Supplemental Methods: Search strategy

We specified two comprehensive search themes:

- *(theme 1)* The first Boolean search used the term "OR" to explode (search by subject heading) and map (search by keyword) relevant terms related to the exposure of interest: "antidepressant" or "antidepressive" or "antidepressant$" or "antidepressant drugs" or "antidepressive agents" or "SSRI" or "selective serotonin re-uptake inhibitor" or "selective serotonin reuptake inhibitor" or "selective serotonin reuptake inhibitor$" or "TCA" or "tricyclic antidepressant" or "tricyclic antidepressant$" or "MAOI" or "monoamine oxidase inhibitor" or "monoamine oxidase inhibitor$" or "monoamine reuptake inhibitor" or "monoamine re-uptake inhibitor".
- *(theme 2)* The second Boolean search was performed using the term "OR" to explode and map relevant terms related to the outcome of interest: "stroke" or "cerebrovascular" or "ictus" or "brain infarction" or "bleeding" or "intracerebral haemorrhage" or "intracerebral bleeding" or "subarachnoid hemorrhage" or "SAH" or "hemorrhage" or "haemorrhage" or "ischemic" or "ischaemic".

These two comprehensive search themes were then combined using the Boolean operator "AND" in varying combinations adapted for the different searches of the electronic databases as follows:

PubMed

1. (antidepressant OR antidepressive) AND (stroke OR cerebrovascular) Filters activated: Humans, English.
2. ((depression AND (therapy OR drug OR medication OR treatment)) AND (ictus OR stroke OR cerebrovascular)) NOT (antidepressant OR antidepressive) Filters activated: Humans, English.
3. (antidepressant OR antidepressive OR SSRI OR selective serotonin reuptake inhibitors) AND (stroke OR cerebrovascular OR bleeding OR intracerebral haemorrhage OR intracerebral bleeding OR subarachnoid hemorrhage OR SAH OR hemorrhage) Filters activated: Humans, English.
4. (antidepressant OR antidepressive OR monoamine reuptake inhibitor OR monoamine oxidase inhibitors OR MAOI OR selective serotonin reuptake inhibitor OR SSRI OR tricyclic antidepressant OR TCA) AND (stroke OR ictus OR brain infarction OR cerebrovascular OR intracerebral OR intracranial OR subarachnoid OR haemorrhage OR hemorrhage OR bleeding OR ischemic OR ischaemic OR hemorrhagic OR haemorrhagic) Filters activated: Humans, English.

This search algorithm contained 405 non-English written articles. In order to have a complete search literature this list was additionally searched. Anyway, based on the English-written title/abstract none of these articles were eligible to be included.

5. (((((((((antidepressive agents[MeSH Terms]) OR antidepressant drugs[MeSH Terms]) OR monoamine reuptake inhibitor) OR monoamine oxidase inhibitor) OR MAOI) OR selective serotonin reuptake inhibitors[MeSH Terms]) OR tricyclic antidepressants[MeSH Terms]) AND Humans[Mesh] AND English[lang])) AND ((((((((((stroke[MeSH Terms]) OR acute stroke[MeSH Terms]) OR cerebral stroke[MeSH Terms]) OR ictus) OR brain infarction[MeSH Terms]) OR cerebrovascular accident[MeSH Terms]) OR cerebrovascular apoplexy[MeSH Terms]) OR intracerebral hemorrhage[MeSH Terms]) OR hemorrhage, intracranial subarachnoid[MeSH Terms]) OR bleeding[MeSH Terms]) AND Humans[Mesh] AND English[lang]) Filters: Humans; English

In this search algorithm all of the articles were written in English.

Ovid platform

6. (antidepressant.sh. OR antidepressant.ab OR antidepressant.kw OR antidepressant.at. OR antidepressive.ab OR antidepressive.kw OR antidepressive.at OR monoamine reuptake inhibitor$.ab OR monoamine reuptake inhibitor$.kw OR monoamine reuptake inhibitor$.at OR tricyclic antidepressant$.ab OR tricyclic antidepressant$.kw OR tricyclic antidepressant$.at OR selective serotonin reuptake inhibitor$.ab OR selective serotonin reuptake inhibitor$.kw OR selective serotonin reuptake inhibitor$.at OR monoamine oxidase inhibitor$.ab OR monoamine oxidase inhibitor$.kw OR monoamine oxidase inhibitor$.at) AND (stroke OR ictus OR brain infarction OR cerebrovascular OR intracerebral OR intracranial OR subarachnoid OR haemorrhage OR bleeding OR ischaemic OR hemorrhagic) {Including Related Terms} limit 1 to (english language and humans)

7. (antidepressant.sh. or antidepressant.ab. or antidepressant.kw. or antidepressant.at. or antidepressive.ab. or antidepressive.kw. or antidepressive.at. or monoamine reuptake inhibitor$.ab. or monoamine reuptake inhibitor$.kw. or monoamine reuptake inhibitor$.at. or tricyclic antidepressant$.ab. or tricyclic antidepressant$.kw. or tricyclic antidepressant$.at. or selective serotonin reuptake inhibitor$.ab. or selective serotonin reuptake inhibitor$.kw. or selective serotonin reuptake inhibitor$.at. or monoamine oxidase inhibitor$.ab. or monoamine oxidase inhibitor$.kw. or monoamine oxidase inhibitor$.at.) and (stroke.sh. or ictus.ab. or ictus.kw. or ictus.at. or brain infarction.sh. or cerebrovascular.ab. or cerebrovascular.kw. or cerebrovascular.at. or intracerebral.ab. or intracerebral.kw. or intracerebral.at. or intracranial.ab. or intracranial.kw. or intracranial.at. or subarachnoid.ab. or subarachnoid.kw. or subarachnoid.at. or hemorrhage.sh. or ischemic.ab. or ischemic.kw. or ischemic.at.) limit 1 to (english language and humans).

Cochrane

8. #1 MeSH descriptor: [Stroke] explode all trees
#2 "ictus" (Word variations have been searched)
#3 MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#4 "cerebrovascular attack" (Word variations have been searched)
#5 "cerebrovascular accident" (Word variations have been searched)

#6 intracerebral haemorrhage (Word variations have been searched)
#7 MeSH descriptor: [Brain Infarction] explode all trees
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Antidepressive Agents] explode all trees
#10 #8 and #9

9. (antidepressant OR antidepressive OR monoamine reuptake inhibitors OR monoamine oxidase inhibitors OR MAOI OR selective serotonin reuptake inhibitors OR SSRI OR tricyclic antidepressants OR TCA) AND (stroke OR ictus OR brain infarction OR cerebrovascular OR intracerebral OR intracranial OR subarachnoid OR hemorrhage OR bleeding OR ischemic OR hemorrhagic) *in titles abstract and keywords

ProQuest

10. (antidepressant OR antidepressive OR monoamine reuptake inhibitor OR monoamine re-uptake inhibitor OR monoamine oxidase inhibitor OR MAOI OR selective serotonin reuptake inhibitor OR selective serotonin re-uptake inhibitor SSRI OR tricyclic antidepressant OR TCA) AND (stroke OR ictus OR brain infarction OR cerebrovascular OR intracerebral OR intracranial OR subarachnoid OR haemorrhage OR hemorrhage OR bleeding OR ischemic OR ischaemic OR hemorrhagic OR haemorrhagic)

Scopus

11. (antidepressant OR antidepressive OR monoamine reuptake inhibitor OR monoamine oxidase inhibitor OR maoi OR selective serotonin reuptake inhibitor OR ssri OR tricyclic antidepressant OR tca) AND (stroke OR ictus OR brain infarction OR cerebrovascular OR intracerebral OR intracranial OR subarachnoid OR haemorrhage OR hemorrhage OR bleeding OR ischemic OR ischaemic OR hemorrhagic OR haemorrhagic) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (EXACTKEYWORD , "Nonhuman") OR EXCLUDE (EXACTKEYWORD , "Animals")

In this database the following abstract “Risk of cardiovascular events in migraine patients treated with prophylactic medications” by Hoffman et al. was listed in the program of the 59th Annual Scientific Meeting of the American Headache Society in June 8 - 11, 2017. The authors were contacted for a possible fully-written text, but we do not receive a response.

Supplemental Table I. Characteristics of included studies								
Author	**Year**	**Study type**	**Country**	**Source population and number of included participants**	**Inclusion and exclusion criteria**	**Definition of outcome**	**Definition of exposure**	**Adjustments**
Bak S	1994-1999	case-control	Europe	residents of Funen County during the '94-'99 who were ≥20 years. 4765 cases 40 000 controls	Excl.: stroke diagnosis that did not fulfill the criteria; stroke during hospitalization, sub/epidural hematoma, head injuries; previous stroke.	diagnosis or autopsy for hemorrhagic, ischemic, SAH or unspecified stroke from '94-'99 codes ICD10th and free of such diagnosis during '73-'93 ICD 8th .	prescriptions for AD inserted in the pharmacological data base. Classified than as *current user* (30 days before IDC); *recent* (31-60d); *past users* (before 61d) *nonusers* (no AD prescription).	age, sex, IDC (3-year band), use of diuretics, beta blockers, calcium channel blockers, ACE inhibitors, antiarrhythmic, antianginal drugs, warfarin, phenprocoumon, antidiabetics, lipid-lowering drugs, low-dose acetyl salicylic acid, and other NSAID's.
Behr S	2004-2006	case-control	Europe	part of the German pharmacoepide miological research database (consisting of claims data from 4 statutory health insurance). 8138 cases 81 373 controls	Excl.: cohort members hospitalized at the index day as the cases were excluded from potential set of controls. Incl.: continuous 6 months insurance before cohort entry.	cases defined as insurant hospitalized for intracerebral hemorrhage (ICD-10 GM code I61 which correspond for intracerebral bleeding).	current use of SSRI assessed in the 90-day period preceding the admission day for intracerebral hemorrhage (ICH).	age, sex, DM, HT, ischemic heart disease, ischemic cerebral infarction, cerebral amyloid angiopathy, cerebral aneurysm, brain tumor, epilepsy, liver diseases, renal failure, alcohol dependence, epistaxis, previous ICH.
Chan CH	2001-2007	cohort	Asia	a subset from the NHIRD, Taiwan with 100, 000 random subjects (5% of all enrollees).	Excl.: any inpatient diagnosis of stroke or 3 outpatient records of stroke before January 1st 2001; no SSRI	first stroke onset identified by meeting criteria 430-432 (hemorrhagic) and	if they received SSRI prescription for at least 2 consecutive months from January	adjusted for angina pectoris, MI, AF, congestive heart failure, PAD, DM, HT, hyperlipidemia, end-stage renal disease, chronic

				630 424 participants	exposure but any diagnosis of mental disorder (290-319 ICD 9th) from January 1st till 2001 December 31st 2007 Incl. :>=20y on January 1st 2001.	433-437 (ischemic) ICD 9th codes	1st till 2001 December 31st 2007.	kidney disease, aspirin, heparin, warfarin and NSAIDs.
Chen Y	1998-2002	case-control	USA	continuous enrollment at least 6m in the medical claim database with a diagnosis of depression . 1086 cases 6515 controls	Excl.: medicaid enrollees; post-stroke depression; if the CVE or the CVE's drug use were before the depression or the antidepressant use.	incident cases with ICD 9th codes as ischemic hemorrhagic or other CVE.	defined as *current user* (antidepressant supply within 30 days before IDC*)*; *recent* (31-60); *past* (61-90) *remote or nonusers* (≥91 or no had no use of any antidepressant prior to their IDC).	matched on age, sex, and index date of depression, medications (aspirin, risperidone), psychiatric (alcohol and substance abuse, anxiety) and medical comorbidities (HT, DM, hypercholesterolemia, cardiac disease).
Coupland C	1996-2008	cohort study	Europe	patients in *QResearch primary care data* which were >=65 years between '96-'08 with first diagnosis of depression or AD prescription if that occurred before the date of depression. 60 746 participants	Excl.: outcome at baseline, >100 y at depression's diagnosis; diagnosis occurred <12m after registration, temporary residents; depression 12m before their index recorded depression; use of AD in the 12 m before depression; schizophrenia, BPD or other psychoses.	Stroke on the basis of recorded Read codes (primary and secondary care) and linked death certificates ICD-9th /10th codes.	defined to be exposed on the date of first AD's prescription (no gaps of >90 days between prescriptions).	sex, age, depression severity, depression before 65, smoking, Townsend deprivation score, CHD, DM, HT, cancer, dementia, Parkinson's disease, hypothyroidism, OCD, epilepsy/seizures, statins, NSAID's, antipsychotics, lithium, aspirin, hypnotics/ anxiolytic, antihypertensive and anticonvulsant therapy.

Coupland C	2000-2012	cohort	Europe	part of *QResearch data* (primary care database), 20-65 years with first depression's diagnosis (occurred at least 12m after registration) or AD prescription if that occurred before the date of depression. 238 963 participants	Excl.: previous depression, schizophrenia, BPD, other psychosis; lithium or antimanic drugs; antidepressant use before: study start date, registration date, before age of 20 or >36 m before the diagnosis of depression; temporary residents; prevalent cases; missing variables; patients receiving MAO.	incident stroke or TIA on the basis of recorded Read codes (primary and secondary care) and linked death certificates ICD-9th /10th codes.	defined to be exposed on the date of first AD's prescription (no gaps of >90 days between prescriptions).	age, sex, year of depression's diagnosis, depression's severity, deprivation, smoking, alcohol, ethnicity, CHD, DM, HT, cancer, epilepsy, hypothyroidism, osteoarthritis, HRT, asthma/COPD, rheumatoid arthritis, osteoporosis, liver and renal disease, OCD, statins, NSAID's, aspirin, antihypertensive, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, antipsychotics, bisphosphonates, anticoagulants.
de Abajo F	1990-1997	case–control	Europe	subjects in UK GPRD aged 18-79 who received a first time AD prescription from January 1st 1990 to October 31st 1997. 65 cases 254 controls	Excl.: past history of ICH, ICD (and TIA), IHD, heart failure, cardiac dysrhythmia, hyperthyroidism, DM, epilepsy, cancer, coagulopathy, chronic liver disease, connective tissue disorders, alcohol abuse, anticoagulant therapy, and pregnancy.	cases defined as idiopathic intracranial hemorrhage (without a primary documented cause of craneo-encephalic trauma, aneurysm, A-V malformation, or thrombocytopenia) referred to a consultant, admitted in the hospital or resulting in death.	prescription by the GP of SSRI or other AD (mainly TIA) classified as: *current* (supply lasted until or ended within 30 days prior to ID) *recent* (ended 31-60 d before the ID) *non users* (remaining subjects). MAO were not included.	age, sex, calendar time, practice hypertension, smoking, BMI, asthma/COPD and current use of NSAIDs including aspirin.

Douglas I	1998-2006	case-control	Europe	every eligible candidate part of the GPRD from 1998-2006 and without previous history of hemorrhagic stroke. 365 195 participants	Excl.: receiving both an SSRI and TCA; receiving an anticoagulant at any point; evidence of trauma, a record of ischemic, unspecified stroke, TIA, or other cerebrovascular event within 30 days before the ID. Incl..: two or more prescriptions for either SSR/TCA and registered at least 12 m before the first SSRI/TCA prescription .	diagnosis of hemorrhagic stroke between 1st January 1998 and 31st December 2006.	SSRI and TCA exposure was classified as a) *current (*prescription date within 30 days before the IDC), *recent (*31 - 60 days before IDC), *unexposed* (no current/recent use); b) *ever/never exposed.*	adjusted for smoking, alcohol, BMI, prior history of TIA or other stroke, hypertension, diabetes, NSAID use, aspirin use, clopidogrel or dipyridamole use, year of first prescription (SSRI or TCA) and total observation time.
Hansen R	2003-2011	cohort study	USA	randomly sampled community dwelling participants by mail/phone from the "Stroke Belt" and other 40 US states. 29 616 participants	Excl.: prevalent stroke cases; participants with missing an in-home medication review, missing follow-up.	medical records and neuroimaging data obtained after a self-reported stroke. Final adjudication based on WHO's definition and/or imaging results. Fatal strokes reported by proxy and mortality files.	in-home medication bottle reviewed by trained technicians measured at study baseline.	age, sex, race, region, education, income, source of care, smoking, alcohol, PA, medication adherence, DM, AF, statins, aspirin, antihypertensive drugs, cholesterol, HDL, HT, BMI, corrected QT, log of: albumin /creatinine; CRP, CHD, aortic aneurysm, PAD, SF12 physical component, moderate to high stress, depressive symptoms, benzodiazepine.

Hung C	2000-2009	cohort study	Asia	subset of the National Health insurance database of 1,000,000 random subjects, (about 5% of all enrollees in the program). 28 145 participants	Excl. :only 1-month SSRI prescription; use of SSRIs after a stroke; head injury or stroke within 2 weeks of the head injury; inpatient /outpatient stroke diagnosis or any diagnosis of mental disorder before study baseline Incl.: ≥age 65 years on January '01.	first stroke event within 1 year after SSRI exposure identified by meeting the occurrence of ICD-9th, codes 430 to 438 in any inpatient or outpatient treatment.	received SSRI prescription for at least two consecutive months during January 1, 2001 to December 31, 2008.	age, sex, and comorbidities in the last 12 months before the first SSRI prescription: myocardial infarction, angina pectoris, atrial fibrillation, peripheral arterial occlusive disease, congestive heart failure, diabetes mellitus, HT, hyperlipidemia, renal diseases, aspirin, heparin, warfarin, NSAID's, and antipsychotics.
Kharofa J	1997-2005	case-control	USA	part of the Genetic and Environmental Risk Factors for Hemorrhagic Stroke study. 916 cases 1776 controls	Excl.: trauma, brain tumor, or vascular malformation as the cause of hemorrhage; hemorrhagic conversion of ischemic stroke; contacted >90 days after the stroke; Incl. ≥18 years of age; residents in the study region and study period; enrolled in the genetic sampling and interview arm.	*retrospective screening of* cases with ICH and SAH from emergency rooms or with the corresponding discharge diagnosis ICD-9th; *prospective screening* for neurosurgery admissions at the busiest hospitals.	all medications (SSRI and others) taken 2 weeks before index date were recorded.	age, race, gender, frequent alcohol use, warfarin, heart disease, history of ischemic stroke, BMI, untreated hypertension, hypercholesterolemia with statins and untreated, current smoker, less than high and high school education.
Khokhar B	2006-2010	cohort study	USA	medicare beneficiaries aged 65 years and older with an inpatient traumatic brain injury (TBI)	Excl.: any antidepressant use 6 m prior to their TBI; did not survive the TBI; had Medicare part C coverage; concomitant use of 2	stroke defined by inpatient claims using ICD-9th CM codes.	new use of antidepressant defined as any use after a 6-month washout period. Antidepressant use ascertained 30-days before and after the TBI hospitalization. Beneficiaries who had a	adjusted for age, race, sex, warfarin, length of hospital stay, discharge to a skilled nursing facility, history of depression, incident depression, AF, Alzheimer, HT. *Ischemic stroke model*- also

				claim from 2006-2010. 64 214 participants	or more different antidepressant Incl.: at least 6 months of Medicare coverage prior to the TBI.		prescription filled during a 30-day period or had a PDC (prescriptions filled and proportion of days covered) greater than 0 were classified as exposed.	included hyperlipidemia, DM, IHD, congestive heart failure, prior ischemic stroke. *Hemorrhagic*: liver disease, chronic kidney disease, alcohol, anemia, coagulation defect, valvular heart disease, neurological disease, and prior hemorrhagic stroke.
Lee Y	2001-2009	cohort study	Asia	beneficiaries of Longitudinal Health Insurance Database with at least 20 years on January 1st 2001 who had a diagnosis of depression or anxiety. *(index date (ID)-initiation of treatment.) 35 405 participants	Excl.: age <20 or undetermined gender; AD prescriptions within one year before the ID; no continuous insurance coverage 1 year before ID; simultaneous use of SSRIs and TCA and no diagnosis of depressive or anxiety disorder.	first hospitalization defined by ICD 9th for ischemic or hemorrhagic stroke as a primary or secondary diagnosis from inpatient discharge database.	patients who began treatment with SSRI or TCA between 2001-2009 under a diagnosis of depressive or anxiety disorder.	adjusted for propensity deciles (history of HT, DM, IHD, cerebrovascular disease, heart failure, AF, migraine, chronic kidney, liver and lung disease, malignancy, use of cyclooxygenase-2 selective and non-selective NSAIL's, antiplatelet agents, anticoagulants, nitrates, antiarrhythmic agents, β-blockers, Ca-channel blockers , ACE inhibitors, angiotensin receptor blockers, insulin, antidiabetics, diuretics, digoxin, lipid-lowering agents, antiepileptic, antipsychotics, estrogen , age, sex, treatment initiation year, and patients' resource utilization) AD's mean daily dose, antihypertensive, antidiabetics, antiplatelet and lipid-lowering drugs.
Mathur R	2005-2015	cohort study	Europa	part of the primary care database at Queen Mary. 524 952 participants	Incl.: >30 years of age in March 2015 free from MI or stroke at study baseline.	diagnosis for stroke obtained from the Red Codes (terminology system used by the GP's).	prescription for antidepressant at study entry.	age, gender, ethnicity, DM, HT, hyperlipidemia, smoking, obesity, Townsend deprivation score, anxiety and depression.
Nabi H	1998-2005	cohort study	Europe	random sample of the finish population, part of Health and Social Support study and 22-54	Excl.: entitlements to special drug reimbursements for CHD, HT and diabetes; hospitalized for CHD or CVE in	patients who were treated in a hospital or died from CVE between 1999 and 2005 with codes I60–I69ICD-10th .	antidepressant prescription collected at study baseline (1998) from the National Drug	sex, age, education, alcohol, sedentary lifestyle, smoking, obesity, HT, diabetes and incident CHD.

				of age at study baseline. 23 282 participants	1998 (from the national discharge register).		Prescription Register (outpatient prescription data ATC code N06A).	
Pan A	2000-2006	cohort study	USA 11 states	female nurses aged 30–55 years in 1976, which responded to a mailed questionnaire regarding their medical history and health practices at '92, '96 and 2000. 80 574 participants	Excl.: participants without information on depressive symptoms, depression diagnosis or ADM use, those with previous stroke, and missing values for covariates at baseline.	incident stroke identified through *self/kin reports*, for which their *medical data, autopsy reports, and death certificates* were retrieved. CVE due to infection, trauma, malignancy, together with silent strokes were excluded.	report of regular use of AD in the '96 questionnaire; regular use of SSRI or other AD (TCA provided as examples) in the 2000 questionnaire. Thereafter this information was updated biennially.	adjusted for age, marital status, parental history of MI, ethnicity, PA, BMI, alcohol, smoking, menopausal status, diet with DASHDS, postmenopausal hormone therapy, aspirin, multivitamin use, HT, hypercholesterolemia, diabetes, cancer and heart diseases.
Quinn G.R	1998-2003	cohort study	USA	part of the Atrial Fibrillation Cohort from July 1996, till December 1997. 13 559 participants	Excl.: previous valve repair or replacement, mitral stenosis, transient perioperative AF, recent hyperthyroidism. Incl.: patients with atrial fibrillation and exposed to warfarin.	hospitalizations for intracranial hemorrhage occurring during warfarin or within 5 days of preceding warfarin identified through the ICD-9th primary and secondary diagnoses.	exposure to SSRI and TCA was defined as ≥1 receipt of the medications based on information in the health plan pharmacy databases. Longitudinal exposure determent by the date of dispensation and number of days supplied between serial prescription (venlafaxine, a SNRI was also included).	adjusted for ATRIA bleeding risk score (anemia, severe renal disease, age, previous bleeding, and hypertension) and time in international normalized ratio range ≥3.0.
Rahman I	2006-2009	cohort study	Europe	Individuals from Swedish Twin Registry and Screening Across Lifespan Twin Study (SALT)	Excl.: individuals with prevalent CVD and who died due to other causes before study baseline (1st January 2006). Incl.: free of CVD and	events were defined as having at least one incident event of ischemic stroke identified through ICD 7-10th and surgical codes.	a) at least one prescription of the ATC-code ''NO6A" in the drug registry (84% from the data). b) self-reported responses gathered in	birth year, gender, smoking status, educational level, HT, DM, BMI, and alcohol intake.

				linked with: national patient, psychiatric, drug death registry. 36 654 participants	part of the SALT interview.		the SALT interview (16% of the data).	
Renoux C	1995-2014	case-control	Canada	Patients registered in CPRD with at least one AD prescription after 18 years of age and being in the practice for at least one year, between January 1, 1995 and October 31, 2014. 3036 cases 89 702 controls	Excl.: prevalent stroke or TIA, prevalent AD users in the year prior to cohort entry, both an SSRI and TCA user on the date of cohort entry.	within the study cohort all patients with a first time Red Code related to non traumatic intracranial hemorrhage, sub/extradural hematoma, hemorrhagic stroke, intracerebral hemorrhage, or SAH.	prescription in the medical records for SSRI, TCA or other AD from the cohort entry till the index date. Further classified as *current* (within 30d before the IDC); *past* (30-90d before the IDC); *non users* (no AD prescription within the 90 d preceding the IDC).	age, sex, year of cohort entry, duration of follow-up, obesity, smoking, alcohol, hyperlipidemia, HT, DM, TIA, AF, CHD, congestive heart failure, PVD, COPD, renal failure, depression, neuropathic pain, cancer, liver disease, hemostasis disorders, cerebral vascular malformation, history of bleeding, health utilization, anticoagulants, antiplatelets, NSAIDs, antipsychotics.
Risselada R	1998-2006	case–control	Europe	persons in the PHARMO database who had at least 3 years of valid database history before the index date.	/	hospitalization for a first SAH (index date), as recorded in the Dutch National Medical Registration with ICD-9-CM code 430.	study participants defined as *current* users (use at index date) of SSRI or TCA versus non-use if they had a prescription in their drug registry.	Adjusted only for age gender and index date

				1004 cases 10 033 controls				
Schalekamp T	1991-2004	case-control	Europe	all persons in the PHARMO Record Linkage system (includes demographic and medical history from community pharmacies of 25 areas in Netherlands). 1848 cases 5818 controls	Incl.:>=18 years old, whit first coumarin prescription from 1991 till 2004 that did not have a hospital admission for major bleeding and available medical history at least 1 y. before the coumarin prescription.	first hospitalization of intracranial bleeding (index date) while being treated with coumarin (clinical modification of the ICD9th diagnostic codes).	drug prescription derived from the PHARMO database and categorized as *current* (if the duration of an AD extended with 10% ended on or beyond the index date) *recent and past users* (if the duration of use extended with 10% from a dispensing date ended within 30 days or more before the index date).	age, sex, coumarin anticoagulant use, time since initiation of coumarin, geographic region, NSAIDs, antiplatelet agents, antibiotics, glucocorticoids, inhibitors/inducers of coumarin metabolism, DM, thyroid disorders, heart failure, and cancer.
Seifert CL	2003-2009	cohort study	Europe	inhabitants of Bavaria, born before 1946 part of the public health insurance. 3852 participants	Incl.: participants who had a complete questionnaire and physical examination in the INVADE trial.	claims data were linked with the hospital discharge diagnosis for ischemic stroke (ICD I63.-).	if the general practitioner reported a prescription of an antidepressant at study baseline.	age, sex, BMI, smoking, HT, DM, hyperlipidemia, previous: myocardial infarction, stroke or TIA, atrial fibrillation, and PA.
Smoller W	1998-2007	cohort study	USA	postmenopausal women aged 50 to 79 years enrolled from 1993 through 1998 in the Women's Health Initiative Study. 136 293 participants	Excl.: drug dependency or mental illness; self-reported cardiovascular outcome; taking AD at baseline, no follow-up visit; missing data on any covariate. Incl.: no AD at baseline and at least 1 follow-up visit.	incidence *non-fatal stroke* obtained from mailed questionnaires, after validated by neurologist and CT/MRI imaging technics; *fatal stroke*-obtained from proxy responders and/or National Death Index search.	defined as use of antidepressant at the first follow-up visit when women were asked to bring all medications to the clinic in their original bottles.	stratified by decile of propensity to be taking any new antidepressant at the start of follow-up and adjusted for SBP, BMI, log of depression screen score, hormone use, migraine or bad headache, aspirin or NSAID and history of stroke or MI.

Trifiro G	1996-2005	case-control	Europe	all individuals ≥65y with at least 1 year of data registered in Integrated Primary Care Information database (IPCI). 996 cases 491 276 controls	Excl.: diagnosis of TIA or stroke in the medical history before study entry; diagnosis of cerebral tumor, before or during the study period.	first-ever ischemic stroke confirmed by CT; or mentioned by specialist; or discharge diagnoses. *If a stroke was preceded by a TIA occurring less than 1 month before, TIA was taken as the index date. Otherwise, TIA was not considered.	information on AD obtained from the outpatient prescription files. Classified than as *current* (30 days before IDC); *past* (>30 days before IDC) and *nonusers* (no AD prescription).	adjusted for HT, angina, history of MI, atrial fibrillation, heart failure, coagulation/platelet abnormalities, COPD, diabetes mellitus, dementia, concomitant use of anticoagulants, systemic corticosteroids, and opioids.
Tully PJ	1996-2009	cohort study	Australia	patients undergoing cardiothoracic surgery (CABG) between January 1st 1996 and 30th December 2008. 4136 participants	Excl.: users of TCA, mood stabilizer, antipsychotic, antihypnotics or other non-SSRI/SNRI, anxiolytic and NSAID (except aspirin).	during hospitalization or within 30 days after surgery defined as permanent stroke, CVA or central neurological deficit persisting for longer than 72 h.	patients were classed into either a SSRI/SNRI or no anti-depressant users among the CABG's patients.	propensity score; age, sex, urgency of surgery, previous MI, respiratory disease, LVEF, DM, renal disease, PVD, CVD, cardiogenic shock, heart failure, HT, smoking, off-pump surgery, statin, aspirin and NSAID's.
Verdel BM	1998-2007	case-control	Europe	participants of the PHARMO Record Linkage System. 28 289 cases 50 786 controls	Incl.: minimum of 365 days of history in the PHARMO record linkage system prior to the index date.	patients ≥18 with a first hospital admission for intracranial bleeding (index day) ICD-9th in the period 1998-2007.	prescription for AD before the index day and classified as: *current* (prescription drug within 90 days before ID); *recent* (91-180 days before the ID); *past* (181 and 365 days prior to ID); *distant past* (>365 days before the ID) *and non-users.*	age, sex, geographical area, index date, duration of exposure, history prior to the index date, NSAIDs, platelet aggregation inhibitors, and vitamin K antagonists (6 months before the index date).

Abbreviations:

AD-antidepresssive drugs

AF-atrial fibrillation

ATC -anatomical therapeutic chemical classification system

BMI-body mass index

BPD- bipolar disorder

CHD-coronary heart disease

COPD-chronic obstructive pulmonary disease

CRP-C-reactive protein

CRPD- clinical practice research datalink

CT-computer tomography

CVD-cardiovascular disease

CVE-cerebrovascular event

DASHDS-dietary approaches to stop hypertension dietary score

D-days

DM-diabetes mellitus

Excl.-exclusion

GP-general practitioner

GRPD-general practice research data base

HDL-high density lipoprotein

HRT-hormone replacement therapy

HT-hypertension

ICD 9^{th} –international classification of diseases 9^{th} revision

ICD-ischemic cerebrovascular disease

ICH-intracranial hemorrhage

IDC-index date of cerebrovascular event

IHD-ischemic heart disease

Incl.-inclusion

INVADE trial-intervention project on cerebrovascular disease and dementia in the district of Ebersberg.

LVEF-left ventricular ejection fraction

MAO- monoamine oxidase inhibitors

MI-myocardial infarction

M-months
MR-magnetic resonance
NDI-national death index
NHIRD- national health insurance research database
NSAIDs-non steroidal anti-inflammatory drugs
OCD-obsessive-compulsive disorder
PAD-peripheral artery disease
PA-physical activity
PVD-peripheral vascular disease
SAH-subarachnoid hemorrhage
SBP-systolic blood pressure
SF12-short form 12
SNRI-serotonin norepinephrine reuptake inhibitors
SSRI-selective serotonin reuptake inhibitors
TCA-tricyclic antidepressants
TIA-transitory ischemic attack
UK-United Kingdom y-year

Supplemental Table II.Quality assessment

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22			
First author	**Items from the STROBE checklist**																							**GRADE**	**Quality**
Bak S [2002]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**22**	●	**High**
Behr S [2010]	1	1	1	1	1	1	1	1	1	1	1	1	0[a]	1	1	1	1	1	1	1	0[b]	1	**19**	●	**High**
Chin CH [2017]	1	1	1	1	1	1	1	1	1	1	1	0[c]	1	1	1	1	1	1	1	1	1	1	**20**	●	Low
Chen Y [2008]	1	1	1	1	1	1	0[d]	1	1	1	1	0[e]	1	0[f]	1	1	0[g]	0[h]	1	1	0[i]	0[j]	**15**	●	Low
Coupland C [2011]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0[k]	1	1	1	1	1	1	1	**21**	●	**High**
Coupland C [2016]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**22**	●	**High**
de Abajo F [2000]	1	1	1	1	1	1	1	0[l]	1	0[m]	1	0[n]	1	0[o]	0[p]	0[q]	1	1	1	1	0[r]	1	**15**	●	Low
Douglas I [2010]	1	1	1	1	1	1	0[s]	0[t]	0[u]	1	0[v]	0[w]	0[x]	1	1	1	1	1	1	1	1	1	**16**	●	Low
Hansesn R[2016]	1	1	1	1	1	1	1	1	1	1	1	1	1	0[y]	1	1	1	1	1	1	1	1	**21**	●	**High**
Hung C[2012]	1	1	1	0[z]	1	1	1	1	1	1	1	0[aa]	0[bb]	0[cc]	0[dd]	1	0[ee]	1	1	1	1	1	**16**	●	Low
Kharofa J [2007]	0[ff]	1	1	0[gg]	1	1	1	1	1	0[hh]	1	0[ii]	0[jj]	0[kk]	1	1	1	1	1	1	1	0[ll]	**15**	●	Low
Khokhar B [2016]	0 mm	1	1	1	1	1	1	1	1	0[nn]	1	1	0[oo]	1	0[pp]	1	1	1	1	1	1	1	**18**	●	Low
Lee Y [2013]	1	1	1	1	1	1	1	1	1	1	1	1	0[qq]	0[rr]	1	1	1	1	1	1	1	1	**20**	●	**High**
Mathur R [2016]	1	1	1	1	1	1	1	1	0[ss]	1	1	0[tt]	0[uu]	1	1	1	1	1	1	1	1	1	**19**	●	**High**
Nabi H [2010]	1	1	1	1	1	1	1	1	0[vv]	1	1	1	0[ww]	0[xx]	0[yy]	1	1	1	1	1	1	1	**18**	●	Low
Pan A [2011]	0[zz]	1	1	1	1	1	1	1	1	1	1	1	1	0[aaa]	0[bbb]	1	1	1	1	1	1	1	**19**	●	**High**
Quinn G.R [2014]	1	1	1	1	1	1	0[ccc]	1	0[ddd]	1	1	0[eee]	0[fff]	0[ggg]	0[hhh]	1	1	1	1	1	0[iii]	1	**15**	●	Low
Rahman I [2013]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0[jjj]	1	1	1	1	1	0[kkk]	1	**20**	●	**High**
Renoux C [2017]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**22**	●	**High**
Risselada R [2009]	1	1	1	1	1	1	0[lll]	1	1	1	1	1	0 mmm	0[nnn]	1	1	1	1	1	1	1	1	**19**	●	Low
Schalekamp T [2008]	1	1	1	1	1	1	0[ooo]	1	1	1	1	1	1	0[ppp]	0[qqq]	1	1	1	1	1	1	1	**19**	●	**High**
Seifert CL [2012]	1	1	1	1	1	1	0[rrr]	1	0[sss]	1	1	1	1	0[ttt]	1	1	1	1	1	1	1	1	**19**	●	**High**
Smoller W [2009]	1	1	1	1	1	1	1	1	1	1	1	1	0[uuu]	1	1	1	1	1	1	1	1	1	**21**	●	**High**
Trifiro G [2010]	1	1	1	1	1	1	1	1	1	0[vvv]	1	1	1	0 www	1	1	1	1	1	1	1	1	**20**	●	**High**
Tully PJ [2012]	0 xxx	1	1	0[yyy]	1	1	1	1	1	1	1	0[zzz]	1	1	0 aaaa	0 bbbb	1	1	1	1	0 cccc	0[dddd]	**15**	●	Low
Verdel BM [2010]	1	1	1	1	1	1	1	1	1	1	1	0 eeee	0[ffff]	1	1	1	1	1	1	1	0 gggg	1	**19**	●	**High**

Quality	STROBE	GRADE
High	>18	
Low	Any number	

[a] The authors explained that they excluded the cohort members who were hospitalized at the index day (the admission for the intracerebral hemorrhage) from the set of the potential controls since they were not at risk of being admitted for bleeding at that point of time. However, the authors were obliged to report the number of excluded members as well as to describe their characteristic (demographic, medical, etc.) in order to address the potential source of bias introduced through the exclusion of these cohort members.
[b] The generalizability of their study results was not discussed.

[c] No sensitivity analysis was discussed in the description of the statistical processing of their data, yet it was mentioned in the discussion part.

[d] Poorly defined confounders.
[e] If a patient was multiple antidepressant user or switched from one antidepressant to another, this patient would have been counted twice. Thus a clear explanations of the used statistical method should have been added. Furthermore, since this is a case-control study a reader will be interested to know why it was decided to be calculate the hazard ratio instead of the odds ratio.
[f] No information for the missing data for each variable of interest (since the data were from medical claims). The reader will be interested in knowing the coverage of the psychiatric comorbidities (anxiety) or the medication that affects the stroke risk (aspirin) and many other potential confounders of this medical claim database.
[g] No report of subgroup analysis, interaction or sensitivity analysis. The only data available is the subcategorization of ischemic and hemorrhagic stroke.
[h] Poorly and confusing summarization of the key results ("24-43% increased risk for CVE"-page n°4 is rather confusing and not well defined).
[i] The generalizability was not discussed.
[j] An information about the source of funding was not provided.

[k] No report of outcome events or summary measures over time.

[l] The authors did not explain how the potential confounders smoking and BMI were assessed and what was their source of data (in the categorization of these variables exist a category with the label "unknown", therefore the reader should be informed about their source and method of assessment).
[m] No explanation how the study size was arrived at.
[n] Taking in consideration the categorization of the variables, no explanation was given how many were "unknown" smokers or obese study members.
[o] No report of the number of the excluded cases and controls due to very numerous exclusion criteria (ischemic heart dieses, cancer, diabetes, alcohol abuse).
[p] No indication of participants with missing data for each variable of interest.
[q] The outcome data were not clearly defined (a mistake was also present arising from the different reported number of the odds ratio with its 95% confidence interval in the text on page n° 3 and in table 1).
[r] The generalizability of their study results was not discussed.

[s] The potential confounders were mentioned, however not defined. Furthermore, hemorrhagic diagnostic stroke code was missing.
[t] No information about methods of assessment of the variables of interest.
[u] No effort to address potential source of bias.

[v] No explanation why and how the quantitative variables were handled in the analysis (e.g. the BMI categorization according the WHO definition is normal (BMI<25kg/m^2), overweight (25–30 kg/m^2) or obese (>30 kg/m^2; in this analysis the BMI was classified as <20 kg/m^2 / 20-25 kg/m^2, and >25 kg/m^2. Therefore, the reader would be interested in knowing the reason for this uncommon categorization.
[w] No described methods for subgroup or sensitivity analysis (since in the discussion one is mentioned), interactions, nor how the missing data was addressed.
[x] No reported numbers of individuals at each stage of study—potentially eligible, examined for eligibility, confirmed eligible, included/excluded in the study, completing follow-up, and analyzed.

[y] The follow-up time was not summarized.

[z] The authors addressed the study design like retrospective observational study.
[aa] Statistical analyses where poorly described without explanation of any methods used to examine the subgroups interaction or sensitivity analysis.
[bb] The authors did not provide the number of the excluded patients from the eligible ones.
[cc] No summarization of the follow-up time (average and total).
[dd] No reported number of outcome events or summary measures over time for the ischemic or hemorrhagic stroke, despite the gradually reported decreased risk for both outcomes.
[ee] No report of other sensitivity or subgroups analysis. The effect of the depression was explored from the same database, but it was not clear the inclusion criteria or how it was statistically analyzed. This analysis was just mentioned in the discussion part.

[ff] No indication for the study design with a commonly used term nor in the abstract or in the study title.
[gg] The key elements for the study design were not mentioned early in the paper.
[hh] No explanation how the study size was arrived at or explanation of a sensitivity analysis (there is flow diagram in reference n°5, but the numbers do not match).
[ii] No explanation how the missing data was addressed (there is self-reported stroke, self-reported BMI, therefore the reader would be interested in knowing the completeness of their interview self-reported data).
[jj] No report of number of individuals at each stage of the study and reasons for non-participation at each stage.
[kk] No indication of participants with missing data in each variable of interest.
[ll] No report of the source of funding.

[mm] No indication of the study's design with a commonly used term in the title or the abstract.
[nn] Now explanation how the study size was arrived at (page n° 2 : no indication for the eligible participants or the number of the excluded beneficiaries with any antidepressant use 6 months prior to their traumatic brain injury, beneficiaries which did not survive the TBI hospital stay, or they had Medicare part C (Medicare Advantage) coverage.)
[oo] No information about stepwise exclusion of study participants not eligible to be included in the final study.

[pp] No report of outcome events or summary measures over time.

[qq] No information on how many of the participants completed the follow-up.
[rr] No summarization of the follow-up time.

[ss] No effort to address potential sources of bias.
[tt] No explanation how they handled the missing variables of interest (e.g. ethnicity).

[uu]No indication of how was derived the number of study participants in the anxiety or depressed study cohort.

[vv] No effort to address potential sources of bias.
[ww] No information about the number of the excluded prevalent cases at study baseline.
[xx] The follow-up time was not summarized. (e.g., average and total amount).
[yy] No reported numbers of outcome events or summary measures over time.

[zz] Absence of a commonly used term for the study's design in the title and the abstract.
[aaa] The average and the total amount of the follow-up time was not reported.
[bbb] No reports of outcome events or summary measures over time.

[ccc] The antidepressant use was not clearly defined since it was not mentioned in the definition of the study exposure what kind of data was included in their pharmacy database (were there included the specialist's beside the GP's prescriptions?). The potential included confounding variables were only mentioned but not described.
[ddd] No effort to address potential source of bias.
[eee] No description of any methods to examine subgroups and interactions. No explanation on how the missing data or losses to follow-up were addressed if there was any.
[fff] No report of how many of the participants completed the follow up.
[ggg] No indication of the participants with missing data for each variable of interest.
[hhh] No report of outcome events or summary measures over time.
[iii] The external validity of their study results was not discussed.

[jjj] Outcome events or summary measures over time were not reported.
[kkk] The generalizability of the study was not discussed. Still they have discussed the possibility of residual confounding due to depression in the people aged 65 and above because it is very probable that they have come in contact only with primary care, not with specialized psychiatric care. In other words this could discuss the limited generalizability in this older population.

[lll] The potential confounding factors, in this case the exposure of SSRI, was not clearly defined. We are in doubt whether the definition of "current user" for the statins is applicable also for the mentioned confounding factors.
[mmm] No information about non-participation at each stage.
[nnn] The follow-up time was not summarized (e.g. average and total amount, or median and standard deviation follow-up time).

[ooo] The referent category is not clearly defined for the current SSRI users (were past and recent SSRI users included in the referent category?).
[ppp] In the table 2 where are presented the characteristics of the study participants, is omitted the number for the recent and past SSRI exposed patients and controls.
[qqq] The authors have reported the number of exposed acenocumarol patients and controls, but not of phenprocoumon which is also included in the definition of the exposure under study.

[rrr] The exposure to antidepressants was not clearly defined (page n° 3: "In addition, depressive symptoms were assumed if the general practitioner reported the prescription of any established antidepressant medication"). It was not mentioned if they were multiple antidepressant users, which code was used or what was the indication for which these medications were prescribed.

[sss] They aimed on a potential effect modifier (the age and sex according to literature data), however the part for the potential source of systematic error (bias) in the design, recruitment, data collection or analysis was not addressed in the text. Anyway, on page n° 3 the authors have mentioned the reason why they have used the cut-off for the Geriatric depression scale (GDS).Yet, this description could not account to avoid bias for antidepressant use since this is only applicable for the depression.
[ttt] The follow-up time is not clearly defined, since the total follow-up was mentioned to be 6 years, and the median 6.13 years?

[uuu] No indicated reason for non-participation at each stage (reasons for losses to follow-up or drop out the study).

[vvv] No information on how the study size was arrived at.
[www] No indication for the missing data for each variable of interest.

[xxx] No indication of the study's design with a commonly used term nor in the title, nor in the abstract.
[yyy] The term "prospectively collected data" is not providing key elements for the study design early in the paper.
[zzz] No information on how the missing data in the study were addressed.
[aaaa] It was not indicated the number of participants with missing data for each variable of interest.
[bbbb] No report of number of outcome events or summary measures over time.
[cccc] The generalizability of the study was not discussed.
[dddd] No information about the funding.

[eeee] No description of any sensitivity analysis.
[ffff] They did not report the number of patients which did not fulfil the inclusion criteria.
[gggg] Study generalizability was not discussed in the discussion part.

Supplemental Table III. Study limitations in observational studies (risk of bias) according to GRADE

[1] The exposure was loosely defined according to nowadays ATC classification. For example: Clomipramine-is a non-selective antidepressant according to the ATC code, but here it was placed in the SSRI category. Venlafaxine is in the "other antidepressant category" ATC N06AX, (here in the SNRI category). Furthermore, nortriptyline and amitriptyline cannot be in a different category.
[2] Residual confounding due to alcohol abuse and smoking (the results from their sensitivity analysis derived from 2 population-based surveys demonstrated that SSRI users were current smokers and alcohol users with either no regular intake or high alcohol consumption), information which were not plausible to be examined from their available data.

[3] Detection bias due to the possibility that the patients who are using anticoagulant therapy, such as phenprocoumon, can undergo imaging procedures more frequently even if they have light symptoms and therefore are diagnosed with intracranial hemorrhage (ICH) more frequently. However, the potential of this "detection bias" is low since usually the ICH has very abrupt onset and sever symptoms.
[4] Residual confounding due to other unmeasured stroke risk factors, mainly smoking, obesity, BMI. The variable "depression" was also not included in the logistic regression analysis.

[5] The major problem in this retrospective cohort study is the initial exclusion of subjects with a diagnosis of mental disorder (290-319 ICD 9th like alcohol or drug induced mental disorders, dementia, but most importantly the major depressive disorder, a strongly reported risk factor for stroke (1)) only among the non-exposed individuals. This step in the conduction of their study had probably introduced a bias in the results, due to the fact that the exposed participants were carrying an additional risk factor for stroke, namely the disease itself.
[6] Residual confounding due to depressive disorder only among the exposed individuals, alcohol abuse, BMI and many others.

[7] This misclassification of prevalent as incident stroke cases could seriously confound their results, because post-stroke depression occurs frequently, and is primarily treated with SSRIs. In this study many cerebrovascular events had the diagnosis of "other cerebrovascular events" (with the code ICD 9th 437.XX (437.0 cerebral atherosclerosis; 437.1 other generalized ischemic cerebrovascular disease; 437.2 hypertensive encephalopathy 437.3 cerebral aneurysm, nonruptured; 437.4 cerebral arteritis; 437.5 moyamoya disease; 437.6 non-pyogenic thrombosis of intracranial venous sinus disease; etc.), which is very heterogeneous group and does not correspond with the definition of the outcome under study.
[8] Residual confounding due to life-style risk factors such as: patient's weight, smoking status, or severity of the cerebrovascular event, the degree of serotonin inhibition and antidepressant dose, the indication for which these antidepressants were being used (confounding by induction) like dysthymia, anxiety disorders, obsessive- compulsive disorder, eating disorders, chronic pain, neuropathic pain and, in some cases, dysmenorrhea, snoring, migraine, attention-deficit hyperactivity disorder. All of the aforementioned cofounding factors wouldn't biased the results greatly, since the study was already adjusted for the most notable stroke risk factors (diabetes, atrial fibrillation, alcohol consumption or the depression itself).

[9] Residual confounding as in every observational study, which is susceptible to confounding by indication, channeling bias and many other unmeasured or unreported confounding factors (alcohol consumption, BMI, obesity, atrial fibrillation).

[10] Residual confounding as in every observational study (some lifestyle risk factors were not measure like physical activity, diet). Authors mentioned residual confounding due to depression severity, since it is not routinely recorded in the general practice but still the analysis was conducted among depressed individuals so the bias would be minimal.

[11] The authors applied very strict entry criteria (exclusion of any of the following conditions: ischemic heart disease, heart failure, cardiac dysrhythmia, hyperthyroidism, diabetes, epilepsy, cancer, coagulopathy, chronic liver disease, connective tissue disorders or alcohol abuse), which can reduce the external validity of the study and also lead to survivor bias.
[12] The definition of the study exposure is introducing non-differential misclassification of the exposure, since it is very plausible that among the non-user's category are present study participants whose supply prescription for any antidepressant ended more than 60 days prior to the intracranial hemorrhage.
[13] Residual confounding can be present due to the indication for the study drug, namely the depression, and many others unmeasured possible stroke risk factors like atrial fibrillation.

[14] In this nested case-control study the source population is a cohort of antidepressant users at some time point with an intention to limit the confounding by indication (when the apparent association with the drug may be due to the condition for which it was prescribed rather than the drug itself). We doubt that this measure had removed this confounding since the antidepressants are prescribed for various reasons such as anxiety, obsessive-compulsive

disease, neuropathic pain etc. Furthermore, the controls in a case-control study should reflect the exposure in the source population, that is they need to be selected independently of the exposure under study in order to avoid "selection bias".

[15] Non-differential exposure misclassification due to medical adherence. Non-differential outcome misclassification since the authors mentioned that it is possible that some hemorrhagic strokes were recorder as non-specific, therefore affecting the control group.

[16] Residual confounding due to unmeasured confounding factors.

[17] Non-deferential misclassification of the exposure due to the measurement of the antidepressive drugs only at study baseline. Because of this cross-sectional antidepressant measurement, the impact of censoring was further explored with sensitivity analysis with 0-2 years, 0-4 years and 0-end of the follow-up period. However, they did not observe any significant antidepressant-related increase of stroke as an outcome (censored at 2 years 1.15 (95%CI 0.81-1.64) censored at 4 years 1.15 (95% CI 0.88-1.50) all years 1.23 (95%CI 0.98-1.55)). This is important from two aspects:
a) A British study suggested that risk of antidepressant-related all-cause mortality, MI, and stroke may be highest in the first 28 days of treatment (2). This means that regardless of exposure misclassification, they likely could have observed the stroke-relevant events early on during participant follow-up if these events were attributable to the antidepressant drugs.
b) A more recent US analysis found that, 66% of antidepressant users continued antidepressant use for more than 2 years (3), leading to a probability that in the first 2 years of the follow-up period they would have caught the majority of antidepressant users and the stroke cases due to this exposure.
Of bigger concern is the exclusion of the prevalent stroke cases at baseline, which were only 8 cases from 29,694 participants (page n°3 of the article). We doubt that this represents the true number of prevalent cases leading the analysis to be subject of differential misclassification of the outcome due to exposure (previous stroke → post-stroke depression →antidepressants) of prevalent/incident cases.

[18] This uniform geriatric population can still introduce "survivor bias". However, their inclusion from a random subset of 100,000 individuals from a large database would attenuate this effect.

[19] Since the exposure like SSRI is a time-dependent variable and in this study, it is measured only at study baseline can be a source of non-differential misclassification.

[20] Residual confounding due to life-style risk factors (alcohol, smoking, BMI). The effect of the depression was explored in a separate sensitivity analysis conducted among individuals without major depressive disorder where it was demonstrated an individual SSRI use increases the stroke risk.

[21] No information about the number of matched controls per case.

[22] Only exposure to antidepressants in the two weeks before the occurrence of the hemorrhagic stroke was considered, which may be not long enough to capture all SSRI users (e.g. recent or past) and can introduce misclassification of the exposure more emphasized among the cases than the controls, if the exposure is a risk factor for the disease.

[23] Failure to match for prognostic factors and/or lack of adjustment in their statistical analysis is derived from the unknown indication for the treatment, therefore leading to residual confounding due to depression, as well as many other stroke risk factors like atrial fibrillation or previous history of stroke (this variable in their analysis was self-reported).

[24] Non-deferential misclassification of the exposure after the thirtieth day after the traumatic brain injury. However, prevalent user bias (when inclusion of prevalent users' biases study results by underestimating early adverse events related to the study drug) is minimized due to the "washout" 6 months' period. The fatal stroke cases, that did not reach the hospital were not included in this analysis.

[25] Residual confounding due to socioeconomic status and lifestyle risk factors such as smoking, diet or physical activity.

[26] No information about how long before the prevalent cases were excluded, i.e. if it was just before the study baseline or earlier. This aspect of the study may have led to prevalent/incident bias. Another issue is referring to the outcome event because the cerebrovascular event is defined as incident primary or secondary stroke diagnosis in the inpatient discharge database. Does that mean that head injury like primary diagnosis and hemorrhagic stroke like secondary diagnosis would fit in the WHO definition of the stroke? Furthermore, the fatal-stroke cases which did not reach the hospital were not recorded in the analysis.

[27] Residual confounding due to life-style risk factors (obesity, smoking, diet or physical activity).

[28] Even if with the prospective collection of their study data was avoided the possibility of reverse casualty, they were not able to determine whether any hospital admission for stroke had occurred prior to study entry. Because of this a prevalent case could have been misclassified as incident, subsequently introducing a "survivor bias" in their analysis.

[29] The exposure under study was only measured at study baseline, not allowing to eliminate the influence of "prevalent use bias". Furthermore, this antidepressant use can vary across their 10 year of follow-up leading probably to non-differential misclassification.
[30] The residual confounding in this observational analysis consist of non-measured life-style risk factors as consumption of alcohol, physical activity and many others.

[31] In the study anyone who had had a coronary heart disease (CHD) or stroke event at baseline (1998) was excluded. However, it was not stated if those who had a cerebrovascular event prior to study baseline were aslo excluded, thus *reverse causality* could have been an issue in their study design. Anyway, since they included individuals till 55 years of age at study baseline, where generally the incidence of stroke remains low, after which it increases dramatically (4) the number of prevalent cases classified as incident should not have introduce serious *survivor bias*. Another problem related to this topic is that the misclassification of the incident/prevalent stroke cases is expected (because post-stroke depression occurs frequently and is primarily treated with SSRIs) to be higher among the exposed population, due to the frequent post-stroke depression along with the antidepressant medication. In that manner, unless we can justify the assumption that the exposure being studied is not associated with recovery or survival, every effort should be made to limit recruitment to incident cases. Additionally, their prescription database had a coverage only on the outpatient prescribed antidepressant medication. This step can capture only the individuals who differ from those hospitalized and treated with antidepressants.
[32] Non-differential misclassification of the exposure, since it is only measured at baseline. Nevertheless, additional analysis at the end of study on the prevalence of antidepressant medication revealed high persistency of those reported at study baseline.
[33] Residual confounding due to the many unmeasured possible stroke risk factors such as the disease itself, since in this study the exposure was defined as having a depression according to the Beck Depression Inventory scale or having a filled antidepressant prescription. The final multivariate model, where the exposure was defined as use of antidepressant drugs, was not adjusted for depression, therefore leading to possible residual confounding.

[34] Relatively homogeneous population of predominantly white registered nurse. Furthermore, selection bias is possible due to the exclusion of large proportion of women without information on depressive symptoms, depression diagnosis or antidepressant medication (ADM), previous stroke and missing covariates at baseline. Still, compared with the population included in the study, the excluded participants had similar age, incidence rate of stroke, but different BMI, prevalence of hypertension, diabetes, and heart disease.
[35] The sensitivity analysis, performed excluding cases of self-reported stroke not confirmed by medical records, did not alter the results, minimizing the risk of bias. The physicians were blinded to risk factor status during the revision of the medical records, which minimize the possibility of detection bias.
[36] Residual confounding from other unmeasured stroke risk factors (atrial fibrillation), even if in the model were included quite enough confounding factors.

[37] Homogeneous population of people with AF on warfarin, which should not introduce selection bias, but rather would be an issue of generalizability, because of poor representation of minorities.
[38] Misclassification of the exposure due to medical adherence. Possible detection bias during the validation procedures of the medical records, since the clinicians were not blinded to the study exposure. However, this will introduce a minimal drift in their study results because they used hard data for the study outcome. Furthermore, their use of primary and secondary diagnosis for intracranial hemorrhage can cover a wide range of conditions that do not fit in their study hypothesis.
[39] The largest problem in this study is the residual confounding due to the disease itself, namely depression, as well as from the many life-style risk factors and comorbidities, which were not included in the multivariable regression model (alcohol consumption, smoking, obesity, diabetes and many others).
[40] No information about possible losses at follow-up.

[41] Recall bias from self-reported data. However, this is not likely to have been major source of bias since combining both data sources, the majority of their reports (84%) were found through the prescribed data registry.
[42] Residual confounding due to:
a) unregistered depression in people older than 65 years of age (the majority of this population only have come in contact with the primary care, therefore their depression diagnosis is omitted in the national patient registry);
b) depression not severe enough to be registered in inpatient or specialized outpatient care;
c) confounding by indication (no records of diagnosis or other medical records for the prescribed agent);
d) residual confounding due to possible change in the life-style risk factors and comorbidities (BMI, diabetes, hypertension) between the SALT interview and study baseline and unmeasured risk factors like atrial fibrillation.

[43] In this study the exposure was recorded through the prescriptions dispensed by the general practice physicians. If the patients with more severe form of depression were referred to a secondary care, their antidepressant medications were not noted in the study database. According to background literature, this depression severity could result in higher risk for a cerebrovascular event (5). In that manner exposure misclassification should be more prevalent among the cases than the selected controls.

[44] Due to the nature of their hospitalization database the cases of SAH that were fatal were not included in the study, limiting the external study validity. However, the cases were *first* ever recorded SAH, minimizing the possibility of introducing a "survivor bias".
[45] The definition of *current* exposure to SSRI use of antidepressant on the index date (the date of SAH hospitalization) did not capture all the exposed study subjects (e.g. recent or past users) and had led to small number of exposed SSRI or TCA cases (32 out of 1004; 10 out of 1004). Also, their pharmaceutical database had coverage only of the outpatient prescribed study drugs. However, this bias is likely to be a non-differential information bias with minimal study impact, since the majority of the antidepressants are prescribed by the GP.
[46] Here the residual confounding is significant due to many uncontrolled and unmeasured potentially SAH risk factors. The main exposure under study is withdrawal of statins and the analysis for the use of SSRI versus non-use is only adjusted for age, gender and index date.

[47] Because the referent category for the SSRI current users was not clearly defined, a doubt remains for the potential source of bias that can be introduced through including the past/recent in the same category. However, they further did a separate analysis for recent and past users.
[48] A number of potential confounding factors that can distort the results were not included, as they were not measured in the study (like many important life style risk factors as smoking, alcohol abuse, BMI, obesity, comorbidities and the indication for which these antidepressants were being used).

[49] Even if the study data was originated from population based data that reduce the possibility of selection bias, still exist potential sources of distortion of the study results. The GP's are first ports of prescribing ADM for those suffering from anxiety and/or depression, yet the authors did not have the information from non-private specialized care, influencing the external validity (generalizability) of the study. This population may be from different social status or have different comorbidities in contrast with the ones who took care in the private clinics (setting with unequal access to medical care).
[50] They did not have the information from the mortality files (fatal stroke cases). This source of bias will only slightly influence the outcome results (those who died or change the insurance was only 1.4% over the entire observation period). Rather more concerning is the baseline measurement of antidepressant medications.

[51] Selection bias due to the study design. All the participants were female postmenopausal nurses.
[52] Self-reported prevalent cases could have been misclassified as incident cases, due to the questionable validity of these self-reported data. Furthermore, the study only determined antidepressant exposure at a single time point. This exposure misclassification during the follow-up would likely produce bias towards the null hypothesis.
[53] Residual confounding due to antidepressant dosage, not full adjusted for depression score (low positive predictive value of the test), and many more unmeasured confounders in the context of the nature of this observational study design.

[54] Relatively homogeneous population of elderly people.
[55] The exposure information data came only from the primary care system. Since the severity level of depression seems to be of significance for increased risk for cardiovascular and cerebrovascular diseases, (5) the cases in this study could reflect a higher undetected exposure prevalence prescribed by the secondary care specialist in comparison with the controls. In the same manner, a missed information on prior cerebrovascular events that occurred long time before the study entry could have been more frequent among the cases than the controls, since a prior cerebrovascular event is a risk factor for stroke recurrence (6).
[56] Unmeasured confounding factors (life-style risk factors, diet, air-pollution or social status).

[57] Since the follow-up period was not clearly defined, a participant in the study could have been follow-up for almost 8 years if its CABG surgery had taken place in 1996, or 3 months if it was in 2008 (median follow-up time 4.7 years, interquartile range 2.3-7.9). Therefore, the possibility of "survivor bias" is high. Furthermore, the exclusion of the participants who were taking TCA could have demonstrated a different association between those who participate and do not participate in the study, because according to literature TCA are usually prescribed to people with lower cardiovascular risk factor profile or who possibly were taking previously SSRI/SNRI and switched very recently before the study baseline. Anyway, this distortion would have not influenced drastically the study results, given that their source population is composed only of high-risk subjects who underwent coronary artery bypass surgery.

[58] Misclassification of the exposure cannot be excluded because it was measured only at study baseline. Anyway, in this study the outcome is defined as 30 days stroke morbidity after the CABG surgery, time in which according to recent literature (2,7,8) the risk for stroke is the highest.

[59] Residual confounding due to past use of antidepressants, antidepressant compliance, socio-economic status, alcohol abuse, obesity, depression and many others. Somatic and vegetative symptoms within a depressive episode are commonly experienced as part of heart diseases and may lead to under-recognition of depression among these patients. Therefore, the residual confounding due to the disease itself is maybe higher in comparison to other studies where this confounding was also not eliminated.

[60] The nature of the study data did not allow examining the possible confounding effect of smoking, alcohol abuse, BMI, some over the counter drugs as well as the possible effect of the depression.

Bibliography:

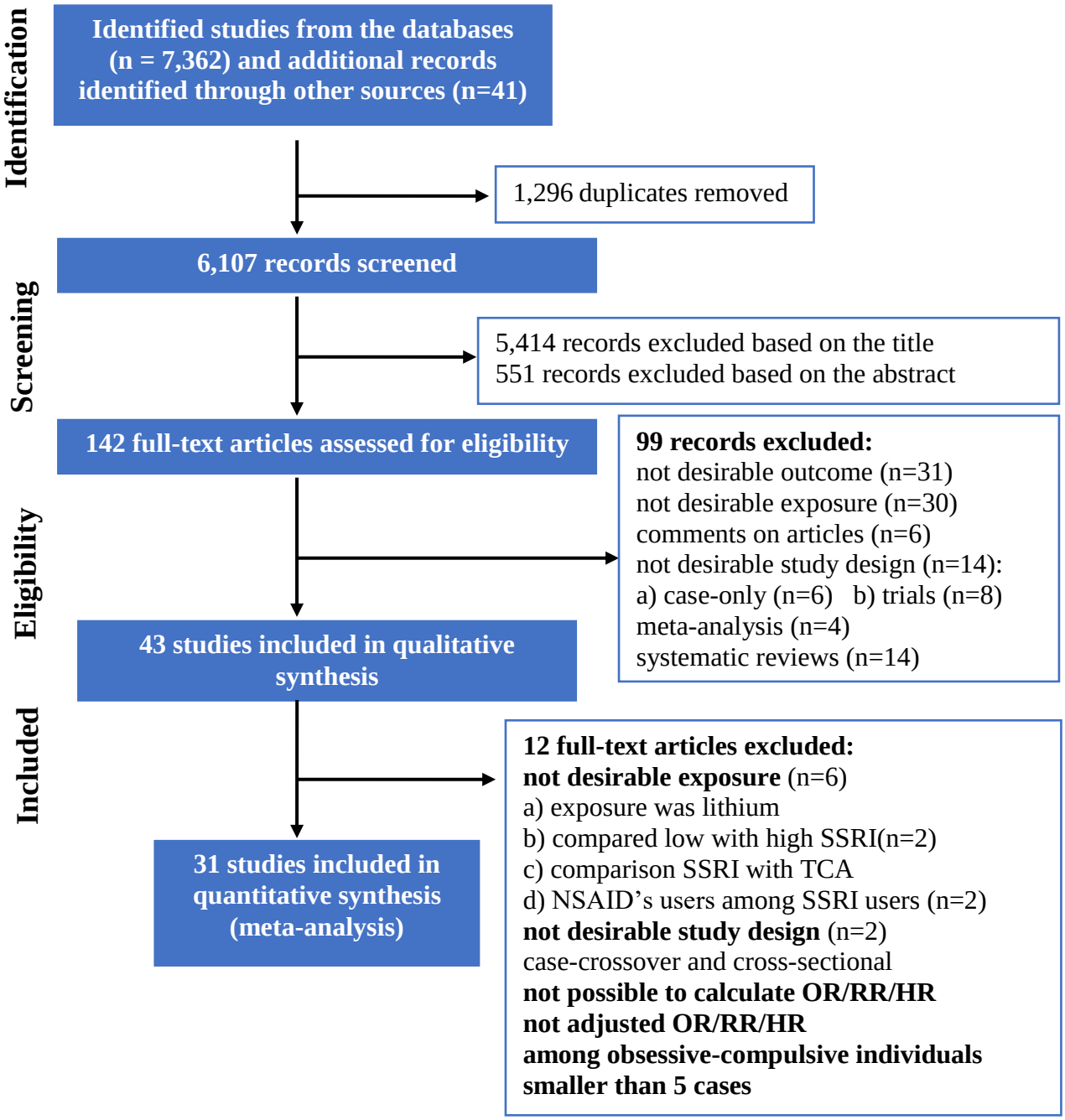
1. Pan A, Sun Q, Okereke O, Rexrode K, Hu F. Depression and risk of stroke morbidity and mortality: A meta-analysis and systematic review. JAMA. 2011;306:1241–9.
2. Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J. Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using primary care database. BMJ. 2016;352:1350i.
3. Mojtabai R, Olfson M. National Trends in Long-Term Use of Antidepressant Medications. J Clin Psychiatry. 2014;75:169–77.
4. Zhang Y, Chapman A-M, Plested M, Jackson D, Purroy F. The Incidence, Prevalence, and Mortality of Stroke in France, Germany, Italy, Spain, the UK, and the US: A Literature Review. Stroke Res Treat. 2012;2012:436125.
5. Almas A, Forsell Y, Iqbal R, Janszky I, Moller J. Severity of Depression, Anxious Distress and the Risk of Cardiovascular Disease in a Swedish Population-Based Cohort. PLoS One. 2015;10:e0140742.
6. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke. 1994;25:333–7.
7. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. Br Med J. 2011;343:d4551.
8. Renoux C, Vahey S, Dell'Aniello S, Boivin J-F. Association of Selective Serotonin Reuptake Inhibitors With the Risk for Spontaneous Intracranial Hemorrhage. JAMA Neurol. 2017;74:173-180.

Supplemental Table IV. Stratified analysis by study quality, region and depression adjustments

	Quality		Region		
	Low	*High*	*Europe*	*USA*	*Other*
Any antidepressant	*meta-* **RR (95% CI)**	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**
Case-Control	0.80 (0.45-1.15) /	1.32 (1.12-1.52) I^2=70,4%	1.32 (1.02-1.62) I^2=76,9%	1.10(0.56-1.64) I^2 = 87,8%	/
Cohort	2.39 (1.96-2.83) I^2=50,6%	1.18 (1.06-1.30) I^2=8,4%	1.08 (0.93-1.23) I^2=0%	1.29 (1.13-1.45) I^2=0%	2.56 (2.34-2.77) I^2=8,5%
Pooled estimate	**1.79 (0.83-2.75)** I^2=95,2%	**1.25 (1.13-1.37)** I^2=55,2%	**1.21 (1.03-1.40)** I^2=62,9%	**1.24 (1.07-1.41)** I^2=53,4%	**2.56 (2.34-2.77)** **I^2=8,5%**
SSRI	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**
Case-Control	0.94 (0.75-1.13) I^2=0,0%	1.33 (1.14-1.53) I^2=63,3%	1.22 (1.01-1.42) I^2=59,2%	1.10 (0.56-1.64) I^2=87,8%	/
Cohort	1.91 (0.91-2.92) I^2=98,7%	1.39 (1.14-1.63) I^2=0,0%	/	1.24(1.01-1.46) I^2=50,3%	2.56 (2.40-2.73) I^2=0,0 %
Pooled estimate	**1.43 (0.84-2.02)** I^2=97,3%	**1.34 (1.19-1.49)** I^2=50,3%	**1.22 (1.01-1.42)** I^2=59,2%	**1.21 (1.02-1.40)** I^2=72,0%	2.56 (2.40-2.73) I^2=0,0 %
TCA	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**	*meta*-**RR (95% CI)**
Case-Control	0.89 (0.66-1.11) I^2=0,0%	1.30 (0.98-1.62) I^2=0,0%	1.34 (0.82-1.34) I^2=15,6%	/	/
Cohort	1.10 (0.74-.1.46) I^2=0%	1.21 (0.89-1.52) I^2=0,0%	/	1.16 (0.92-1.40) I^2=0%	/
Pooled estimate	**0.95 (0.76-1.14)** I^2=0%	**1.25 (1.03-1.48)** I^2=0,0%	**1.34 (0.82-1.34)** **I^2=15,6%**	**1.16 (0.92-1.40)** **I^2=0%**	/
Any antidepressant	**Adjusted for depression**	**Among depressed**			
Case-control	1.35 (1.21-1.49) /				
Cohort	1.17 (0.98-1.35) I^2=43,7%	1.33(1.12-1.55) I^2=88%			
Pooled estimate	1.23 (1.07-1.39) I^2=58,1%				
SSRI-any stroke	**Adjusted for depression**	**Among depressed**	***TCA-any stroke***	**Adjusted for depression**	**Among depressed**
Case-control	1.35 (1.21-1.49) /	1.43 (0.79-2.07) I^2=47%	***Case-control***	/	1.33 (1.07-1.58) I^2=0%
Cohort	1.24 (0.98-1.49) I^2=64,3%	1.25 (1.05-1.45) I^2=84,5%	***Cohort***	1.20(0.88-1.52) I^2=0%	1.18 (0.93-1.44) I^2=54,4%
Pooled estimate	1.27 (1.07-1.47) I^2 =77,1%	**1.27 (1.11-1.43)** I^2=76,6%	***All***	**/**	**1.21 (1.02-1.40)** I^2=47,3%

Table legend: ***meta***-RR-meta Risk Ratio; 95%CI-Confidence Interval

Supplemental Figure I. PRISMA Flow-chart of study inclusions



1 Flow-chart of study inclusion

Records excluded

No desirble outcome
(1–31)
Not desirable exposure
(32–61)
Comments on articles
(62–67)
Case-only
(68–73)
Trials
(74–81)
Meta-analysis
(82–85)
Systematic reviews
(86–99)

Full-text articles excluded

Exposure was litium (100)
Compared low to high SSRI (101,102)
Compared SSRI with TCA (103)
Non-steroid anti-inflammatory drugs among SSRI users (104,105)
Case-crossover (106)
Cross-sectional study (107)
Not possible to calculate OR/RR/HR (108)
Not adjusted OR/RR/HR (109)
Among obsessive-compulsive individuals (110)
Smaller than 5 cases (111)

1. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. Stroke. 1994;25:1099–104.
2. Skop BP, Brown TM. Potential Vascular and Bleeding Complications of Treatment With Selective Serotonin Reuptake Inhibitors. Psychosomatics. 1996;37:12–6.
3. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, et al. Depressive Symptoms, Health Behaviors, and Risk of Cardiovascular Events in Patients With Coronary Heart Disease. JAMA. 2008;300:2379–88.
4. Wallerstedt SM, Gleerup H, Sundström A, Stigendal L, Ny L. Risk of clinically relevant bleeding in warfarin-treated patients-influence of SSRI treatment. Pharmacoepidemiol Drug Saf. 2009;18:412–6.
5. Barbui C, Andretta M, De Vitis G, Rossi E, D'Arienzo F, Mezzalira L, et al. Antidepressant Drug Prescription and Risk of Abnormal Bleeding. J Clin Psychopharmacol. 2009;29:33–8.
6. Jerrell JM, McIntyre RS. Cardiovascular and neurological adverse events associated with antidepressant treatment in children and adolescents. J Child Neurol. 2009;24:297–304.

7. Krantz DS, Whittaker KS, Francis JL, Rutledge T, Johnson BD, Barrow G, et al. Psychotropic medication use and risk of adverse cardiovascular events in women with suspected coronary artery disease: outcomes from the Women's Ischemia Syndrome Evaluation (WISE) study. Heart. 2009;95:1901–6.
8. Cochran KA, Cavallari LH, Shapiro NL, Bishop JR. Bleeding Incidence With Concomitant Use of Antidepressants and Warfarin. Ther Drug Monit. 2011;33:433–8.
9. Hamer M, Batty GD, David Batty G, Seldenrijk A, Kivimaki M. Antidepressant medication use and future risk of cardiovascular disease: the Scottish Health Survey. Eur Heart J. 2011;32:437–42.
10. Labos C, Dasgupta K, Nedjar H, Turecki G, Rahme E. Risk of bleeding associated with combined use of selective serotonin reuptake inhibitors and antiplatelet therapy following acute myocardial infarction. CMAJ. 2011;183:1835–43.
11. Paolucci S. Role, indications, and controversies of antidepressant therapy in chronic stroke patients. Eur J Phys Rehabil Med. 2013;49:233–41.
12. Péquignot R, Tzourio C, Péres K, Ancellin M-L, Perier M-C, Ducimetière P, et al. Depressive symptoms, antidepressants and disability and future coronary heart disease and stroke events in older adults: the Three City Study. Eur J Epidemiol. 2013;28:249–56.
13. Bingefors K, Isacson D, Knorring L V, Smedby B, Wicknertz K. Antidepressant-treated patients in ambulatory care. Mortality during a nine-year period after first treatment. Br J Psychiatry. 1996;169:647–54.
14. Löppönen P, Tetri S, Juvela S, Huhtakangas J, Saloheimo P, Bode MK, et al. Association between warfarin combined with serotonin-modulating antidepressants and increased case fatality in primary intracerebral hemorrhage: a population-based study. J Neurosurg. 2014;120:1358–63.
15. Mortensen JK, Larsson H, Johnsen SP, Andersen G. Impact of prestroke selective serotonin reuptake inhibitor treatment on stroke severity and mortality. Stroke. 2014;45:2121–3.
16. Tang WK, Liu XX, Chen YK, Abrigo J, Chu WCW, Mok VCT, et al. Pontine microbleeds and depression in stroke. J Geriatr Psychiatry Neurol. 2014;27:159–64.
17. Aarts N, Akoudad S, Noordam R, Hofman A, Ikram MA, Stricker BH, et al. Inhibition of serotonin reuptake by antidepressants and cerebral microbleeds in the general population. Stroke. 2014;45:1951–7.
18. Gahr M, Zeiss R, Lang D, Connemann BJ, Hiemke C, Muche R, et al. Association between haemorrhages and treatment with selective and non-selective serotonergic antidepressants: Possible implications of quantitative signal detection. Psychiatry Res. 2015;229:257–63.
19. Gahr M, Zeiss R, Lang D, Connemann BJ, Hiemke C, Freudenmann RW, et al. Risk of bleeding related to selective and non-selective serotonergic antidepressants: a case/non-case approach using data from two pharmacovigilance databases. Pharmacopsychiatry. 2015;48:19–24.
20. Akoudad S, Aarts N, Noordam R, Ikram MA, Tiemeier H, Hofman A, et al. Antidepressant Use Is Associated With an Increased Risk of Developing Microbleeds. Stroke. 2016;47:251–4.
21. Nissen SE, Wolski KE, Prcela L, Wadden T, Buse JB, Bakris G, et al. Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients With Cardiovascular Risk Factors: A Randomized Clinical Trial. JAMA. 2016;315:990–1004.
22. Würtz M, Schmidt M, Grove EL, Horváth-Puhó E, Christiansen CF, Sørensen HT.

Preadmission use of selective serotonin reuptake inhibitors and short-term mortality in diabetic patients hospitalized due to stroke. J Intern Med. 2016;280:407–18.
23. May HT, Bair TL, Reiss-Brennan B, Knight S, Anderson JL, Horne BD, et al. The association of antidepressant and statin use with death and incident cardiovascular disease varies by depression severity. Psychol Health Med. 2017;22:919–31.
24. Zimmer B, Kant R, Zeiler D, Brilmyer M. Antidepressant efficacy and cardiovascular safety of venlafaxine in young vs old patients with comorbid medical disorders. Int J Psychiatry Med. 1997;27:353–64.
25. Samuel NG, Seifert CF. Risk of Bleeding in Patients on Full-Dose Enoxaparin With Venous Thromboembolism and Selective Serotonin Reuptake Inhibitors. Ann Pharmacother. 2017;51:226–31.
26. Roose SP, Glassman AH, Attia E, Woodring S, Giardina E-G V., Bigger JT. Cardiovascular Effects of Fluoxetine in Depressed Patients With Heart Disease. Am J Psychiatry. 1998;155:660–5.
27. Lake MB, Birmaher B, Wassick S, Mathos K YA. Bleeding and Selective Serotonin Reuptake Inhibitors in Childhood and Adolescence. J Child Adolesc Psychopharmacol. 2000;10:35–8.
28. Layton D, Clark DW, Pearce GL, Shakir SA. Is there an association between selective serotonin reuptake inhibitors and risk of abnormal bleeding? Results from a cohort study based on prescription event monitoring in England. Eur J Clin Pharmacol. 2001;57:167–76.
29. Meijer WEE, Heerdink ER, Nolen WA, Herings RMC, Leufkens HGM, Egberts ACG. Association of Risk of Abnormal Bleeding With Degree of Serotonin Reuptake Inhibition by Antidepressants. Arch Intern Med. 2004;164:2367–70.
30. Kurdyak PA, Juurlink DN, Kopp A, Herrmann N, Mamdani MM. Antidepressants, warfarin, and the risk of hemorrhage. J Clin Psychopharmacol. 2005;25:561–4.
31. Avdibegović E, Bećirović E, Selimbasić Z, Hasanović M, Sinanović O. Cerebral cortical atrophy and silent brain infarcts in psychiatric patients. Psychiatr Danub. 2007;19:49–55.
32. Simonsick EM, Wallace RB, Blazer DG, Berkman LF. Depressive symptomatology and hypertension-associated morbidity and mortality in older adults. Psychosom Med. 1995;57:427–35.
33. Everson SA, Roberts RE, Goldberg DE, Kaplan GA. Depressive symptoms and increased risk of stroke mortality over a 29-year period. Arch Intern Med. 1998;158:1133–8.
34. Dam H, Harhoff M, Andersen PK, Kessing LV. Increased risk of treatment with antidepressants in stroke compared with other chronic illness. Int Clin Psychopharmacol. 2007;22:13–9.
35. Salaycik KJ, Kelly-Hayes M, Beiser A, Nguyen A-H, Brady SM, Kase CS, et al. Depressive Symptoms and Risk of Stroke: The Framingham Study. Stroke. 2007;38:16–21.
36. Cherr GS, Zimmerman PM, Wang J, Dosluoglu HH. Patients with depression are at increased risk for secondary cardiovascular events after lower extremity revascularization. J Gen Intern Med. 2008;23:629–34.
37. Wouts L, Oude Voshaar RC, Bremmer MA, Buitelaar JK, Penninx BWJH, Beekman ATF. Cardiac disease, depressive symptoms, and incident stroke in an elderly population. Arch Gen Psychiatry. 2008;65:596–602.
38. Bos MJ, Linden T, Koudstaal PJ, Hofman A, Skoog I, Breteler MMB, et al. Depressive symptoms and risk of stroke: the Rotterdam Study. J Neurol Neurosurg Psychiatry. 2008;79:997–1001.

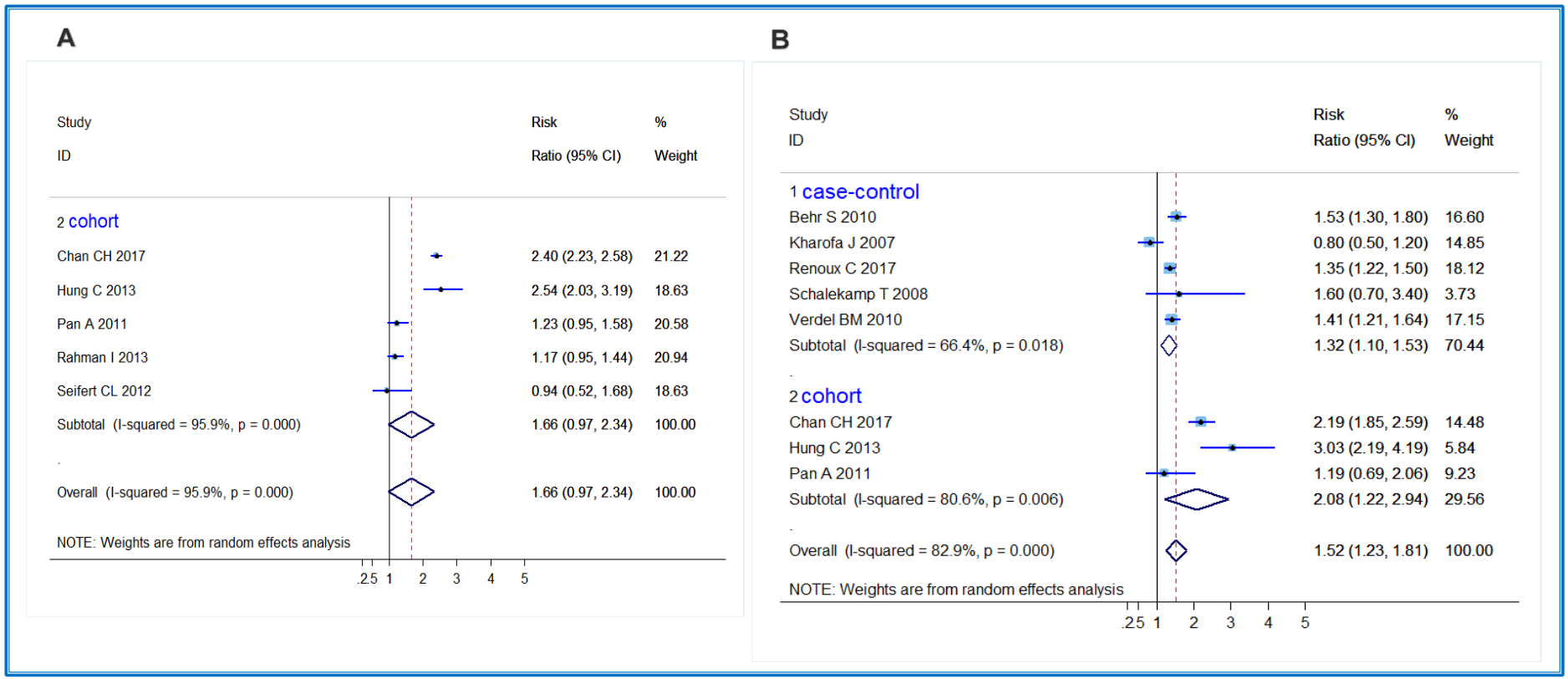
39. Surtees PG, Wainwright NWJ, Luben RN, Wareham NJ, Bingham SA, Khaw K-T. Psychological distress, major depressive disorder, and risk of stroke. Neurology. 2008;70:788–94.
40. Steffens DC, Chung H, Krishnan KRR, Longstreth WT, Carlson M, Burke GL. Antidepressant treatment and worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. Stroke. 2008;39:857–62.
41. Peters R, Pinto E, Beckett N, Swift C, Potter J, McCormack T, et al. Association of depression with subsequent mortality, cardiovascular morbidity and incident dementia in people aged 80 and over and suffering from hypertension. Data from the Hypertension in the Very Elderly Trial (HYVET). Age Ageing. 2010;39:439–45.
42. Mease PJ, Zimetbaum PJ, Duh MS, Vekeman F, Guérin A, Boerstoel-Streefland M, et al. Epidemiologic Evaluation of Cardiovascular Risk in Patients Receiving Milnacipran, Venlafaxine, or Amitriptyline: Evidence from French Health Data. Ann Pharmacother. 2011;45:179–88.
43. Majed B, Arveiler D, Bingham A, Ferrieres J, Ruidavets J-B, Montaye M, et al. Depressive symptoms, a time-dependent risk factor for coronary heart disease and stroke in middle-aged men: the PRIME Study. Stroke. 2012;43:1761–7.
44. Simons LA, McCallum J, Friedlander Y, Simons J. Risk factors for ischemic stroke: Dubbo Study of the elderly. Stroke. 1998;29:1341–6.
45. Li C-T, Bai Y-M, Tu P-C, Lee Y-C, Huang Y-L, Chen T-J, et al. Major depressive disorder and stroke risks: a 9-year follow-up population-based, matched cohort study. PLoS One. 2012;7:e46818.
46. Jackson CA, Mishra GD. Depression and risk of stroke in midaged women: a prospective longitudinal study. Stroke. 2013;44:1555–60.
47. Henderson KM, Clark CJ, Lewis TT, Aggarwal NT, Beck T, Guo H, et al. Psychosocial Distress and Stroke Risk in Older Adults. Stroke. 2013;44:367–72.
48. Graham DJ, By K, McKean S, Mosholder A, Kornegay C, Racoosin JA, et al. Cardiovascular and mortality risks in older Medicare patients treated with varenicline or bupropion for smoking cessation: an observational cohort study. Pharmacoepidemiol Drug Saf. 2014;23:1205–12.
49. Taipale H, Vuorikari H, Tanskanen A, Koponen M, Tiihonen J, Kettunen R, et al. Prevalence of Drug Combinations Increasing Bleeding Risk Among Warfarin Users With and Without Alzheimer's Disease. Drugs Aging. 2015;32:937–45.
50. Péquignot R, Dufouil C, Prugger C, Pérès K, Artero S, Tzourio C, et al. High Level of Depressive Symptoms at Repeated Study Visits and Risk of Coronary Heart Disease and Stroke over 10 Years in Older Adults: The Three-City Study. J Am Geriatr Soc. 2016;64:118–25.
51. Daskalopoulou M, George J, Walters K, Osborn DP, Batty GD, Stogiannis D, et al. Depression as a Risk Factor for the Initial Presentation of Twelve Cardiac, Cerebrovascular, and Peripheral Arterial Diseases: Data Linkage Study of 1.9 Million Women and Men. PLoS One. 2016;11:e0153838.
52. Lee Y-C, Lin C-H, Lin M-S, Lu Y, Chang C-H, Lin J-W. Comparison of the effects of serotonin-norepinephrine reuptake inhibitors versus selective serotonin reuptake inhibitors on cerebrovascular events. J Clin Psychiatry. 2016;77:e1-7.
53. Dong Y-H, Bykov K, Choudhry NK, Donneyong MM, Huybrechts KF, Levin R, et al. Clinical Outcomes of Concomitant Use of Warfarin and Selective Serotonin Reuptake

Inhibitors: A Multidatabase Observational Cohort Study. J Clin Psychopharmacol. 2017;37:200–9.
54. Leong C, Alessi-Severini S, Enns MW, Nie Y, Sareen J, Bolton J, et al. Cerebrovascular, Cardiovascular, and Mortality Events in New Users of Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors: A Propensity Score-Matched Population-Based Study. J Clin Psychopharmacol. 2017;37:332–40.
55. Whooley MA, Browner WS. Association between depressive symptoms and mortality in older women. Study of Osteoporotic Fractures Research Group. Arch Intern Med. 1998;158:2129–35.
56. Jonas BS, Mussolino ME. Symptoms of depression as a prospective risk factor for stroke. Psychosom Med. 2000;62:463–71.
57. Ohira T, Iso H, Satoh S, Sankai T, Tanigawa T, Ogawa Y, et al. Prospective study of depressive symptoms and risk of stroke among japanese. Stroke. 2001;32:903–8.
58. Stewart RAH, North FM, West TM, Sharples KJ, Simes RJ, Colquhoun DM, et al. Depression and cardiovascular morbidity and mortality: cause or consequence? Eur Heart J. 2003;24:2027–37.
59. Nilsson FM, Kessing L V. Increased risk of developing stroke for patients with major affective disorder-a registry study. Eur Arch Psychiatry Clin Neurosci. 2004;254:387–91.
60. Almeida OP, Xiao J. Mortality Associated with Incident Mental Health Disorders After Stroke. Aust New Zeal J Psychiatry. 2007;41:274–81.
61. Arbelaez JJ, Ariyo AA, Crum RM, Fried LP, Ford DE. Depressive symptoms, inflammation, and ischemic stroke in older adults: a prospective analysis in the cardiovascular health study. J Am Geriatr Soc. 2007;55:1825–30.
62. Smoller JW. Do Antidepressants Raise the Risk of Stroke? Am J Psychiatry. 2011;168:457–9.
63. Hatcher S, Arroll B. Newer antidepressants for the treatment of depression in adults. BMJ. 2012;344:d8300.
64. Hankey GJ. Selective Serotonin Reuptake Inhibitors and Risk of Cerebral Bleeding. Stroke. 2014;45:1917–8.
65. Bray BD. Study design cannot support link between intracranial haemorrhage, antidepressants, and NSAIDs. BMJ. 2015;h4445.
66. Lewis LS. Combined use of antidepressants and NSAIDs: NNT for intracranial haemorrhage. BMJ. 2015;h4444.
67. Mercer SW, Payne RA, Nicholl BI, Morrison J. Risk of intracranial haemorrhage linked to co-treatment with antidepressants and NSAIDs. BMJ. 2015;h3745.
68. Hirsch MS, Walter RM, Hasterlik RJ. Subarachnoid hemorrhage following ephedrine and MAO inhibitor. JAMA. 1965;194:1259.
69. Ottervanger JP, Stricker BH, Huls J, Weeda JN. Bleeding attributed to the intake of paroxetine. Am J Psychiatry. 1994;151:781–2.
70. Tielens JA. Vitamin C for paroxetine- and fluvoxamine-associated bleeding. Am J Psychiatry. 1997;154:883–4.
71. de Maistre E, Allart C, Lecompte T, Bollaert P-E. Severe bleeding associated with use of low molecular weight heparin and selective serotonin reuptake inhibitors. Am J Med. 2002;113:530–2.
72. Kundhal P, Sockalingam S, Krishnadev N, Demarchi R, Bhalerao S. Monoamine Oxidase Inhibitors and Subarachnoid Hemorrhage. Can J Psychiatry. 2004;49:573–4.

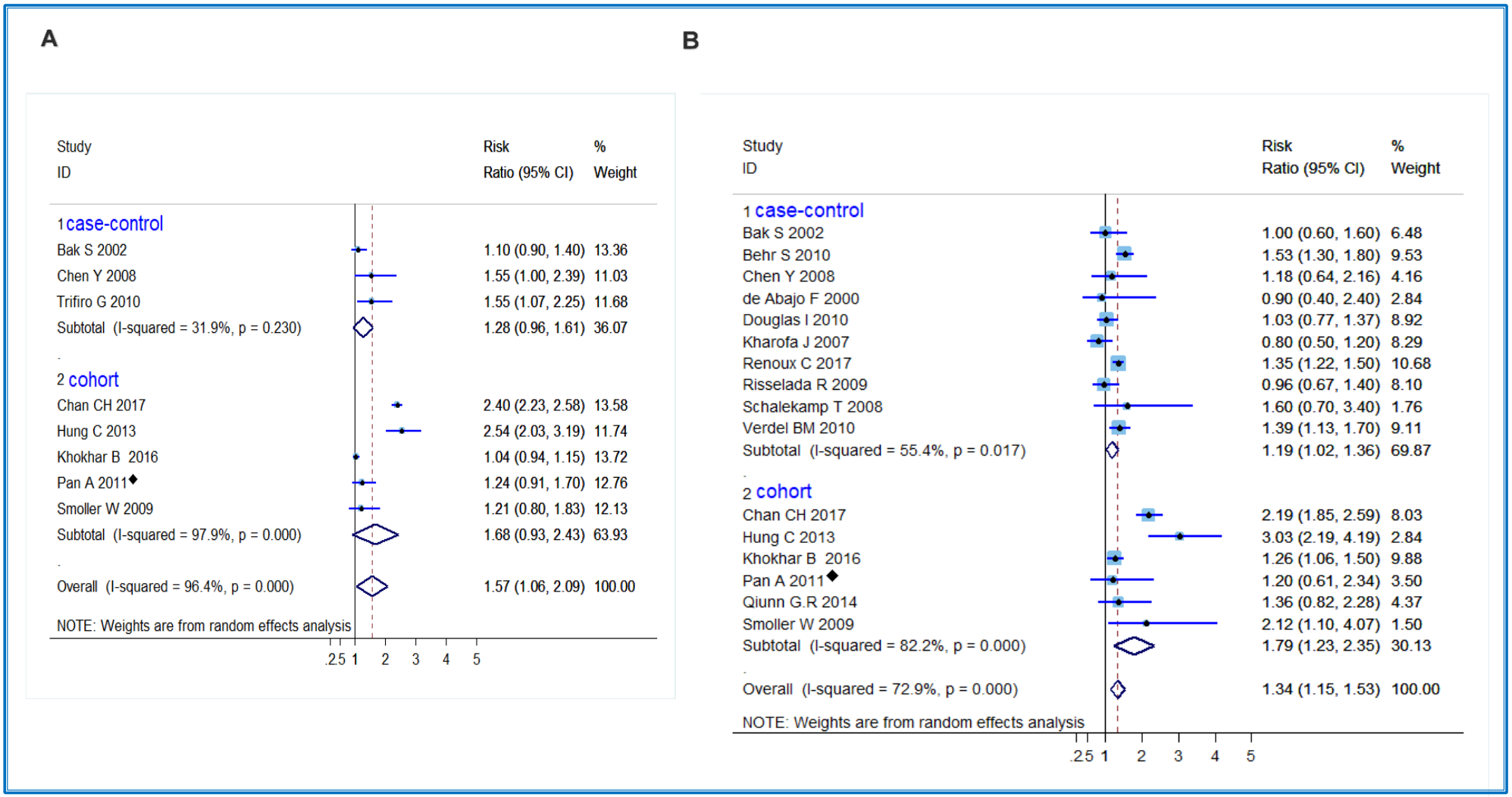
73. Ceylan ME, Alpsan-Omay MH. Bleeding induced by SSRIs. Eur Psychiatry. 2005;20:570–1.
74. Veith RC, Raskind MA, Caldwell JH, Barnes RF, Gumbrecht G, Ritchie JL. Cardiovascular Effects of Tricyclic Antidepressants in Depressed Patients with Chronic Heart Disease. N Engl J Med. 1982;306:954–9.
75. Reding MJ, Orto LA, Winter SW, Fortuna IM, Di Ponte P, McDowell FH. Antidepressant therapy after stroke. A double-blind trial. Arch Neurol. 1986;43:763–5.
76. Fruehwald S, Gatterbauer E, Rehak P, Baumhackl U. Early fluoxetine treatment of post-stroke depression--a three-month double-blind placebo-controlled study with an open-label long-term follow up. J Neurol. 2003;250:347–51.
77. Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and Poststroke Depression: A Placebo-Controlled Trial of Antidepressants. Am J Psychiatry. 2003;160:1823–9.
78. Thébault JJ, Guillaume M, Levy R. Tolerability, safety, pharmacodynamics, and pharmacokinetics of rasagiline: a potent, selective, and irreversible monoamine oxidase type B inhibitor. Pharmacotherapy. 2004;24:1295–305.
79. Rampello L, Alvano A, Chiechio S, Raffaele R, Vecchio I, Malaguarnera M. An evaluation of efficacy and safety of reboxetine in elderly patients affected by "retarded" post-stroke depression. A random, placebo-controlled study. Arch Gerontol Geriatr. 2005;40:275–85.
80. Murray V, von Arbin M, Bartfai A, Berggren A-L, Landtblom A-M, Lundmark J, et al. Double-blind comparison of sertraline and placebo in stroke patients with minor depression and less severe major depression. J Clin Psychiatry. 2005;66:708–16.
81. Perahia DG, Bangs ME, Zhang Q, Cheng Y, Ahl J, Frakes EP, et al. The risk of bleeding with duloxetine treatment in patients who use nonsteroidal anti-inflammatory drugs (NSAIDs): analysis of placebo-controlled trials and post-marketing adverse event reports. Drug Healthc Patient Saf. 2013;5:211–9.
82. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and Risk of Stroke Morbidity and Mortality. JAMA. 2011;306:1241–9.
83. Hackam DG, Mrkobrada M. Selective serotonin reuptake inhibitors and brain hemorrhage: a meta-analysis. Neurology. 2012;79:1862–5.
84. Shin D, Oh YH, Eom C-S, Park SM. Use of selective serotonin reuptake inhibitors and risk of stroke: a systematic review and meta-analysis. J Neurol. 2014;261:686–95.
85. Biffi A, Scotti L, Corrao G. Use of antidepressants and the risk of cardiovascular and cerebrovascular disease: a meta-analysis of observational studies. Eur J Clin Pharmacol. 2017;73:487–97.
86. Ramasubbu R. Cerebrovascular effects of selective serotonin reuptake inhibitors: a systematic review. J Clin Psychiatry. 2004;65:1642–53.
87. Thanacoody HKR, Thomas SHL. Tricyclic antidepressant poisoning : cardiovascular toxicity. Toxicol Rev. 2005;24:205–14.
88. Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M. Antidepressants for depression in physically ill people. Cochrane Database Syst Rev. 2010;CD007503.
89. Mead GE, Hsieh C-F, Lee R, Kutlubaev M, Claxton A, Hankey GJ, et al. Selective Serotonin Reuptake Inhibitors for Stroke Recovery: A Systematic Review and Meta-analysis. Stroke. 2013;44:844–50.
90. Mitsch AL. Antidepressant adverse drug reactions in older adults: implications for RNs and APNs. Geriatr Nurs (Minneap). 2013;34:53–61.
91. Álamo C, López-Muñoz F, García-García P, García-Ramos S. Risk-benefit analysis of

antidepressant drug treatment in the elderly. Psychogeriatrics. 2014;14:261–8.
92. Weinrieb RM, Auriacombe M, Lynch KG, Lewis JD. Selective serotonin re-uptake inhibitors and the risk of bleeding. Expert Opin Drug Saf. 2005;4:337–44.
93. Serebruany VL. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? Am J Med. 2006;119:113–6.
94. Swenson JR, Doucette S, Fergusson D. Adverse cardiovascular events in antidepressant trials involving high-risk patients: a systematic review of randomized trials. Can J Psychiatry. 2006;51:923–9.
95. Fernandez A, Bang SE, Srivathsan K, Vieweg WVR. Cardiovascular side effects of newer antidepressants. Anatol J Cardiol. 2007;7:305–9.
96. Wernicke J, Lledó A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. Drug Saf. 2007;30:437–55.
97. Kamath J, Handratta V. Desvenlafaxine succinate for major depressive disorder: a critical review of the evidence. Expert Rev Neurother. 2008;8:1787–97.
98. Von Ruden AE, Adson DE, Kotlyar M. Effect of Selective Serotonin Reuptake Inhibitors on Cardiovascular Morbidity and Mortality. J Cardiovasc Pharmacol Ther. 2008;13:32–40.
99. Andrade C, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. J Clin Psychiatry. 2010;71:1565–75.
100. Lan C-C, Liu C-C, Lin C-H, Lan T-Y, McInnis MG, Chan C-H, et al. A reduced risk of stroke with lithium exposure in bipolar disorder: a population-based retrospective cohort study. Bipolar Disord. 2015;17:705–14.
101. Chen Y, Guo JJ, Patel NC. Hemorrhagic stroke associated with antidepressant use in patients with depression: does degree of serotonin reuptake inhibition matter? Pharmacoepidemiol Drug Saf. 2009;18:196–202.
102. Castro VM, Gallagher PJ, Clements CC, Murphy SN, Gainer VS, Fava M, et al. Incident user cohort study of risk for gastrointestinal bleed and stroke in individuals with major depressive disorder treated with antidepressants. BMJ Open. 2012;2:e000544.
103. Barbui C, Percudani M, Fortino I, Tansella M, Petrovich L. Past use of selective serotonin reuptake inhibitors and the risk of cerebrovascular events in the elderly. Int Clin Psychopharmacol. 2005;20:169–71.
104. Shin J-Y, Park M-J, Lee SH, Choi S-H, Kim M-H, Choi N-K, et al. Risk of intracranial haemorrhage in antidepressant users with concurrent use of non-steroidal anti-inflammatory drugs: nationwide propensity score matched study. BMJ. 2015;351:h3517.
105. Schmidt M, Johansen MB, Lash TL, Christiansen CF, Christensen S SH. Antiplatelet drugs and risk of subarachnoid hemorrhage: a population-based case-control study. J Thromb Haemost. 2010;8:1468–74.
106. Wu C-S, Wang S-C, Cheng Y-C, Gau SS-F. Association of cerebrovascular events with antidepressant use: a case-crossover study. Am J Psychiatry. 2011;168:511–21.
107. Acharya T, Acharya S, Tringali S, Huang J. Association of antidepressant and atypical antipsychotic use with cardiovascular events and mortality in a veteran population. Pharmacotherapy. 2013;33:1053–61.
108. Wassertheil-Smoller S, Shumaker S, Ockene J, Talavera GA, Greenland P, Cochrane B, et al. Depression and Cardiovascular Sequelae in Postmenopausal Women. Arch Intern Med. 2004;164:289–98.

109. Liebetrau M, Steen B, Skoog I. Depression as a risk factor for the incidence of first-ever stroke in 85-year-olds. Stroke. 2008;39:1960–5.
110. Chu C-S, Chou P-H, Lin C-H, Cheng C, Tsai C-J, Lan T-H, et al. Use of Selective Serotonin Reuptake Inhibitors and Risks of Stroke in Patients with Obsessive Compulsive Disorder: A Population-Based Study. PLoS One. 2016;11:e0162239.
111. Hauta-Aho M, Tirkkonen T, Vahlberg T, Laine K. The effect of drug interactions on bleeding risk associated with warfarin therapy in hospitalized patients. Ann Med. 2009;41:619–28.

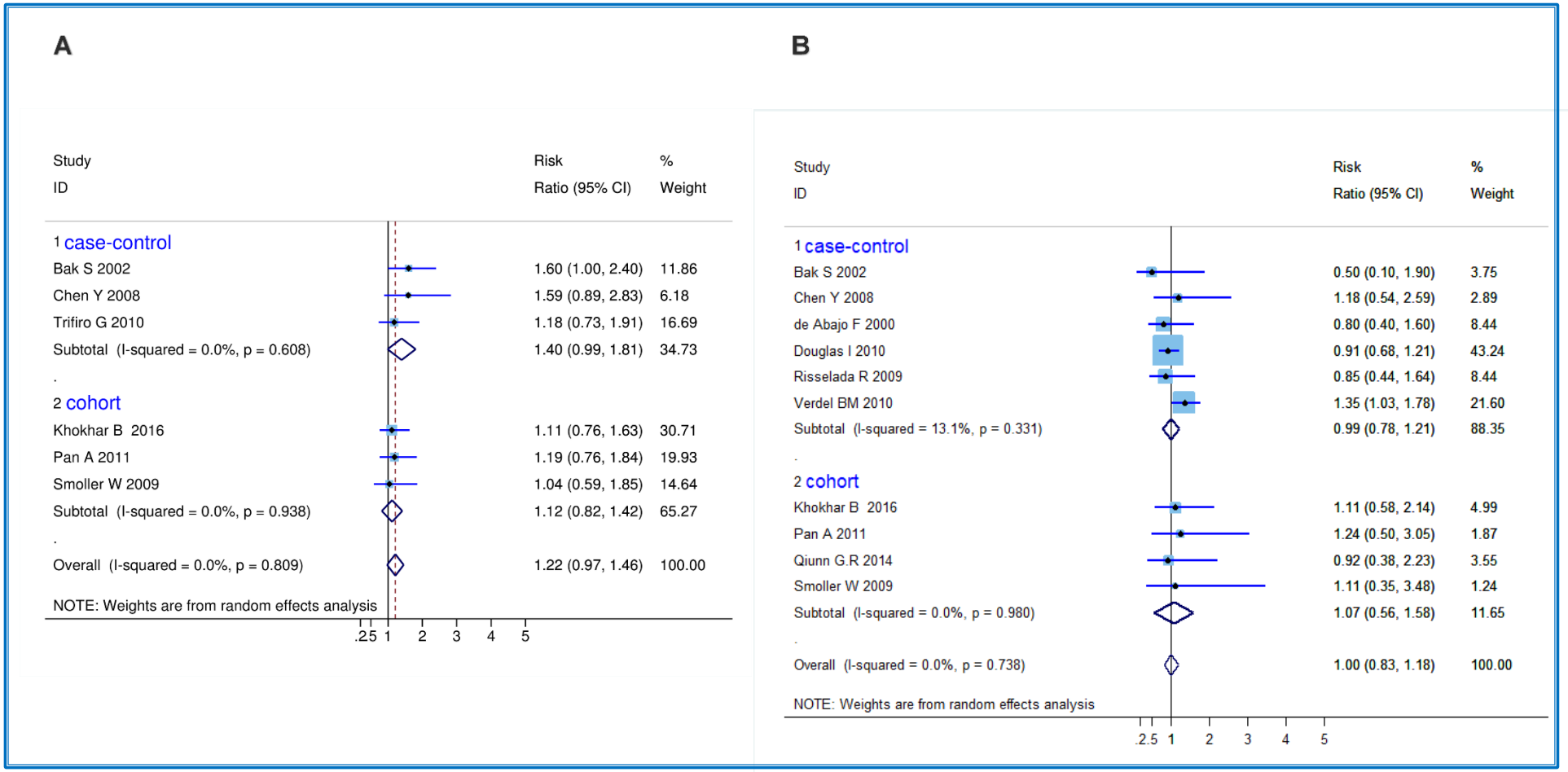


Supplemental Figure II.



Supplemental Figure III.

◆Additional data from Shin et al. 2014 (analysis adjusted for depression



Supplemental Figure IV.

Figure legends:

Supplemental Figure I. PRISMA Flow-chart of study inclusions PRISMA Flow-chart of study inclusions; SSRI-Selective Serotonin Reuptake Inhibitors; TCA-Tricyclic Antideressives; NSAID's-Nonsteroidal anti-inflammatory drug; OR-Odds Ratio; RR- Risk Ratio; HR-Hazard Ratio.

Supplemental Figure II.

Panel A) Forest plot I. Any antidepressant-ischemic stroke; Study ID: First author, year of publication; **Panel B) Forest plot II. Any antidepressant-hemorrhagic stroke;** Study ID: First author, year of publication.

Supplemental Figure III

Panel A) Forest plot III. SSRI-ischemic stroke; Study ID: First author, year of publication, ♦Additional data from Shin et al. 2014 (analysis adjusted for depression); **Panel B) Forest plot IV.SSRI-hemorrhagic stroke;** Study ID: First author, year of publication, ♦Additional data from Shin et al. 2014 (analysis adjusted for depression).

Supplemental Figure IV

Panel A) Forest plot V. TCA- ischemic stroke; Study ID: First author, year of publication; **Panel B) Forest plot VI. TCA- hemorrhagic stroke;** Study ID: First author, year of publication.