PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Psychotropic drug use following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study
AUTHORS	Højen, Anette Arbjerg; Søgaard, Mette; Melgaard, Line; Lane, Deirdre; Sørensen, Erik; Goldhaber, Samuel; Larsen, Torben

VERSION 1 - REVIEW

REVIEWER	Paolo Bucciarelli, MD Hemophilia and Thrombosis Center Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (Italy)
REVIEW RETURNED	01-Oct-2018

GENERAL COMMENTS	In this study, Hojen et al. explore the long-term mental wellbeing of adolescent and young adults after a first episode of venous thromboembolism (VTE), and compare it with that of an age- and sex-matched group of young patients with insulin-dependent diabetes mellitus (IDDM). The study is carried out in the frame of a Danish nationwide registry-based cohort study, and using registry data on psychotropic drug use as a proxy to describe long-term mental well being. The main result is that the risk of psychotropic drug purchase is higher among VTE patients than among IDDM patients. This finding suggests the need of an adequate support in this particularly fragile age. The study is well done, the paper well written and the message is definitely important. I have the following comments: 1. Methods, page 5: were all VTE episodes objectively diagnosed? Please clarify. 2. Methods, page 5: why were pregnancy/puerperium and OC use not included among risk factors for VTE? This is particularly important considering the higher prevalence of female sex among young patients with VTE (68% vs 38% of IDDM patients). 3. Did any patient with IDDM have cardiovascular events that might have had an impact on their mental wellbeing? 4. Statistical analysis, page 6: was the pseude-value regression a variant of a Cox regression? 5. Table 1: Did “PE” include both PE alone and DVT + PE?

REVIEWER	Suzanne Cannegieter LUMC, the Netherlands
REVIEW RETURNED	08-Oct-2018

GENERAL COMMENTS	In this nationwide cohort study the authors studied the long-term well-being of young patients with either VTE or insulin-dependent diabetes (IDDM), using psychotropic drug purchase as proxy for their well-being. The results show that such drug usage was somewhat higher for VTE patients than for IDDM patients. Although I understand the need to study the long-term well-being of chronically ill or acutely ill young patients, which is an important topic, I have several concerns about the research question, and hence I wonder what the value is of this study and these results: 1) why is drug usage as registered in the prescription database used as an endpoint? Such medication gives an impression on psychiatric co-morbidity in these subjects, but this is serious mental disease, and far removed from 'well-being'. 2) why are these two conditions compared, and is not a general group without any diagnosis used as comparison group? Perhaps the prevalence of psychotropic drug use that is found is very close to that of the general population of this age. 3) Many patients with VTE, especially young patients, suffer from underlying co-morbidity when they develop VTE. Also only hospital diagnoses were taken into account whereas VTE is often treated in an out-patient setting. So VTE is likely to be a marker for more serious disease in these patients. 4) Significance is not an issue with these large numbers and its importance should therefore not be overstated. 5) The results are expressed as 'ever use', which leads to a suggestion that almost 20% of patients uses these drugs after 5 years. I assume that a large proportion has stopped, and only had a short term prescription. This information should be provided for both groups. 6) The risk difference gets smaller after adjustment: this suggests that confounding plays a role (i.e., the two patient groups cannot simply be compared) which makes it likely that not all confounding was taken into account (this was very limited anyway). 7) The conclusion that 'long-term focus on the mental well-being is important in young VTE patients' may therefore just as well apply to other young patients or healthy subjects. No clinical implications should therefore be suggested.

REVIEWER	Carlos Martinez Institute for Epidemiology, Statistics and Informatics GmbH, Frankfurt, Germany I have received grants from Bayer, Bristol-Myers-Squibb, grants from CSL Behring, grants from Merz Pharma
REVIEW RETURNED	09-Oct-2018

GENERAL COMMENTS	Comments: 1. The authors should clarify why patients with IDDM are a meaningful comparison group for patients with VTE with respect to subsequent psychotropic drug use. The rationale provided in the

	introduction is insufficient given the differences in the onset of IDDM and VTE, the minimum duration of treatment with insulin and anticoagulants and different routes of drug administration. 2. Other potential confounders not adjusted for in the analysis are pregnancy and drug addiction. Both are associated with VTE and psychotropic drug use, and may be common in the age group of 13-33 years. Therefore, additional adjustment in the analysis is required. 3. The analyses presented account for mortality via censoring but mortality should be accounted for as a competing risk instead, as death precludes psychotropic drug use and the proportion of patients dying during the observational period is likely to be higher in the VTE group than in the IDDM group. 4. The diagnosis of IDDM requires an insulin prescription claim within 30 days following the DM diagnosis and immortal person-time may result. This should be discussed. 5. The definition of IDDM does not include pregnancy-related DM, for example O24.4 ("Gestational diabetes mellitus") or O24.9 ("Unspecified diabetes mellitus in pregnancy, childbirth and the puerperium") but no rationale for this exclusion is provided. 6. VTE is defined as deep vein thrombosis and pulmonary embolism. The current selection of ICD codes for the definition of the VTE cohort includes an incomplete set of unusual VTE sites, such as I63.6 ("Cerebral infarction due to cerebral venous thrombosis, nonpyogenic"), but does not include cerebral venous thrombosis without mentioning of cerebral infarction or abdominal vein thromboses. Furthermore, ICD codes O22.3 or O87.1 for deep vein thrombosis and embolism in pregnancy are missing. 7. Sub-analysis on OAC treatment: a. Given the original aim of the presented study it is unclear why the sub-analysis on OAC treatment was conducted. A comparison between treated and untreated VTE may require a different approach and analysis: consider using matching and the clinical and baseline characteristics at 1 year after VTE rather than the baseline characteristics (at VTE) for adjustment. b. In addition, patients in the group treated with OAC 1 year after VTE are likely to represent a specific subgroup of VTE patients, for example those that had a recurrent VTE in-between, as long-term anticoagulation is not recommended for all VTEs. 8. Authors should clarify why the age group 13-33 years was chosen. 9. Patients with a history of psychiatric diagnosis before VTE/IDDM were excluded from the cohorts. Why were psychiatric diagnoses not used in addition to psychotropic drug prescriptions to further define the outcome of interest, i.e. to include untreated mental disease? 10. Authors should discuss if VTEs and IDDMs recorded in hospitals comprise a selection of more severe forms of both diseases and how this selection could have altered the study findings. 11. It is unclear if patients in the VTE group were censored when a subsequent IDDM occurred (and vice versa). 12. Patients with psychiatric diagnoses or psychotropic drug use in the 2 years before VTE/IDDM were excluded. Were the study cohorts restricted to those with at least 2 years of history before the index VTE/IDDM in the database? 13. Supplementary table 1 includes procedure codes which are not ICD-codes. The classification of surgical procedures used should be stated.

	14. Please state which link function was used in the pseudo-value regression. 15. There are differences between numbers presented in the abstract/results and numbers presented in Table 2. "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%)." 16. The term "index date" (probably the day of initial VTE/IDDM) is used throughout the manuscript but was not defined. 17. Page 7 line 30: "Patients with VTE patients [...]". 18. The legend of Supplementary table 1 includes the footnote "c" ("Within 8 weeks before and 42 weeks after diagnosis (data from the Danish Medical Birth Registry)"). However, the "Danish Medical Birth Registry" is not mentioned in the method section. Furthermore, “c” is not used throughout the table.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Paolo Bucciarelli, MD

Institution and Country: Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (Italy) Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below In this study, Hojen et al. explore the long-term mental wellbeing of adolescent and young adults after a first episode of venous thromboembolism (VTE), and compare it with that of an age- and sex-matched group of young patients with insulin-dependent diabetes mellitus (IDDM). The study is carried out in the frame of a Danish nationwide registry-based cohort study, and using registry data on psychotropic drug use as a proxy to describe long-term mental well being. The main result is that the risk of psychotropic drug purchase is higher among VTE patients than among IDDM patients. This finding suggests the need of an adequate support in this particularly fragile age. The study is well done, the paper well written and the message is definitely important. I have the following comments:

1. Methods, page 5: were all VTE episodes objectively diagnosed? Please clarify.

Response: We thank the reviewer for the positive reception of our work. The diagnosis of VTE were based on discharge diagnoses recorded in the National Patient Registry. As such, the diagnoses were therefore not objectively diagnosed. However, validation studies of the VTE diagnosis in the Danish National Patient Register have shown positive predictive values of 88 % to 90%, which we have discussed in the limitation section of the revised manuscript.

For references please see:

Sundbøll et al: BMJ Open 2016; 6(11): e012832.

Schmidt et al.:J Thromb Haemost 2014: 12(8): 1207–15.

2. Methods, page 5: why were pregnancy/puerperium and OC use not included among risk factors for VTE? This is particularly important considering the higher prevalence of female sex among young patients with VTE (68% vs 38% of IDDM patients).

Response: We apologize for not making this clear. The reviewer makes a valid point about the importance of hormones and pregnancy in this age group. Nonetheless, because the course of pregnancy-related VTE and gestational diabetes are different from VTE and insulin dependent diabetes mellitus, and also due to the risk of postpartum depression, we excluded patients who were pregnant. We have clarified this in the revised manuscript (page 7 line 6). We did not include OC use, as we did not consider it a risk factor for VTE of importance for the study outcome mental health.

3. Did any patient with IDDM have cardiovascular events that might have had an impact on their mental wellbeing?

Response: The reviewer raises an important question. Nonetheless, we find that it is beyond the scope of this paper to compare rates of cardiovascular events in patients with VTE vs. IDDM. Nevertheless, this would clearly be relevant and important to address in future studies.

4. Statistical analysis, page 6: was the pseudo-value regression a variant of a Cox regression?

Response: The Cox regression model produces event hazard rates as a measure of absolute risk. However, in the presence of censoring, e.g., competing risks or loss to follow-up, the event status at the end of follow-up is unknown for some individuals. Such missing values imply that the event rates do not translate directly into absolute risk, meaning the probability that a given person will experience an event within a stated period of time. Risk as a measure of disease frequency has the advantage that it is readily understood from a clinical perspective. The pseudo-value method removes the potential pitfalls of using event rates to quantify the absolute risk by replacing missing values with imputed pseudo-values. Thus, the pseudo-value method reduces to simple regression on the event status indicator when there is no censoring, while at the same time handling censored observations, which allows for producing survival curves and estimating risk probabilities at a fixed point in time.

For further discussion, we refer to:

Klein JP, et al.; Stat Med 2007; 26: 4505–19.

Andersen PK et al.; Biometrika 2003; 90: 15–27.

5. Table 1: Did “PE” include both PE alone and DVT + PE?

Response: We apologize for not making this clear. Patients with PE included patients with a primary hospital discharge diagnosis of PE. These patients could have a secondary diagnosis of DVT. We have clarified this in the manuscript. (page 6 line 18)

Reviewer: 2

Reviewer Name: Suzanne Cannegieter

Institution and Country: LUMC, the Netherlands Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below In this nationwide cohort study the authors studied the long-term well-being of young patients with either VTE or insulin-dependent diabetes (IDDM), using psychotropic drug purchase as proxy for their well-being. The results show that such drug usage was somewhat higher for VTE patients than for IDDM patients.

Although I understand the need to study the long-term well-being of chronically ill or acutely ill young patients, which is an important topic, I have several concerns about the research question, and hence I wonder what the value is of this study and these results:

1) why is drug usage as registered in the prescription database used as an endpoint? Such medication gives an impression on psychiatric co-morbidity in these subjects, but this is serious mental disease, and far removed from ‘well-being’.

Response: We understand the reviewer´s line of thought and after careful consideration, we have changed the phrasing well-being to mental health. As such, psychotropic drug purchase was an indication of mental impairment. We recognize that this likely underestimate the ‘true’ incidence of mental impairment as other treatment options are recommended for milder cases especially among adolescents. However, we infer that such underestimation would be non-differential across the patients with VTE and IDDM.

2) why are these two conditions compared, and is not a general group without any diagnosis used as comparison group? Perhaps the prevalence of psychotropic drug use that is found is very close to that of the general population of this age.

Response: The reviewer make an important point. We have previously, shown that the risk of psychotropic drug use in young VTE patients is substantially than the general population of this age (5-year risk of 22.1% vs. 11.3%)(Højen et al.; Thromb Res 2015; 135: 643–7). This led to the question of whether the risk of psychotropic drug use among young VTE patients was comparable to that of chronically ill patients. As chronic illness such as diabetes mellitus in adolescence and young adulthood have continuously been associated with significant long-term psychological, emotional and behavioral problems, we choose this as our comparison group. We have elaborated on the rationale underlying our choice of comparison cohort in the introduction of the revised manuscript.

3) Many patients with VTE, especially young patients, suffer from underlying co-morbidity when they develop VTE. Also only hospital diagnoses were taken into account whereas VTE is often treated in an out-patient setting. So VTE is likely to be a marker for more serious disease in these patients.

Response: We understand the reviewer’s line of thought and agree that part of the young VTE patients may have other underlying diseases. However, it is important to note that in Denmark, all patients with VTE are diagnosed and treated in a hospital-based setting and therefore both in- and out-patients with VTE are included in the study. Furthermore, the aim of the study was not to access a causal relation between VTE and impaired mental health, but to compare the mental health status among young VTE patients compared to young IDDM patients among whom the impact on mental health of the latter is well established. To ensure that risk differences were assessed between comparable VTE patients and IDDM patients we adjusted for the effect of provoking factors that could possibly influence mental health including; diagnosis of cancer, rheumatoid arthritis, inflammatory bowel disease, resent trauma or resent surgery.

4) Significance is not an issue with these large numbers and its importance should therefore not be overstated.

Response: We agree with the reviewer and have revised the use of the word significance accordingly.

5) The results are expressed as ‘ever use’, which leads to a suggestion that almost 20% of patients uses these drugs after 5 years. I assume that a large proportion has stopped, and only had a short term prescription. This information should be provided for both groups.

Response: Thank you for your comment. Focus in this study was on showing and comparing the proportion of VTE and IDDM patients who at any point in the years after diagnosis showed impaired mental health, not the duration of mental health impairment. As such, in figure 2, we show the cumulative risk of first psychotropic drug prescription after diagnosis as a function of time.

6) The risk difference gets smaller after adjustment: this suggests that confounding plays a role (i.e., the two patient groups cannot simply be compared) which makes it likely that not all confounding was taken into account (this was very limited anyway).

Response: We agree with the reviewer, however, as noted above, the aim of our study was not the investigate the causal relation between VTE per se and psychotropic drug purchase, rather the association. Adjusting for the effect of recent provocations' was not an attempt to adjust for confounding and thereby explore the causal relationship between VTE and the risk of psychotropic drug purchase. It was to ensure that risk differences were assessed between comparable VTE and IDDM patients. We have carefully revised the manuscript to ensure that this is reflected throughout the paper.

7) The conclusion that 'long-term focus on the mental well-being is important in young VTE patients' may therefore just as well apply to other young patients or healthy subjects. No clinical implications should therefore be suggested.

Response: We have carefully considered this comment and have revised the text regarding clinical implications (page 10, lines 7-12) as suggested by the reviewer.

Reviewer: 3

Reviewer Name: Carlos Martinez

Institution and Country: Institute for Epidemiology, Statistics and Informatics GmbH, Frankfurt, Germany Please state any competing interests or state 'None declared': I have received grants from Bayer, Bristol-Myers-Squibb, grants from CSL Behring, grants from Merz Pharma

Please leave your comments for the authors below

Comments:

1.The authors should clarify why patients with IDDM are a meaningful comparison group for patients with VTE with respect to subsequent psychotropic drug use. The rationale provided in the introduction is insufficient given the differences in the onset of IDDM and VTE, the minimum duration of treatment with insulin and anticoagulants and different routes of drug administration.

Response: We thank the reviewer for this suggestion and have revised the introduction accordingly. Mental health co-morbidity is well established as a prevalent problem in IDDM patients and is of importance for disease management and prognosis. Decreased quality of life and psychological impairment have been reported in younger VTE patients and mental health co-morbidity among VTE patients have been associated with both increased mortality, and poor disease management. Thus, similar to young chronically ill patients with diabetes mellitus, the mental health of adolescents and young adults with VTE could be impaired in long-term, potentially resulting in a poorer prognosis and complicating disease management.

2.Other potential confounders not adjusted for in the analysis are pregnancy and drug addiction. Both are associated with VTE and psychotropic drug use, and may be common in the age group of 13-33 years. Therefore, additional adjustment in the analysis is required.

Response: We apologized for not making it clear that our study was restricted to non-pregnant patients given that the course of pregnancy-related VTE and gestational diabetes are different from VTE and insulin dependent diabetes mellitus, and due to the risk of postpartum depression. We have clarified this in the revised manuscript (page 7 line 6). Likewise, we excluded patients with drug addiction in order to new-onset mental impairment as noted in the study population paragraph in the

revised manuscript (page 7 line 4). ICD-10 codes for addiction are found in supplementary table 1 (line 16)

3.The analyses presented account for mortality via censoring but mortality should be accounted for as a competing risk instead, as death precludes psychotropic drug use and the proportion of patients dying during the observational period is likely to be higher in the VTE group than in the IDDM group.

Response: The reviewer makes a valid point about the importance of accounting for mortality as a competing risk. However, because the study population comprised a young population, the death rates during the observation period were very low and comparable in the two groups. VTE n = 127 (2.4%) IDDM n= 246 (2.2%).

4.The diagnosis of IDDM requires an insulin prescription claim within 30 days following the DM diagnosis and immortal person-time may result. This should be discussed.

Response: The reviewer makes a valid point about the risk of immortal person-time. However, we would infer that in the current study this is mainly a theoretical problem, because of the very low mortality rate in this young population. A count of IDDM patients who died within 30 days following the diagnosis showed that this only concerned 12 patients corresponding to 0.18% of the IDDM patient population.

5.The definition of IDDM does not include pregnancy-related DM, for example O24.4 ("Gestational diabetes mellitus") or O24.9 ("Unspecified diabetes mellitus in pregnancy, childbirth and the puerperium") but no rationale for this exclusion is provided.

Response: As noted in our response to the reviewer´s second comment, we excluded all pregnant women due to the distinct clinical course of pregnancy-related VTE and gestational diabetes, as well the risk of postpartum depression. We apologize for not making this clear and have clarified this in the revised manuscript (page 7 line 6).

6.VTE is defined as deep vein thrombosis and pulmonary embolism. The current selection of ICD codes for the definition of the VTE cohort includes an incomplete set of unusual VTE sites, such as I63.6 ("Cerebral infarction due to cerebral venous thrombosis, nonpyogenic"), but does not include cerebral venous thrombosis without mentioning of cerebral infarction or abdominal vein thromboses. Furthermore, ICD codes O22.3 or O87.1 for deep vein thrombosis and embolism in pregnancy are missing.

Response: We thank the reviewer for drawing our attention to the codes for VTE.. During the review process, we have therefore revised the ICD codes excluding the more unusual VTE sites, and re-run the analyses, which did not materially change the results.

As noted above pregnancy-related VTE and gestational were excluded. We have clarified this in the revised manuscript (page 7 line 6).

7.Sub-analysis on OAC treatment:

a.Given the original aim of the presented study it is unclear why the sub-analysis on OAC treatment was conducted. A comparison between treated and untreated VTE may require a different approach and analysis: consider using matching and the clinical and baseline characteristics at 1 year after VTE rather than the baseline characteristics (at VTE) for adjustment.

b.In addition, patients in the group treated with OAC 1 year after VTE are likely to represent a specific subgroup of VTE patients, for example those that had a recurrent VTE in-between, as long-term anticoagulation is not recommended for all VTEs.

Response: We thank you for pointing this out. We agree with the reviewer's concerns and have therefore decided to remove this sub-analysis from the revised manuscript.

8.Authors should clarify why the age group 13-33 years was chosen.

Response: We agree, and have clarified this in the Introduction. (Page 1 line 4)

9.Patients with a history of psychiatric diagnosis before VTE/IDDM were excluded from the cohorts. Why were psychiatric diagnoses not used in addition to psychotropic drug prescriptions to further define the outcome of interest, i.e. to include untreated mental disease?

Response: Thank you for your comment. The information available in the registers is unfortunately only hospital diagnoses of psychiatric disease, which would underestimate the full extent of mental health impairment. In Denmark, relatively few patients are admitted to a psychiatric ward without receiving psychotropic. As such, we only excluded 6 VTE patients and 10 IDDM patients on the basis of a psychiatric diagnosis, with no concurrent psychotropic drug prescription (see flow chart)

10.Authors should discuss if VTEs and IDDMs recorded in hospitals comprise a selection of more severe forms of both diseases and how this selection could have altered the study findings.

Response: In Denmark, all patients with VTE are diagnosed and treated in a hospital-based setting and both in- and out-patients with VTE are therefore included in the study. The same applies for young patients with insulin dependent diabetes who are treated and cared for in specialized clinics in hospital-based settings.

11.It is unclear if patients in the VTE group were censored when a subsequent IDDM occurred (and vice versa).

Response: We apologize for not making this clear. Patients were not censored if they subsequently suffered from VTE or IDDM.

12.Patients with psychiatric diagnoses or psychotropic drug use in the 2 years before VTE/IDDM were excluded. Were the study cohorts restricted to those with at least 2 years of history before the index VTE/IDDM in the database?

Response: Thank you for your comment. 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.

13.Supplementary table 1 includes procedure codes which are not ICD-codes. The classification of surgical procedures used should be stated.

Response: Changes were made as suggested.

14.Please state which link function was used in the pseudo-value regression.

Response: We apologize for this omission. This information has been added. (page 7 line 23)

15.There are differences between numbers presented in the abstract/results and numbers presented in Table 2. "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%)."

Response: We apologize for this inconsistency. The numbers have been changed in the table as well as the manuscript corresponding to the reviewers' comment (number 6).

16.The term "index date" (probably the day of initial VTE/IDDM) is used throughout the manuscript but was not defined.

Response: We thank the reviewer for pointing this out. The index date was defined as the date of the VTE diagnosis or diabetes diagnosis, respectively. We have clarified this in the revised manuscript (page 6, line 23).

17.Page 7 line 30: "Patients with VTE patients [...]".

Response: Changes were made as suggested.

18.The legend of Supplementary table 1 includes the footnote "c" ("Within 8 weeks before and 42 weeks after diagnosis (data from the Danish Medical Birth Registry)"). However, the "Danish Medical Birth Registry" is not mentioned in the method section. Furthermore, “c” is not used throughout the table.

Response: The footnote has been deleted.

VERSION 2 – REVIEW

REVIEWER	Suzanne Cannegieter Dept of Clinical Epidemiology, LUMC, the Netherlands
REVIEW RETURNED	06-Dec-2018

GENERAL COMMENTS	I thank the authors for the alterations they made to the manuscript which have covered most of my concerns. However, I am still not completely satisfied with their reaction on two points, which I would like to see addressed as a limitation in the Discussion section: 1) ‘Ever use’ was the endpoint of choice, hence knowledge on duration of use was lacking, which may have been different between the groups. This hampers correct interpretation of the data. 2) The authors state that they were not interested in the causality of the association and therefore did not want to look into confounding. However, they took out pregnant and drug-using patients in order to make the groups comparable, and also adjusted for provoking risk factors, for the same reason. Making groups comparable is the same as taking confounding into account, so this does not make much sense. It should be made more explicit to what extent their results should be causally interpreted.

REVIEWER	Carlos Martinez Institute for Epidemiology, Statistics and Informatics GmbH I have received grants from Bayer, Bristol-Myers-Squibb, grants from CSL Behring, grants from Merz Pharma
REVIEW RETURNED	10-Dec-2018

GENERAL COMMENTS	Comments to responses: 1. The rationale provided in the revised introduction is still insufficient for the reader to understand why patients with IDDM and why the age group of 13 to 33 were chosen as a meaningful comparison group for patients with VTE with respect to

	subsequent psychotropic drug use. Please expand. The meaning of the first sentence is unclear, suggest deleting. Also provide reference for the statement "This phase often continues into the early thirties" 2. OK 3. Despite the similar proportions of overall mortality, there might be a difference in the timing of mortality between VTE and IDDM. VTE deaths may occur earlier than IDDM deaths. A sensitivity analysis accounting for mortality as competing risk should be performed to show the reader that the handling of mortality in the analysis does not affect the results. 4. It is not surprising that 30-day mortality after DM diagnosis in the IDDM group is low (beside the young age) given that the IDDM patients had to survive until the prescription claim for insulin to become members of the IDDM cohort. Furthermore, "immortal" time here also means the time without being at risk for impaired mental health recording between DM diagnosis and the first insulin claim. Consider shifting the index day of IDDM patients to the day of the first insulin claim after the initial DM diagnosis and make respective index day adjustments to the VTE cohort, e.g. random shift of index day in VTE patients based on the distribution of time between DM diagnosis and first insulin claim in the IDDM cohort. 5. OK 6. The revised code sets still includes unusual or unspecified sites, such as I823 or I829. However, VTE is defined to include deep venous thrombosis (DVT) and pulmonary embolism (PE). The point is to clearly define the study cohorts. Whether or not the exclusion or further codes materially change the results is secondary. In addition, as procedure codes are available, consider using procedure codes related to thrombectomy of deep veins or of pulmonary emboli for the identification of VTE. 7. OK 8. Consider deleting the first sentence in the introduction as not related to your study aims and the subsequent sentence. Please add a reference for the statement "This phase often continues into the early thirties". See comment 1. 9. OK. In addition, R06AD is included as a psychotropic drug. However, R06AD is clinically used as a systemic antihistamine and not as an antipsychotic medication. Please explain rationale. 10. Please add this information to the discussion, as this study strength may be unknown to readers that are not familiar with the Danish health system. 11. Please add this aspect to the study limitations, including how this influenced your results. 12. OK 13. Thank you for separating the procedure codes. Please provide coding system and reference for the procedure codes listed. 14. OK 15. OK 16. See comment 4. 17. OK 18. OK Other: Abstract – Summary, not summery Sorry for not picking up the following major comment earlier: I wonder if the main results presented in table 2 are spurious and age-dependent but unrelated to IDDM or VTE. Therefore, please adjust all “Adjusted risk differences” in table 2 for age at index day, and discuss age as a potential confounder.

	Expand abbreviations in footnote of table 2.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name: Suzanne Cannegieter

Institution and Country: Dept of Clinical Epidemiology, LUMC, the Netherlands

Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below

I thank the authors for the alterations they made to the manuscript which have covered most of my concerns. However, I am still not completely satisfied with their reaction on two points, which I would like to see addressed as a limitation in the Discussion section:

1) ‘Ever use’ was the endpoint of choice, hence knowledge on duration of use was lacking, which may have been different between the groups. This hampers correct interpretation of the data.

Response: We acknowledge the reviewer’s comment and have added the following sentence as a study limitation: “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 (page 11 line 10)”

2) The authors state that they were not interested in the causality of the association and therefore did not want to look into confounding. However, they took out pregnant and drug-using patients in order to make the groups comparable, and also adjusted for provoking risk factors, for the same reason. Making groups comparable is the same as taking confounding into account, so this does not make much sense. It should be made more explicit to what extent their results should be causally interpreted.

Response: We thank the reviewer for this point, and as suggested we have included the following concluding sentence in the limitations section: “Given these limitations, it is important to emphasize that based this observational study we cannot infer a causal interpretation of the observed association between VTE and impaired mental health (page 11 line 15)”

Reviewer: 3

Reviewer Name: Carlos Martinez

Institution and Country: Institute for Epidemiology, Statistics and Informatics GmbH

Please state any competing interests or state ‘None declared’: I have received grants from Bayer, Bristol-Myers-Squibb, grants from CSL Behring, grants from Merz Pharma

Please leave your comments for the authors below

Comments to responses:

1. The rationale provided in the revised introduction is still insufficient for the reader to understand why patients with IDDM and why the age group of 13 to 33 were chosen as a meaningful comparison group for patients with VTE with respect to subsequent psychotropic drug use. Please expand. The meaning of the first sentence is unclear, suggest deleting. Also, provide reference for the statement "This phase often continues into the early thirties"

Response: We thank the reviewer for the suggestions regarding the introduction and have revised the introduction accordantly, including deleting the first sentence.

3. Despite the similar proportions of overall mortality, there might be a difference in the timing of mortality between VTE and IDDM. VTE deaths may occur earlier than IDDM deaths. A sensitivity analysis accounting for mortality as competing risk should be performed to show the reader that the handling of mortality in the analysis does not affect the results.

Response: We have carefully reflected on the reviewer's comment, and have revised the analyses in order to take the competing risk of death into account. We have therefore also estimated the cumulative incidence functions of psychotropic drug use by means of the Aalen-Johansen estimator, assuming death as competing risks, instead of basing this on the Kaplan-Meier estimator. (page 8 line 1 and revised Figure 2).

4. It is not surprising that 30-day mortality after DM diagnosis in the IDDM group is low (beside the young age) given that the IDDM patients had to survive until the prescription claim for insulin to become members of the IDDM cohort. Furthermore, "immortal" time here also means the time without being at risk for impaired mental health recording between DM diagnosis and the first insulin claim.

Consider shifting the index day of IDDM patients to the day of the first insulin claim after the initial DM diagnosis and make respective index day adjustments to the VTE cohort, e.g. random shift of index day in VTE patients based on the distribution of time between DM diagnosis and first insulin claim in the IDDM cohort.

Response: In our cohort, the mean time from DM diagnosis to first insulin prescription was 11 days. As suggested by the reviewer, we have shifted the index day of IDDM patients to the day of first insulin claim after DM diagnosis and made index day adjustments in the VTE cohort to match this, by randomly shifting according to the distribution of time between DM diagnosis and insulin claim in the IDDM cohort. This is described in the statistical methods section page 7, lines 1-3.

6. The revised code sets still includes unusual or unspecified sites, such as I823 or I829. However, VTE is defined to include deep venous thrombosis (DVT) and pulmonary embolism (PE). The point is to clearly define the study cohorts. Whether or not the exclusion or further codes materially change the results is secondary. In addition, as procedure codes are available, consider using procedure codes related to thrombectomy of deep veins or of pulmonary emboli for the identification of VTE.

Response: We acknowledge the reviewer's comments and have removed ICD codes I823 and I829 accordingly. With regard to thrombectomy, this is very rarely performed in Denmark and all patients referred to this procedure will have an ICD diagnosis of VTE. Inclusion of this procedure will therefore not provide additional observations in our data set and will not be useful to improve the validity of the VTE diagnosis.

8. Consider deleting the first sentence in the introduction as not related to your study aims and the subsequent sentence. Please add a reference for the statement "This phase often continues into the early thirties". See comment 1.

Response: We thank the reviewer for the suggestions regarding the introduction we have deleted the first sentence and added a reference to support the statement "This phase often continues into the early thirties".

9. OK. In addition, R06AD is included as a psychotropic drug. However, R06AD is clinically used as a systemic antihistamine and not as an antipsychotic medication. Please explain rationale.

Response: We thank the reviewer for pointing our attention to the improper inclusion of R06AD, which has been removed in the revised analyses.

10. Please add this information to the discussion, as this study strength may be unknown to readers that are not familiar with the Danish health system.

Response: We agree with the reviewer and have added this as a strength of our study (page 11 line 16-18)

11. Please add this aspect to the study limitations, including how this influenced your results.

Response: In response to the reviewer's suggestion, we have added the following sentence to the limitations section: "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. (page 11 line 10-12)". In response to reviewer 2's comments, we have further added the following concluding remark in the limitations section: "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". Hopefully these additions to the study limitations underlines that we cannot assess the causality of our findings because for instance, patients with VTE may have been diagnosed with other diseases during follow-up which we do not account for.

13. Thank you for separating the procedure codes. Please provide coding system and reference for the procedure codes listed.

Response: We apologize for this omission. In Denmark procedure codes are coded according to the Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures. We have added this in the methods section along with a reference providing more detailed information. Please refer to page 6 line 4.

Other: Abstract – Summary, not summery

Response: We apologize for this typo which has been corrected.

Sorry for not picking up the following major comment earlier: I wonder if the main results presented in table 2 are spurious and age-dependent but unrelated to IDDM or VTE. Therefore, please adjust all "Adjusted risk differences" in table 2 for age at index day, and discuss age as a potential confounder. Expand abbreviations in footnote of table 2.

Response: We thank you for pointing this out. We have included age in the adjusted risk differences, and rephrased the reasoning on page 7 line 19.

VERSION 3 - REVIEW

REVIEWER	Suzanne Cannegieter Dept of Clinical Epidemiology, LUMC, the Netherlands
REVIEW RETURNED	25-Mar-2019

GENERAL COMMENTS	In response to my earlier comments the authors added the following sentence to the Limitations Section: "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". This is sufficient, although a bit short, but I think that this limitation is actually more important than the two that are now given in the 'Strengths and limitations of the study' section, so I would suggest that they replace the last one that is there now with this one.

REVIEWER	Carlos Martinez Institute for Epidemiology, Statistics and Informatics GmbH I have received grants from Informatics GmbH has received grants from Bayer, Bristol-Myers Squibb, CSL Behring, and grants from Merz Pharma
REVIEW RETURNED	26-Mar-2019

GENERAL COMMENTS	Results, second paragraph starting “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 comparison of crude risk differences is not meaningful given that the point estimates of the crude risk differences decreased after adjustment from 2.6 to 1.9 and from 4.6 to 1.9 for 1 and 5 years of follow up respectively. “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%, adjusted 95% CI: 0.5-3.3).“ Need to mention that risk differences were adjusted for age. “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).” Meaning of “similar risks” is unclear. Do you refer to adjusted risk differences? How was 'similar defined? Which test did you use to conclude that the risks were similar? Most adjusted risk differences were not statistically significant. Discussion - consider residual confounding as a study limitation. Abstract – results: The presentation of the results is not balanced and need to be rewritten. For example, the first sentence refers to VTE, however respective estimates for IDDM are not presented. Crude risk differences are provided although adjusted estimates are more meaningful.

	“The findings of comparable risk of psychotropic drug use remained robust when adjusting for the effect of sex and risk factors for VTE...” The statement on “comparable risks” is not correct given that there were statistically significantly increased overall adjusted risk differences at 1 and 5 years of follow up. See comments on the results section. It is not obvious that the findings remained robust after adjustment. Decreasing differences indicate confounding and that there may still be residual confounding. a. Page 7 lines 10-13: "date of diagnosis of VTE or IDDM" should be "index date" (i.e. the shifted date) instead. b. Page 8 line 4: Number of individuals in the VTE cohort to be updated (5172 is the old count) c. Figure 1: Please double check the numbers in the VTE path as these do not add up. d. Table2: I. Please double check the unadjusted 5 year risk difference estimates for "provoked VTE" (4.1) and "unprovoked VTE" (4.2) as the overall estimate (4.6) is higher than both. Or have not all VTE patients been allocated to either provoked or unprovoked? II. Abbreviations DVT, IBD, PE and RA to be explained in the footnote

VERSION 3 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name: Suzanne Cannegieter

Institution and Country: Dept of Clinical Epidemiology, LUMC, the Netherlands Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below In response to my earlier comments the authors added the following sentence to the Limitations Section: "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".

This is sufficient, although a bit short, but I think that this limitation is actually more important than the two that are now given in the 'Strengths and limitations of the study' section, so I would suggest that they replace the last one that is there now with this one.

Response: We thank the reviewer for drawing our attention to this and have revised the section “Strength and limitation of the study” accordingly.

Reviewer: 3

Reviewer Name: Carlos Martinez

Institution and Country: Institute for Epidemiology, Statistics and Informatics GmbH Please state any competing interests or state ‘None declared’: I have received grants from Informatics GmbH has received grants from Bayer, Bristol-Myers Squibb, CSL Behring, and grants from Merz Pharma

Please leave your comments for the authors below

Results, second paragraph starting “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 comparison of crude risk differences is not meaningful given that the point estimates of the crude risk differences decreased after adjustment from 2.6 to 1.9 and from 4.6 to 1.9 for 1 and 5 years of follow up respectively.

Response: Although we understand the reviewer’s line of thought, we do not entirely agree. In clinical practice, we still find the crude results informative as they depict the young VTE patients as a vulnerable group in regards of mental health status. As such, we prefer to keep the presentation of both crude and adjusted results. To avoid misunderstanding, we have added clarified that the first estimates are the crude results, and as commented by the reviewer, we explicitly describe in the results that adjustment attenuates the observed differences.

“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%, adjusted 95% CI: 0.5-3.3).“ Need to mention that risk differences were adjusted for age.

Response: We apologize for this omission. Age have been added. (page 8 line 15)

“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).” Meaning of “similar risks” is unclear. Do you refer to adjusted risk differences? How was 'similar defined? Which test did you use to conclude that the risks were similar? Most adjusted risk differences were not statistically significant.

Discussion - consider residual confounding as a study limitation.

Response: We apologize for not making this clear. We have changed the wording of “similar risks” and provide a more specific description – 5 year adjusted risk differences in the revised manuscript. (page 8 line 21)

Abstract – results:

The presentation of the results is not balanced and need to be rewritten. For example, the first sentence refers to VTE, however respective estimates for IDDM are not presented. Crude risk differences are provided although adjusted estimates are more meaningful.

“The findings of comparable risk of psychotropic drug use remained robust when adjusting for the effect of sex and risk factors for VTE...” The statement on “comparable risks” is not correct given that there were statistically significantly increased overall adjusted risk differences at 1 and 5 years of follow up. See comments on the results section. It is not obvious that the findings remained robust after adjustment. Decreasing differences indicate confounding and that there may still be residual confounding.

Response: The reviewer makes a valid point and we have revised the abstract accordantly.

a.Page 7 lines 10-13: "date of diagnosis of VTE or IDDM" should be "index date" (i.e. the shifted date) instead.

Response: Changes were made as suggested

b. Page 8 line 4: Number of individuals in the VTE cohort to be updated (5172 is the old count)

Response: Changes were made as suggested

c.Figure 1: Please double check the numbers in the VTE path as these do not add up.

Response: We thank the reviewer for his thorough review of our results. We have checked the numbers, and because the patients can present more than one “Risk factor for VTE” these will not add up.

d. Table2:

I. Please double check the unadjusted 5 year risk difference estimates for "provoked VTE" (4.1) and "unprovoked VTE" (4.2) as the overall estimate (4.6) is higher than both. Or have not all VTE patients been allocated to either provoked or unprovoked?

Response: Again, we thank the reviewer for his thorough review of our results. We realize that there were a typing error in the point estimate for the unprovoked group. This has been corrected from 4.2 to 4.8. Thank you for drawing our attention to this.

II.Abbreviations DVT, IBD, PE and RA to be explained in the footnote

Response: Changes were made as suggested