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ORIGINAL COMMUNICATION

Use of selective serotonin reuptake inhibitors and risk of stroke: a systematic review and meta-analysis

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Abstract Since several studies have inconsistently reported the association between the use of selective serotonin reuptake inhibitors (SSRIs) and the risk of stroke, we performed a meta-analysis on this issue. We identified studies by searching three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) from their inception to August, 2013. Pooled effect estimates were obtained by using random-effects meta-analysis. Thirteen relevant studies (three case–control, six nested case–control, and four cohort studies) were finally included in our study. In our meta-analyses, the use of SSRIs was associated with an increased risk of all types of stroke [adjusted odds ratio (aOR), 1.40; 95 % confidence interval (CI), 1.09–1.80], ischemic stroke (aOR 1.48; 95 % CI 1.08–2.02), and hemorrhagic stroke (aOR 1.32; 95 % CI 1.02–1.71). Between the two subtypes of hemorrhagic stroke, that is, intracerebral and subarachnoid, the increased risk of intracerebral hemorrhage was associated with the use of SSRIs (aOR 1.30; 95 % CI 1.02–1.67). When the analysis was restricted to the studies in which potential confounding by depression was considered, the risks were still higher in SSRI users than in non-users and the heterogeneities among studies were significantly decreased. Since there was heterogeneity among studies and a possible confounding effect from depression could not be fully excluded, further well-designed studies are needed to confirm this association.

Keywords Stroke · Selective serotonin reuptake inhibitors · Antidepressants · Meta-analysis

Introduction

Depression has become highly prevalent in the recent days, with a lifetime incidence higher than 16 % in the general population [1, 2]. Among the several drugs used in the treatment of depression, selective serotonin reuptake inhibitors (SSRIs) have been widely prescribed because of their safety and tolerability. With the increasing use of SSRIs, many studies have been conducted to investigate the effects of SSRIs on patients. Given that SSRIs are frequently prescribed to patients with cerebrovascular diseases, their cerebrovascular effects are among the major concerns. SSRI administration may increase the risk of bleeding, including hemorrhagic stroke, owing to their antiplatelet effects [3–5]. Meanwhile, SSRI-induced serotonergic activation may also cause ischemic stroke via arterial vasoconstriction [5–7]. However, these SSRI effects on the risk of ischemic or hemorrhagic stroke remain to be elucidated.

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To our knowledge, only one meta-analysis has been conducted on this area of research thus far, in which total brain hemorrhage was related to SSRI exposure, whereas hemorrhagic stroke was not [8]. Furthermore, the authors focused only on several types of brain hemorrhage rather than on stroke [8]. Therefore, we first investigated the association between the use of SSRIs and the risk of stroke, including ischemic and hemorrhagic strokes, by performing a meta-analysis.

Methods

Search strategy and data sources

We searched MEDLINE, EMBASE, and the Cochrane Library from their inception until August 2013, using the search terms described in Supplemental Method 1. We also reviewed the bibliographies of relevant articles to locate additional publications.

Study selection

We included observational studies that met all of the following criteria: (1) a case–control or cohort study; (2) studies that investigated the association between the use of SSRIs and the risk of ischemic, hemorrhagic, or all types of stroke; and (3) those that reported outcome measures with adjusted relative risk (aRR) or adjusted odds ratio (aOR) and 95 % confidence interval (CI). To avoid any confusion between hemorrhagic stroke and other types of brain hemorrhage, hemorrhagic stroke was regarded as the pure combination of intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Even if some studies only reported the risk of one subtype of hemorrhagic stroke, either ICH or SAH, we included their results when estimating the risk of hemorrhagic stroke. Other studies reported the use of SSRIs in relation to the risk of intracranial hemorrhage, including not only hemorrhagic stroke but also other types of brain hemorrhage. In these cases, we contacted the authors and asked them whether they could provide the results regarding hemorrhagic stroke. If the authors did not provide the results, we excluded their studies from our analysis.

Data extraction and quality assessment

Two investigators (DS and YHO) independently evaluated the eligibility of all the studies retrieved from the databases. They resolved any disagreements in consultation with the other co-authors (SMP and CSE).

We assessed the methodological quality based on the Newcastle-Ottawa Scale (NOS) [9]. Low quality was defined as NOS score <8.0; and high quality, as NOS score ≥ 8.0 (maximum score, 9).

Main and subgroup analyses

In the main analysis, we investigated the association between the use of SSRIs and the risk of ischemic or hemorrhagic stroke. We also estimated the risk of all types of stroke from the studies that reported combined results ($n = 6$) [5, 10–14]. In addition, the analysis was restricted to the studies in which authors controlled potential confounding by depression [7, 11–15], since depression itself may be a risk factor for stroke [2]. If a study provided data regarding the risk of stroke according to time window of exposure to SSRIs (e.g., current, recent, or past use), we used the results of current users in the main analysis. The patient was regarded as the "current user" if SSRI administration ended within 30 days before the date the stroke occurred. Some studies did not specify the time window of exposure to SSRIs and were hence classified as the "not specified" group. We performed a subgroup meta-analysis based on whether the studies specified the time window of exposure to SSRIs (specified or not specified). We also performed subgroup analyses based on the type of study design (case–control, nested case–control, or cohort study); the geographic location where the study was conducted [Eastern (Asia) or Western (Europe and the United States)]; the adjustment of drugs that could increase the risk of bleeding (none, aspirin, and aspirin plus anticoagulants); the number of adjusted risk factors of hypertension, diabetes, hyperlipidemia, obesity, smoking, and alcohol consumption (adjusted variables, ≥ 3 or <3); the methodological quality of the study (high or low); age [general population group (age $\geq$18–20 years or not restricted) or old age group (age $\geq$50–65 years)]; sex (female or either); the stroke assessment method (using a database or self-report); and the exposure assessment method (using a database or self-report). With regard to hemorrhagic stroke, we performed an additional analysis according to the subtype of hemorrhagic stroke (ICH or SAH).

Statistical analyses

We computed a pooled aOR with the 95 % CIs from the aORs/aRRs and those reported in the studies. Given that the outcome of interest was sufficiently rare, we assumed that the difference between the various measures of risk in our study was not significant. We combined studies that provided stratum-specific estimates by using the inverse variance method. Heterogeneity of results across the studies was examined by using the Higgins I^2 value [16]. Because of the heterogeneity of the results among the studies, we estimated the pooled aOR on the basis of

random-effects model using the DerSimonian–Laird method [17]. Publication bias of the studies included in the final analysis was evaluated using the Egger test [18]. We performed a random-effects meta-regression analysis to assess the effect of the following study characteristics on the results: study design, time window of exposure, geographic location, adjustment for drugs, number of risk factors for adjustment, study quality, age, sex, stroke assessment method, exposure assessment method, and subtype of hemorrhagic stroke. We used the Stata version 12.1 (StataCorp, College Station, Texas, USA) for the statistical analysis.

Results

Identification of relevant studies

Figure 1 shows a flow diagram of how we identified relevant studies. A total of 7,722 articles were identified, and 13 studies were included in the final analysis [5, 7, 10–15, 19–23]. We contacted the authors of four articles [20, 23–25] to ask for data on the risk of hemorrhagic stroke, because only the risk of other types of brain hemorrhage was reported in those studies. Authors of two articles [20, 23] responded and provided the adjusted estimates.

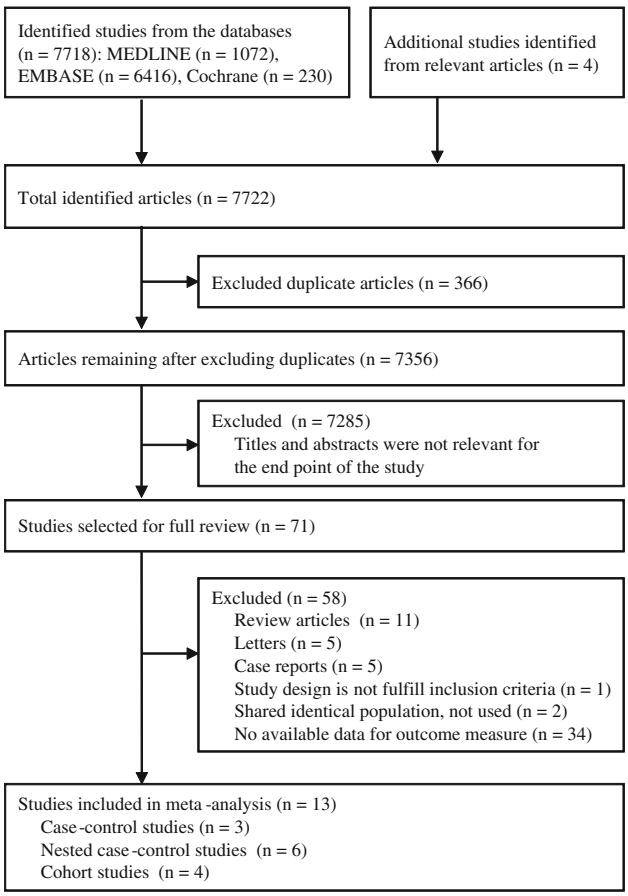

Fig. 1 Flow diagram of studies identified and selected

Characteristics of studies included in the analyses

The descriptive data for the studies are summarized in Table 1. The mean NOS score was 7.07 for the 13 studies (maximum score, 9; Supplemental Table 1). Six studies tried to control the potential confounding due to depression by (1) adjusting for severity of depression [12–14] and/or (2) exclusively selecting patients with depression (depression as the indication of treatment) [7, 11, 12, 15]. Among those studies, we contacted the authors of two studies in which these results were not presented [13, 15], and one group provided us the additional data [13].

Main analysis

In a random-effects meta-analysis, we found a significant association between the use of SSRIs and the risk of ischemic stroke (aOR 1.48; 95 % CI 1.08–2.02; $I^2 = 83.9$ %; Fig. 2A), hemorrhagic stroke (aOR 1.32; 95 % CI 1.02–1.71; $I^2 = 74.9$ %; Fig. 2B), and all types of stroke (aOR 1.40; 95 % CI 1.09–1.80; $I^2 = 93.2$ %; Fig. 3). When the analysis was restricted to the studies in which authors controlled the potential confounding by depression, the use of SSRIs was associated with increased risk of ischemic stroke (aOR 1.39; 95 % CI 1.14–1.71; $I^2 = 3.8$ %), hemorrhagic stroke (aOR 1.43; 95 % CI 0.98–2.08; $I^2 = 1.8$ %), and all types of stroke (aOR 1.22; 95 % CI 1.13–1.31; $I^2 = 15.3$ %) (Fig. 4).

Subgroup meta-analyses

Supplemental Table 2 shows the results of the subgroup meta-analyses. In the subgroup meta-analyses according to the type of study design, we observed a significant positive association between the use of SSRIs and the risk of ischemic stroke in the nested case–control studies (aOR 1.31; 95 % CI 1.02–1.69; $I^2 = 43.0$ %). The risk of hemorrhagic stroke increased in the nested case–control (aOR 1.26; 95 % CI 1.03–1.56; $I^2 = 33.2$ %) and cohort studies (aOR 2.12; 95 % CI 1.25–3.61; $I^2 = 66.0$ %).

Current SSRI use increased the risk of ischemic (aOR 1.26; 95 % CI 1.07–1.49; $I^2 = 14.8$ %) or all types of stroke (aOR 1.20; 95 % CI 1.01–1.43; $I^2 = 61.3$ %) in the subgroup meta-analysis of the studies that specified the time window of exposure to SSRIs. Although the risk of hemorrhagic stroke was not associated with current use of SSRIs (aOR 1.02; 95 % CI 0.86–1.22; $I^2 = 0.0$ %), the risk of ICH was still significantly higher in SSRI users once we differentiated between ICH and SAH. The degree of

Table 1 Characteristics of studies included in the final analysis of SSRIs and stroke

Study	Country Population	Study design	Outcomes	No. of SSRI users/ nonusers	Risk or odds ratios (95 % CI)	Study period	Adjustment
Bak et al. [10]	Denmark $n = 44{,}765$ (age ≥20 years)	Nested case–control	All stroke	NR	1.0 (0.8–1.2)	1994–1999	Age, sex, index date, and use of other drugs (diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, anti-arrhythmics, anti-anginal medication, warfarin, phenprocoumon, anti-diabetics, lipid-lowering drugs, low-dose acetyl salicylic acid, and other anti-inflammatory drugs)
			ICH	Cases: 21/606 Controls: 742/38,058	1.0 (0.6–1.6)		
			Ischemic stroke	Cases: 100/2,460 Controls: 742/38,058	1.1 (0.9–1.4)		
Behr [19]	Germany $n = 89{,}511$	Nested case–control	ICH	Cases: 198/7,940 Controls: 1,084/ 80,289	1.53 (1.30–1.80)	2004–2006	Age, interactions between phenprocoumon exposure and age, sex, diabetes, hypertension, ischemic heart disease, ischemic cerebral infarction, cerebral amyloid angiopathy, cerebral aneurysm, brain tumor, epilepsy, liver diseases, renal failure, alcohol dependence, epistaxis, previous intracerebral hemorrhage, other hemorrhage, and concurrent use of platelet aggregation inhibitors, heparin, NSAIDs, acetyl salicylic acid, diuretics, corticosteroids, statins
Chen et al. [11]	US $n = 7{,}601$	Nested case–control	All stroke	Cases: 352/729 Controls: 1,585/ 4,794	1.24 (1.07–1.44)	1998–2002	Age, sex, index date, history of depression, antidepressants, other medications that are known or proposed to affect risk of stroke (e.g., aspirin, anticoagulants, risperidone), other psychiatric comorbidities (e.g., anxiety, alcohol abuse, substance abuse), and medical comorbidities (e.g., hypertension, diabetes, dyslipidemia, ventricular hypertrophy, other cardiac diseases, obesity)
			Hemorrhagic stroke	Cases: 26/65 Controls: 115/426	1.18 (0.64–2.16)		
			Ischemic stroke	Cases: 54/110 Controls: 232/734	1.55 (1.00–2.39)		
Coupland et al. [12]	UK $n = 60{,}746$ (age ≥65 years)	Cohort study	All Stroke	1,384/2,811	1.17 (1.10–1.26)	1996–2008	Sex, age, year, severity of depression, depression before age 65 years, smoking status, Townsend deprivation score, coronary heart disease, diabetes, hypertension, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive–compulsive disorder, epilepsy/ seizures, statins, non-steroidal, anti-inflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, and hypnotics/anxiolytics
De Abajo et al. [20]	UK $n = 319$ (age 18–79 years)	Nested case–control	Hemorrhagic stroke	Cases: 7/44 Controls: 24/160	0.91 (0.30–2.66)	1990–1997	Age, sex, calendar time, practice, hypertension, smoking, body mass index, asthma or COPD, migraines, NSAID use
			SAH	NR	0.8 (0.2–3.2)		
			ICH	Cases: 3/19 Controls: 9/76	0.8 (0.1–5.6)		

Table 1 continued

Study	Country Population	Study design	Outcomes	No. of SSRI users/ nonusers	Risk or odds ratios (95 % CI)	Study period	Adjustment
Douglas et al. [15]	UK *n* = 1,988	Nested case–control	Hemorrhagic stroke	Cases: 102/255 Controls: 386/1,245	1.11 (0.82–1.50)	1992–2006	Age, sex, registration date, practice, 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), observation time
Hung et al. [5]	Taiwan *n* = 28,145 (age >65 years)	Cohort study	All stroke Hemorrhagic stroke Ischemia stroke	NR NR NR	2.66 (2.21–3.20) 3.03 (2.19–4.19) 2.54 (2.03–3.19)	2001–2009	Age, sex, atrial fibrillation, myocardial infarction, chronic heart failure, angina pectoris, peripheral arterial occlusive disease, diabetes, hypertension, hyperlipidemia, chronic kidney disease, end stage renal disease, use of aspirin, heparin, warfarin, NSAID, antipsychotics
Kharofa et al. [21]	US *n* = 3,335	Case–control	Hemorrhagic stroke	Cases: 71/844 Controls: 158/1,618	0.8 (0.5–1.2)	2002–2005	Age, sex, race, SSRIs, antiplatelet drugs (ASA, clopidogrel, dipyridamole),frequent alcohol use, warfarin, heart disease, history of ischemic stroke, body mass index, treated and untreated hypertension, hypercholesterolemia, statin use, smoking, education
Pan et al. [2, 13]	US *n* = 80,574 (age 54–79 years; women)	Cohort study	All stroke Hemorrhagic stroke Ischemic stroke	97/893 10/109 45/468	1.39 (1.13–1.72) 1.25 (0.65–2.41) 1.23 (0.90–1.67)	2000–2006	Age, marital status, parental history of myocardial infarction, ethnicity, physical activity level, body mass index, alcohol consumption, smoking status, menopausal status, postmenopausal hormone therapy, current aspirin use, current multivitamin use, dietary approaches to stop hypertension dietary score, and history of hypertension, hypercholesterolemia, diabetes, cancer, and heart diseases
Risselada et al. [22]	The Netherlands *n* = 11,037	Case–control	SAH	Cases: 32/972 Controls: 335/9,698	0.96 (0.67–1.40)	1998–2006	Age, sex, calendar date, SSRI
Schalekamp et al. [23]	The Netherlands *n* = 7,666	Case–control	Hemorrhagic stroke	Cases: 240/NR Controls: 776/NR	1.59 (0.71–3.58)	1991–2004	Age, sex, coumarin exposure, duration of coumarin exposure, geographic region, index date, current use of SSRIs, NSAIDs, antiplatelet agents, antibiotics, glucocorticoids, gastro-protective agents, inhibitors and inducers of coumarin metabolism, and the comorbidities diabetes mellitus, thyroid disorders, heart failure, and cancers
Smoller et al. [14]	US *n* = 136,293 (age 50–79 years; women)	Cohort study	All stroke Hemorrhagic stroke Ischemic stroke	F/up visit: 64/2,232 NR NR	1.45 (1.08–1.97) 2.12 (1.10–4.07) 1.21 (0.80–1.83)	1993–1998	SSRIs, decile of propensity score, hormone use, log of depression screen score, BMI, history of MI or stroke, systolic blood pressure, migraine or bad headaches, aspirin or NSAID use

Table 1 continued

Study	Country Population	Study design	Outcomes	No. of SSRI users/ nonusers	Risk or odds ratios (95 % CI)	Study period	Adjustment
Trifiro et al. [7]	The Netherlands *n* = 492,272 (age ≥65 years)	Nested case–control	Ischemic stroke	Cases: 29/844 Controls: 9,410/ 437,718	1.55 (1.07–2.25)	1996–2005	Age, sex, index date, hypertension, angina, history of myocardial infarction, atrial fibrillation, heart failure, coagulation/platelet abnormalities, COPD, diabetes mellitus, dementia, and concomitant use of anticoagulants, systemic corticosteroids, and opioids

SSRIs selective serotonin reuptake inhibitors, *NR* not reported, *ICH* intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *F/up* follow up

heterogeneity was always lower among these studies compared with that of the studies that did not specify the time window of exposure to SSRIs ($I^2 = 14.5$ vs. 89.5 % for ischemic stroke; 0.0 vs. 79.9 % for hemorrhagic stroke; $I^2 = 61.3$ vs. 97.0 % for all types of stroke, respectively).

In the subgroup analysis according to study location (Western or Eastern), the risk of ischemic, hemorrhagic, or all types of stroke increased among the SSRI users in both subgroups, although the increased risk of hemorrhagic stroke was marginally significant in the Western studies (aOR 1.19; 95 % CI 0.98–1.44; $I^2 = 44.5$). After excluding a study conducted in an Eastern country, the I^2 values were largely reduced from 83.0 to 0.0 % for ischemic stroke, from 74.9 to 44.5 % for hemorrhagic stroke, and from 93.2 to 43.8 % for all types of stroke.

In the subgroup analysis according to the age of the study population, the risk of ischemic, hemorrhagic, or all types of stroke was higher in the old age group of SSRI users (aOR: 1.58, 1.72, and 1.58, respectively) than in the general population age group (aOR: 1.24, 1.15, and 1.13, respectively). Positive association between the use of SSRIs and the risk of ischemic or all types of stroke was significant only in the old-age group (aOR 1.58; 95 % CI 1.06–2.36 and aOR 1.58; 95 % CI 1.06–2.36, respectively).

In the subgroup meta-analysis according to the subtype of hemorrhagic stroke, the risk of ICH, but not SAH, increased with statistical significance (aOR 1.30; 95 % CI 1.02–1.67; $I^2 = 28.7$ %).

Meta-regression analysis

The meta-regression of the potential effect modifiers on the log estimate for the risk of hemorrhagic stroke showed a statistically significant difference between the studies that specified the time window of exposure to SSRIs and the studies that did not ($P = 0.01$; Supplemental Table 3). We also found a significant effect of the study location on the risk of ischemic, hemorrhagic, or all types of stroke ($P = 0.01$ for all; Supplemental Table 3).

Publication bias

No evidence of publication bias was found in the results of the Egger test, since the P values for the bias were not significant for the studies of ischemic, hemorrhagic, and all types of stroke (P for bias = 0.709, 0.493, and 0.392, respectively).

Discussion

In our study, the use of SSRIs was associated with increased risks of ischemic and hemorrhagic strokes. Between the two subtypes of hemorrhagic stroke, the risk of ICH increased with statistical significance in the SSRI users, whereas the risk of SAH did not. We also found that the use of SSRIs was positively associated with the risk of all types of stroke, irrespective of the type. These results were more obvious in the old age group than in the general population group. Based on the 2000–2008 statistics [26], we can broadly suppose that 70 cases of ischemic stroke and 10 cases of ICH occur for every 100,000 individuals not receiving SSRIs. If we assume a 1.48- and 1.30-fold increase in the risks of ischemic stroke and ICH due to SSRIs, respectively, one case of ischemic stroke occurs in every 2,976 patients treated with SSRIs and one case of ICH occurs in every 33,333 SSRI users. Although the events are rare, it should not be just underestimated considering the frequent use of SSRIs, with the fact that 27.0 million US patients were treated with antidepressants in 2005 [27].

Several studies have suggested that the use of SSRIs is associated with increased risk of bleeding [3–5]. Because mature platelets are not capable of producing serotonin, they are dependent on the reuptake of plasma serotonin [24]. However, SSRIs deplete platelet serotonin by blocking the serotonin receptor, which potentially leads to abnormal aggregation and prolonged bleeding time [28]. A previous meta-analysis indicated that SSRI exposure was

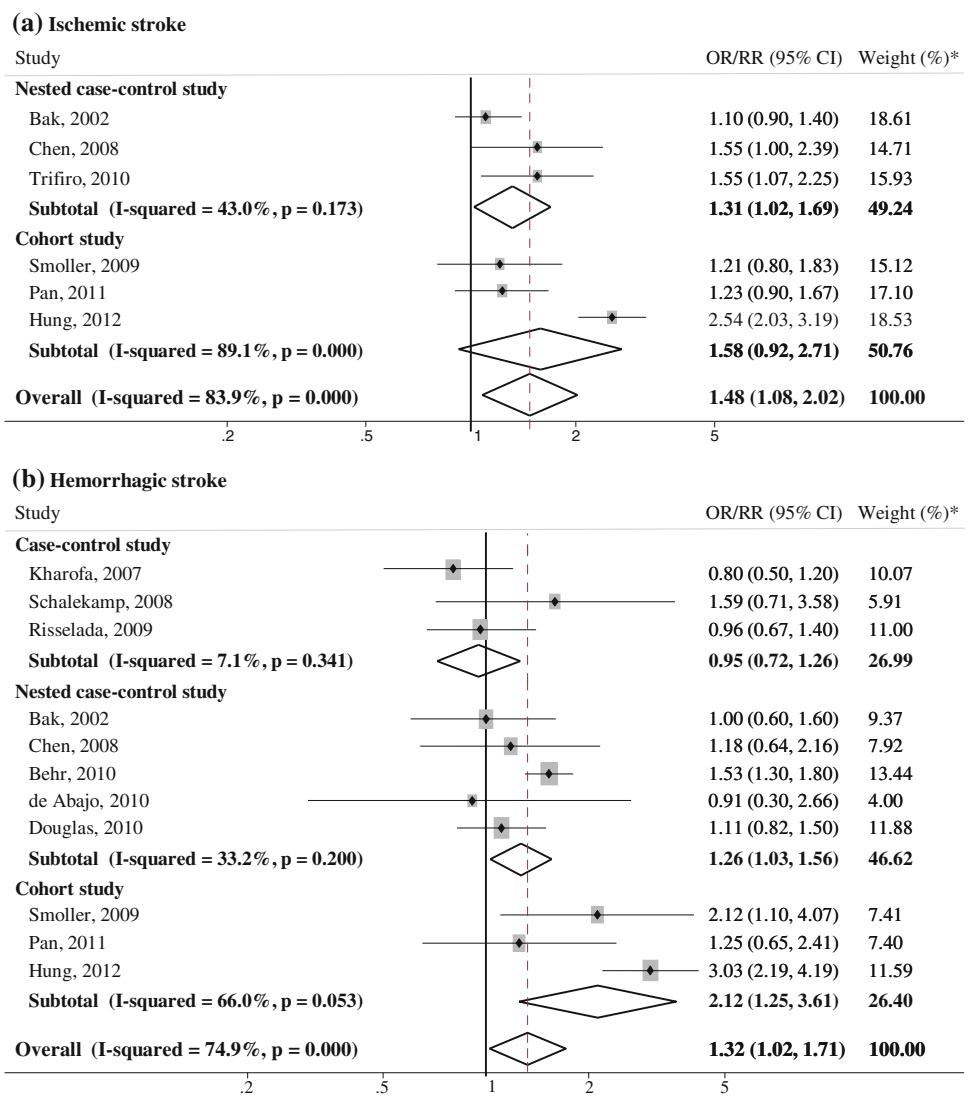

Fig. 2 Risk of ischemic and hemorrhagic strokes among those who used SSRIs according to study design. *OR* Odds ratio, *RR* relative risk. *Asterisk* weights are from random effects analysis

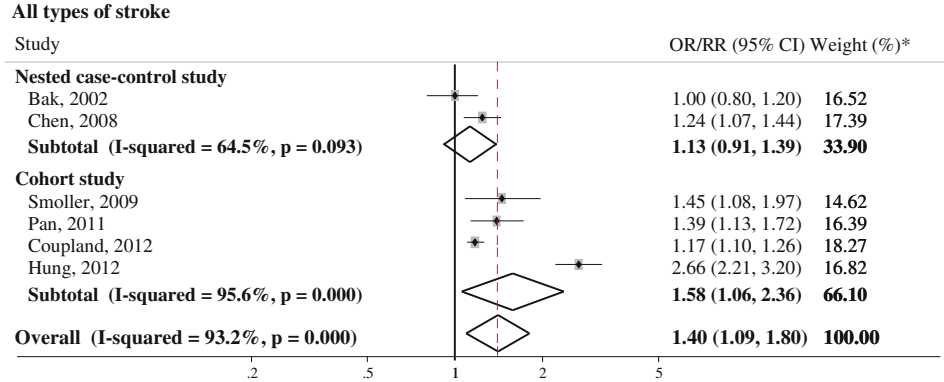

Fig. 3 Risk of all types of stroke among those who used SSRIs according to study design. *OR* Odds ratio, *RR* relative risk. *Asterisk* weights are from random effects analysis

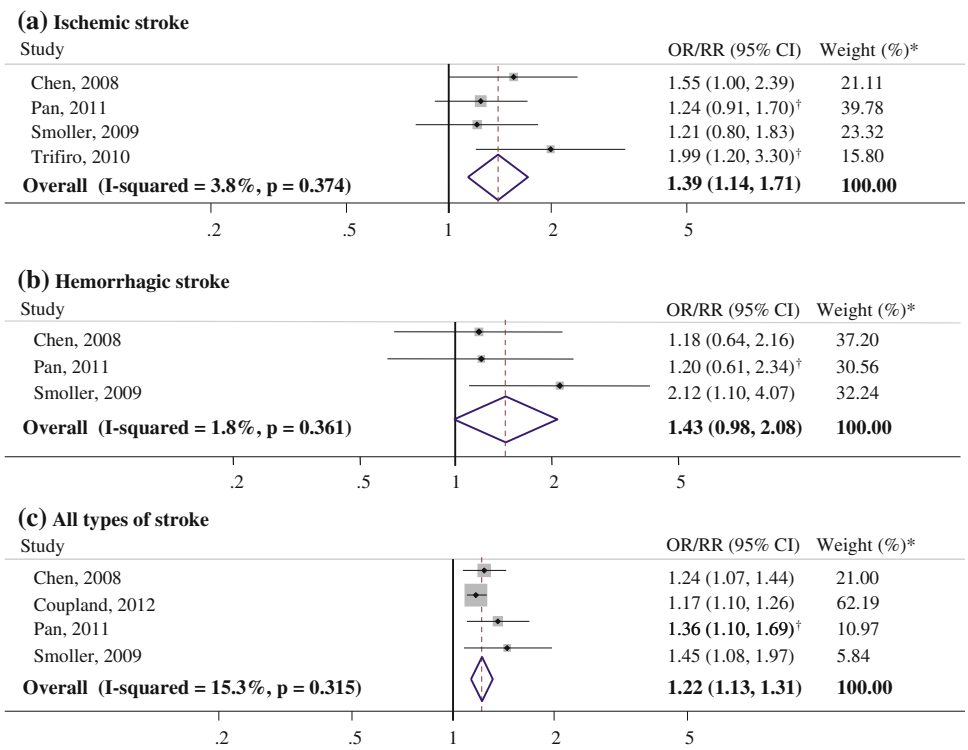

Fig. 4 Risk of stroke among SSRI users in the studies where potential confounding by depression was controlled. *OR* Odds ratio, *RR* relative risk. *Asterisk* weights are from random effects analysis. *Dagger* additional data from the study

associated with an increased risk of intracranial hemorrhage and ICH [8]. These results are partially consistent with the results of our study, in which we found a positive association between the use of SSRIs and the risk of hemorrhagic stroke, especially ICH.

Considering the antiplatelet effect of SSRIs, their use would be protective for thrombotic events theoretically. However, serotonin is also a potent vasoactive amine of large arteries of the brain [29], and SSRIs may cause vasoconstriction in cerebral arteries, which lead to ischemic stroke [6]. Our study revealed that the risk of ischemic stroke was high in the SSRI users. According to the subgroup analysis in our study, current SSRI use was significantly associated with an increased risk of ischemic stroke, although we could not find this association among the studies that did not specify the time window of exposure as either current or past use. These results support the hypothesis that the vasoconstrictive effect of SSRIs may cause ischemic stroke because it is not a cumulative effect and thus can be expected only with the current use of the drugs.

Importantly, depression may confound the association between SSRI use and the risk of stroke, since depression itself has been shown to increase the risk of stroke [2]. In our study, we performed a subgroup meta-analysis of the studies in which potential confounding due to depression was controlled by adjusting for severity of depression and/or by exclusively selecting patients with depression. In this subgroup analysis, SSRIs still increased the risks of ischemic and all types of stroke with statistical significance, as well as hemorrhagic stroke with marginal significance, and the heterogeneities among studies decreased significantly. To further address this problem, we found some evidence from the relevant articles. Some studies found that the risk of stroke was increased more in patients on SSRIs than those on tricyclic antidepressants, after adjusting for severity of depression [12–14]. Another study revealed that the risk of stroke was also increased in SSRI users who had no diagnosis of major depressive disorder [5]. In addition, the use of SSRIs was associated with increased risk of stroke in a recent case-crossover study, in which all between-subject time-invariant confounding factors were controlled due to the characteristics of the study design [30]. To sum up, all these findings, along with our results, suggest that the use of SSRIs may increase the risk of stroke independent of depression. Since no study thus far could have completely ruled out the potential confounding by depression, however, residual confounding still remains and this unresolved problem should be addressed more in the future studies. Similarly, it is unclear whether the well-known association between depression and stroke was confounded by possible adverse effects of SSRIs, because most studies did not control the use of antidepressants when assessing the association. Therefore, further well-designed studies are required to evaluate the adverse cerebrovascular effects of depression and SSRIs while controlling for each other as much as possible.

Despite the possible adverse cerebrovascular effects of SSRIs, the use of SSRIs may be beneficial for the patients with recent stroke by preventing post-stoke depression [31] and enhancing motor and cognitive recovery with modulation of brain plasticity [32–34]. Considering that a recent study showed increased risk of major bleeding and mortality among SSRI users after stroke [35], more studies are needed to balance between potential beneficial and adverse effects of using SSRIs in those patients.

We obtained high I^2 values for the risks of ischemic and hemorrhagic strokes (83.0 and 74.9 %, respectively). As described above, heterogeneity among studies significantly decreased when we restricted the analysis to the studies in which possible confounding by depression was controlled. To reveal further the reasons for these heterogeneities, we additionally performed subgroup meta-analyses and meta-regression. First, not specifying the time window of exposure as current, recent, or past use in some studies may be a possible reason for the heterogeneity. Second, the study location may be another important reason for the heterogeneity, because the I^2 values were reduced significantly in the subgroup meta-analysis according to the study location (Western or Eastern). It was confirmed by the meta-regression analysis. Well-known large differences in lifestyle and the incidence, composition, fatality, and mortality of stroke between Western and Eastern countries could have affected the heterogeneity [36, 37]. Finally, the I^2 values for the risk of ICH or SAH were low ($I^2 = 28.7$ and 18.5, respectively). It means that combining the results of the two different subtypes to estimate the risk of hemorrhagic stroke may increase heterogeneity. Along with those explanations, we believe that this association should not be underrated simply because of the high heterogeneity, since five of the six studies consistently showed a positive association between the use of SSRIs and the risk of all types of stroke.

One could suggest that the treatment duration and daily dose of SSRIs may affect the risk of stroke. According to the relevant studies [7, 10, 12, 20], the daily dose of SSRIs did not affect the risk of stroke and the duration effect of the SSRI treatment seems to be controversial. In our study, it was impossible to investigate dose and duration effects on the risk of stroke given that the number of studies with detailed information about treatment dose and duration was not enough to perform a meta-analysis. Similarly, although different types of SSRIs may affect the risk of stroke differently due to their distinct affinities to the serotonin transporter, not enough data have been available so far to examine the possible differences according to the type of SSRIs.

Our meta-analysis had several strengths. First, it is the only meta-analysis of the association between the use of SSRIs and the risk of stroke, including ischemic and hemorrhagic strokes. Second, the present study examined the associations in greater detail by performing subgroup analyses. Despite its strengths, our study only included observational studies that are considered to have potential for bias, and thus, further well-designed studies are needed.

In conclusion, the use of SSRIs was associated with the increased risks of ischemic, hemorrhagic, and all types of stroke. Given that SSRIs are still effective and safe drugs with diverse indications, proper use of SSRIs should carefully consider necessity and patients' status. Since there was heterogeneity among studies and potential confounding by depression could not be fully excluded, well-designed studies are required to confirm this association.

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Conflicts of interest None.

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