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# Psychotic, mood and anxiety disorders and venous thromboembolism: a systematic review and meta-analysis

Running title: **Psychiatric disorders and venous thromboembolism**

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# ABSTRACT

## *Objective*

Several studies have shown that psychiatric disorders can be associated with venous thromboembolism (VTE) risk, i.e. pulmonary embolism (PE) and/or deep vein thrombosis (DVT). In this study, we provide a systematic review and meta-analyses of the studies addressing this issue.

## *Methods*

All studies addressing the risk of VTE phenomena (whole VTE, PE, DVT, fatal VTE) in subjects with psychotic, mood and anxiety disorders published between 1998 and 2019 were reviewed and included in the meta-analyses. Main characteristics of the studies and data concerning VTE risk were extracted. The methodological qualities of the studies were also analysed.

A random-effects meta-analysis model was used. A meta-analysis was conducted separately for each disorder, as well as separately for unadjusted and adjusted studies. Meta-analyses were repeated considering only good-quality studies. Heterogeneity was assessed.

## *Results*

Sixteen studies were reviewed and 15 included in the meta-analyses. Psychotic and bipolar disorders were significantly associated with VTE risk (VTE, DVT, PE, fatal VTE for psychotic disorder, ORs between 1.29 and 2.20; VTE, DVT and PE for bipolar disorder, ORs between 1.22 and 2.14). Depression and anxiety disorders were associated with VTE risk only in adjusted analyses (DVT and PE for depression, ORs = 1.29; VTE and PE for anxiety disorders, ORs between 1.14 and 1.49).

## *Conclusions*

The risk of VTE among subjects with psychiatric disorders may be explained by hypercoagulability and stasis, with both being related to, and independent of, treatment side-effects. VTE risk should be taken into consideration in the treatment of people with psychiatric disorders.

## *Keywords*

Venous thromboembolism disease; Deep venous thrombosis; Pulmonary embolism; Psychotic disorders; Bipolar disorders; Depression.

## ***Abbreviations***

- DVT: Deep vein thrombosis;
- FGA: First-generation antipsychotics;
- HR: Hazard-ratio;
- HPA: Hypothalamic-pituitary-adrenal;
- MRR: Mortality rate ratio;
- NOS: Newcastle-Ottawa Scale ;
- PE: Pulmonary embolism;
- PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses;
- PTSD: Post-traumatic stress disorder;
- RR: Relative-risk;
- SGA: Second-generation antipsychotics;
- SMR: Standardized mortality ratios;
- SSRIs: Selective Serotonin Reuptake Inhibitors;
- VTE: Venous thromboembolism.

# INTRODUCTION

Psychiatric disorders are associated with premature mortality. A recent cohort study in Denmark shows that the mortality rate ratio (MRR) of people with psychiatric disorders was 2.53 (95 % CI [2.52-2.54]), with variations according to the particular disorder (e.g., schizophrenia: MRR = 2.57, or mood disorders: MRR = 1.92) (1). Considering all psychiatric disorders, the causes of this excessive mortality can be external (i.e., suicide, accidents or homicide) or natural, including circulatory (i.e., cardiovascular or cerebrovascular: MRR = 2.45, 95 % CI [2.43-2.47]) and diabetes (MRR = 2.61, 95 % CI [2.53-2.69]). A longitudinal study of subjects with psychotic or bipolar disorders in London found standardized mortality ratios (SMR) of 2.65 (95 % CI [2.45-2.86]) for circulatory system causes, 3.38 (95 % CI [3.04-3.74]) for respiratory system causes, and 1.45 (95 % CI [1.32-1.60]) for cancers deaths (2).

Venous thromboembolism (VTE), i.e. pulmonary embolism (PE) and/or deep vein thrombosis (DVT), are the third most common cardiovascular disorders, after coronary artery disease and heart failure, with an overall annual incidence of between 100 and 200 per 100,000 inhabitants (3,4). VTE is associated with high mortality rates. In a Canadian longitudinal study based on general populations registers, the 30-day and 1-year fatality was 2.0 % and 9.2 %, and was higher when PE alone was considered (5).

Several studies and meta-analysis have shown that some psychotropic medications were associated with VTE phenomena, particularly concerning first- and second-generation antipsychotics (FGA: Odds-ratio (OR) = 1.74, 95 % CI [1.28-2.37], SGA: OR = 2.07, 95 % CI [1.74-2.52]) (6), or antidepressants drugs (Relative-risk (RR) = 1.27, 95 % CI [1.06-1.51]) (7). Other factors, such as low-grade inflammation, sedentary lifestyle, tobacco and substance use comorbidities, or metabolic syndrome are also associated with VTE phenomena (8–13). These various factors are frequently and differentially associated with different psychiatric disorders. Consequently, it would be interesting to gather and synthesize the different studies pertaining to the risk of VTE among patients with psychiatric disorders, independently of the risk factors.

## *Aims of the study*

107           In the present systematic review and meta-analysis, our aim was to determine the risk of  
108 whole venous thromboembolism, pulmonary embolism, deep vein thrombosis, and fatal venous  
109 thromboembolism associated with different psychiatric disorders.

110

# METHODS

We developed and followed a standard meta-analysis protocol previously registered (prospero registration number CRD42020136915, see Supplementary material).

## *Inclusion and exclusion criteria*

The inclusion criteria of the different studies in this systematic review were:

- original studies;
- clinical prospective or retrospective studies;
- studies analysing the risk of VTE, PE, DVT, and/or fatal VTE among subjects/patients with psychiatric disorders in comparison to subjects/patients without psychiatric disorders (i.e., that published numbers of patients with and without VTE phenomena and with or without psychiatric disorders);
- targeted psychiatric disorders were: psychotic disorders, bipolar disorders, depression, anxiety disorders and catatonia.

In addition to these criteria, and in order to be meta-analysed, the different psychiatric disorders need to be studied by at least two studies. Consequently, a psychiatric disorder with only one study would be added in the systematic review but not included in the meta-analysis.

The exclusion criteria were:

- no control population;
- clinical psychiatric population (i.e. patients hospitalized in psychiatry settings, or subjects with psychiatric disorders) as control population;
- in vitro studies;
- no statistical comparison of VTE rates;
- case reports or case series;
- studies in populations of patients with a history of VTE disease (DVT and/or PE);
- no details on the different types of psychiatric disorders (psychiatric disorders treated as a whole, without precision), and/or no data on psychiatric disorders.

## *Search strategy and study selection*

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were applied for systematic reviews and meta-analyses. The search covered two databases: MEDLINE and EMBASE. Only English language articles published between June 1, 1998 and December 31, 2019 were included. The search terms were designed to provide maximum sensitivity in the detection of studies (see Supplementary material for the details of the search strategy). Duplicates were removed.

All articles found in the databases searched were reviewed. This was first based on title and abstract screening, and secondly on full-texts. Two researchers (CK and BP) independently carried out the selection of the studies and the extraction of data. Discrepancies were subsequently addressed and discussed with a third researcher (HP).

### ***Systematic review***

The considered outcomes were: main characteristics of the studies (including prospective vs. retrospective, source of the data, duration of follow-up), number of patients with and without each considered psychiatric disorder in groups with and without VTE phenomena (whole VTE, DVT, PE, and/or fatal VTE), main characteristics of case and controls (age, sex and available clinical characteristics), adjustment factors, and statistic rates (hazard-ratio (HR), OR, RR, and 95 % CI), and p-values.

The methodological quality of studies was conducted with the Newcastle-Ottawa Scale (NOS). This scale has been developed to assess the quality of nonrandomised studies with its design, content and ease of use directed to the incorporation of the quality assessments in the interpretation of meta-analytic results. Studies were judged on three broad dimensions: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. To separate studies according to their quality, values were attributed to each grade of the notation (a = 1, b = 2, c = 3, and d = 4). Based on the mean score in the different studied characteristics in NOS, studies were median-spited and separated in two samples (i.e., low and good quality studies).

### ***Meta-analyses***

We used a random-effects meta-analysis model, which assumes that the observed estimates of VTE, DVT, PE and fatal VTE can vary across studies because of real differences in



each study as well as sampling variability. Analyses were conducted separately for the different psychiatric disorders. To examine the putative role of confounding factors, unadjusted and adjusted estimates were meta-analysed separately for each outcome (i.e. VTE, DVT, PE and fatal VTE) and each psychiatric disorder. We expected differences in the confounding variables taken into account in the adjusted model of the different studies. The robustness of the meta-analyses was determined by including only studies of good quality based on the NOS. Heterogeneity was assessed using the  $I^2$  statistic, which represents the percentage of variation across studies due to heterogeneity, and ranges from 0 to 100 %; higher values indicate greater heterogeneity across studies (14). Publication bias was assessed using funnel plots. Statistical analyses were performed using the R package “meta” for unadjusted ORs, and the R package “metaphor” (ORs were log-transformed following Chen and Peace (15) methods) for ORs that were adjusted on confounding variables.

# RESULTS

## *Studies selection*

The search revealed 6,211 potential studies. After duplicates were removed, and titles and abstracts screened, 398 records were selected. These 398 full-texts were then reviewed to assess eligibility according to inclusion and exclusion criteria. Of these 398 records, 381 were excluded, leaving 17 studies in the qualitative analysis. As adjustment disorder and post-traumatic stress disorder (PTSD) were each analysed in only one article (16), they were not studied in the meta-analysis. No selected article assessed catatonia. As the study of Enga et al. (17) studied self-reported depression and loneliness without medical assessment, it was not included in the meta-analysis. Thus, 15 articles were included in the meta-analysis. See details in PRISMA diagram (**Figure 1**).

## - FIGURE 1 -

## *Systematic review*

Of the 17 studies included in the qualitative analysis, 15 studies concerned VTE (16–30), and 2 concerned fatal VTE (31,32). Sixteen were (prospective or retrospective) cohort studies, and one was a nested case-control study. The psychiatric disorders considered were depression (N = 12), schizophrenia (N = 10), anxiety disorders (N = 5), bipolar disorders (N = 4), and adjustment disorder and PTSD (N = 1). All of the studies used registers as source of data, except one that used interview to assess depression. Seven selected studies concerned post-operative risk of VTE. Six studies concerned only inpatients, whilst 10 studies involved inpatients and outpatients.

The details of the articles included in the systematic review are available in **Table 1**.

## - TABLE 1 -

## *Meta-Analysis*

Of the 15 studies included in the meta-analysis, 13 studies concerned VTE (18–30), and 2 fatal VTE (31,32). Among the 13 studies on non-fatal VTE, 6 assessed whole VTE phenomena without details on DVT and/or PE, 5 assessed DVT and PE, and 2 assessed only PE. The 15 articles included in the meta-analysis have been assessed according to NOS. Overall, 3 studies were considered as representative of the target population. The comparability of the groups and the follow-up (adequacy and period) were judged appropriate in the 15 studies. More details of the different fields assessed by NOS are available in supplementary table (*Supplementary Table 1*).

Detailed results of the different meta-analyses are shown in **Table 2**. Funnel plots of unadjusted meta-analyses of associations between VTE and psychiatric disorders are depicted in **Figure 2**. The meta-analyses of the good quality studies and the forest and funnel plots of adjusted meta-analyses are available in supplementary materials (*Supplementary Figure 1 and Table 2*). The different adjustment factors used in the adjusted analyses was available in supplementary table (*Supplementary Table 3*).

## - TABLE 2 AND FIGURE 2 -

In unadjusted analyses, VTE was associated with psychotic disorders (OR = 2.20, 95 % CI [1.06-4.59]), in contrast to DVT, PE, and fatal VTE. Heterogeneity was high (above 99 %). The funnel plot was consistent with this high heterogeneity (**Figure 2**), but did not indicate any publication bias in favour of a positive association. Considering only adjusted analyses, VTE, DVT, PE, and fatal VTE were all associated with psychotic disorders (ORs between 1.29 and 2.88). In comparison with unadjusted analyses, heterogeneity was reduced ( $I^2 = 21.3$  % for VTE, 79.1 % for DVT, and 47.4 % for PE). Considering only good quality studies, VTE, DVT and PE were associated with psychotic disorders in both unadjusted and adjusted analyses (ORs between 1.82 and 2.78 in unadjusted analyses, ORs between 1.49 and 2.02 in adjusted analyses). There were no good quality studies concerning fatal VTE and psychotic disorders.

In unadjusted analyses, VTE was associated with depression (OR = 1.86, 95 % CI [1.19-2.92]), in contrast to DVT, PE, and fatal VTE. Heterogeneity was high ( $I^2$  above 99 %). As with psychotic disorders, the funnel plot shows this high heterogeneity, without indication of a publication bias. Considering only adjusted analyses, VTE, DVT and PE were associated with

depression (ORs between 1.19 and 1.29), in contrast to fatal VTE. In comparison with unadjusted analyses, heterogeneity was reduced ( $I^2 = 43.6\%$  for VTE, and  $92.1\%$  for PE, only 1 study for DVT). When only good quality studies were considered, no studies were considered DVT, PE and fatal VTE, whereas VTE was found not to be associated with depression in both unadjusted and adjusted analyses.

In unadjusted analyses, no VTE phenomena were associated with anxiety disorders (OR = 0.64, 95 % CI [0.29-1.42]). Heterogeneity was high ( $I^2$  above 99 %). The number of studies ( $N = 3$ ) makes the funnel plot difficult to interpret. There were no studies concerning fatal VTE and anxiety disorders. Considering only adjusted analyses, VTE and PE were considered only in one study, and were found associated with anxiety disorders (ORs between 1.14 and 1.49). Considering only good quality studies, VTE and PE were also considered in only one study in both unadjusted and adjusted analyses (whilst DVT was not studied). VTE was associated with anxiety disorders only in adjusted analyses (OR = 1.14, 95 % CI [1.00-1.29]), while PE was associated in both unadjusted and adjusted analyses (ORs between 1.42 and 1.49).

In unadjusted analyses, all VTE phenomena, except fatal VTE, were associated with bipolar disorders (ORs between 1.48 and 1.59). Heterogeneity was high (above 99 %). As for anxiety disorder, the number of studies ( $N = 2$ ) makes the funnel plot difficult to interpret. Considering only adjusted analyses, VTE and DVT were considered only in one study, with only DVT associated with bipolar disorders (OR = 2.14, 95 % CI [1.87-2.45]). PE was associated with bipolar disorders (OR = 2.06, 95 % CI [1.26-3.37]), with high level of heterogeneity ( $I^2 = 93.3\%$ ). When considering only good quality studies, PE remained associated with bipolar disorders in both unadjusted and adjusted analyses (ORs between 1.22 and 1.29), whilst VTE was not associated with bipolar disorder in unadjusted and adjusted analyses, and DVT was not considered.

## DISCUSSION

The systematic review and meta-analysis indicate significant associations between psychiatric disorders and VTE, DVT and PE risk. Among the psychiatric disorders, psychotic disorders were associated with the highest and most consistent ORs (except for the meta-analysis of unadjusted analyses on DVT and PE). Bipolar disorders were also associated with an increased risk of VTE, DVT and PE in the meta-analyses of unadjusted and adjusted studies, with the exception of the meta-analysis of adjusted studies on VTE risk. Meta-analyses of unadjusted analyses of depression and anxiety disorders did not show any significant associations, whereas meta-analyses of adjusted analyses of indicated associations of DVT and PE with depression, as well as VTE and PE for anxiety disorders.

Several mechanisms have been proposed to explain these associations. To develop VTE, pathophysiological studies assume that one or a combination of Virchow's triad – hypercoagulability, stasis of blood flow and vein wall injury – are necessary (33,34). Psychiatric disorders may be particularly associated with hypercoagulability and stasis factors.

### ***Psychotic disorders and venous thromboembolism***

Regarding psychotic disorders and schizophrenia, antipsychotics – in particular SGA – have been associated with VTE risk in several studies (6,35), although not all (36,37). As the side-effects of antipsychotics include sedation, negative symptoms and sedentary behaviour (38,39), they can increase the risk of venous stasis. Moreover, sedentary behaviour has been associated with inflammation-induced hypercoagulability (40,41), indicating that the well-known heightened level of inflammation evident in schizophrenia may interact with sedentary behaviours. Additionally, the putative hypercoagulability associated with antipsychotic use has been directly linked to enhanced platelet aggregation and to increased levels of anti-phospholipid antibodies (34,42). However, results across several studies are inconsistent in regard to antipsychotic-induced hypercoagulability, and thereby the antipsychotic-driven VTE risk among patients with psychotic disorders. In a sample of patients with schizophrenia, Halacheva et al. (43) did not find any association between antipsychotics and anti-phospholipid antibodies. In a sample of healthy volunteers, a reduced aggregability, and associated decreased

hypercoagulability, of blood samples was present after treatment with clozapine or olanzapine (44). In a study comparing the level of blood factors that are associated with coagulation and inflammation in schizophrenia patients treated chronically with antipsychotics and in their drug-naïve first-degree relatives, Carrizo et al. (40) did not find a homogeneous profile of inflammation and coagulation according to the different groups. However, these authors did find that the observed blood abnormalities were related to an elevated BMI in both patients and relatives. Moreover, Masopust et al. (45) studied the levels of activation of the coagulation factors in patients with acute psychotic disorders, who were antipsychotic naïve. Coagulation factors were higher among patients in comparison to controls, suggestive of a medication independent VTE risk in patients with acute psychotic disorders. Thus, the proposed association of antipsychotic use driving hypercoagulability is questionable. Gaertner et al. (46) estimated the incidence of VTE phenomena among 12,320 patients in psychiatric institutions. Although they found an incidence rate of VTE around 20 times higher than in the general population, they did not observe any association between psychotropic drugs and VTE risk. Overall, the role of antipsychotic use in the pathoetiology of VTE is questionable, indicating that the association between psychotic disorder and VTE may be explained at least partly by treatment-independent mechanisms. In the present systematic review, we report the results of one large population based nested case-control study (21), which found a significant association between VTE and psychotic disorders *after adjusting for antipsychotics use* (OR = 1.34, 95 % CI [1.15-1.55]). The authors proposed that the association between psychotic disorders and VTE may be explained by other factors, such as lifestyle habits, high BMI, or tobacco use (40,45,46). Negative symptoms may also be involved, as they are associated with sedentary behaviour (47), as well as hyperprolactinemia, metabolic syndrome, and physical restraint (48–50).

Another explanation, that concerns psychotic and non-psychotic disorders, may lie in risk factors and/or comorbidities shared by psychiatric disorders and VTE. For instance, psychotic, mood and anxiety disorders are associated with hypothalamic-pituitary-adrenal (HPA) axis dysregulation and related hypercortisolism (51–54), and hypercortisolism is associated with hypercoagulability (55,56). Likewise, low education and economic level, occupational status, obesity, metabolic syndrome, smoking, or alcohol use disorders have been linked to both VTE and psychiatric disorders (57–64). A correlate of lower socio-economic status is residence within

areas of heightened air pollution, which is also a common risk factor for both VTE and psychiatric disorders (65,66).

### ***Mood and anxiety disorders and venous thromboembolism***

The association of VTE with mood disorders parallels its association with psychotic disorders. Several studies have found significant associations between various types of antidepressants, including Selective Serotonin Reuptake Inhibitors (SSRIs), tricyclic, and other antidepressants, with VTE (7,67). However, other studies have shown no such significant associations (28,36,46,68). Of note, patients with anxiety disorders often use antidepressant and antipsychotic drugs (69,70). In an observational prospective study of patients addressed for thrombophilia investigation after a VTE episode, von Känel et al. (71) examined the role of depressive symptoms in VTE recurrence. Antidepressant use was an exclusion criterion. These authors showed that depressive symptoms were predictive of VTE recurrence, showing a “dose-effect” relationship. The results of this study, in line with the data of Enga et al. (17), support the role of medication-independent depressive symptoms in VTE risk. Again, an increase of sedentary symptoms has been proposed to underpin this association, as well as an increase in hypercoagulability induced by stress and heightened sympathetic nervous system (72,73). Such stress-driven pathophysiological changes may also underpin the association of anxiety disorders with hypercoagulability. In the study by Gaertner et al. (46) on VTE incidence in psychiatric institutions, almost one third of VTE were diagnosed during the first 48h of hospitalization, and 50 % during the first week of hospitalization, highlighting an association of VTE with the high levels of stress, dysphoria and depressive symptoms that are often evident at this time.

Other studies on psychotropic treatments of mood disorders, including benzodiazepines and mood stabilizers, showed little association with VTE risk (with the exception of one study in pregnant women, where VTE displayed a significant associations with benzodiazepine derivatives) (74,75).

### ***Limitations***

Some limitations of this study should be acknowledged. While it concerns an important topic, relative few studies have been included in this systematic review and meta-analysis. Anxiety (N = 5) and bipolar disorders (N = 4) have been poorly studied and some psychiatric

disorders, such as PTSD, catatonia, have not been studied. Moreover, as noted in the systematic review, and as confirmed by the high level of heterogeneity, inclusion criteria and clinical settings of the studies were different. Similarly, in the adjusted analyses, the heterogeneity was lower, but still high, which is consistent with different adjustment factors. Meta regressions, which could have helped to clarify the role of treatment in VTE risk could not be utilized. Other limitations arising from unavailable data, include the analysis of different adjustment factors, and psychiatric subgroups, including with and without psychotropic drug use.

## ***Conclusion***

Overall, in this systematic review and meta-analysis, the risk of VTE, DVT and PE associated with psychotic, mood, and anxiety disorders was addressed for the first time. The absolute risks of VTE of each studied psychiatric disorders, estimated based on the meta-analysis of unadjusted analyses, were as follow: psychotic disorders: OR = 2.20, 95 % CI [1.06-4.59]; depression: OR = 1.86, 95 % CI [1.19-2.92]; bipolar disorders: OR = 1.49, 95 % CI [1.23-1.80]; and anxiety disorders: OR = 0.64, 95 % CI [0.29-1.42]. Regarding details, psychotic and bipolar disorders were associated with VTE, DVT and PE risk. Depression and anxiety disorders, in adjusted analyses, show associations of DVT and PE for depression, and VTE and PE for anxiety disorders. Such results highlight the need for clinicians to be vigilant in the monitoring of VTE risk across a wide range of psychiatric disorders, which, as with other cardiovascular diseases, should have a focus that emphasizes prevention. Prevention measures, based on the use of compression stockings, hydration, behavioral activation, and sometimes prophylactic anticoagulation should be applied, especially in the case of physical restraint (76,77).



**Conflict of interest:** None

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**Authors' contribution:**

- Concept and design of the study: CK, HP and BP
- Systematic review: CK, HP and BP
- Analysis and interpretation of data: HP and BP
- First draft: CK and BP
- Critical review: CK, HP, AA, AP, ML, FS.

## FIGURES LEGENDS

### **Figure1**

Title: PRISMA flowchart of literature search process

Abbreviations: DVT = Deep venous thrombosis, PE = Pulmonary embolism, VTE = Venous thromboembolism events

### **Figure 2**

Title: Funnel plots of unadjusted meta-analyses of association between psychiatric disorders and venous thromboembolism

### **Supplementary Figure 1**

Title: Forest and funnel plots of adjusted meta-analyses of association between psychiatric disorders and venous thromboembolism

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