had prior psychiatric diagnosis
5,065 individuals enrolled with venous thromboembolism
7,616 eligible individuals aged 13-33 years with incident insulin-dependent diabetes
997 had prior psychotropic drug prescription
10 had prior psychiatric diagnosis
6,609 individuals enrolled with insulin-dependent diabetes



Cumulative incidence of psychotropic drug purchase in patients with venous thromboembolism and patients with insulin-dependent diabetes mellitus

139x101mm (300 x 300 DPI)

Supplementary table 1: ICD-10, ATC and procedure codes used in the study

ICD-10, ATC and procedure codes			
	ICD 10 Codes	**ATC Codes**	**Surgical procedure Codes**
Deep Venous Thrombosis	I801 I802 I803 I808 I809 I822		
Pulmonary Embolism	I26		
Insulin depended diabetes mellitus	E100, E101, E109, E110, E111, E119	A10	
Psychotropic drugs Antidepressants Antipsychotics Anxiolytics Sedatives		 N06A N05A N05B N05CD, N05CF	
Psychiatric diagnosis Schizophrenia Bi-polar Depression Anxiety Addiction	 F20 F30, F31 F322, F323, F332 F333 F40, F41, F93 F10-F19		
Risk factors for VTE Cancer[a] Inflammatory bowel disease[a] Rheumatoid arthritis[a] Major surgery[b] Trauma[b]	 C K50, K51 M05, M06 S, T0, T10, T11, T12, T13, T14		 A, B, F, G, H, J, K, L,M,N,P

[a]*Within 1 year before diagnosis*
[b]*Within 90 days before diagnosis*

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STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study Design	4	Present key elements of study design early in the paper	1, 2, 4, 5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	5-6
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7

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Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study Size	10	Explain how the study size was arrived at	6-7
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6 N/A N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, Flowchart
		(b) Give reasons for non-participation at each stage	Flowchart
		(c) Consider use of a flow diagram	Flowchart
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

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Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	tabel 2
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key Results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Psychotropic drug use following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study

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Secondary Subject Heading:	Nursing
Keywords:	Adolescents, Diabetes, Thromboembolism < CARDIOLOGY, Psychology, Young Adult

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Psychotropic drug use following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study

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Running title: Comparison of young VTE and diabetes patients' psychotropic drug use

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Abstract

Objectives: Critical and chronic illness in youth such as diabetes can lead to impaired mental health. Despite the potentially traumatic and life-threatening nature of venous thromboembolism (VTE), the long-term mental health of adolescents and young adults with VTE is unclear. We compared the long-term mental health of adolescents and young adults with VTE versus adolescents and young adults with insulin-dependent diabetes mellitus (IDDM) using psychotropic drug purchase as proxy for mental health.

Design: Nationwide registry-based cohort study.

Setting: Denmark 1997-2015

Participants: All patients aged 13-33 years with an incident diagnosis of VTE (n=5,065) or IDDM (n=6,609)

Exposure: First time primary hospital diagnosis of VTE or IDDM.

Primary and secondary outcome measures: Adjusted absolute risk and risk difference at 1 and 5 years follow-up for first psychotropic drug purchase comparing patients with VTE and patients with IDDM.

Results: The absolute 1-year risk of psychotropic drug use was 6.2% among VTE patients versus 3.6% among patients with IDDM, at 5 years this was 19.3% 14.7%, respectively. After adjusting for the effect of sex, age, and risk factors for VTE this corresponded to a 1-year risk differences of 1.9% (95 % confidence interval (CI): 0.1%-3.3%). At 5-years follow-up the risk difference was, 1.9% (95% CI: 0.5%-3.3%).

Conclusion: One-fifth of adolescents and young adults with incident VTE had claimed a prescription for a psychotropic drug within 5 years, a risk comparable to that of young patients with IDDM.

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Keywords: Adolescents; Diabetes; Embolism and Thrombosis; Psychology; Venous Thromboembolism; Young Adult

Strengths and limitations of the study

- The study included all patients aged 13-33 years with a first-time hospital diagnosis of venous thromboembolism or insulin-dependent diabetes mellitus in Denmark in 1997-2015
- The study had complete long-term follow-up on psychotropic drug purchase
- The study lacked data regarding socioeconomic position, which has been associated with increased mental health problems in these patient groups.
- Finally, the study lacked data on duration of psychotropic drug use and other diseases occurring during follow-up, which may have been associated with the need for psychotropic therapy.

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Introduction

Mental co-morbidity is well established as a prevalent problem in young patients with insulin-dependent diabetes (IDDM), with documented negative effect on disease management and prognosis [1–3]. Venous thromboembolism (VTE), which include deep venous thrombosis (DVT) and pulmonary embolism (PE), is not traditionally considered a chronic illness. However, 25-50% of patients with DVT live with chronic complications in terms of post-thrombotic syndrome, and 0.4-4.0% of patients with PE develop chronic thromboembolic pulmonary hypertension [4]. Additionally, adolescents and young adults with VTE have to manage anticoagulant treatment and live with the perpetual risk of recurrent VTE, which may reach an incidence rate of 6.7 per 100 persons years among patients younger than 30 years [5]. Thus, from a transition theory perspective, adolescent and young adults with VTE are likely to be similar to IDDM patients in experiencing multiple and simultaneous transitions, making them particularly vulnerable to psychosocial distress [6]. In addition to the health-illness transition of VTE, the young patients will face the developmental transition of adolescence and young adulthood marked by intimacy, generativity, and career consolidation, which today often continues into the early thirties[7].

Younger patients with VTE have been shown to have a decreased quality of life and psychological impairment compared with the general population of same age [8,9].
Similar to IDDM patients, symptoms of anxiety and depression among VTE patients have been associated with poor disease management and mortality [10,11]. Thus, similar to young chronically ill patients with IDDM, the mental health of adolescents and young adults with VTE could be impaired in long-term.

We hypothesized that adolescents and young adults with VTE would have a similar risk of psychotropic drug purchase as chronically ill adolescents and young adults with IDDM. In the

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present nationwide cohort study, we therefore compared the long-term mental health of adolescents and young adults with VTE to young patients with IDDM. To assess mental health status, we used information about psychotropic drug purchase derived from a Danish registry as a proxy for mental health

Methods

Registry Data sources

We used three nationwide Danish registries in this study [12]: 1)The Danish National Patient Register, which contains detailed information on 99% of all somatic hospital admissions since 1977 along with diagnoses, coded according to the International Classification of Diseases (ICD) and surgical procedures coded according to the Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures[13]; 2) The Danish National Prescription Registry, which contains data on redeemed prescriptions in Denmark since 1995, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System [14]; and 3) The Danish Civil Registration System, which holds information on gender, date of birth, death, and emigration of all Danish residents [15]. Data were linked using a unique civil registration number assigned to all Danish residents at birth or immigration and used in all Danish national registries.

In accordance with Danish law, no ethical approval is required for non-biomedical registry studies. The study was approved by the Danish Data Protection Agency (File No. 2012-41-0633).

Study population

We identified all patients aged 13-33 years with a first-time diagnosis of VTE or IDDM in the period January 1, 1997, to December 31, 2015. Patients with VTE were identified by a first-time primary hospital diagnosis of DVT or PE. If a patient had a diagnosis of both DVT and PE, preference was given to PE. Risk factors for VTE included major surgery, fracture, or trauma

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within 90 days before the VTE diagnosis or a diagnosis of cancer, inflammatory bowel disease or rheumatoid arthritis within one year prior to the VTE diagnosis. Patients with IDDM were identified by a first-time hospital diagnosis of diabetes mellitus and a prescription claim for insulin within 30 days after diagnosis and no insulin prescription before 30 days prior to date of diagnosis. The index date for IDDM patients was defined as the date of first insulin prescription purchase after the diabetes diagnosis. The index date for VTE patients was based on day of VTE diagnosis and randomly shifted according to the distribution of time between diabetes diagnosis and insulin prescription purchase in the IDDM cohort. We excluded patients who had not been residents in Denmark for at least 2 years before the date of VTE or IDDM in order to ensure sufficient lookback time for diagnoses and medications, as well as patients who died on the day of diagnosis. To identify new-onset impaired mental health, we further excluded patients with prior psychiatric diagnosis (depression, anxiety, bi-polar disorder, schizophrenia, and addiction) and patients who had purchased psychotropic drugs (antidepressants, anxiolytics, sedatives, antipsychotics) within 2 years before the date of VTE or IDDM diagnosis. Further, we excluded patients with gestational diabetes mellitus and pregnancy-related VTE because of the distinct clinical course of pregnancy-related VTE and gestational diabetes, as well the risk of postpartum depression. Supplementary table 1 provides information on codes used in the study.

Outcome

The primary endpoint was a composite endpoint of psychotropic drug purchase, as a proxy for impaired mental health, recorded in the Danish National Prescription Registry following the index date. The secondary outcome was the specific types of psychotropic drugs: antipsychotics, anxiolytics, sedatives, and antidepressants.

Statistical Analysis

Descriptive characteristics of the study population at date of diagnosis of VTE or IDDM were

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presented using means and standard deviations for continuous measures and counts and percentages for categorical measures. Time to first psychotropic drug purchase was measured from index date. Patients were censored at the time of death, emigration, or end of study (December 31, 2015), whichever came first. Cumulative incidence functions (by means of the Aalen-Johansen estimator), assuming death as competing risks, were used to depict risk of psychotropic drug purchase within 10 years. We used pseudo-value regression approach with identity link function on a risk difference scale to assess the association between diagnosis type (VTE or IDDM) and the risk of a psychotropic drug purchase within 1 and 5 years taking into account the competing risk of death. The pseudo-value regression technique reduces to simple regression on the event status indicator when there is no censoring and accounts for censored observations before 1 and 5 years, respectively [16]. To assess to which extent the observed association could be explained by sex, age or recent provocation, we also conducted multivariate regression of pseudovalues, adjusting for the effect of sex (binary), age (continuous), and 'recent provocation' (binary). We repeated the analysis with stratification according to sex, age (13-25 or 26-33 years) VTE type (DVT or PE), and VTE-status (provoked or unprovoked).

Stata/MP version 13 was used for the statistical analysis (Stata Corporation, College Station, TX).

Patient and public involvement

Patients and public were not directly involved in the development of the research question and outcome measures or design of this nationwide cohort study.

Results

We identified 6,297 patients with VTE and 7,616 patients with IDDM. After exclusion of patients who died on the day of diagnosis and patients with prior psychiatric diagnoses or a psychotropic drug purchase within 2 years prior to the diagnosis, the study population comprised 5,065 VTE patients, of which 76.6% had DVT and 23.4% had PE, and 6,609 IDDM patients (Figure 1).

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Patients with VTE were slightly older compared with patients with IDDM (mean age 25.7 years vs. 23.7 years), and a substantially higher proportion were females (68.5% vs. 38.1%) (Table 1). Approximately one-fifth of patients with VTE had an underlying recorded risk factor, such as trauma (12.2%) or major surgery (12.9%). In comparison, only 4.0% of patients with IDDM had a diagnosis of trauma, and 2.4% had major surgery (Table 1).

The absolute risk of psychotropic drug use among patients with VTE was 6.2% at 1 year of follow-up and 19.3% after 5 years of follow-up. The cumulative incidence curve revealed a higher risk of psychotropic drugs among patients with VTE compared with patients with IDDM (Figure 2). At 1 year follow-up, the crude risk difference was 2.6% (95 % confidence interval (CI): 1.3%-3.9%). Extending follow-up to 5 years did not materially change this conclusion; the crude 5-year risk-difference was 4.6% (95% CI: 2.3%-6.9%) (Table 2). The finding of a higher psychotropic drug use among patients with VTE compared with IDDM was attenuated when adjusting for the effect of sex, age and risk factors for VTE (1-year risk difference 1.9%, 95% CI: 0.1-3.3; 5 year risk difference 1.9%, 95% CI: 0.5-3.3). Analyses stratified by sex, age, presence of provoking factors (Table 2), also revealed slightly increased 5-year adjusted risk of psychotropic drug purchase among VTE patients compared with IDDM patients, though the risk differences were not statistically significant except for males in whom the long-term risk of psychotropic drugs was significantly higher among the VTE patients (Table 2).

Antidepressants were the most frequently purchased drug class in both patient groups (VTE: 48%, IDDM: 58%) followed by sedatives (VTE: 24%, IDDM: 20%), anxiolytics (VTE: 19%, IDDM: 13%), antipsychotics (VTE: 5%, IDDM: 6%), and combined prescription of more than one drug class (VTE: 3% IDDM 3%). The absolute risk and risk difference comparing VTE patients and

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IDDM patients stratified by psychotropic drug class did not materially change the overall conclusions (data not shown).

Discussion

To our knowledge, this is the first study to compare the mental health of adolescents and young adults with VTE to that of patients receiving a diagnosis of a chronic disease such as IDDM. Our nationwide cohort study revealed that the long-term mental health of adolescents and young adults with VTE was comparable to that of IDDM patients as evidenced by a slightly higher risk of psychotropic drug use among the VTE patients, which persisted over time and was evident across strata of age and type of VTE.

Our findings extend the results from previous studies, indicating that mental health impairment does not diminish over time among VTE patients [9,17,18]. Compared to IDDM patients among whom long-term co-morbid mental health problems are well documented [1,3], we noted comparable psychotropic use among patients with VTE. Indeed, our study revealed that one fifth of adolescents and young adults with VTE claim a prescription for a psychotropic drug within 5 years. This is of major concern, as it is well established that impaired mental health has an effect on outcome as well as disease management in medically ill patients [19]. Accordingly, symptoms of depression and anxiety among VTE patients have been associated with both increased mortality and poor disease management [10,11]. Thus, impaired mental health possibly plays an important role for disease management and long-term prognosis in a considerable number of young VTE patients as the proportion with impaired mental health was comparable to that of patients with IDDM. These findings indicate a need for further studies to prevent, or at least, to minimize psychological distress in patients with VTE.

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At odds with studies from the general population, where higher levels of depression and lower quality of life are found in women than men [20], we found no difference in psychotropic drug use among men and women with VTE. This lack of gender-related differences in mental health following VTE is in accordance with prior observations of mental quality of life following VTE [21–23], and subject to further investigation.

Study limitations

Misclassification of VTE and IDDM diagnoses cannot be ruled out. Danish validation studies have previously found a positive predictive value of the VTE diagnosis of 88% to 90% [24,25], and ascertainment of diabetes mellitus by purchase of insulin in combination with a primary hospital discharge diagnosis has been shown to have a positive predictive value of 95%-97% [26,27]. We defined impaired mental health by prescription purchase of psychotropic drugs but do not know whether the patients actually took the medication. However, in the present study, we infer that a prescription for a psychotropic drug would be an indication of impaired mental health. We did not assess the duration of psychotropic drug use and other diseases occurring during follow-up, which may have been associated with the need for psychotropic therapy. We also lacked data on socioeconomic factors. Low socioeconomic position has been associated with increased mental health problems, e.g., higher depression rates among young patients with IDDM [28] and low health related quality of life in young women with pregnancy-related DVT [29]. Given these limitations, it is important to emphasize that based on this observational study we cannot infer a causal interpretation of the observed association between VTE and impaired mental health.

The major strengths of this study are the large sample size and complete coverage in the Danish hospital discharge and prescription purchase registries including all in- and outpatients with VTE or IDDM, which enabled a complete long-term follow-up on psychotropic drug purchases.

Conclusion

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This nationwide cohort study showed that one-fifth of adolescents and young adults with incident VTE had claimed a prescription for a psychotropic drug within 5 years, indicating an impact on mental health comparable to that of young patients with IDDM.

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Competing interests

Dr Lane has received investigator-initiated educational grants from Boehringer- Ingelheim and Bristol-Myers Squibb, served on speaker bureaus for Boehringer-Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer and has consulted for Bristol-Myers Squibb, Bayer, Boehringer-Ingelheim and Daiichi-Sankyo. Professor Goldhaber has received research support from BiO2 Medical, Boehringer-Ingelheim, BMS, BTG EKOS, Daiichi, National Heart Lung and Blood Institute of the National Institutes of Health, Janssen, Thrombosis Research Institute and served as a consultant for Bayer, Boehringer-Ingelheim, BMS, Daiichi, Janssen, Novartis, Portola, Zafgen. Associate Professor Larsen has been an investigator for Janssen Scientific Affairs and Boehringer-Ingelheim, and served on speaker bureaus for AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, Roche Diagnostics, Siemens Diagnostics and Takeda. Other authors – none declared.

Contributorship Statement

All authors designed the study; A.A. Højen, L. Melgaard M. Søgaard and T.B. Larsen obtained and analyzed the data; and all authors interpreted the data. A.A. Højen drafted the manuscript, and L. Melgaard, M. Søgaard, D.A. Lane, S.Z. Goldhaber, E.E. Sørensen and T.B. Larsen critically revised it.

Data Sharing Statement

No additional data are available.

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Figure legends

Figure 1. Flowchart of patients included in the final study population

Figure 2. Cumulative incidence of psychotropic drug purchase in patients with venous thromboembolism and patients with insulin-dependent diabetes mellitus

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Table 1: Study population characteristics

Variable	VTE	IDDM
N	5,065	6,609
Mean age (SD)	25.7 (5.2)	23.7 (6.5)
Age group, n (%)		
13-25 years	2,258 (44.6)	3,627 (54.9)
26-33 years	2,807 (54.4)	2,982 (45.1)
Females, n (%)	3,470 (68.5)	2,516 (38.1)
Risk factor for VTE, yes, n (%)	1,179 (23.3)	449 (6.8)
Trauma	618 (12.2)	267 (4.0)
Surgery	652 (12.9)	156 (2.4)
Cancer	64 (1.3)	16 (0.2)
Inflammatory bowel disease	49 (1.0)	26 (0.7)
Rheumatoid arthritis	8 (0.1)	5 (0.1)
DVT, n (%)	3,881 (76.6)	-
PE, n (%)	1,184 (23.4)	-

DVT: deep venous thrombosis, IDDM: insulin-dependent diabetes mellitus PE: pulmonary embolism, SD: standard deviation, VTE: venous thromboembolism

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Table 2. Risk of psychotropic drug purchase following a diagnosis of venous thromboembolism or insulin dependent diabetes mellitus in youth or adolescence

Characteristic	1 year follow-up				5 year follow-up			
	Psychotropic drug purchase (%)		Unadjusted risk difference	Adjusted risk difference[a]	Psychotropic drug purchase (%)		Unadjusted risk difference	Adjusted risk difference[a]
	VTE	IDDM	VTE vs. IDDM (95% CI)	VTE vs. IDDM (95% CI)	VTE	IDDM	VTE vs. IDDM (95% CI)	VTE vs. IDDM (95% CI)
Overall	6.2	3.6	2.6 (1.3-3.9)	1.9 (0.1-3.3)	19.3	14.7	4.6 (2.3-6.9)	1.9 (0.5-3.3)
Male	6.9	2.9	4.1 (1.8-6.4)	3.0 (0.7-5.4)	18.5	11.9	6.6 (2.7-10.4)	3.0 (0.7-5.4)
Female	5.9	4.9	1.0 (-0.1-2.7)	0.3 (-1.5-2.1)	19.7	19.5	0.2 (-2.9-3.4)	0.3 (-0.2-2.1)
Age 13-25 years	6.1	2.7	3.4 (1.5-5.2)	1.7 (0.1-3.7)	17.9	12.9	5.1 (1.9-8.3)	1.7 (-0.4-3.7)
Age 26-33 years	6.4	4.8	1.5 (-0.3-3.4)	0.7 (-0.1-2.8)	20.4	17.1	3.4 (0.1-6.8)	0.7 (-0.0-2.8)
Provoked VTE	6.3	3.6	2.4 (-0.2-5.0)	1.1 (-0.2-3.9)	18.8	14.7	4.1 (-0.7-8.9)	1.1 (-0.6-3.9)
Unprovoked VTE	6.0	3.6	2.7 (1.2-4.1)	1.5 (-0.1-3.0)	19.5	14.7	4.8 (1.6-6.8)	1.5 (-0.1-3.0)
DVT	6.1	3.6	2.6 (1.2-4.1)	1.2 (-0.1-2.7)	18.9	14.7	4.1 (1.2-4.1)	1.2 (-0.1-2.7)
PE	6.3	3.6	2.4(0.1-5.0)	1.0 (-0.2-3.6)	20.8	14.7	6.1 (1.7-10.6)	0.9 (-0.7-3.6)

CI: confidence interval, DVT: deep venous thrombosis, IDDM: insulin-dependent diabetes mellitus, PE: pulmonary embolism, VTE: venous thromboembolism

[a]Adjusted for sex, age, recent provocation (trauma, surgery, cancer, inflammatory bowel disease or rheumatoid arthritis) except when stratifying variable

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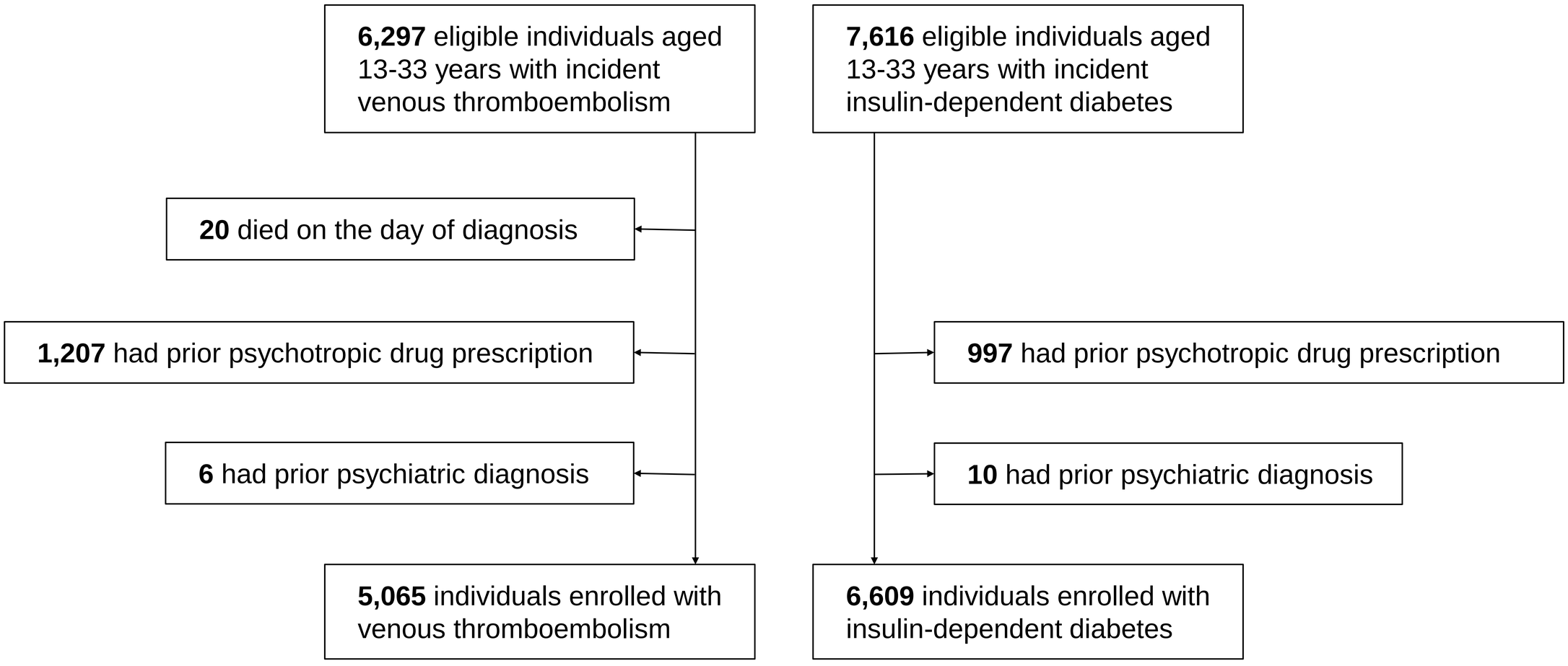
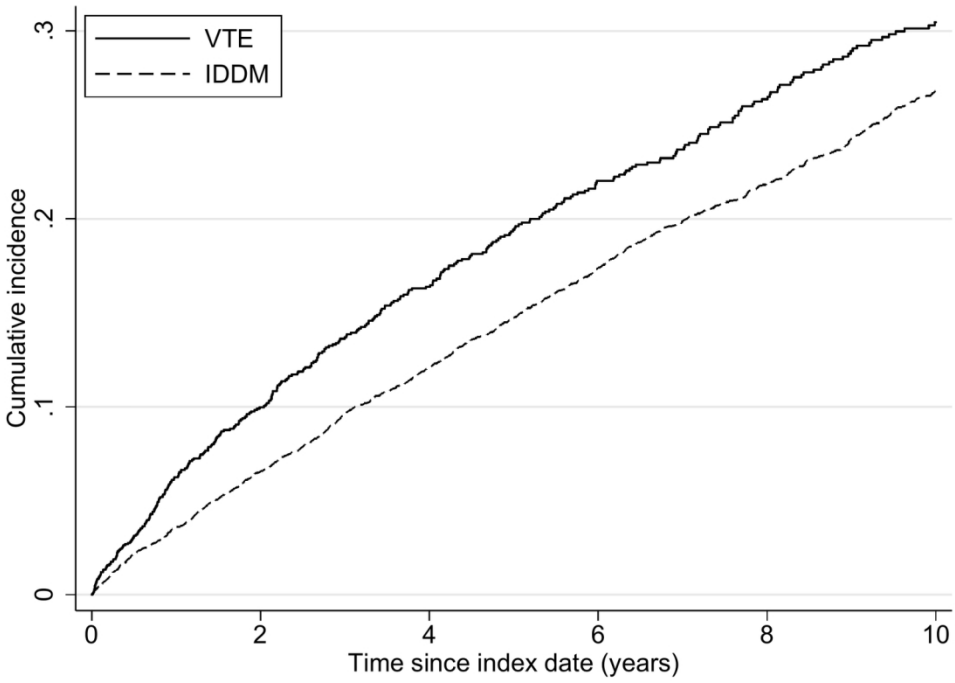

6,297 eligible individuals aged 13-33 years with incident venous thromboembolism
20 died on the day of diagnosis
1,207 had prior psychotropic drug prescription
6 had prior psychiatric diagnosis
5,065 individuals enrolled with venous thromboembolism
7,616 eligible individuals aged 13-33 years with incident insulin-dependent diabetes
997 had prior psychotropic drug prescription
10 had prior psychiatric diagnosis
6,609 individuals enrolled with insulin-dependent diabetes



Cumulative incidence of psychotropic drug purchase in patients with venous thromboembolism and patients with insulin-dependent diabetes mellitus

139x101mm (300 x 300 DPI)

Supplementary table 1: ICD-10, ATC and procedure codes used in the study

ICD-10, ATC and procedure codes			
	ICD 10 Codes	**ATC Codes**	**Surgical procedure Codes**
Deep Venous Thrombosis	I801 I802 I803 I808 I809 I822		
Pulmonary Embolism	I26		
Insulin depended diabetes mellitus	E100, E101, E109, E110, E111, E119	A10	
Psychotropic drugs Antidepressants Antipsychotics Anxiolytics Sedatives		 N06A N05A N05B N05CD, N05CF	
Psychiatric diagnosis Schizophrenia Bi-polar Depression Anxiety Addiction	 F20 F30, F31 F322, F323, F332 F333 F40, F41, F93 F10-F19		
Risk factors for VTE Cancer[a] Inflammatory bowel disease[a] Rheumatoid arthritis[a] Major surgery[b] Trauma[b]	 C K50, K51 M05, M06 S, T0, T10, T11, T12, T13, T14		 A, B, F, G, H, J, K, L,M,N,P

[a]*Within 1 year before diagnosis*
[b]*Within 90 days before diagnosis*

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STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study Design	4	Present key elements of study design early in the paper	1, 2, 4, 5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	5-6
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7

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Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study Size	10	Explain how the study size was arrived at	6-7
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6 N/A N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, Flowchart
		(b) Give reasons for non-participation at each stage	Flowchart
		(c) Consider use of a flow diagram	Flowchart
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

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Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	tabel 2
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key Results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

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