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Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence

Running Title: Depression, antidepressant use, and VTE

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ABSTRACT

Purpose: Evidence on the association between depression, antidepressant use and venous thromboembolism (VTE) risk is conflicting. We conducted a systematic review and meta-analysis of published observational studies evaluating the associations of depression and antidepressant use with VTE risk.

Design: Eligible studies were identified in a literature search of MEDLINE, Embase, Web of Science and reference list of relevant studies up to April 2018. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated aggregated using random effects models.

Results: Eight observational studies with data on 960 113 non-overlapping participants and 9027 VTE cases were included. The pooled RR (95% CI) for VTE comparing antidepressant use with no antidepressant use was 1.27 (1.06-1.51). Tricyclic antidepressants, selective serotonin reuptake inhibitors and other antidepressants were each associated with an increased VTE risk; 1.16 (1.06-1.27), 1.12 (1.02-1.23), and 1.59 (1.21-2.09) respectively. In pooled analysis of three studies that compared patients with depression versus individuals without depression, the RR for VTE was 1.31 (1.13-1.53).

Conclusion: Pooled observational evidence suggests that depression and use of antidepressants are each associated with an increased VTE risk. The effect of antidepressant drugs on VTE may be a class effect. The mechanistic pathways underlying these associations deserve further evaluation.

Systematic review registration: PROSPERO 2018: CRD42018095595

Keywords depression; antidepressants; observational study; venous thromboembolism; deep vein thrombosis; pulmonary embolism

KEY MESSAGES

- Emerging evidence suggests that depression and antidepressant use may be associated with venous thromboembolism (VTE) risk, but the evidence is conflicting.
- This first systematic review and meta-analysis of observational studies shows that depression and use of antidepressants are each associated with an increased risk of VTE.
- There may be a class effect of antidepressant drugs on VTE.

Introduction

Venous thromboembolism (VTE), which comprises of deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of morbidity, mortality and associated with high health costs.(1, 2) VTE is regarded as a multifactorial disorder which is determined by genetic, biological, and environmental factors.(3) Despite advances in the knowledge of risk factors for VTE and its treatment, it remains a global public health problem.(4) Against a background risk from established factors such as immobilisation, trauma, surgery, hormonal therapy, obesity, and inherited thrombophilia,(5) several other factors might be involved in the development of VTE; this is because in a substantial number of VTE cases, the causes are unknown;(6) and the occurrence of VTE is not decreasing.(7) This suggests that there are still several yet to be identified factors that are involved in the aetiology of VTE. A number of studies have shown that psychosocial factors such as stress, depression, anxiety, and low socioeconomic status might be associated with VTE development.(8-11) It has been postulated that these factors promote hypercoagulable states through autonomic and neuroendocrine pathways.(12) Emerging evidence suggests that depression and antidepressant use may be associated with the development of VTE. A number of population-based observational studies have reported on the associations of depression and antidepressant use with subsequent risk of VTE, but the results have been conflicting. Whereas some studies have shown evidence of associations,(11, 13-16) others have found no significant relationships.(17-19) The evidence is uncertain and there is a need to summarize all published data on the topic. In this context, we performed a systematic review and meta-analysis of all available published observational evidence to clarify and quantify the extent of potential associations of depression and antidepressant use with the risk of incident VTE.

Methods

Data sources and searches

This review is registered in the PROSPERO prospective register of systematic reviews (CRD42018095595) and was conducted using a predefined protocol and in accordance with PRISMA and MOOSE guidelines (20, 21). We searched MEDLINE, Embase and Web of Science up to April

2018 for population-based observational studies that have evaluated the associations of depression and/or antidepressant use with risk of VTE outcomes. The computer-based searches combined terms and combined key words related to the exposure (e.g., "depression", "antidepressant") and outcome (e.g., "venous thromboembolism", "deep vein thrombosis", "pulmonary embolism") in humans without language restriction or publication date. Further details on the search strategy are presented in **Supplementary Table S1**. Studies which were reported only as abstracts and not published in their full text formats or which were unobtainable as full text copies were excluded. We scanned the reference lists of selected studies and review articles for additional studies.

Study selection and eligibility criteria

Observational longitudinal (prospective cohort, retrospective cohort, nested case-control, or case-control) studies were eligible for inclusion if they assessed the association of depression and/or antidepressant use with first VTE, DVT, or PE events in adults. Studies that reported on recurrent VTE were excluded. The initial screening of titles and abstracts was performed by two independent authors (S.K.K. and S.S.), after which potentially relevant articles were acquired for full text evaluation. The two independent authors assessed each article using the inclusion criteria and any disagreements regarding eligibility of an article was discussed and agreement reached by adjudication of a third author (K.K.).

Data extraction and quality assessment

Using a standardized form, we extracted data on study characteristics such as publication year, study design, geographical location, baseline age, proportion of males, duration of follow-up, sample size and number of VTE events, and risk estimates. Venous thromboembolism outcomes were extracted as reported by the eligible studies. The primary outcome of this analysis was composite VTE (DVT and/or PE). We also extracted data on the specific endpoints of DVT and PE. Risk estimates for the greatest degree of adjustment were extracted. In the case of multiple publications involving the same study, the most up-to-date or comprehensive information was abstracted. We assessed study quality

using the nine-star Newcastle–Ottawa Scale (NOS)(22) which uses three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality.

Statistical analysis

The summary measures were presented as relative risks (RRs) with 95% confidence intervals (CIs). Hazard ratios (HRs) and odds ratios (ORs) were assumed to approximate the same measure of RR following Cornfield's rare disease outcome assumption(23) and also given the fact that the hazard can be treated as the instantaneous risk of an event. The inverse variance weighted method was used to combine summary measures using random-effects models to account for the effect of between-study heterogeneity.(24) We quantified statistical heterogeneity between studies was using the I^2 statistic.(25) We also estimated 95% prediction intervals which are used to determine the degree of heterogeneity, as they provide a region in which about 95% of the true effects of a new study are expected to be found.(26, 27) We conducted subgroup analyses by study level characteristics with sufficient data using random-effects meta-regression.(28) All statistical tests were two-sided and used a significance level of $P<0.05$ and STATA release 14 (StataCorp LP, College Station, TX, USA) software was used for all statistical analyses.

Results

Study identification and selection

Our initial search identified 283 potentially relevant citations (**Figure 1**). After screening the titles and abstracts, 11 articles remained for further evaluation. We reviewed these articles and excluded 3 articles because: (i) outcome was not relevant (n = 1); (ii) study design was not appropriate (n = 1); (iii) study duplicated a previous publication using the same cohort (n = 1). In total, there were 8 eligible articles, which included one article that was identified from manual scanning of the reference

lists. The included articles are based on 8 unique observational studies comprising 960 113 participants and 9027 VTE cases.(11, 13-19) There were 1050 DVT and 79 PE cases.

Study characteristics and quality

Table 1 provides details of the eligible studies. The mean age of participants at baseline ranged from approximately 48 to 68 years, for studies reporting these data. Four studies were based in Europe (UK, Norway, and France), two in Asia (Taiwan), one in North America (Canada), and one in the Pacific (New Zealand). Five studies explored antidepressant use as an exposure, two studies explored depression, and one study explored both antidepressant use and depression. Average duration of follow-up to the development of VTE ranged from 0.9 to 13.5 years. The degree of covariate adjustment varied, but majority of studies adjusted for VTE established risk factors such as age, body mass index, smoking status, and comorbidities. Overall, we judged all of the included studies to be of adequate quality (quality score: 6-8).

Depression, antidepressants, and VTE risk

In pooled analysis of six studies (828 327 participants and 8273 VTE cases), the RR for VTE comparing users of antidepressants with non-users was 1.27 (95% CI: 1.06 to 1.51) (**Figure 2**). The 95% prediction interval for the pooled RR was 0.73 to 2.18%, suggesting that the true RR for any single new study will usually fall within this range. There was evidence of heterogeneity between the contributing studies (I^2=79%, 53 to 90%; p<0.001). On exclusion of two studies that employed a case-control design and assigned a quality score of 6 each, the RR for VTE comparing users of antidepressants with non-users was 1.28 (95% CI: 1.05 to 1.55). In analysis by type of risk estimate reported (HRs vs ORs), the pooled risk estimate of VTE comparing users of antidepressants with non-users for studies reporting HRs was 1.17 (95% CI: 1.09 to 1.27) and that for studies reporting ORs was 1.31 (95% CI: 1.14 to 1.49) (p-value for meta-regression=0.593). Comparing users of antidepressants with non-users, the RRs for DVT (one study) and PE (one study) were 1.02 (95% CI: 0.91 to 1.13) and 4.90 (95% CI: 1.10 to 22.50) respectively. In pooled analysis of two studies (740945

participants and 4905 VTE cases), comparing women who used antidepressants versus women who did not use them, the RR for VTE was 1.44 (95% CI: 1.29 to 1.61).(14, 15) One study reported a RR of 1.38 (95% CI: 0.96 to 1.97) for VTE comparing men who used antidepressants with men who did not use antidepressants.(14) In analysis by antidepressant class; tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and other antidepressants (comprising of monoamine oxidase inhibitors, triazolopyridine, serotonin norepinephrine reuptake inhibitors, or norepinephrine dopamine reuptake inhibitors) were each associated with an increased risk of VTE (**Figure 3**), with no significant difference between them (*p*-value for meta-regression=0.328).

Comparing depression with no depression (3 studies; 865 878 participants; and 4676 VTE cases), the pooled RR for VTE was 1.31 (95% CI: 1.13 to 1.53) with a 95% prediction interval of 0.49 to 3.51%. (**Figure 2**). There was no significant evidence of heterogeneity between the contributing studies (I^2=0%, 0 to 90%; *p*=0.44). One study reported estimates for the specific outcomes of DVT and PE and no significant associations were demonstrated between depression and these endpoints.(13) In pooled analysis of two studies (777,578 participants and 4,125 VTE cases),(13, 15) the RR for VTE in women comparing depression with no depression was 1.21 (95% CI: 1.02 to 1.45). One study reported a RR of 1.65 (95% CI: 1.12 to 2.44) for VTE comparing men with depression versus men no depression.(13)

Discussion

Though a limited number of studies have generally suggested that depression and use of antidepressant drugs may each be associated with an excess risk of VTE, the findings have mostly been mixed and inconclusive. Indeed, some studies have reported significant associations, whereas others have reported null associations. In the largest study conducted to date which comprised over 700 000 women followed for an average of approximately 7 years, it was reported that women who used antidepressants had an increased risk of VTE.(15) However, women who reported treatment for depression but not on antidepressants had no significantly increased risk of VTE. By aggregating data

from all available epidemiological observational studies, we have shown that antidepressant use (vs non-users) as well as depression (vs no depression) are each associated with an increased risk of VTE. The associations were more consistent in women. Furthermore, all three classes of antidepressants (TCAs, SSRIs, and others) were associated with an increased risk of VTE, with no statistically significant difference in their associations. These findings indeed add to accumulating evidence that a relationship exists between depression, antidepressant use, and VTE.

An inflammatory hypothesis has been postulated in the pathogenesis of VTE.(29, 30) Whether the associations we have demonstrated is driven by the antidepressant drugs or depression itself or both is not very clear. It is difficult to determine this based on evidence from the studies included in this review. Based on results from the Million Women Study,(15) which showed that women who reported treatment for depression but not on antidepressants did not experience a significant increased VTE risk, it has been suggested that the driving force behind VTE development could be due to antidepressants rather than the condition itself.(31) Parkin and colleagues hypothesized the observed association between antidepressant use and risk of PE could be due to the chemical similarities between TCAs (commonly used in treating depression) and phenothiazines.(16) Phenothiazines, which are antipsychotics, have been postulated to increase the risk of VTE via increased aggregation of platelets,(32) the presence of anticardiolipin antibodies,(33) and exacerbation of venous stasis as a result of the sedative effect.(33) Given that the classes of antidepressant are pharmacologically distinct and the evidence suggests that VTE risk is similar across the various classes of antidepressants, it has also been argued that increased VTE risk may be related to depression itself and not due to the antidepressant drugs.(31) A number of pathways have been proposed to explain the role of depression in the development of VTE. Depression could impair immobility,(34) which is an established risk factor for VTE. Patients with depression are known to have high rates of hyperhomocysteinemia,(35) which has been suggested to be associated with an increased risk of VTE.(36) Patients with depression may have an elevated VTE risk due to greater platelet activation and increased procoagulant activity.(37) Furthermore, it is also possible that the observed associations are due to confounding factors such as poor underlying health status, lifestyle, or diet and problems

with mobilization, which are common characteristics in some of these patients. The evidence on the mechanistic pathways linking depression, antidepressant use, and VTE risk are still speculative.

Whether the associations are causal or may be just an epiphenomenon, these findings are very relevant and underscore the deleterious effects of both depression and antidepressant use on VTE risk. Though antidepressant drug groups are pharmacologically distinct in addition to their varying effects, our findings suggest there may be a class effect of antidepressant drugs on VTE. Depressive disorders are one of leading cause of the global burden of disease and constitute an important cause of years lived with disability.(38) Antidepressant drugs have multiple indications, which include anxiety, pain, and neuralgia and their use is on the increase on a global scale.(39, 40) Before patients are prescribed antidepressants, prescribers may need to conduct further evaluation to determine the excess risk of VTE in these patients. However, further studies are still warranted to establish the role of depression and antidepressant use in VTE development, their potential causative pathways, and if there is a class effect of antidepressants on VTE. Furthermore, additional research is needed to ascertain whether it is depression or antidepressant use which drives an increase in VTE risk. These would need to involve studies that are able to assess both exposures and provide a way of isolating the effects of one exposure from the other. For example, assessing the effect on individuals who are not depressed but use antidepressants for a condition such as neurologic or gastrointestinal disease.

To our knowledge, we have conducted the first systematic review and meta-analysis to summarise the evidence on the associations of depression and antidepressant use with the risk of VTE. Though the evidence was limited, we were able to harmonize data to perform a quantitative analysis, which enhanced power and provided more robust associations compared to the associations reported by individual studies. For studies of antidepressant use, we were able to conduct sensitivity analyses by type of study design and risk estimates reported and the results were observed to persist. However, the few number of studies prevented further evaluation of the associations in clinically relevant subgroups such as age, sex, diagnosis of depression (clinical diagnosis vs. diagnosis based on self-reported questionnaires), type of VTE (provoked vs unprovoked), severity of depression, and duration of depression. There was limited data on the specific outcomes of DVT and PE and therefore their

associations could not be evaluated in much detail. In addition, pooled analysis was based on variably adjusted data reported by the eligible studies, therefore prone to confounding by unmeasured factors. However, majority of studies adjusted for relevant confounding factors. Furthermore, the limited number of studies (< 10) precluded assessment of publication bias. Finally, estimated prediction intervals of the pooled RRs of the associations contained values below 1 and so, although on average there seemed to be evidence of associations of depression and antidepressant use with VTE risk, this may not always be so in other studies. Further research is needed to replicate these associations and identify causes of the heterogeneity between studies.

Conclusions

Pooled observational evidence suggests that depression and use of antidepressants are each associated with an increased risk of VTE. The effect of antidepressant drugs on VTE may be a class effect. The mechanistic pathways underlying these associations deserve further evaluation.

Disclosure of interest

The authors report no conflicts of interest.

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Figure legends

Figure 1. PRISMA flow diagram

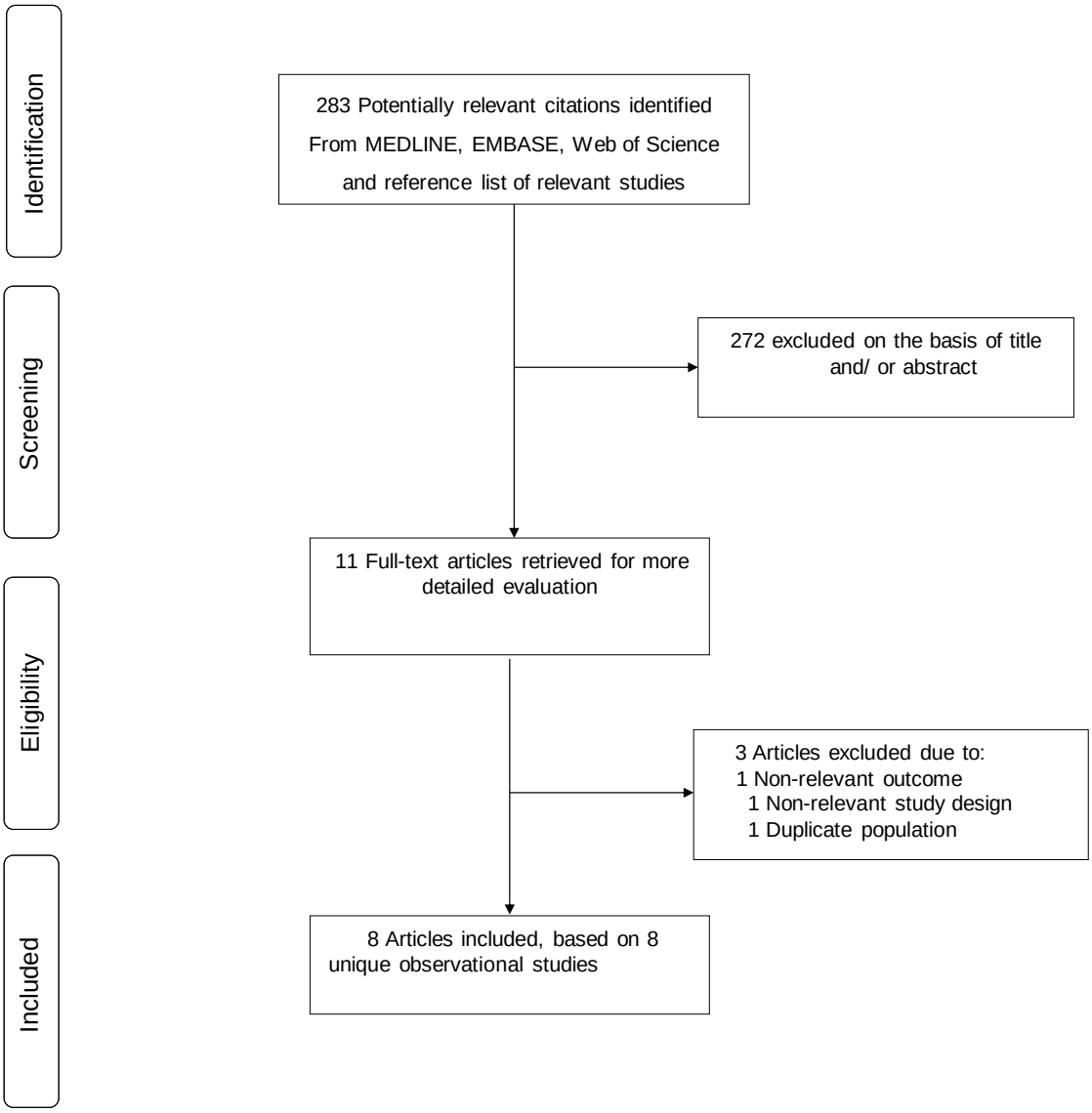
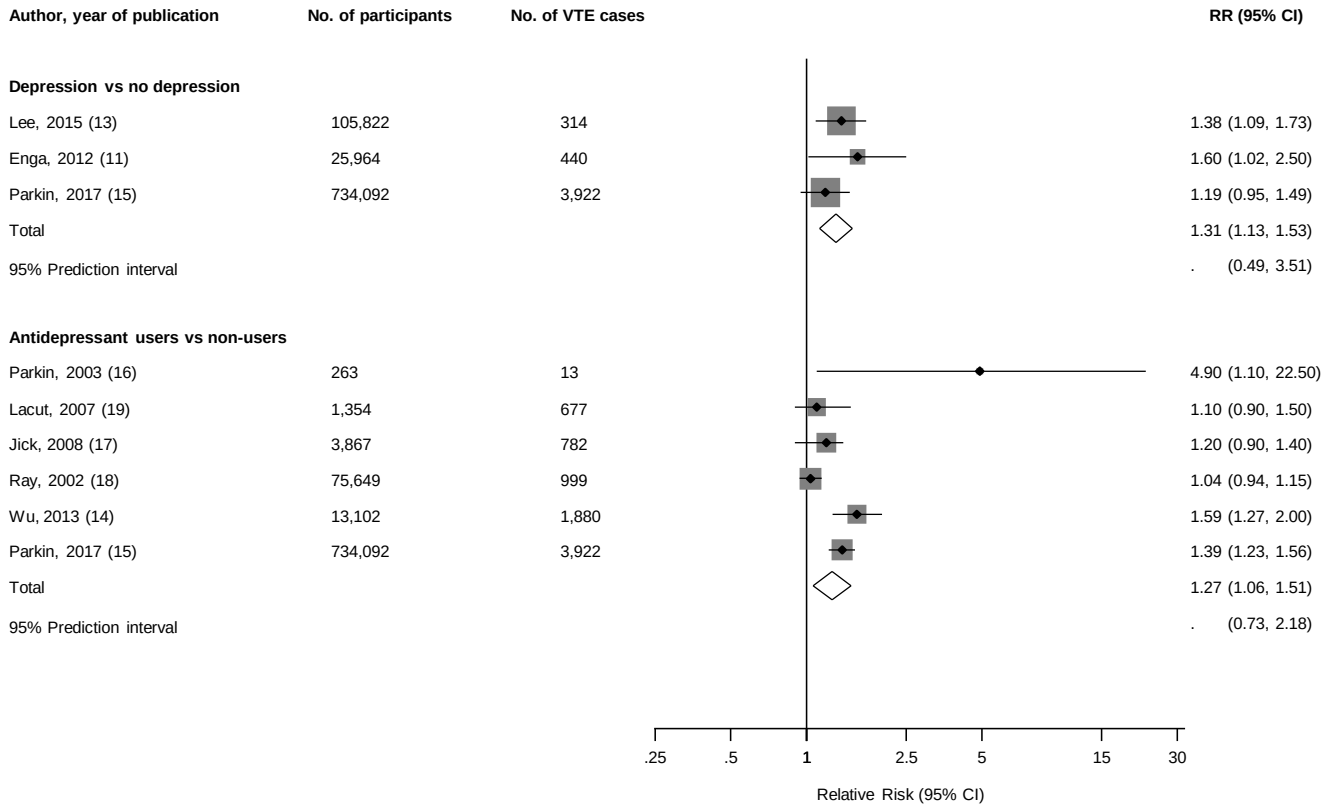
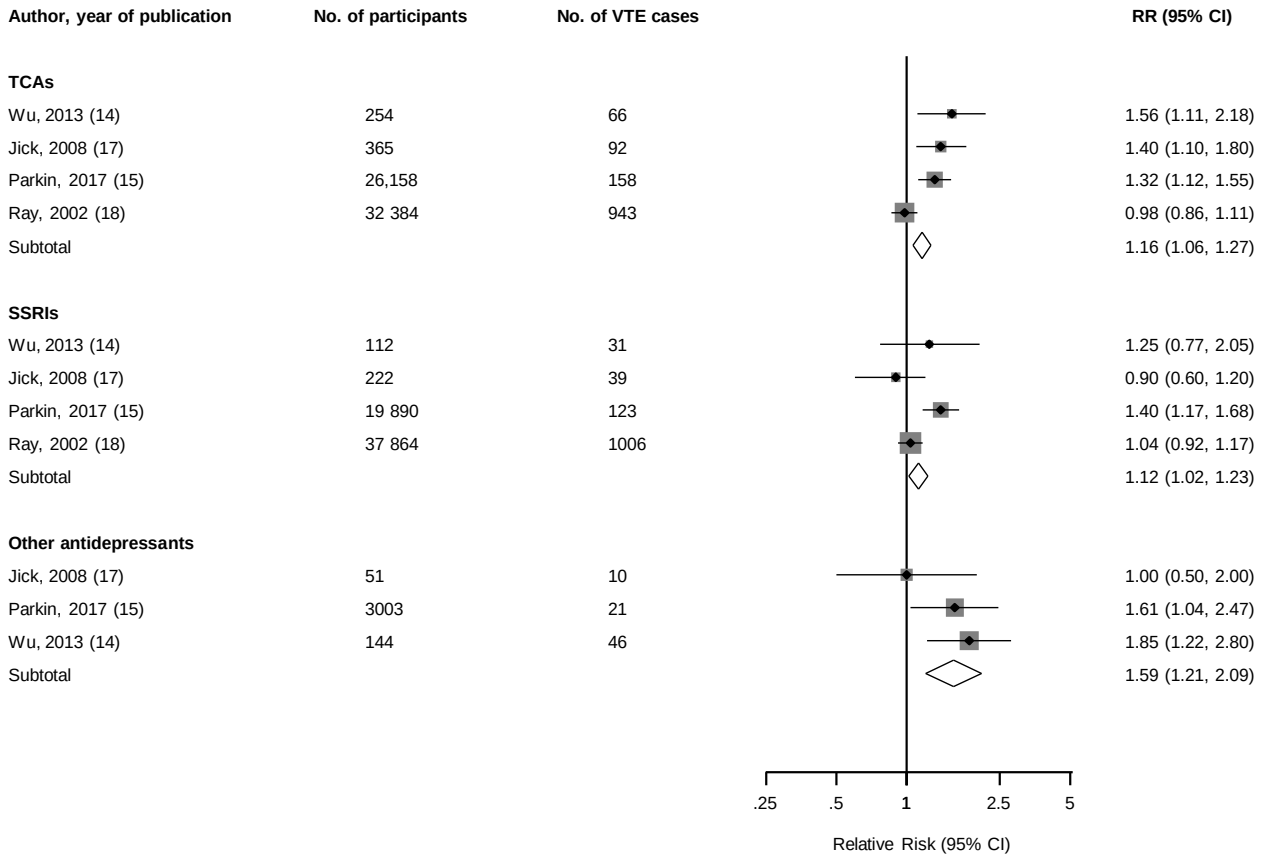


Figure 2. Associations of depression and antidepressant use with risk of venous thromboembolism



CI, confidence interval (bars); RR, relative risk; VTE, venous thromboembolism

Figure 3. Associations of antidepressant groups with risk of venous thromboembolism



CI, confidence interval (bars); RR, relative risk; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; VTE, venous thromboembolism

Table 1. Characteristics of studies included in review

Lead Author, Publication Date (Reference)	Name of study or source of participants	Location	Study design	Year of baseline survey	Baseline age range (years)	% male	Follow up (years)	Exposure	Outcomes reported	Type of risk estimate	No. of VTE events	Total participants	Covariates adjusted for	Study quality
Enga, 2012 (10)	Tromso	Norway	Prospective cohort	1994-1995	25-96	NR	12.4	Depression	VTE		440	25 964	Age, sex, BMI, oestrogens, lifestyle and co-morbidities	8
Lee, 2015 (12)	LHID 2000	Taiwan	Retrospective cohort	2000	48.0*	38.4	11.0	Depression	VTE, DVT, and PE		314	105 822	Age, sex, comorbidities of atrial fibrillation, hypertension, diabetes, CVA, heart failure, cancer	8
Wu, 2013 (13)	LHID 2005	Taiwan	Nested case-control	2001	63.3‡	47.7	8.0	Antidepressant use	VTE	OR	1,880	13 102	Disease risk score based on comorbid medical and psychiatric illnesses (controls were matched on age and sex)	8
Parkin, 2017 (14)	Million Women Study	UK	Prospective cohort	1996-2001	59.9*	0.0	7.3	Depression and antidepressant use	VTE	HR	3,922	734 092	Age, BMI, smoking, alcohol consumption, frequency of strenuous physical activity, hormone therapy, diabetes mellitus, high blood pressure, and socioeconomic status, and stratified by recruitment region	8
Parkin, 2003 (15)	GP database	New Zealand	Case-control	1990-1998	15-59	NR	12.2-13.5	Antidepressant use	PE	OR	13†	263†	Weight, combined oral contraceptive use and hormone replacement (controls matched on sex and year of birth)	6
Jick, 2008 (16)	UK GPRD	UK	Nested case-control	1990-2005	≤ 70	34.8	NR	Antidepressant use	VTE	OR	782	3867	Smoking, BMI (controls matched on age, sex, practice attended by case patient, index data, and duration of previous computerized record)	6
Ray, 2002 (17)	Administrative database	Canada	Retrospective cohort	1994-2000	≥ 65	75.0	0.9	Antidepressant use	VTE and DVT	HR	999	75 649	Age, sex, currently residing within a long-term facility, recent prior hospitalization, concurrent diagnosis of cancer, and concurrent prescription of ASA, warfarin, estrogen or lithium	7
Lacut, 2007 (18)	University Hospital	France	Case-control	2000-2004	68.0*	43.3	NR	Antidepressant use	VTE	OR	677	1354	BMI, factor V Leiden, and prothrombin G20210A gene variation (controls were matched on age and gender)	6

*, average age; †, these numbers are based on subjects without major risk factors for VTE; ‡, mean age of VTE cases; ASA, acetylsalicylic acid; BMI, body mass index; CVA, cerebral vascular accident; DVT, deep vein thrombosis; GP, general practitioner; HR, hazard ratio; LHID, Longitudinal Health Insurance Database; NR, not reported; OR, odds ratio; PE, pulmonary embolism; UK GPRD, United Kingdom General Practice Research Database; VTE, venous thromboembolism