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Current antipsychotic agent use and risk of venous thromboembolism and pulmonary embolism: a systematic review and meta-analysis of observational studies

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Abstract

Background: Antipsychotic agents (APS) are widely used drugs to treat psychotic symptoms and can effectively reduce both positive and negative symptoms of schizophrenia. For decades, some studies suggested that there is a relationship between using APS and the risk of venous thromboembolism (VTE) and pulmonary embolism (PE). However, results remain inconclusive.

Method: This review has been registered in International Prospective Register of Systematic Reviews (PROSPERO, ID: CDR42020155620). Relevant studies were identified among observational studies published up to 1 October 2019 in the databases MEDLINE, EMBASE, and Cochrane Library. Random or fixed-effects models were used to calculate the pooled odds ratio (OR).

Results: In total, 28 observational studies were included. The results showed that compared with non-users, current APS users have significantly increased risks of VTE [OR 1.55 95% confidence interval (CI) 1.36, 1.76] and PE (OR 3.68, 95% CI 1.23, 11.05). Subgroup analyses suggested that new users were associated with a higher risk of VTE (OR 2.06, 95% CI 1.81, 2.35). For individual drugs, increased risk of VTE and PE was observed in taking haloperidol, risperidone, olanzapine, prochlorperazine but not in chlorpromazine, quetiapine or aripiprazole. However, careful interpretation is needed because of high heterogeneity among studies and scarce data.

Conclusion: The present comprehensive meta-analysis further indicates a significantly increased risk of VTE and PE in current APS users compared with non-users. Subgroup analyses suggest that new users are more likely to develop VTE. However, due to significant heterogeneity among studies, conclusions should be considered with caution.

Keywords: antipsychotic agents, meta-analysis, pulmonary embolism, systematic review, venous thromboembolism

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Introduction

Antipsychotic agents (APS) are a group of drugs with a wide range of indications used mainly for psychotic symptom treatment, and are recommended for treating schizophrenia, bipolar disorder, resistant depression, autism spectrum disorder, Tourette's disorder *et al.*[1–4] Most APS can effectively reduce both positive and negative symptoms of schizophrenia.[5] However, as APS use is widespread, the safety of APS must be considered. The life expectancy of schizophrenia patients has been shown to be 14.5 years less than that of the healthy population,[6] and sudden unexpected death was found to be correlated with multiple APS in a meta-analysis.[7] Pulmonary embolism (PE) is a severe condition that can lead

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to sudden death and can be caused by a venous thromboembolism (VTE) that has broken free from the vein wall.

Many cases of sudden death caused by PE related to APS exposure have been reported for decades,[8–12] but the relationship between APS usage and risk of VTE and PE is still controversial. The first epidemiological study of APS associated with VTE risk was conducted by Walker *et al.* in 1997, showing that current clozapine exposure related to a five-fold increase in risk of fatal PE compared with past exposure to clozapine.[13] Thereafter, Zornberg and Jick performed a nested case-control study to investigate whether any APS have an influence on VTE and concluded first-generation antipsychotic medication (FGA) exposure increased the risk of VTE significantly.[14] However, a few studies failed to recognize this association.[15,16] To identify the precise VTE and PE risk in APS users, Zhang *et al.* conducted a meta-analysis of seven case-control studies, indicating that the risk of VTE was increased 2.39-fold in APS users.[17] Afterward, Barbui *et al.* performed a systematic review and meta-analysis of 17 observational studies in 2014 and ascertained that APS users were at higher risk for VTE [odds ratio (OR) 1.54, 95% confidence intervals (CIs) 1.28–1.86] than non-users but not for PE (OR 4.90, 95% CIs 0.77–30.98). More pronounced VTE risk was found for both FGA (OR 1.74, 95% CIs 1.28–2.37) and second-generation antipsychotic medication (SGA) (OR 2.07, 95% CIs 1.74–2.52).[18] Moreover, the same group of researchers conducted a nested case-control study and updated the meta-analysis to suggest that APS users have a higher risk for PE (OR 3.68, 95% CIs 1.22–11.07).[19] However, high heterogeneity of included studies limited the reliability of the practice. Recently, a meta-analysis updated this risk to 1.53-fold for VTE and 3.69-fold for PE[20] but failed to include several observational studies.[13,21–25] In addition, studies that have recurrent VTE as the outcome were not included in the analysis.[26–28]

Thus, a comprehensive meta-analysis of all observational studies is needed to ascertain the correlation of APS with VTE and PE risk. Studies with recurrent VTE risk as the outcome were also evaluated in subgroup analysis. Furthermore, VTE risk associated with APS of different types, potencies, doses, usage durations, and individual APS exposure were also assessed to provide more information on clinical practice.

Methods

Data sources and searches

This review has been registered in PROSPERO (International Prospective Register of Systematic Reviews, ID: CDR42020155620)[29] and conducted by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[30] and Meta-Analyses of Observational Studies in Epidemiology (MOOSE).[31] Articles published up to 1 October 2019 in the databases MEDLINE, EMBASE, and Cochrane Library were searched. The keywords used in the search were "antipsychotic agents," "antipsychotic drugs," "antipsychotics" AND "thrombosis," "deep venous thrombosis," "venous thrombosis," "pulmonary embolism," and the full electronic search strategy is in the supplemental materials. In addition, further relevant studies were found in the references of retrieved articles.

Eligible criteria and quality assessment

The following inclusion criteria were used to select eligible studies: (1) observational design, (2) APS users *versus* a non-users group, (3) evaluation of the relationship between APS and risk of VTE and PE, (4) Risk ratios (RR), ORs, or hazard ratios (HR) with corresponding CIs were reported or these values could be calculated with sufficient information.

Two authors (LYZ and XJ) independently selected the eligible studies following the criteria above and assessed the quality of included studies. As recommended by the Cochrane Collaborations, the Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality of the included studies. A study with a below-average NOS score was defined as low quality, and a study with a NOS score at or above the average was defined as high quality.

Data extraction

Two authors (LYZ and XJ) extracted data independently, and discrepancies were resolved through discussion with the third author (XY). Data related to the characteristics and reported results of each study were extracted. The following data were extracted: study name, data source, study design, study population characteristics, total population, ascertainment of APS exposure, outcome, definition of outcome, VTE risk factors exclusion, controlled variables, raw data, unadjusted OR, RR or

HR with corresponding 95% CIs and adjusted OR, RR or HR with corresponding 95% CIs in the analysis.

Statistical analysis

Review Manager (RevMan) Version 5.2 software was utilized for all statistical analyses. The occurrence of VTE or PE in current APS users compared with unexposed individuals or past APS users was the outcome measure of this analysis. Adjusted ORs, RRs, or HRs with their corresponding 95% CIs were synthesized for analysis. Moreover, raw data were also used to calculate unadjusted ORs. Because the outcome of interest was rare, the OR, RR, and HR can be regarded as equivalent. The inverse variance method was used for combining studies, and both fixed and random-effects models were performed for pooling. Heterogeneity was assessed by Cochran's Q chi-square test and I^2 index.[32] When I^2 value was above 50% and $p \leqslant 0.1$, there was considered to be significant heterogeneity among the study results, and a random-effects model was performed for pooling. Otherwise, a fixed-effects model was used. Subgroup meta-analyses were performed according to the following: (1) recurrent VTE, (2) cohort study design, (3) case-control study design, (4) high quality of study methodology, (5) gender, (6) age, (7) psychiatric disorder category, (8) types of APS (FGA only, SGA only, combined), (9) duration of current APS use [new users (defined as participants who had no APS prescription from the current usage time window to at least 1 year before the index date), continuing users (defined as exposure to APS during both the current usage time window and from the current usage time window to at least 1 year before the index date)], (10) potency of APS (high potency, low potency), (11) dose of APS, and (12) individual APS. Sensitivity analysis was performed by eliminating one study in turn to estimate the stability and reliability of the results of the meta-analysis. Publication bias of the included studies was investigated by funnel plot.

Results

Search results

The three databases were searched by using the keywords, and a total of 2275 potentially relevant articles were identified after duplicates were removed. Of all these articles, 2202 were excluded by the screening of titles and abstracts. Of these, 19 articles are conference abstracts, 116 articles are a letter or note, 352 are case reports, 685 are reviews, and 1030 articles are obviously not relevant. Thereafter, 73 articles were included in the full-text assessed. Of these, 45 studies were excluded because of the reasons reported in the diagram (Figure 1). Therefore, 28 studies[13–16,19,21–28,33–47] were eligible for inclusion and quality assessment.

Characteristics of included studies

Table 1 shows the characteristics of the 28 studies included in the meta-analysis. Of all the included studies, 17 were case-control studies,[14,16,19,21,22,24,33–35,37–42,45,46] of which nine had a nested case-control design.[14,16,19,21,40–42,45,46] Eleven were cohort studies.[13,15,23,25–28,36,43,44,47] In terms of data sources, 20 studies identified patients from databases,[13–16,19,21,23,25,26,28,36,37,40–47] four studies identified patients from hospital medical records,[22,24,27,38] two used autopsy records,[35,39] one study used both police records and hospital records,[34] and one used previous cohort study data. The patient populations of most of these studies were heterogeneous, and diagnostic categories were not restricted. In addition, two studies included dementia patients only,[45,47] six studies focused on elderly patients,[15,36,41,45–47] and two studies focused on female APS users,[23,46] of which one study included menopausal women[46] and the other study focused on pregnant women.[23] While the majority of included studies ascertained VTE and PE by diagnostic codes, six studies used PE diagnostic codes only,[13,19,34,35,39,44] and 18 studies excluded or controlled mainly confounding factors of VTE and PE.[14–16,19,21,23,27,28,34,36,37,40–43,45–47] Three studies employed recurrent VTE as the outcome. One study is a re-analysis of the Leiden Thrombophilia Study (LETS), a case-control study on patients with venous thrombosis, rather than a case-control design directly for the purpose on the VTE risk of antipsychotics. Supplemental materials show the results of the NOS score that was used to assess the quality of observational studies. The mean score was 6.6 for the 28 studies.

Main results

Figure 2 shows the ORs of VTE and PE risks with APS used in individual studies and summary estimates. Twenty-one studies (22 estimates) provided data eligible for the risk of VTE analysis, showing that compared with non-users, current APS use can significantly increase the risk of VTE by about 50% (OR 1.55 95% CIs 1.36, 1.76).

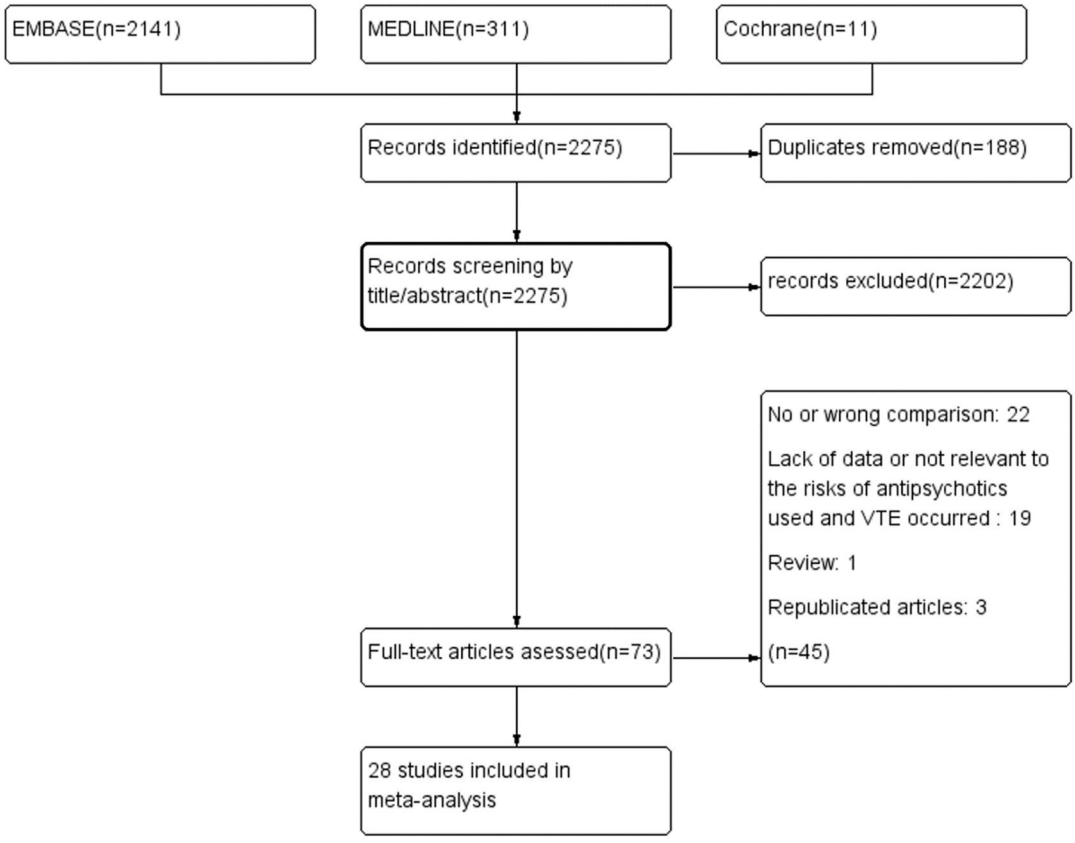


Figure 1. Flow diagram of relevant studies identification.

However, a high heterogeneity was observed ($p < 0.00001$; $I^2 = 85\%$).

Suitable data were extracted from four studies for PE risk estimates and showed that current APS use also increased the risk of PE (OR 3.68, 95% CIs 1.23, 11.05), but the heterogeneity was significantly high ($p < 0.00001$; $I^2 = 90\%$).

Subgroup meta-analysis

The results of the subgroup meta-analyses are shown in Table 2. The risk of recurrent VTE was increased for APS users based on three studies' data analysis (OR 1.62 95% CIs 1.18, 2.24), and no heterogeneity was observed ($p = 0.66$, $I^2 = 0\%$). Subgroup analysis of both cohort (OR 1.50, 95% CIs 1.22, 1.83) and case-control (OR 1.58, 95% CIs 1.33, 1.89) designs shows that APS also significantly increases the risk of VTE. A similar result was observed in the high-quality subgroup (OR 1.50, 95% CIs 1.30, 1.72). Both male (OR 1.80, 95% CIs 1.52, 2.14) and female (OR 1.63, 95% CIs 1.37, 1.93) patients taking APS were found to have significantly increased risk of VTE. This association was not found in elderly patients (OR 1.33, 95% CIs 0.99, 1.79). However, high heterogeneity was observed ($p < 0.00001$, $I^2 = 95\%$). When studies were grouped by diagnostic categories, a significant increase in VTE risk was observed among schizophrenia patients (OR 1.34, 95% CIs 1.15, 1.55), but not among dementia patients (OR 1.44, 95% CIs 0.99, 2.08). One study researched the VTE risk in patients with bipolar disorder, and the result showed that the VTE risk is not significantly increased in bipolar disorder (OR 1.22, 95% CIs 0.91, 1.65).

In the subgroup of meta-analyses concerning categories of APS, using FGA (OR 1.47, 95% CIs 1.21, 1.78) and SGA (OR 1.62, 95% CIs 1.28, 2.05) both significantly increased the risk of VTE. A similar association was observed for combination use of two types of APS (OR 2.01, 95% CIs 1.47, 2.75). When studies were grouped by usage duration, new users were more vulnerable to VTE (OR 2.06 95% CIs 1.81, 2.35) than continuing

Table 1. Characteristics of studies.

Study	Data source	Design	Population characteristics	Total population	Ascertainment of antipsychotic agents exposure	Outcome	Outcome definition	VTE risk factors exclusion	Controlled variables	High quality
Walker *et al.*[13]	Clozaril National Registry (CNR)	Retrospective cohort study	The fetal PE rates of current and recent clozapine exposure group *versus* past clozapine exposure group	67,072 patients	Current use clozapine (since last clozapine exposure within 14 days)	PE	ICD codes	Over 54 years of age	Race, sex, and age	No
Wolstein *et al.*[25]	Arzneimittelsicherheit in der Psychiatrie in Germany	Prospective cohort study	Severe adverse drug reactions among inpatients of 35 psychiatric hospitals in Germany and Switzerland	13,081 received clozapine, 59,637 received other antipsychotic medication, 30,282 were not treated with antipsychotic medication	Unclear	VTE	Unclear	No	No	No
Zornberg and Jick[14]	UK-based General Practice Research Database	Nested case-control study	Patients younger than 60 who used at least one first-generation or second-generation antipsychotic medication between 1 January 1990 and 31 October 1998; controls matched by age, sex, general practice attended, and index date	42 individuals with idiopathic venous thromboembolism and 168 matched controls	Current use: 1–60 days before the index date	VTE	ICD codes, & objective tests	Individuals over 60, trauma, pregnancy, surgery, coagulopathies, congestive heart failure, myocardial infarction, cancer, renal failure, epilepsy, diabetes mellitus, cystic fibrosis, multiple sclerosis, psychotic episode, alcohol and substance use disorders, previously VTE occurred	Age, sex, general practice attended, years in GPRD, and index date, smoking status, BMI, estrogens exposure, antidepressant, hypertension	Yes
Thomassen *et al.*[33]	Leiden University Medical Center	Case-control study	Outpatients who suffered first-episode VTE as the case group, each case matched a control by gender and age	474 VTE cases 474 controls	Current use (unclear definition)	VTE	Objective tests defined	Older than 70, malignancies, recurrent VTE	Unclear	No
Ray *et al.*[15]	Linked health care administrative databases	Retrospective cohort study	Individuals aged 65 years and over exclusively prescribed either antipsychotic drugs or antidepressant drugs; thyroid replacement hormones as the control group	22,514 antipsychotic agents used; 75,649 antidepressant drugs used; 33,033 thyroid hormones used as control	Current use (previously used in 180 days)	VTE	ICD codes	Cancer, previously VTE/PE in 3 years. Used warfarin in 1 year.	Age, sex, living in residential facility, recent prior hospitalization, cancer and prescription of ASA, warfarin, estrogen, lithium	Yes
Parkin *et al.*[34]	Coroner and police records, death certificates and hospital records in New Zealand	Case-control study	New Zealand men and women aged 15–59 years who died from PE between 1 January 1990 and 31 December 1998, each case matched 4 controls by sex and year of birth	75 fetal PE cases 300 controls	Current use (previously 3 months)	PE	ICD codes & objective tests	No	Weight, combined oral contraceptive use and hormone replacement therapy during the 3 months before the index date	No

(Continued)

Table 1. (Continued)

Study	Data source	Design	Population characteristics	Total population	Ascertainment of antipsychotic agents exposure	Outcome	Outcome definition	VTE risk factors exclusion	Controlled variables	High quality
Hamanaka *et al.*[35]	Autopsy records from January 1998 to December 2002 in Japan	Case-control study	Reviewed sudden death autopsy records. Cases were defined by massive thrombus that filled the lumen of the major pulmonary vessels	1125 autopsy records. 34 antipsychotic medication users, 28 cases were defined as death from PE	Unclear	PE	Autopsy records	Unclear	Age, gender, BMI	No
Liperoti *et al.*[36]	Systematic Assessment of Geriatric Drug Use *via* Epidemiology (SAGE) database, which contains data from the Minimum Data Set (MDS)	Retrospective cohort study	Over 65 years of age nursing home residents, 6 months follow-up	19,940 exposed to antipsychotic agents and 112,078 non-user control	New users (previous 7 days)	VTE	ICD-9	Schizophrenia patients	Age, sex, BMI, functional and cognitive status, history of deep venous thrombosis, hip fracture, COPD, cancer, and drugs (anticoagulants, aspirin antiplatelets, estrogens. co-morbidities (dementia, depression, peripheral vascular disease, cerebrovascular disease, heart failure, diabetes mellitus)	Yes
Lacut *et al.*[37]	EDITH study (well-documented VTE cases occurring between May 2000 and December 2004 in Brest University Hospital)	Case-control study	Over 18 years of age hospitalized patients who suffered from VTE. Controls were matched with the cases by age and gender, and had no major acquired risk factors as previously defined	677 VTE cases; 677 non-VTE controls	Current users and have to have been using for more than 1 week prior to admission	VTE	Objective tests	Surgery, plaster cast, pregnancy, delivery, active malignancy in past 3 months	BMI factor V Leiden and prothrombin G20210A gene variation	Yes
Masopust *et al.*[38]	Hradec Kraáloveé university hospital's electronic information system during 1 January 1996–31 December 2004	Case-control study	Patients hospitalized with DVT/PE between 18–60 years of age as the case group, arterial hypertension patients as control group	266 VTE cases 274 controls	Current users defined as taking any antipsychotic medication for at least 4 weeks	VTE or PE	Hospital medical records	No	No	No
Jönsson *et al.*[39]	Autopsy records within National Board of Forensic Medicine in Sweden	Case-control study	Age between 18 and 65 autopsy PE cases	279 PE patients, 14 160 controls	Postmortem analyses	Fetal PE	ICD codes	Injuries and intoxications as the cause of death were excluded	Age, sex	No

(Continued)

Table 1. (Continued)

Study	Data source	Design	Population characteristics	Total population	Ascertainment of antipsychotic agents exposure	Outcome	Outcome definition	VTE risk factors exclusion	Controlled variables	High quality
Jönsson *et al.*[40]	Denmark medical databases	Nested case-control study	First-time diagnosis of VTE for cases. Each case matched 10 controls on age, sex and county	5999 cases of VTE/ PE 59,990 controls	Medical databases' data. Antipsychotic drug exposure defined as any antipsychotic taken within 365 days before the VTE-related hospital admission date	VTE	ICD codes	Surgery, major trauma, fractures, pregnancy within the prior 3 months; cancer within, prior to, and following 3 months	Myocardial infarction, stroke, COPD, peripheral atherosclerosis in the legs, heart failure, diabetes and current use of statins, low-dose acetylsalicylic acid, postmenopausal hormone replacement therapy and vitamin K antagonists	Yes
Kleijer *et al.*[41]	PHARMO institute's record linkage system	Nested case-control study	Patients aged over 60 years of age who started with prescription for an APD between January 1998 and December 2008. Controlled group matched on age, sex, and duration of registration in the database	1032 cases of VTE; 4125 controls	Current users (divided in five categories: 0–7, 8–14, 15–30, 31–90, and >90 days before the index date) ascertain by databases records	VTE	ICD codes	No	Immobilization, recent trauma surgery, hormone replacement therapy. Cancer cardiovascular disease, COPD, bacterial infection and medication treated for infection. Male, prior hospitalization for any reason within 3 months, vitamin K antagonists or heparins treatment	Yes
Parker *et al.*[42]	QResearch database	Nested case-control study	Patients with the first-episode VTE between January 1996 and July 2007 in the database were identified by the case group. Each case matched 4 controls by single year of age, calendar time, sex, and practice	25,532 cases of VTE 89,491 matched controls	Any antipsychotic medication prescriptions issued in the 24 months before the index date, current use defined as 3 months before the index date	VTE	Post-mortem records Diagnostic codes	Insufficient data; past warfarin used, previous cancer, coronary heart disease, stroke, congestive cardiac failure; hip surgery, hip or lower limb fracture, or pregnancy within the previous 6 months	Socioeconomic status, the co-morbidity and drug variables, the number of complete months of data before the index date, mental health indication	Yes
Hippisley-Cox and Coupland[43]	QResearch database	Cohort study	Cohort of patients aged 25–84 years drawn from patients registered with general practices between 1 January 2004 and 30 April 2010	2,314,701 patients; 14,756 cases of VTE	Current use (previous 30 days)	VTE	ICD codes	History of venous thromboembolism, oral anticoagulation drugs, pregnancy, delivery	Age, body mass index, smoking status, medical history, current medication	Yes
Allenet *et al.*[44]	'Premier's Perspective' database (US clinical and economic database from about 500 acute care hospitals)	Retrospective cohort study	Attended a hospital consultation or been hospitalized at least once in 2006, over 18 years of age, participating in the Premier project	450,951 patients in antipsychotic agents users cohort, 28,272,820 in non-antipsychotic users cohort	Any antipsychotic medication used identified by database records	PE	ICD codes	No	Age, sex, the individual components of the Charlson co-morbidity index	No

(Continued)

Table 1. (Continued)

Study	Data source	Design	Population characteristics	Total population	Ascertainment of antipsychotic agents exposure	Outcome	Outcome definition	VTE risk factors exclusion	Controlled variables	High quality
Schmedt and Garbe[45]	German Pharmacoepidemiological Research Database	Nested case-control study	>65 years of age dementia patients hospitalized with a main discharge diagnosis for DVT or PE as the case group. Each case matched 4 controls by year of birth, sex, SHI, and calendar time of the VTE	1028 cases of VTE; 4109 controls	Any antipsychotic medication prescription within the 365 days before the index date, current use defined as 3 months before the index date.	VTE	ICD codes	No	Co-morbidities, schizophrenia, bipolar disorder, previous VTE, fracture, surgery, hospitalization, drugs	Yes.
Wu *et al.*[21]	National Health Insurance Research Database	Nested case-control study	Cohort was comprised of participants over 16 years of age between January 2001 and December 2010. Cases were defined as VTE patients. Every case matched 6 controls by age and gender	2162 cases of VTE 12,966 controls	At least 1 day of antipsychotic drug supply within the 12 months prior to the index date	VTE	ICD codes	Cases with diagnosis of VTE before 2000.12, less than 16 years of age, participation in the database for less than 1 year	Co-morbid medical, psychiatric illnesses, medication use, health care utilization within 1 year	Yes
Ishiguro *et al.*[16]	Clinical Practice Research Datalink	Nested case-control study	Age between 20 and 59 years VTE cases with no major risk factors for VTE as cases. Each case matched 4 controls on age, sex, general practice, calendar time, and length of medical history	868 cases of VTE, 3158 controls	Current/Recent/Past exposure was defined as receipt of a prescription whose filled use extended to within 60/61–120/121–365 days before the index date	VTE	Database records and anticoagulation therapy requirement	Proximate causes for VTE, clinical risk factors, substance abuse, rheumatic immune disease	Smoking status, BMI, history of hypertension, hyperlipidemia, phlebitis, schizophrenia, bipolar disorder, depression, and other psychoses. Estrogen-containing drugs and antidepressant drugs	Yes
Conti *et al.*[19]	Regional Health Service (RHS) databases of Lombardy, Italy	Nested case-control study	Age ⩾18 hospitalized for non-fatal or fatal PE during follow-up in the database. Each case matched up to 20 controls by age at cohort entry and gender	232 PE cases 4353 controls matched by age and gender controls	Current/recent/past users were defined as one or more prescriptions within 3/4–12/over 13 months before the index date)	PE	ICD codes	Previously PE or DVT, pregnancy, leg/hip fracture, neoplasm; use of warfarin or other antithrombotic drugs	Psychiatric hospitalization, co-morbidities, drug prescription	Yes

(Continued)

Table 1. (Continued)

Study	Data source	Design	Population characteristics	Total population	Ascertainment of antipsychotic agents exposure	Outcome	Outcome definition	VTE risk factors exclusion	Controlled variables	High quality
Vigod *et al.*[23]	population health administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, Ontario	Prospective cohort study	Women who delivered singleton infants in Ontario and had at least two consecutive prescriptions of antipsychotic medication between conception and delivery as exposure patients, each matched 1 control by HDPS algorithm	Antipsychotic users: 1021 non-users: 1021	At least two consecutive prescriptions for an antipsychotic drug filled between the conception date and the delivery date	VTE	ICD codes	No	SSRI and non-SSRI antidepressants, mood stabilizer or benzodiazepine medication	Yes
Wang *et al.*[46]	Taiwan National Health Insurance Research Database	Nested case-control study	Postmenopausal women who used any antipsychotic medication in the year between 1 January 2001 and 31 December 2010 as case group. Each case was matched with up to 10 controls by age, cohort entry date, presence of cancer, and any major surgery	2520 cases of VTE; 24,233 controls	Any antipsychotic use in the year before the index date	VTE	ICD codes	VTE diagnosis in the year before cohort entry	Major risk factors for VTE, mental health conditions, use of co-medications, fracture/surgery, paralysis/CVC/comorbid	Yes
Dennis *et al.*[47]	Secure Anonymized Information Linkage databank based at the Health Information Research Unit, Swansea University	Retrospective cohort study	People registered to a SAIL supplying GP practice and aged over 57 years at the onset of the study period (1 January 2003)	3735 in antipsychotic drug exposure group; 5939 in no antipsychotic exposure group	Unclear definition	VTE	ICD codes	Prior diagnosis of schizophrenia, bipolar affective disorder, cancer	Age, gender and comorbidities, use of hypnotics, anxiolytics and benzodiazepines	No
Nakamura *et al.*[26]	The EBM provider healthcare database	Retrospective cohort study	Patients diagnosed with VTE between 1 April 2008 and 30 September 2013 in acute care hospitals in Japan	3554 cases of VTE, 350 antipsychotic user patients, 3204 non-users	Unclear	Recurrent VTE	ICD codes	VTE event during the 180-day period after enrollment	Sex and diabetes	No
Premuš Marušič *et al.*[22]	Surgical department at the Murska Sobota General Hospital	Case-control study	DVT or PE within 180 days after surgical treatment as the case group, surgical patients who did not develop DVT or PE as controls	144 cases of VTE; 142 control group	Unclear	VTE	Unclear	Polytrauma, history of VTE, inherited thrombophilia, proven malignancy	No	No

(Continued)

Table 1. (Continued)

Study	Data source	Design	Population characteristics	Total population	Ascertainment of antipsychotic agents exposure	Outcome	Outcome definition	VTE risk factors exclusion	Controlled variables	High quality
Mollard *et al.*[27]	Brest University Hospital	Cohort study	Patients with a first symptomatic VTE event were enrolled in the study. Non-users were defined as having no antipsychotic drugs prescribed during the follow-up. Exposure was defined as having at least one prescription of antipsychotic drugs after the end of anticoagulation treatment	61 antipsychotic exposure patients; 675 non-antipsychotic-used patients	At least one prescription of antipsychotic drugs after the end of anticoagulation treatment	Recurrent VTE	Objective tests	Anticoagulant treatment within 3 months for reason other than recurrent VTE, cancer, no stopping of anticoagulation	Age, sex, BMI, duration of anticoagulant therapy, initial presentation of VTE, and family history of VTE	Yes
Ferraris *et al.*[28]	Prospective institutional registry of venous thromboembolic disease in a tertiary teaching hospital in Buenos Aires, Argentina	Retrospective cohort study	Adult patients (older than 17 years) with a confirmed diagnosis of VTE between 2010.01 and June 2017. New users of antipsychotic medication defined as having at least one documented dispensing event after the index date, no antipsychotic medication exposure as the control group	136 new users of antipsychotic agents, 967 people who had never used antipsychotic medication	At least one documented dispensing event in the institutional pharmacy's registry after the index date	Recurrent VTE	Objective test	Antipsychotic agents used before index date, VTE occurring in first 3 days after the index date, past antipsychotic medication users	Age, sex, alcohol use, tobacco status, hypertension, known risk factors of VTE, type of treatment initiated from the institutional registry. Lipid lowering drugs, antiplatelet agents, antidepressants, hypnotics	Yes
Rarrick *et al.*[24]	Internal medicine ambulatory clinic at an academic medical center	Case-control study	Patients with a primary care provider assigned in addition to being seen at least twice within the previous 3 years between 2012.01 and 2017.12	314 cases of VTE; 6765 non-VTE controls	Chart review, current user definition was unclear	VTE	ICD codes	age <18 years, pregnancy, malignancy	Age, gender, obesity, and cigarette smoking, hyperlipoidemia, hypertension, diabetes mellitus	No

PE, pulmonary embolism; VTE, venous thromboembolism; GPRD, UK-based General Practice Research Database; BMI, body mass index; ASA, Acetylsalicylic acid; COPD, chronic obstructive pulmonary disease; APD, antipsychotic drug; DVT, deep venous thrombosis; SHI, German statutory health insurances; HDPS, high dimensional propensity score; SSRI, selective serotonin reuptake inhibitor; CVC, central venous catheter; SAIL, Secure Anonymised Information Linkage; GP, general practitioner

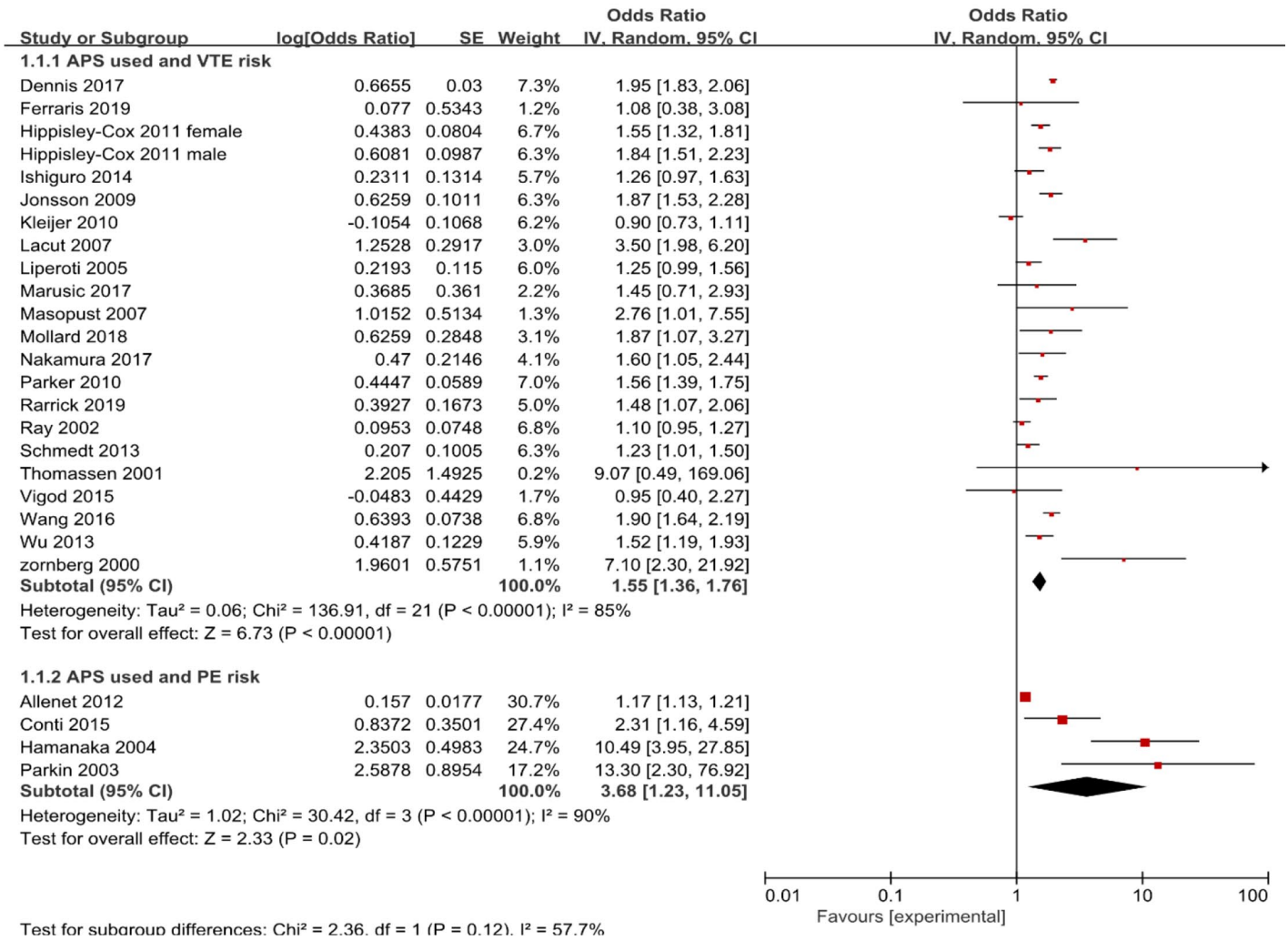


Figure 2. Forest plot of the association between current antipsychotic agents (APS) used and risk of venous thromboembolism (VTE) and pulmonary embolism (PE).
CI, confidence interval; OR, odds ratio.

users (OR 1.29, 95% CIs 1.04, 1.61). Significantly increased risk of VTE was found in high-potency (OR 1.31, 95% CIs 1.22, 1.41) but not in low-potency (OR 1.65, CIs 95% 0.99, 2.77) APS. Association of the dose of APS use with VTE risk was also assessed. The results showed the risk of VTE was significantly higher in both high-dose (OR 1.86, 95% CIs 1.12, 3.09) and low-dose (OR 1.45, 95% CIs 1.11, 1.90) APS. For the association between individual drugs and VTE and/or PE risks, only a few studies provided analyses. Increased risk of VTE and PE was observed for haloperidol (OR 1.64, 95% CIs 1.20, 2.23), risperidone (OR 1.63, 95% CIs 1.16, 2.31), olanzapine (OR 1.63, 95% CIs 1.12, 2.37), and prochlorperazine (OR 1.90, 95% CIs 1.06, 3.40). A significant association was not found for chlorpromazine (OR 1.36, 95% CIs 0.98, 1.87), quetiapine (OR 1.61, 95% CIs 0.57, 4.55) or aripiprazole (OR 2.79, 95% CIs 0.31, 25.37). However, substantial heterogeneity was found for most of these analyses. Further details of subgroup analyses of individual studies and summary estimates are shown in Figure 3.

Sensitivity analysis and publication bias

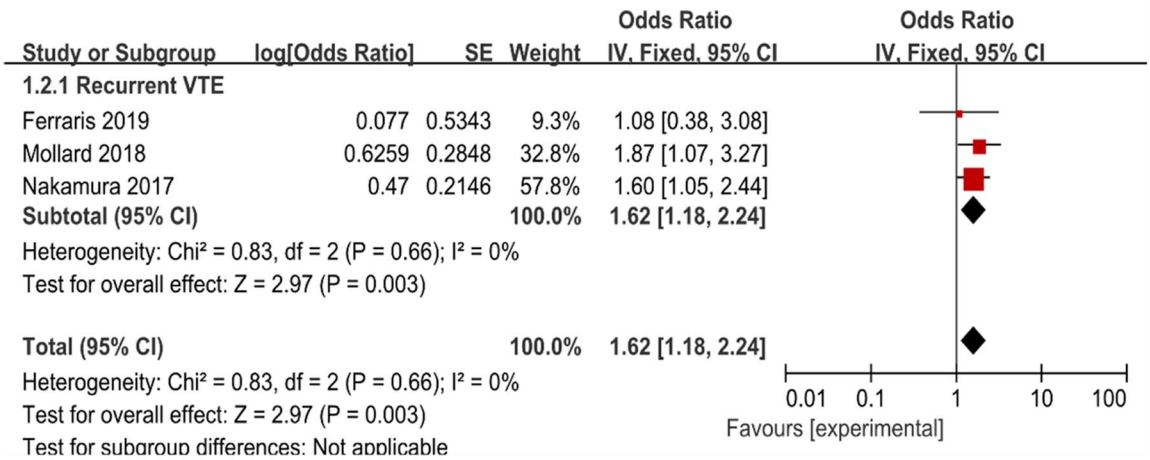
Sensitivity analysis was performed by eliminating each study in turn. The pooled ORs of association between APS exposure and VTE risks were not altered after omitting each individual study in turn. However, for APS and PE risks, the ORs

Table 2. Association between antipsychotic agent use and VTE and/or PE in subgroup meta-analysis.

Category	Outcome	No. of studies	Pooled OR (95% CI)	Heterogeneity I^2 (%)	Model used
Total	VTE	21	1.55 (1.36–1.76)	85%	Random effects
	PE	4	3.68 (1.23–11.05)	90%	Random effects
Recurrent VTE	VTE	3	1.62 (1.18, 2.24)	0%	Fixed effects
Cohort	VTE	8	1.50 (1.22, 1.83)	88%	Random effects
Case-control	VTE	12	1.58 (1.33, 1.89)	82%	Random effects
High-quality studies	VTE	15	1.50 (1.30–1.72)	82%	Random effects
Gender					
Male	VTE	2	1.80 (1.52, 2.14)	0%	Fixed effects
Female	VTE	4	1.63 (1.37, 1.93)	51%	Random effects
Elder	VTE	6	1.33 (0.99, 1.79)	95%	Random effects
Psychiatric disorders					
Schizophrenia	VTE	2	1.34 (1.15, 1.55)	0%	Fixed effects
Dementia	VTE	3	1.44 (0.99, 2.08)	94%	Random effects
Types of APS					
FGA only	VTE	9	1.47 (1.21–1.78)	80%	Random effects
SGA only	VTE	8	1.62 (1.28–2.05)	69%	Random effects
Combined	VTE	6	2.01 (1.47–2.75)	53%	Random effects
Duration of current use APS					
New users	VTE	5	2.06 (1.81, 2.35)	44%	Fixed effects
Continuing users	VTE	5	1.29 (1.04, 1.61)	82%	Random effects
Potency of APS					
High potency APS	VTE	5	1.31 (1.22, 1.41)	43%	Fixed effects
Low potency APS	VTE	5	1.65 (0.99, 2.77)	79%	Random effects
Dose of APS					
High dose using of APS	VTE	5	1.86 (1.12, 3.09)	81%	Random effects
Low dose using of APS	VTE	5	1.45 (1.11, 1.90)	78%	Random effects
Individual APS used					
Haloperidol	VTE and PE	5	1.64 (1.20, 2.23)	87%	Random effects
Risperidone	VTE and PE	5	1.63 (1.16, 2.31)	86%	Random effects
Olanzapine	VTE and PE	5	1.63 (1.12, 2.37)	78%	Random effects
Prochlorperazine	VTE	3	1.90 (1.06, 3.40)	95%	Random effects
Chlorpromazine	VTE	3	1.36 (0.98, 1.87)	58%	Random effects
Quetiapine	VTE and PE	2	1.61 (0.57, 4.55)	95%	Random effects
Aripiprazole	VTE and PE	2	2.79 (0.31, 25.37)	92%	Random effects

APS, antipsychotic agents; FGA, first-generation antipsychotic agents; PE, pulmonary embolism; SGA, second-generation antipsychotic agents; VTE, venous thromboembolism.

Recurrent VTE



study design, high-quality study

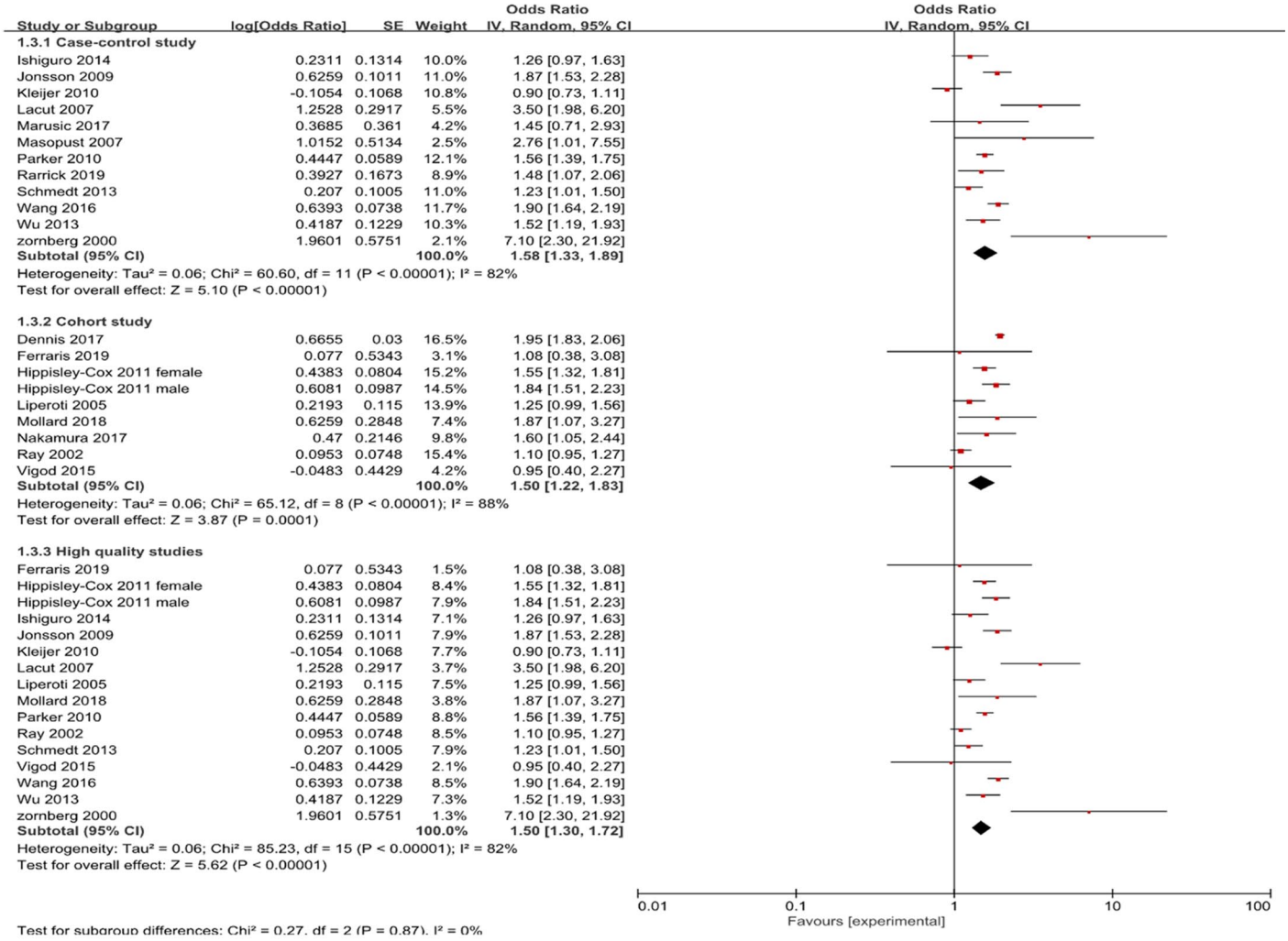
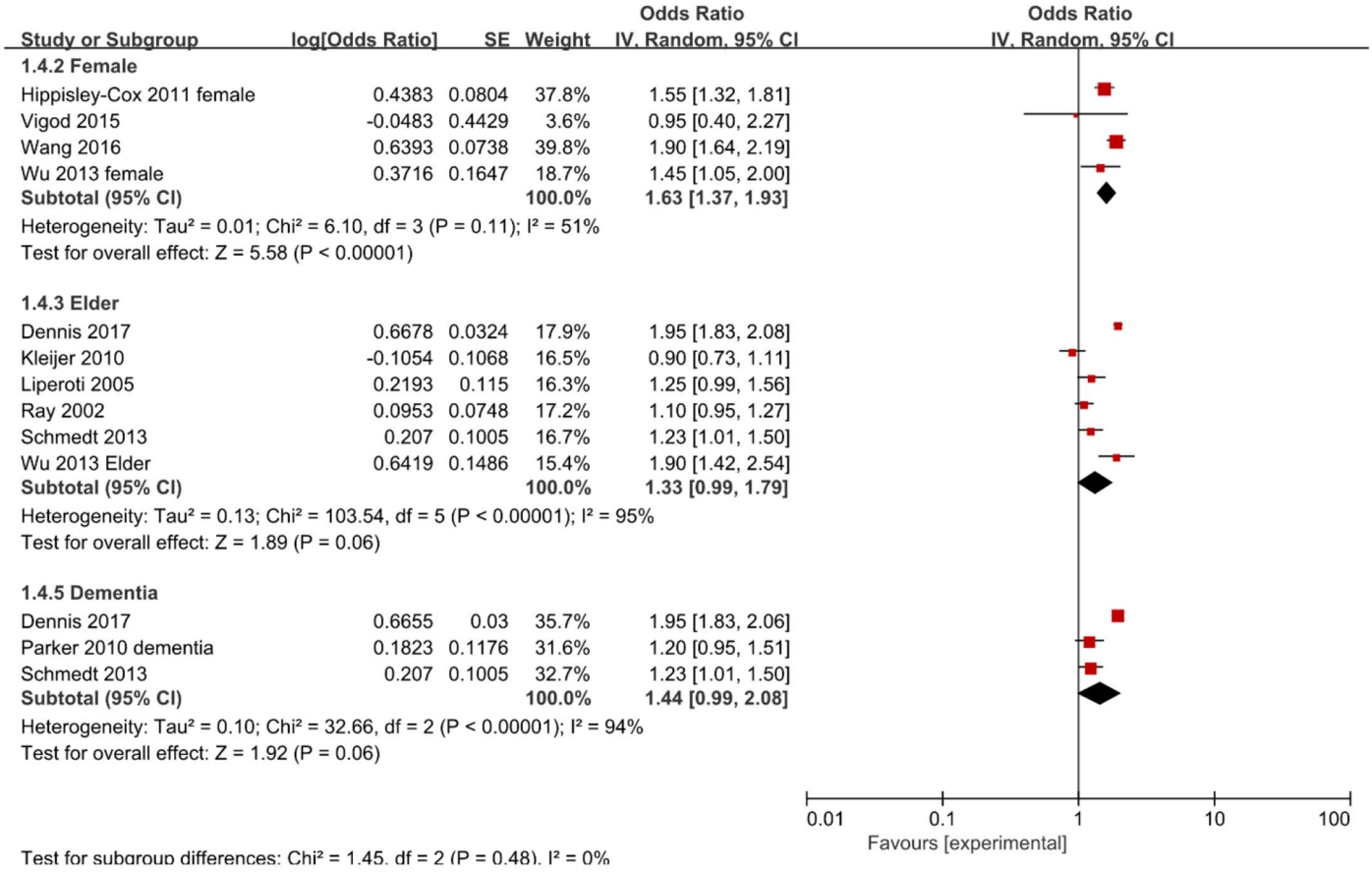
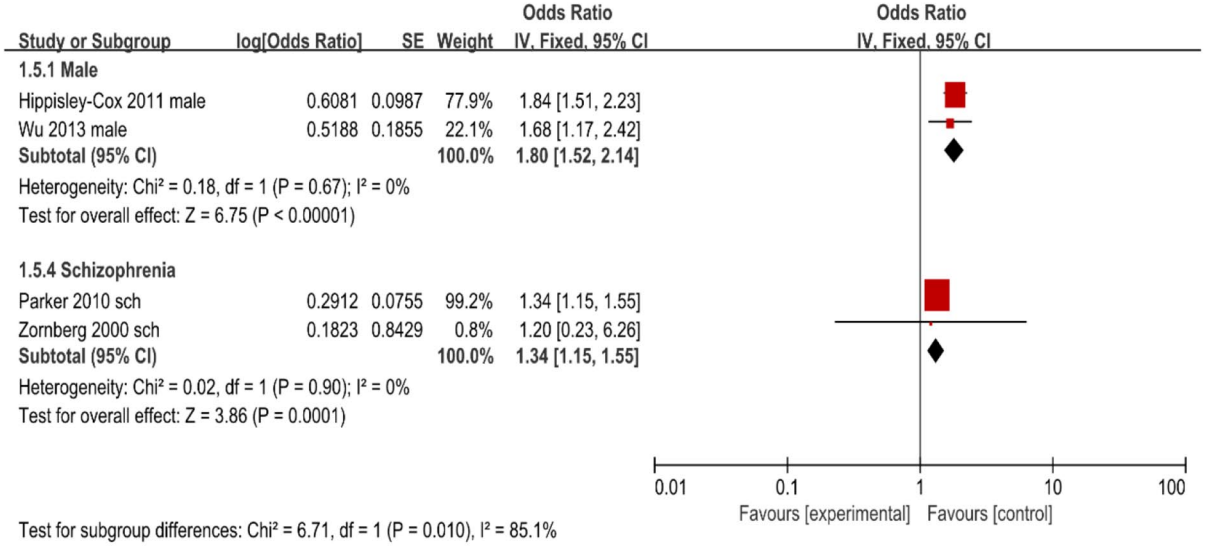


Figure 3. (Continued)

Study population pooled by random effects model



Study population pooled by fixed effects model



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Types of antipsychotic agents

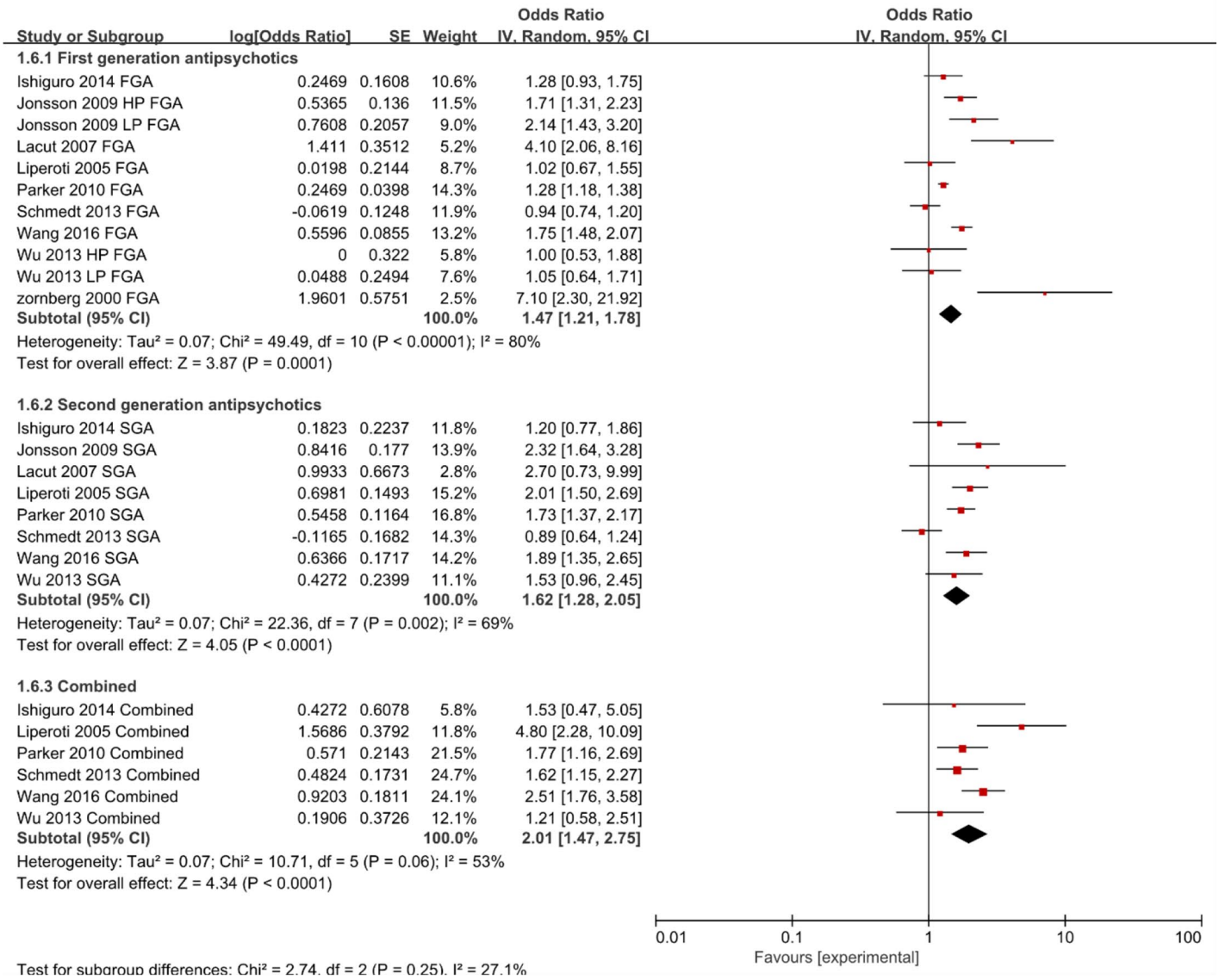
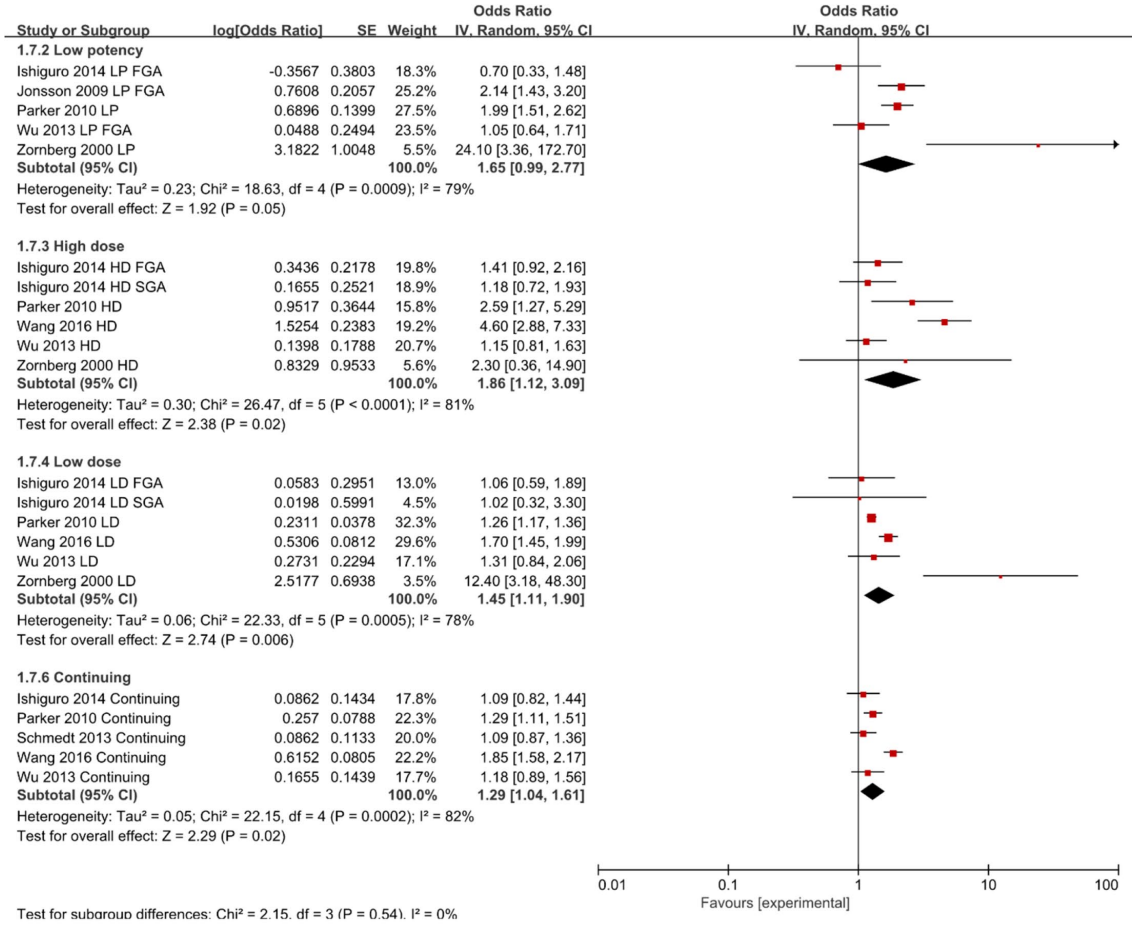


Figure 3. (Continued)

Potency, dose, and duration of APS use pooled by random effects model



Potency, dose, and duration of APS use pooled by fixed effects model

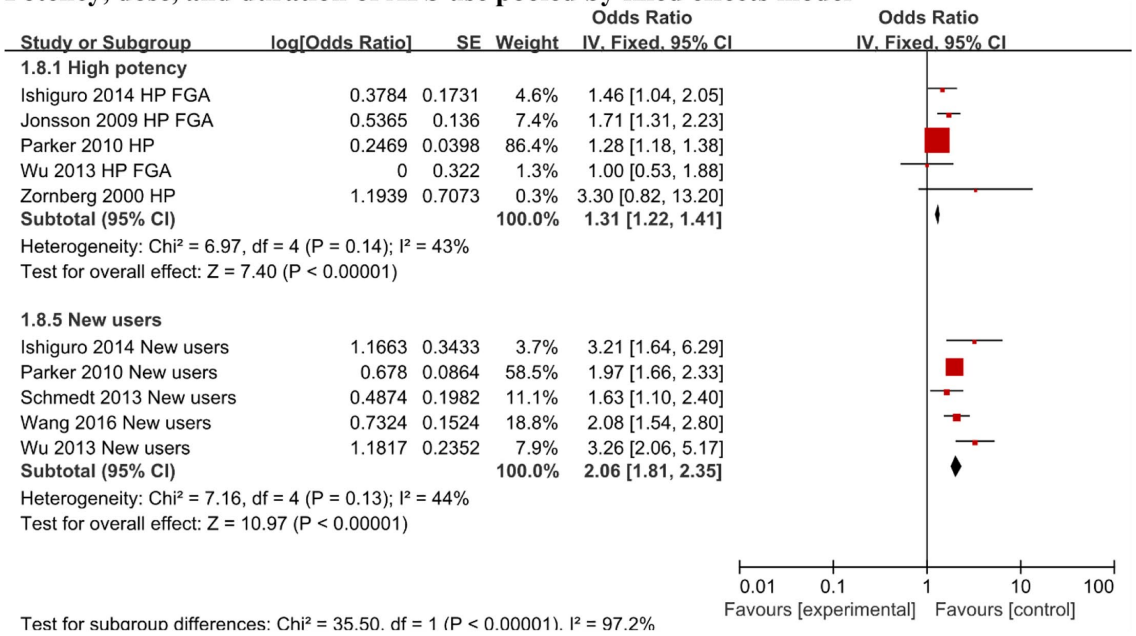


Figure 3. (Continued)

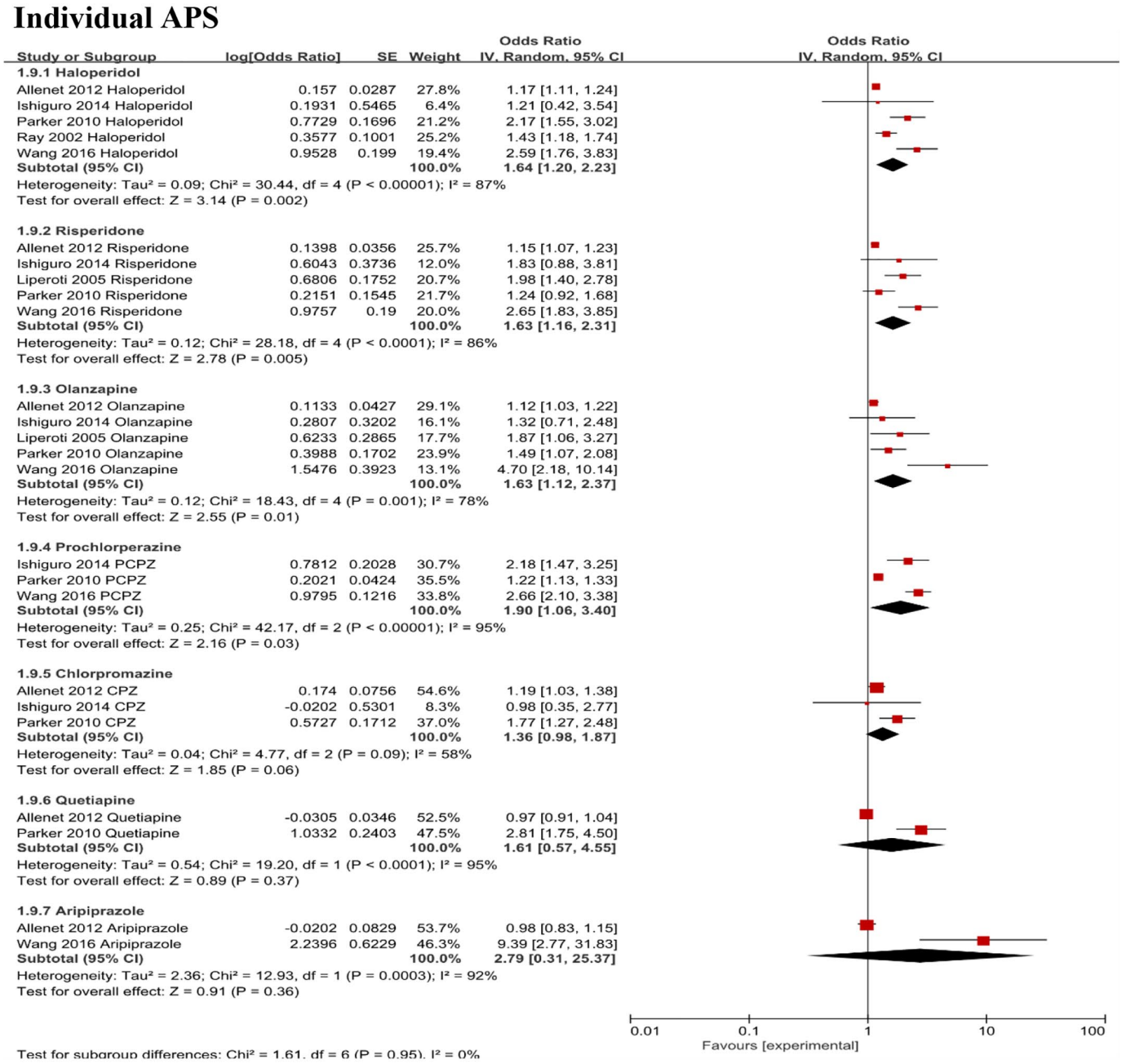


Figure 3. Forest plot of individual studies and summary estimates of subgroup analyses on recurrent venous thromboembolism (VTE), study design, high-quality study, study population, types of antipsychotic agents (APS), potency, dose, and duration of APS use, individual APS.

CPZ, chlorpromazine; FGA, first-generation antipsychotics; HD, high dose; HP, high potency; LD, low dose; LP, low potency; PCPZ, prochlorperazine; Sch, schizophrenia; SGA, second-generation antipsychotics.

were altered after eliminating three individual studies[19,34,35] in turn, indicating that the result was not stable. The funnel plot was used to assess the publication bias, and the results were shown in Figure 4. Visual inspection of the funnel plot showed obvious asymmetry. Therefore, the publication bias needs to be considered.

Discussion

The aim of this meta-analysis is to ascertain the risk of VTE and PE among users of APS compared with non-users. Cohort and case-control studies were included in the review. Except for two studies with unclear definition,[22,25] most of the studies identified VTE and PE by International

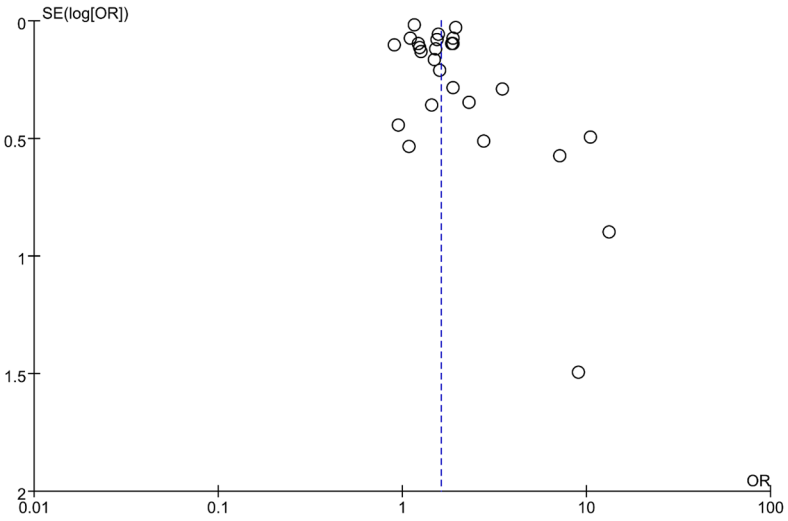


Figure 4. Funnel plot on the publication bias of all included studies.

Classification of Diseases codes, medical records, and objective tests, which can result in reliable VTE and PE diagnoses. The results of this study indicate that the risk of both VTE and PE is higher for APS users than non-users, with a pooled OR estimate of 1.55 (95% CIs 1.36, 1.76) for VTE and 3.68 (95% CIs 1.23, 11.05) for PE. For individual drugs, increased risk of VTE and PE was observed in taking haloperidol, risperidone, olanzapine, prochlorperazine, but not in chlorpromazine, quetiapine, or aripiprazole.

This finding is consistent with previously published meta-analyses that found correlations between APS use and VTE risk.[17,18,20] However, compared with the most recent meta-analysis,[20] nine additional studies were identified in this rev iew.[13,21–28] Our subgroup analysis also suggests that APS exposure increases the risk of VTE recurrence. This finding further implicates APS as an independent factor contributing to VTE. Subgroup analysis of cohort, case-control and high-quality studies also showed that VTE risk significantly increased in APS users, which strengthens the confidence of the results. However, the results still need to be interpreted with care because of high heterogeneity among the included studies. Our finding that APS use increased risk of PE is also consistent with previous studies, though the strength of this finding is limited by high heterogeneity among included studies and wide CIs.[19,20] The present sensitivity analysis also suggested that this result is not stable, which indicates that the result of high risk of PE is not reliable.

As far as we know, this is the first meta-analysis of pooled comprehensive data based on five studies about APS new users and VTE risk reported by observational studies, indicating that VTE risk appears to be greater in new users.[16,21,42,45,46] This result suggests that APS users in the initial stage are more vulnerable to VTE. Several possible explanations might be involved in this result. Continuing APS users were not observed to have as high a risk for VTE as new APS users, indicating that tolerance is increased with longer APS exposure. Another possible explanation is that some psychotic symptoms are related to VTE. Increased risk for VTE among patients with concurrent depressive, bipolar, and schizophrenic disorders was reported that implied psychiatric symptoms might take part in the process of VTE risk.[48] Psychiatric symptoms relieved after APS treatment may partially explain the higher risk in new APS users. In addition, the VTE test usually was arranged in the first few days of medication treatment, potentially leading to a biased overestimation of VTE risk in the initial stage. Interestingly, a similar finding was reported in a meta-analysis about APS exposure and myocardial infarction (MI) risk.[49] A common pathway might contribute to both MI and VTE in APS users.

FGA use and SGA use were both related to the risk of VTE, and the effect sizes are quite similar. Compared with the most recent review, three additional studies for evaluating VTE with FGA[21,40,45] and two additional studies with SGA[21,45] were included, and a consistent result was observed. The study conducted by Ballard *et al.* was not included in this analysis because this study was performed as a clinical trial rather than an observational study.[50] Although the subgroup analyses showed that a combination of two types of APS increased risk of VTE two-fold, this result cannot be explained by the combined use of FGA and SGA because of overlapping CIs. Studies reporting the relationship between individual APS use and VTE or PE outcome were all included in the analysis to supplement scarce data. Statistical differences were observed in the subgroup of haloperidol, risperidone, olanzapine, prochlorperazine users compared with APS non-users, but not in the subgroup of chlorpromazine, quetiapine, and aripiprazole users. Although definitive conclusions cannot be drawn because there was high heterogeneity among the included studies and scarce data, this result calls for clinicians to remain cautious about using certain drugs. In addition, a recent systematic review showed that 34 cases of

PE occurred after clozapine treatment and nearly half of them did not have other co-morbidities for PE, indicating that clozapine exposure may be associated with a high risk of PE.[51] However, among the few observational studies that provide data on this issue, one study conducted in 1997 did not provide CIs,[13] and the strength of another study was limited by methodological quality.[44] The proper risk of using clozapine for VTE and/or PE cannot yet be determined.

The mechanism of VTE risk and exposure to APS remains unclear. Psychotic disorders and APS might both play a role in the occurrence of VTE. Possible mechanisms that have been reported include immobilization, metabolic syndrome, antiphospholipid antibody increases, and hyperprolactinemia. Immobilization leads to circulatory stasis, which as one of Virchow's triad is a well-known risk factor contributing to VTE. Many kinds of APS have been indicated to have a side effect of sedation, which can cause immobilization.[5] Also, symptoms of mental illness, such as negative symptoms of schizophrenia, dementia, and major depressive disorder, could lead to social withdrawal and immobilization. There is a significantly increased risk of weight gain involved in using a variety of APS, especially SGA, a relationship that has been known for decades. Metabolic syndrome and obesity could contribute to increased platelet activity *via* the inflammation process.[52] Platelet aggregation plays a direct role in coagulation hyperactivity, which has been reported in APS users. Blood platelet aggregation was observed to increase after clozapine treatment,[53] but a conflicting result was suggested in an *in vitro* study,[54] showing that this question remains controversial. In addition, first-episode drug-naïve schizophrenia patients have been shown to have higher expression of platelet integrins αIIb and βIIIa compared with healthy individuals, suggesting that psychiatric disorders might be involved in platelet aggregation hyperactivity.[55]

Antiphospholipid syndrome is frequently observed as an increase in anticardiolipin antibodies (aCL) and most commonly manifests as VTE, potentially relating to increased VTE risk among APS users. A significant positive relationship between serum IgM aCL and serum clozapine level was shown in a clinical trial,[53] but the opposite result was reported in another one.[56] Hyperprolactinemia is another underlying reason for APS use being related to high risk of VTE. It has been reported that hyperprolactinemia may contribute to coagulation disorder.[57] In addition, a positive correlation was observed between prolactin levels and some coagulation activation markers in male patients taking APS but not in females.[58] The other possible mechanisms include hyperhomocysteinemia, inflammatory process *et al.*, but the actual mechanism is still not clear.[59,60] More evidence needs to be provided to clarify the exact mechanism of the relationship between APS use and VTE risk.

This analysis has some limitations that should be considered. The most noticeable one is the high heterogeneity among included studies, which is similar to the previous meta-analysis.[18,20] The heterogeneity can be observed in various aspects. First, the populations in each study are quite different. As reported above, VTE risk could be increased in first-episode drug-naïve schizophrenia patients. Hence the different study populations could result in different baseline VTE risks. Second, the definition of current use is inconsistent. We collected data on current APS exposure rather than recent or past exposure to mitigate heterogeneity caused by different durations of APS exposure. However, the definition of current exposure also was not consistent among studies; thus, VTE risk in APS users might be underestimated since greater risk was observed for short-term APS use. In addition, for some subgroup analyses, different definitions of subgroup exposure among included studies contributed to significant heterogeneity. For instance, for the subgroup analysis of the dose group, three studies defined a high dose as a chlorpromazine-equivalent dose over 100 mg.[14,16,21] One study defined low-dose and high-dose group by chlorpromazine-equivalent dose $\leqslant$150 mg, $>$300 mg.[46] Another one considered the low-dose group as $\leqslant$25% of the maximum recommended in British National Formulary, and high dose as maximum and over.[42] It is worth noting that the present study directly combined the data in high and low-dose groups of these five publications that might result in statistical bias. Third, the inconsistent nature of non-users leads to different interpretations of the findings in each cohort study, which can also result in heterogeneity. For example, Ray *et al.*[15] used a thyroid hormone-prescribed population as a control group and interpreted their results relative to those prescribed thyroid hormones, and suggested that antipsychotic medication intake is not related to a higher risk of VTE.[15] Fourth, the effect size in the association between APS use and PE risk is not reliable. There are only four studies that provided data on the correlation of APS

exposure with PE risk alone, but some studies used PE and deep venous thrombosis as the outcome. Consequently, hardly separated PE in mixed outcomes leads to inaccurate assessment of PE risk. In addition, only a few studies provided data on VTE risk of individual drugs, resulting in inadequate strength to determine the safety of individual drugs. In addition, although the Cochrane Collaboration has recommended NOS as a methodological quality assessment tool for observational studies, the low reliability between individual reviewers shows that the tool is not objective enough.[61] Moreover, the weights of each study in pooling OR cannot be based on the study quality, which might cause the result to be easily influenced by low-quality studies. Based on these considerations, further studies could focus on specific populations of APS users, for example, schizophrenia patients. It will help to know the exact risk of taking certain drugs. In addition, studies about individual APS that have only PE as the outcome also need to be conducted to provide more evidence based in clinical practice.

This comprehensive systematic review provides more information and strengthens the evidence on APS use and VTE risk for guideline developers, policymakers, and clinicians. In addition, the subgroup analyses draw clinician attention to an initial period of APS use and provide clues into the risk of individual APS. Therefore, the necessary physical health monitoring is needed to provide for psychiatric patients prescribed continuing antipsychotic medication in clinical practice. For example, the Two-level DVT Wells score assessment, D-dimer test and the proximal leg vein ultrasound scan can be considered for these patients, especially new antipsychotic drug users, in order to comprehensively evaluate the risk of VTE and PE.[62]

Conclusion

The comprehensive meta-analysis indicates that both the significantly increased VTE and PE risk were found in current APS users compared with non-users. Subgroup analyses suggest that new users are more likely to develop VTE. Using haloperidol, risperidone, olanzapine, or prochlorperazine significantly increased the risk for VTE, but not chlorpromazine, quetiapine, or aripiprazole. However, high heterogeneity among studies and scarce data for individual APS calls for cautious interpretation of the findings from this review. Further studies could focus on specific populations of APS users and VTE risk of individual APS. In addition, more studies listing only PE as the outcome need to be conducted to provide more evidence based in clinical practice.

Author Contributions

Xiangrong Zhang, Congjie Wang, and Yinzhao Liu contributed to the design of the study. Yinzhao Liu, Jun Xu, Yue Xu, Ju Gao, Chao Zhou, Xiaowei Tang, Jiu Chen, Chunming Xie, Fuquan Zhang managed the data collection, analysis, and interpretation. Kacey Fang checked the data analysis and interpretation. Yinzhao Liu drafted the manuscript. Xiangrong Zhang, Congjie Wang and Kacey Fang contributed to revising the manuscript. All authors have approved the final manuscript.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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