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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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1 **Psychotic, mood and anxiety disorders and venous**
2 **thromboembolism:**
3 **a systematic review and meta-analysis**

4
5 Running title: **Psychiatric disorders and venous thromboembolism**

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28

29 **ABSTRACT**

30

31 ***Objective***

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

36 ***Methods***

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

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

45 ***Results***

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

52 ***Conclusions***

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

57

58 ***Keywords***

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

61

62 ***Abbreviations***

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

77

78 INTRODUCTION

79

80 Psychiatric disorders are associated with premature mortality. A recent cohort study in
81 Denmark shows that the mortality rate ratio (MRR) of people with psychiatric disorders was 2.53
82 (95 % CI [2.52-2.54]), with variations according to the particular disorder (e.g., schizophrenia:
83 MRR = 2.57, or mood disorders: MRR = 1.92) (1). Considering all psychiatric disorders, the
84 causes of this excessive mortality can be external (i.e., suicide, accidents or homicide) or natural,
85 including circulatory (i.e., cardiovascular or cerebrovascular: MRR = 2.45, 95 % CI [2.43-2.47])
86 and diabetes (MRR = 2.61, 95 % CI [2.53-2.69]). A longitudinal study of subjects with psychotic
87 or bipolar disorders in London found standardized mortality ratios (SMR) of 2.65 (95 % CI
88 [2.45-2.86]) for circulatory system causes, 3.38 (95 % CI [3.04-3.74]) for respiratory system
89 causes, and 1.45 (95 % CI [1.32-1.60]) for cancers deaths (2).

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

96 Several studies and meta-analysis have shown that some psychotropic medications were
97 associated with VTE phenomena, particularly concerning first- and second-generation
98 antipsychotics (FGA: Odds-ratio (OR) = 1.74, 95 % CI [1.28-2.37], SGA: OR = 2.07, 95 % CI
99 [1.74-2.52]) (6), or antidepressants drugs (Relative-risk (RR) = 1.27, 95 % CI [1.06-1.51]) (7).
100 Other factors, such as low-grade inflammation, sedentary lifestyle, tobacco and substance use
101 comorbidities, or metabolic syndrome are also associated with VTE phenomena (8–13). These
102 various factors are frequently and differentially associated with different psychiatric disorders.
103 Consequently, it would be interesting to gather and synthesize the different studies pertaining to
104 the risk of VTE among patients with psychiatric disorders, independently of the risk factors.

105

106 *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

111 **METHODS**

112

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

115

116 ***Inclusion and exclusion criteria***

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

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

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

129 The exclusion criteria were:

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

139

140 ***Search strategy and study selection***

141 The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses)
142 guidelines were applied for systematic reviews and meta-analyses. The search covered two
143 databases: MEDLINE and EMBASE. Only English language articles published between June 1,
144 1998 and December 31, 2019 were included. The search terms were designed to provide
145 maximum sensitivity in the detection of studies (see Supplementary material for the details of the
146 search strategy). Duplicates were removed.

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

151

152 ***Systematic review***

153 The considered outcomes were: main characteristics of the studies (including prospective
154 vs. retrospective, source of the data, duration of follow-up), number of patients with and without
155 each considered psychiatric disorder in groups with and without VTE phenomena (whole VTE,
156 DVT, PE, and/or fatal VTE), main characteristics of case and controls (age, sex and available
157 clinical characteristics), adjustment factors, and statistic rates (hazard-ratio (HR), OR, RR, and
158 95 % CI), and p-values.

159 The methodological quality of studies was conducted with the Newcastle-Ottawa Scale
160 (NOS). This scale has been developed to assess the quality of nonrandomised studies with its
161 design, content and ease of use directed to the incorporation of the quality assessments in the
162 interpretation of meta-analytic results. Studies were judged on three broad dimensions: the
163 selection of the study groups, the comparability of the groups and the ascertainment of either the
164 exposure or outcome of interest for case-control or cohort studies respectively. To separate
165 studies according to their quality, values were attributed to each grade of the notation (a = 1, b =
166 2, c = 3, and d = 4). Based on the mean score in the different studied characteristics in NOS,
167 studies were median-spited and separated in two samples (i.e., low and good quality studies).

168

169 ***Meta-analyses***

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

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

184

185 **RESULTS**

186

187 *Studies selection*

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

197

198 **- FIGURE 1 -**

199

200 *Systematic review*

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

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

210

211 **- TABLE 1 -**

212

213 *Meta-Analysis*

214 Of the 15 studies included in the meta-analysis, 13 studies concerned VTE (18–30), and 2
215 fatal VTE (31,32). Among the 13 studies on non-fatal VTE, 6 assessed whole VTE phenomena
216 without details on DVT and/or PE, 5 assessed DVT and PE, and 2 assessed only PE. The 15
217 articles included in the meta-analysis have been assessed according to NOS. Overall, 3 studies
218 were considered as representative of the target population. The comparability of the groups and
219 the follow-up (adequacy and period) were judged appropriate in the 15 studies. More details of
220 the different fields assessed by NOS are available in supplementary table (*Supplementary Table*
221 *1*).

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

228

229 - TABLE 2 AND FIGURE 2 -

230

231 In unadjusted analyses, VTE was associated with psychotic disorders (OR = 2.20, 95 %
232 CI [1.06-4.59]), in contrast to DVT, PE, and fatal VTE. Heterogeneity was high (above 99 %).
233 The funnel plot was consistent with this high heterogeneity (**Figure 2**), but did not indicate any
234 publication bias in favour of a positive association. Considering only adjusted analyses, VTE,
235 DVT, PE, and fatal VTE were all associated with psychotic disorders (ORs between 1.29 and
236 2.88). In comparison with unadjusted analyses, heterogeneity was reduced ($I^2 = 21.3$ % for VTE,
237 79.1 % for DVT, and 47.4 % for PE). Considering only good quality studies, VTE, DVT and PE
238 were associated with psychotic disorders in both unadjusted and adjusted analyses (ORs between
239 1.82 and 2.78 in unadjusted analyses, ORs between 1.49 and 2.02 in adjusted analyses). There
240 were no good quality studies concerning fatal VTE and psychotic disorders.

241 In unadjusted analyses, VTE was associated with depression (OR = 1.86, 95 % CI [1.19-
242 2.92]), in contrast to DVT, PE, and fatal VTE. Heterogeneity was high (I^2 above 99 %). As with
243 psychotic disorders, the funnel plot shows this high heterogeneity, without indication of a
244 publication bias. Considering only adjusted analyses, VTE, DVT and PE were associated with

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

250 In unadjusted analyses, no VTE phenomena were associated with anxiety disorders (OR
251 = 0.64, 95 % CI [0.29-1.42]). Heterogeneity was high (I^2 above 99 %). The number of studies (N
252 = 3) makes the funnel plot difficult to interpret. There were no studies concerning fatal VTE and
253 anxiety disorders. Considering only adjusted analyses, VTE and PE were considered only in one
254 study, and were found associated with anxiety disorders (ORs between 1.14 and 1.49).
255 Considering only good quality studies, VTE and PE were also considered in only one study in
256 both unadjusted and adjusted analyses (whilst DVT was not studied). VTE was associated with
257 anxiety disorders only in adjusted analyses (OR = 1.14, 95 % CI [1.00-1.29]), while PE was
258 associated in both unadjusted and adjusted analyses (ORs between 1.42 and 1.49).

259 In unadjusted analyses, all VTE phenomena, except fatal VTE, were associated with
260 bipolar disorders (ORs between 1.48 and 1.59). Heterogeneity was high (above 99 %). As for
261 anxiety disorder, the number of studies (N = 2) makes the funnel plot difficult to interpret.
262 Considering only adjusted analyses, VTE and DVT were considered only in one study, with only
263 DVT associated with bipolar disorders (OR = 2.14, 95 % CI [1.87-2.45]). PE was associated
264 with bipolar disorders (OR = 2.06, 95 % CI [1.26-3.37]), with high level of heterogeneity ($I^2 =$
265 93.3%). When considering only good quality studies, PE remained associated with bipolar
266 disorders in both unadjusted and adjusted analyses (ORs between 1.22 and 1.29), whilst VTE
267 was not associated with bipolar disorder in unadjusted and adjusted analyses, and DVT was not
268 considered.

269

270 **DISCUSSION**

271

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

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

285

286 ***Psychotic disorders and venous thromboembolism***

287 Regarding psychotic disorders and schizophrenia, antipsychotics – in particular SGA –
288 have been associated with VTE risk in several studies (6,35), although not all (36,37). As the
289 side-effects of antipsychotics include sedation, negative symptoms and sedentary behaviour
290 (38,39), they can increase the risk of venous stasis. Moreover, sedentary behaviour has been
291 associated with inflammation-induced hypercoagulability (40,41), indicating that the well-known
292 heightened level of inflammation evident in schizophrenia may interact with sedentary
293 behaviours. Additionally, the putative hypercoagulability associated with antipsychotic use has
294 been directly linked to enhanced platelet aggregation and to increased levels of anti-phospholipid
295 antibodies (34,42). However, results across several studies are inconsistent in regard to
296 antipsychotic-induced hypercoagulability, and thereby the antipsychotic-driven VTE risk among
297 patients with psychotic disorders. In a sample of patients with schizophrenia, Halacheva et al.
298 (43) did not find any association between antipsychotics and anti-phospholipid antibodies. In a
299 sample of healthy volunteers, a reduced aggregability, and associated decreased

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

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

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

332

333 ***Mood and anxiety disorders and venous thromboembolism***

334 The association of VTE with mood disorders parallels its association with psychotic
335 disorders. Several studies have found significant associations between various types of
336 antidepressants, including Selective Serotonin Reuptake Inhibitors (SSRIs), tricyclic, and other
337 antidepressants, with VTE (7,67). However, other studies have shown no such significant
338 associations (28,36,46,68). Of note, patients with anxiety disorders often use antidepressant and
339 antipsychotic drugs (69,70). In an observational prospective study of patients addressed for
340 thrombophilia investigation after a VTE episode, von Känel et al. (71) examined the role of
341 depressive symptoms in VTE recurrence. Antidepressant use was an exclusion criterion. These
342 authors showed that depressive symptoms were predictive of VTE recurrence, showing a “dose-
343 effect” relationship. The results of this study, in line with the data of Enga et al. (17), support the
344 role of medication-independent depressive symptoms in VTE risk. Again, an increase of
345 sedentary symptoms has been proposed to underpin this association, as well as an increase in
346 hypercoagulability induced by stress and heightened sympathetic nervous system (72,73). Such
347 stress-driven pathophysiological changes may also underpin the association of anxiety disorders
348 with hypercoagulability. In the study by Gaertner et al. (46) on VTE incidence in psychiatric
349 institutions, almost one third of VTE were diagnosed during the first 48h of hospitalization, and
350 50 % during the first week of hospitalization, highlighting an association of VTE with the high
351 levels of stress, dysphoria and depressive symptoms that are often evident at this time.

352 Other studies on psychotropic treatments of mood disorders, including benzodiazepines
353 and mood stabilizers, showed little association with VTE risk (with the exception of one study in
354 pregnant women, where VTE displayed a significant associations with benzodiazepine derivatives)
355 (74,75).

356

357 ***Limitations***

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

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

368

369 ***Conclusion***

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

383

384 **Conflict of interest:** None

385

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387 profit sectors.

388

389 **Authors' contribution:**

390 - Concept and design of the study: CK, HP and BP

391 - Systematic review: CK, HP and BP

392 - Analysis and interpretation of data: HP and BP

393 - First draft: CK and BP

394 - Critical review: CK, HP, AA, AP, ML, FS.

395 **FIGURES LEGENDS**

396

397 **Figure1**

398 Title: PRISMA flowchart of literature search process

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

401

402 **Figure 2**

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

405

406 **Supplementary Figure 1**

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

409

410 REFERENCES

- 411 1. Plana-Ripoll O, Pedersen CB, Agerbo E, Holtz Y, Erlangsen A, Canudas-Romo
412 V, Andersen PK, Charlson FJ, Christensen MK, Erskine HE, Ferrari AJ, Iburg KM, Momen N,
413 Mortensen PB, Nordentoft M, Santomauro DF, Scott JG, Whiteford HA, Weyerer N, McGrath JJ,
414 Laursen TM. A comprehensive analysis of mortality-related health metrics associated with
415 mental disorders: a nationwide, register-based cohort study. *The Lancet*. 2019;394:1827–35.
- 416 2. Das-Munshi J, Chang C-K, Dutta R, Morgan C, Nazroo J, Stewart R, Prince MJ.
417 Ethnicity and excess mortality in severe mental illness: a cohort study. *The Lancet Psychiatry*.
418 2017;4:389–99.
- 419 3. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, Greer
420 IA, Heit JA, Hutchinson JL, Kakkar AK, Mottier D, Oger E, Samama M-M, Spannagl M, VTE
421 Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe. The
422 number of VTE events and associated morbidity and mortality. *Thrombosis and Haemostasis*.
423 2007;98:756–64.
- 424 4. Delluc A, Tromeur C, Ven FL, Gouillou M, Paleiron N, Bressollette L, Nonent
425 M, Salaun P-Y, Lacut K, Leroyer C, Gal GL, Couturaud F, Mottier D, Group for the E study.
426 Current incidence of venous thromboembolism and comparison with 1998: a community-based
427 study in Western France. *Thrombosis and Haemostasis*. 2016;116:967–74.
- 428 5. Alotaibi GS, Wu C, Senthilselvan A, McMurtry MS. Secular Trends in Incidence
429 and Mortality of Acute Venous Thromboembolism: The AB-VTE Population-Based Study. *The*
430 *American Journal of Medicine*. 2016;129:879.e19-879.e25.
- 431 6. Barbui C, Conti V, Cipriani A. Antipsychotic drug exposure and risk of venous
432 thromboembolism: a systematic review and meta-analysis of observational studies. *Drug Safety*.
433 2014;37:79–90.
- 434 7. Kunutsor SK, Seidu S, Khunti K. Depression, antidepressant use, and risk of
435 venous thromboembolism: systematic review and meta-analysis of published observational
436 evidence. *Annals of Medicine*. 2018;50:529–37.
- 437 8. Healy D, Le Noury J, Harris M, Butt M, Linden S, Whitaker C, Zou L, Roberts
438 AP. Mortality in schizophrenia and related psychoses: data from two cohorts, 1875-1924 and
439 1994-2010. *BMJ open*. 2012;2.

- 440 9. Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, Kupfer DJ. Can
441 bipolar disorder be viewed as a multi-system inflammatory disease? *Journal of Affective*
442 *Disorders*. 2012;141:1–10.
- 443 10. Saghazadeh A, Rezaei N. Inflammation as a cause of venous thromboembolism.
444 *Critical Reviews in Oncology/Hematology*. 2016;99:272–85.
- 445 11. Song K, Rong Z, Yao Y, Shen Y, Zheng M, Jiang Q. Metabolic Syndrome and
446 Deep Vein Thrombosis After Total Knee and Hip Arthroplasty. *The Journal of Arthroplasty*.
447 2016;31:1322–25.
- 448 12. Bonaldi C, Pasquereau A, Hill C, Thomas D, Moutengou E, Thanh VN, Olié V.
449 Hospitalizations for cardiovascular diseases attributable to tobacco smoking in France in 2015.
450 *European Journal of Preventive Cardiology*. 2019;2047487319885462.
- 451 13. Fond G, Godin O, Boyer L, Berna F, Andrianarisoa M, Coulon N, Brunel L,
452 Bulzacka E, Aouizerate B, Capdevielle D, Chereau I, D’Amato T, Dubertret C, Dubreucq J,
453 Faget C, Leignier S, Lançon C, Mallet J, Misdrahi D, Passerieux C, Rey R, Schandrin A, Urbach
454 M, Vidailhet P, Llorca PM, Schürhoff F, Leboyer M, Andrianarisoa M, Aouizerate B, Bazin N,
455 Berna F, Blanc O, Brunel L, Bulzacka E, Capdevielle D, Chereau-Boudet I, Chesnoy-Servanin
456 G, Danion JM, D’Amato T, Deloge A, Delorme C, Denizot H, Dorey JM, Dubertret C, Dubreucq
457 J, Faget C, Fluttaz C, Fond G, Fonteneau S, Gabayet F, Giraud-Baro E, Hardy-Bayle MC,
458 Lacelle D, Lançon C, Laouamri H, Leboyer M, Le Gloahec T, Le Strat Y, Llorca PM, Mallet J,
459 Metairie E, Misdrahi D, Offerlin-Meyer I, Passerieux C, Peri P, Pires S, Portalier C, Ramet L,
460 Rey R, Roman C, Sebilleau M, Schandrin A, Schürhoff F, Tessier A, Tronche AM, Urbach M,
461 Vaillant F, Vehier A, Vidailhet P, Vilà E, Yazbek H, Zinetti-Bertschy A, the FACE-SZ
462 (FondaMental Academic Centers of Expertise for Schizophrenia) Group. Chronic low-grade
463 peripheral inflammation is associated with ultra resistant schizophrenia. Results from the FACE-
464 SZ cohort. *European Archives of Psychiatry and Clinical Neuroscience*. 2019;269:985–92.
- 465 14. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in
466 meta-analyses. *BMJ (Clinical research ed.)*. 2003;327:557–60.
- 467 15. Chen D-G (Din), Peace KE. *Applied Meta-Analysis with R*. CRC Press; 2013.
468 331 p.
- 469 16. Gradus JL, Farkas DK, Svensson E, Ehrenstein V, Lash TL, Milstein A, Adler N,
470 Sørensen HT. Associations between stress disorders and cardiovascular disease events in the

- 471 Danish population. *BMJ Open*. 2015;5.
- 472 17. Enga KF, Brækkan SK, Hansen-Krone IJ, Hansen J-B. Emotional states and
473 future risk of venous thromboembolism: the Tromsø Study. *Thrombosis and Haemostasis*.
474 2012;107:485–93.
- 475 18. Strudsholm U, Johannessen L, Foldager L, Munk-Jørgensen P. Increased risk for
476 pulmonary embolism in patients with bipolar disorder. *Bipolar Disorders*. 2005;7:77–81.
- 477 19. Daumit GL, Pronovost PJ, Anthony CB, Guallar E, Steinwachs DM, Ford DE.
478 Adverse events during medical and surgical hospitalizations for persons with schizophrenia.
479 *Archives of General Psychiatry*. 2006;63:267–72.
- 480 20. Khaykin E, Ford DE, Pronovost PJ, Dixon L, Daumit GL. National estimates of
481 adverse events during nonpsychiatric hospitalizations for persons with schizophrenia. *General
482 Hospital Psychiatry*. 2010;32:419–25.
- 483 21. Parker C, Coupland C, Hippisley-Cox J. Antipsychotic drugs and risk of venous
484 thromboembolism: nested case-control study. *BMJ (Clinical research ed.)*. 2010;341:c4245.
- 485 22. Menendez ME, Neuhaus V, Bot AGJ, Vrahas MS, Ring D. Do Psychiatric
486 Comorbidities Influence Inpatient Death, Adverse Events, and Discharge After Lower Extremity
487 Fractures? *Clinical Orthopaedics and Related Research*. 2013;471:3336–48.
- 488 23. Menendez ME, Neuhaus V, Bot AGJ, Ring D, Cha TD. Psychiatric disorders and
489 major spine surgery: epidemiology and perioperative outcomes. *Spine*. 2014;39:E111-122.
- 490 24. Stundner O, Kirksey M, Chiu YL, Mazumdar M, Poultsides L, Gerner P,
491 Memtsoudis SG. Demographics and perioperative outcome in patients with depression and
492 anxiety undergoing total joint arthroplasty: a population-based study. *Psychosomatics*.
493 2013;54:149–57.
- 494 25. Browne JA, Sandberg BF, D’Apuzzo MR, Novicoff WM. Depression is
495 associated with early postoperative outcomes following total joint arthroplasty: a nationwide
496 database study. *The Journal of Arthroplasty*. 2014;29:481–83.
- 497 26. Buller LT, Best MJ, Klika AK, Barsoum WK. The influence of psychiatric
498 comorbidity on perioperative outcomes following primary total hip and knee arthroplasty; a 17-
499 year analysis of the National Hospital Discharge Survey database. *The Journal of Arthroplasty*.
500 2015;30:165–70.
- 501 27. Hsu W-Y, Lane H-Y, Lin C-L, Kao C-H. A population-based cohort study on

- 502 deep vein thrombosis and pulmonary embolism among schizophrenia patients. *Schizophrenia*
503 *Research*. 2015;162:248–52.
- 504 28. Lee CW-S, Liao C-H, Lin C-L, Liang J-A, Sung F-C, Kao C-H. Depression and
505 risk of venous thromboembolism: a population-based retrospective cohort study. *Psychosomatic*
506 *Medicine*. 2015;77:591–98.
- 507 29. Klement MR, Bala A, Blizzard DJ, Wellman SS, Bolognesi MP, Seyler TM.
508 Should We Think Twice About Psychiatric Disease in Total Hip Arthroplasty? *The Journal of*
509 *Arthroplasty*. 2016;31:221–26.
- 510 30. Drinane JJ, Pham T-H, Schalet G, Rezak K. Depression is associated with worse
511 outcomes among women undergoing breast reconstruction following mastectomy. *Journal of*
512 *Plastic, Reconstructive & Aesthetic Surgery*. 2019;72:1292–98.
- 513 31. Søgaaard M, Skjøth F, Kjældgaard JN, Larsen TB, Hjortshøj SP, Riahi S. Atrial
514 fibrillation in patients with severe mental disorders and the risk of stroke, fatal thromboembolic
515 events and bleeding: a nationwide cohort study. *BMJ open*. 2017;7:e018209.
- 516 32. Sundbøll J, Schmidt M, Adelborg K, Pedersen L, Bøtker HE, Videbech P,
517 Sørensen HT. Impact of pre-admission depression on mortality following myocardial infarction.
518 *The British Journal of Psychiatry: The Journal of Mental Science*. 2017;210:356–61.
- 519 33. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis.
520 *Lancet*. 2012;379:1835–46.
- 521 34. Jönsson AK, Schill J, Olsson H, Spigset O, Hägg S. Venous Thromboembolism
522 During Treatment with Antipsychotics: A Review of Current Evidence. *CNS Drugs*.
523 2018;32:47–64.
- 524 35. Zhang R, Dong L, Shao F, Tan X, Ying K. Antipsychotics and venous
525 thromboembolism risk: a meta-analysis. *Pharmacopsychiatry*. 2011;44:183–88.
- 526 36. Ray JG, Mamdani MM, Yeo EL. Antipsychotic and Antidepressant Drug Use in
527 the Elderly and the Risk of Venous Thromboembolism. *Thrombosis and Haemostasis*.
528 2002;88:205–9.
- 529 37. Ferraris A, Szmulewicz AG, Posadas-Martínez ML, Serena MA, Vazquez FJ,
530 Angriman F. The Effect of Antipsychotic Treatment on Recurrent Venous Thromboembolic
531 Disease: A Cohort Study. *The Journal of Clinical Psychiatry*. 2019;80.
- 532 38. Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, Samara M,

533 Barbu C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM.
534 Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-
535 treatments meta-analysis. *The Lancet*. 2013;382:951–62.

536 39. Vancampfort D, Firth J, Schuch FB, Rosenbaum S, Mugisha J, Hallgren M,
537 Probst M, Ward PB, Gaughran F, Hert MD, Carvalho AF, Stubbs B. Sedentary behavior and
538 physical activity levels in people with schizophrenia, bipolar disorder and major depressive
539 disorder: a global systematic review and meta-analysis. *World Psychiatry*. 2017;16:308–15.

540 40. Carrizo E, Fernández V, Quintero J, Connell L, Rodríguez Z, Mosquera M,
541 Acosta A, Baptista T. Coagulation and inflammation markers during atypical or typical
542 antipsychotic treatment in schizophrenia patients and drug-free first-degree relatives.
543 *Schizophrenia Research*. 2008;103:83–93.

544 41. Stubbs B, Gardner-Sood P, Smith S, Ismail K, Greenwood K, Farmer R,
545 Gaughran F. Sedentary behaviour is associated with elevated C-reactive protein levels in people
546 with psychosis. *Schizophrenia Research*. 2015;168:461–64.

547 42. Shen H, Li R, Xiao H, Zhou Q, Cui Q, Chen J. Higher serum clozapine level is
548 associated with increased antiphospholipid antibodies in schizophrenia patients. *Journal of*
549 *Psychiatric Research*. 2009;43:615–19.

550 43. Halacheva K, Dimova S, Tolev T, Dimov D, Nikolova M. Elevated
551 anticardiolipin antibodies in schizophrenic patients before and during neuroleptic medication.
552 *Psychiatry Research*. 2009;169:51–55.

553 44. Dietrich-Muszalska A, Rabe-Jablonska J, Nowak P, Kontek B. The first- and
554 second-generation antipsychotic drugs affect ADP-induced platelet aggregation. *The World*
555 *Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of*
556 *Biological Psychiatry*. 2010;11:268–75.

557 45. Masopust J, Malý R, Andrýs C, Vališ M, Bažant J, Hosák L. Markers of
558 thrombogenesis are activated in unmedicated patients with acute psychosis: a matched case
559 control study. *BMC Psychiatry*. 2011;11:2.

560 46. Gaertner S, Piémont A, Faller A, Bertschy G, Hallouche N, Mirea C, Le Ray I,
561 Cordeanu E-M, Stephan D. Incidence and risk factors of venous thromboembolism: Peculiarities
562 in psychiatric institutions. *International Journal of Cardiology*. 2017;248:336–41.

563 47. Kluge A, Kirschner M, Hager OM, Bischof M, Habermeyer B, Seifritz E, Walther

- 564 S, Kaiser S. Combining actigraphy, ecological momentary assessment and neuroimaging to study
565 apathy in patients with schizophrenia. *Schizophrenia Research*. 2018;195:176–82.
- 566 48. Hem E, Steen O, Opjordsmoen S. Thrombosis associated with physical restraints.
567 *Acta Psychiatrica Scandinavica*. 2001;103:73–76.
- 568 49. Wallaschofski H, Eigenthaler M, Kiefer M, Donn  M, Hentschel B, Gertz HJ,
569 Lohmann T. Hyperprolactinemia in Patients on Antipsychotic Drugs Causes ADP-Stimulated
570 Platelet Activation That Might Explain the Increased Risk for Venous Thromboembolism: Pilot
571 Study. *Journal of Clinical Psychopharmacology*. 2003;23:479.
- 572 50. Ageno W, Di Minno MND, Cihan A, Ju Jang M, Hansen J-B, Steffen LM, Vay 
573 A, Rattazzi M, Pabinger I, Oh D, Di Minno G, Br kkan SK, Cushman M, Bonet E, Pauletto P,
574 Squizzato A, Francesco D. Association Between the Metabolic Syndrome, Its Individual
575 Components, and Unprovoked Venous Thromboembolism. *Arteriosclerosis, Thrombosis, and*
576 *Vascular Biology*. 2014;34:2478–85.
- 577 51. Tirabassi G, Boscaro M, Arnaldi G. Harmful effects of functional
578 hypercortisolism: a working hypothesis. *Endocrine*. 2014;46:370–86.
- 579 52. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between
580 childhood trauma and depression: Insights from HPA axis studies in humans.
581 *Psychoneuroendocrinology*. 2008;33:693–710.
- 582 53. Cherian K, Schatzberg AF, Keller J. HPA axis in psychotic major depression and
583 schizophrenia spectrum disorders: Cortisol, clinical symptomatology, and cognition.
584 *Schizophrenia Research*. 2019;213:72–79.
- 585 54. Belvederi Murri M, Prestia D, Mondelli V, Pariante C, Patti S, Olivieri B, Arzani
586 C, Masotti M, Respino M, Antonioli M, Vassallo L, Serafini G, Perna G, Pompili M, Amore M.
587 The HPA axis in bipolar disorder: Systematic review and meta-analysis.
588 *Psychoneuroendocrinology*. 2016;63:327–42.
- 589 55. Trementino L, Arnaldi G, Appolloni G, Daidone V, Scaroni C, Casonato A,
590 Boscaro M. Coagulopathy in Cushing’s syndrome. *Neuroendocrinology*. 2010;92 Suppl 1:55–59.
- 591 56. Świ tkowska-Stodulska R, Sworczak K. Disorders of Hemostasis in Overt and
592 Subclinical Hypercortisolism. *Experimental and Clinical Endocrinology & Diabetes*.
593 2013;121:588–94.
- 594 57. Lorant V, Deli ge D, Eaton W, Robert A, Philippot P, Anseau M.

595 Socioeconomic inequalities in depression: a meta-analysis. *American Journal of Epidemiology*.
596 2003;157:98–112.

597 58. Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, Correlates, Disability,
598 and Comorbidity of DSM-IV Alcohol Abuse and Dependence in the United States: Results From
599 the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General*
600 *Psychiatry*. 2007;64:830–42.

601 59. Rosengren A, Fredén M, Hansson P-O, Wilhelmsen L, Wedel H, Eriksson H.
602 Psychosocial factors and venous thromboembolism: a long-term follow-up study of Swedish
603 men. *Journal of Thrombosis and Haemostasis*. 2008;6:558–64.

604 60. Holst AG, Jensen G, Prescott E. Risk Factors for Venous Thromboembolism.
605 *Circulation*. 2010;121:1896–1903.

606 61. Zöller B, Li X, Sundquist J, Sundquist K. Socioeconomic and occupational risk
607 factors for venous thromboembolism in Sweden: A nationwide epidemiological study.
608 *Thrombosis Research*. 2012;129:577–82.

609 62. Godin O, Henry C, Leboyer M, Azorin J-M, Aubin V, Bellivier F, Polosan M,
610 Courtet P, Gard S, Kahn J-P, Loftus J, Passerieux C, Costagliola D, Etain B. Sleep quality,
611 chronotype and metabolic syndrome components in bipolar disorders during the remission
612 period: Results from the FACE-BD cohort. *Chronobiology International*. 2017;34:1114–24.

613 63. Mallet J, Le Strat Y, Schürhoff F, Mazer N, Portalier C, Andrianarisoa M,
614 Aouizerate B, Berna F, Brunel L, Capdevielle D, Chereau I, D’Amato T, Denizot H, Dubreucq J,
615 Faget C, Gabayet F, Lançon C, Llorca PM, Misdrahi D, Rey R, Roux P, Schandrin A, Urbach M,
616 Vidailhet P, Fond G, Dubertret C, Andrianarisoa M, Aouizerate B, Bazin N, Berna F, Blanc O,
617 Brunel L, Bulzacka E, Capdevielle D, Chereau-Boudet I, Chesnoy-Servanin G, Danion JM,
618 D’Amato T, Deloge A, Delorme C, Denizot H, Dorey JM, Dubertret C, Dubreucq J, Faget C,
619 Fluttaz C, Fond G, Fonteneau S, Gabayet F, Giraud-Baro E, Lacelle D, Lançon C, Laouamri H,
620 Leboyer M, Le Gloahec T, Le Strat Y, Llorca PM, Mallet J, Metairie E, Misdrahi D, Offerlin-
621 Meyer I, Passerieux C, Peri P, Pires S, Portalier C, Ramet L, Rey R, Roman C, Schandrin A,
622 Schürhoff F, Tessier A, Tronche AM, Urbach M, Vaillant F, Vehier A, Vidailhet P, Vilà E,
623 Yazbek H, Zinetti-Bertschy A. Cigarette smoking and schizophrenia: a specific clinical and
624 therapeutic profile? Results from the FACE-Schizophrenia cohort. *Progress in Neuro-*
625 *Psychopharmacology and Biological Psychiatry*. 2017;79:332–39.

- 626 64. Callaghan RC, Veldhuizen S, Jeysingh T, Orlan C, Graham C, Kakouris G,
627 Remington G, Gatley J. Patterns of tobacco-related mortality among individuals diagnosed with
628 schizophrenia, bipolar disorder, or depression. *Journal of Psychiatric Research*. 2014;48:102–10.
- 629 65. Khan A, Plana-Ripoll O, Antonsen S, Brandt J, Geels C, Landecker H, Sullivan
630 PF, Pedersen CB, Rzhetsky A. Environmental pollution is associated with increased risk of
631 psychiatric disorders in the US and Denmark. *PLOS Biology*. 2019;17:e3000353.
- 632 66. Crous-Bou M, Harrington LB, Kabrhel C. Environmental and Genetic Risk
633 Factors Associated with Venous Thromboembolism. *Seminars in Thrombosis and Hemostasis*.
634 2016;42:808–20.
- 635 67. Wu C-S, Chang C-M, Chen C-Y, Wu EC-H, Wu K-Y, Liang H-Y, Chao Y-L,
636 Chung W-SI, Tsai H-J. Association between antidepressants and venous thromboembolism in
637 Taiwan. *Journal of Clinical Psychopharmacology*. 2013;33:31–37.
- 638 68. Lacut K, Gal GL, Couturaud F, Cornily G, Leroyer C, Mottier D, Oger E.
639 Association between antipsychotic drugs, antidepressant drugs and venous thromboembolism:
640 results from the EDITH case–control study. *Fundamental & Clinical Pharmacology*.
641 2007;21:643–50.
- 642 69. Perna G, Alciati A, Riva A, Micieli W, Caldirola D. Long-Term Pharmacological
643 Treatments of Anxiety Disorders: An Updated Systematic Review. *Current Psychiatry Reports*.
644 2016;18:23.
- 645 70. Pignon B, Tezenas du Montcel C, Carton L, Pelissolo A. The Place of
646 Antipsychotics in the Therapy of Anxiety Disorders and Obsessive-Compulsive Disorders.
647 *Current Psychiatry Reports*. 2017;19:103.
- 648 71. von Känel R, Margani A, Stauber S, Meyer FA, Demarmels Biasiutti F, Vökt F,
649 Wissmann T, Lämmle B, Lukas PS. Depressive symptoms as a novel risk factor for recurrent
650 venous thromboembolism: a longitudinal observational study in patients referred for
651 thrombophilia investigation. *PloS One*. 2015;10:e0125858.
- 652 72. Thrall G, Lane D, Carroll D, Lip GYH. A systematic review of the effects of
653 acute psychological stress and physical activity on haemorrhology, coagulation, fibrinolysis and
654 platelet reactivity: Implications for the pathogenesis of acute coronary syndromes. *Thrombosis
655 Research*. 2007;120:819–47.
- 656 73. von Känel R. Acute mental stress and hemostasis: When physiology becomes

657 vascular harm. *Thrombosis Research*. 2015;135:S52–55.

658 74. Jensen TB, Gerds TA, Grøn R, Bretler D-M, Schmiegelow MD, Andersson C,
659 Azimi A, Gislason G, Torp - Pedersen C, Olesen JB. Risk factors for venous thromboembolism
660 during pregnancy. *Pharmacoepidemiology and Drug Safety*. 2013;22:1283–91.

661 75. Ugras M, Yakinci C. Protein C, protein S and other pro- and anticoagulant
662 activities among epileptic children using sodium valproate. *Brain and Development*.
663 2006;28:549–53.

664 76. Ishida T, Suzuki T, Watanabe K, Sakurai H, Uchida H, Mimura M. Prophylactic
665 use of heparin for deep vein thrombosis in restrained psychiatric patients: a chart review. *General*
666 *Hospital Psychiatry*. 2014;36:690–93.

667 77. Tezenas du Montcel C, Kowal C, Leherle A, Kabbaj S, Frajerman A, Le Guen E,
668 Hamdani N, Schürhoff F, Leboyer M, Pelissolo A, Pignon B. Isolement et contention mécanique
669 dans les soins psychiatriques : modalités de prescription, prise en charge et surveillance. *La*
670 *Presse Médicale*. 2018;47:349–62.

671