Risk of First Onset Stroke in SSRI-Exposed Adult Subjects:
Survival Analysis and Examination of Age and Time Effects

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ABSTRACT

Objective: Exposure to selective serotonin reuptake inhibitors (SSRIs) has been shown to increase the risk of stroke. In this study, we investigated age and time effects on the risk of first onset stroke in SSRI-exposed (SSRIEXP) adult subjects.

Methods: We analyzed an 8-year cohort from the National Health Insurance Research Database, Taiwan. Patients were defined as SSRIEXP subjects if they received SSRI prescriptions for at least 2 consecutive months during January 1, 2001, to December 31, 2007. Otherwise, they were categorized as SSRI-nonexposed (SSRINONE) subjects. Stroke diagnosis was made according to *ICD-9* codes 430–432 (hemorrhagic stroke) and 433–437 (ischemic stroke).

Results: Kaplan-Meier survival analysis showed a greater probability of first onset stroke in SSRIEXP than SSRINONE subjects ($P < .001$). The higher incidence rates in SSRIEXP subjects persisted to the 3 year time point. Ischemic/hemorrhagic stroke cumulative incidence ratios were also higher during the first 3 years in SSRIEXP subjects. Analysis of adjusted hazard ratios indicated that younger SSRIEXP subjects were more likely to experience stroke, with a slight increase of risk in subjects older than 65 years. Stratified analysis of ischemic stroke and hemorrhagic stroke resulted in a similar hazard ratio trend.

Conclusions: Use of SSRIs independently increases the risk of stroke across age strata. The risk is higher in younger adult subjects, and the stroke is more likely to be ischemic than hemorrhagic. The underlying mechanisms of stroke may be related to cerebral microbleeding or an overcorrection of hemostasis function.

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Stroke ranks as the second cause of death worldwide after ischemic heart disease.[1] The proportion of ischemic (lack of blood flow) stroke is generally higher than hemorrhagic (leakage of blood) stroke across populations.[2] The advisory guidelines for primary prevention of stroke published by the American Heart Association/American Stroke Association point out several nonmodifiable risk factors (eg, genetic predisposition), modifiable risk factors (eg, atrial fibrillation [AF][3,4]), and potentially modifiable risk factors (eg, excessive alcohol consumption) for stroke.[5] In addition, many other heart diseases also increase the risk of stroke.[4,6]

A body of research has reported that individuals with depression have an increased risk of stroke; some of these studies concluded that depression is an independent risk factor for stroke without accounting for pharmacologic effects of antidepressants in their statistics.[7] Selective serotonin reuptake inhibitors (SSRIs) are widely used in the treatment of depressive disorder[8] and have been accepted by the general public as a safe class of therapeutics for decades. However, findings from cohort studies, including the Women's Health Initiative study[9] and the Integrated Primary Care Information database of the Netherlands,[10] and analytic results from a managed care medical claims database in the United States[11] have indicated that SSRIs probably have more potential hazards to human health than previously thought. Recently, a Taiwan research team found a transient effect of antidepressants including SSRIs (exposure 1–14 days before first hospitalization for stroke to exposure 15–28 days before first hospitalization for stroke) in increasing risk of stroke, using a case-crossover design.[12] Moreover, recent meta-analyses by Hackam and Mrkobrada[13] and Shin et al[14] have confirmed the increased risk of stroke in SSRI users. To obtain a clearer picture of this health issue, we examined the effects of age, time, and comorbidity on the risk of stroke in SSRI users with a defined period of SSRI exposure. The results should contribute more information to the current understanding of stroke risk in SSRI users.

METHODS

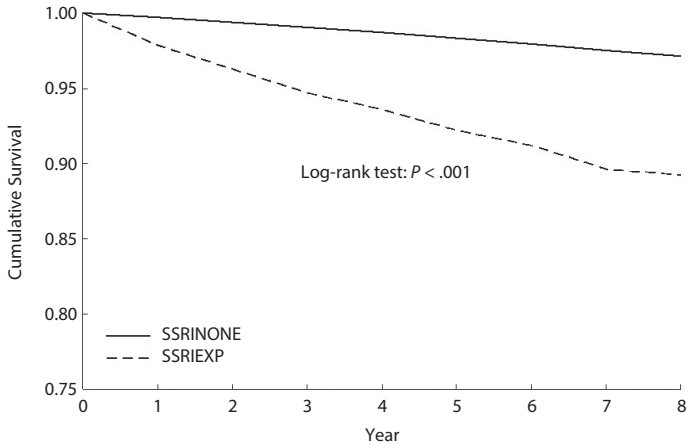
Study Population and Design

The Taiwan government launched a single-payer National Health Insurance (NHI) program on March 1, 1995. Up to 2007, 22.6 million of the 22.96 million

Clinical Points

- The characteristics of stroke in SSRI users are unclear.
- This study found that most stroke events in SSRI users occurred at the early stage of SSRI exposure. Younger users were more likely to suffer from stroke, and the stroke was more likely to be ischemic than hemorrhagic.
- SSRIs are generally safe for treating depression. Precautions and monitoring are recommended.

Figure 1. Kaplan-Meier Survival Analysis of SSRIEXP and SSRINONE Subjects for First Onset Stroke Events



Abbreviations: SSRIEXP = selective serotonin reuptake inhibitor–exposed, SSRINONE = selective serotonin reuptake inhibitor–nonexposed.

population in Taiwan had enrolled in this program. The National Health Research Institutes, Taiwan, manage the authorization of the National Health Insurance Research Database (NHIRD) for research use. We obtained a subset of the NHIRD with 1,000,000 random subjects, accounting for about 5% of all enrollees in the NHI program. The database contains information on medical claims for ambulatory care, inpatient care, dental services, and prescription drugs, as well as registration files, of enrollees insured from January 1996 to December 2008. There were no statistically significant differences in age, gender, or costs between the sample group and all enrollees (data not shown).

This is an 8-year retrospective cohort observation study. The sampling procedures are summarized in Supplementary eFigure 1. Subjects were included if they were 20 years or older on January 1, 2001. Subjects were categorized as SSRI exposed (SSRIEXP) when they first received an SSRI prescription (paroxetine, fluoxetine, sertraline, citalopram, escitalopram, or fluvoxamine) for at least 2 consecutive months to ensure a sufficient length of SSRI exposure during January 1, 2001, to December 31, 2007. Otherwise, they were categorized as SSRI nonexposed (SSRINONE). For SSRIEXP subjects, the date of first SSRI prescription was defined as the entry date for this study. The first onset stroke diagnosis was identified by meeting *ICD-9* codes 430–432 (hemorrhagic stroke) or 433–437 (ischemic stroke) in any inpatient or outpatient treatment during the 8-year period. Code 438, stroke unspecified, was not included in this study because the etiology is unknown. The endpoint of follow-up was occurrence of first stroke event, death, or end of study on December 31, 2008. The date of death was defined as the ending date of insurance coverage because the NHI coverage period for most of the stroke patients ended within a month of the patient's death.[15] This is evident from the analysis of the date of death and the date of end of NHI coverage in stroke patients who died within 1 year after discharge. Ninety-seven percent of the records demonstrated the same date of death and date of end of NHI coverage. Thus, the end of NHI coverage is a good proxy for a patient's survival.

Confounding Factors

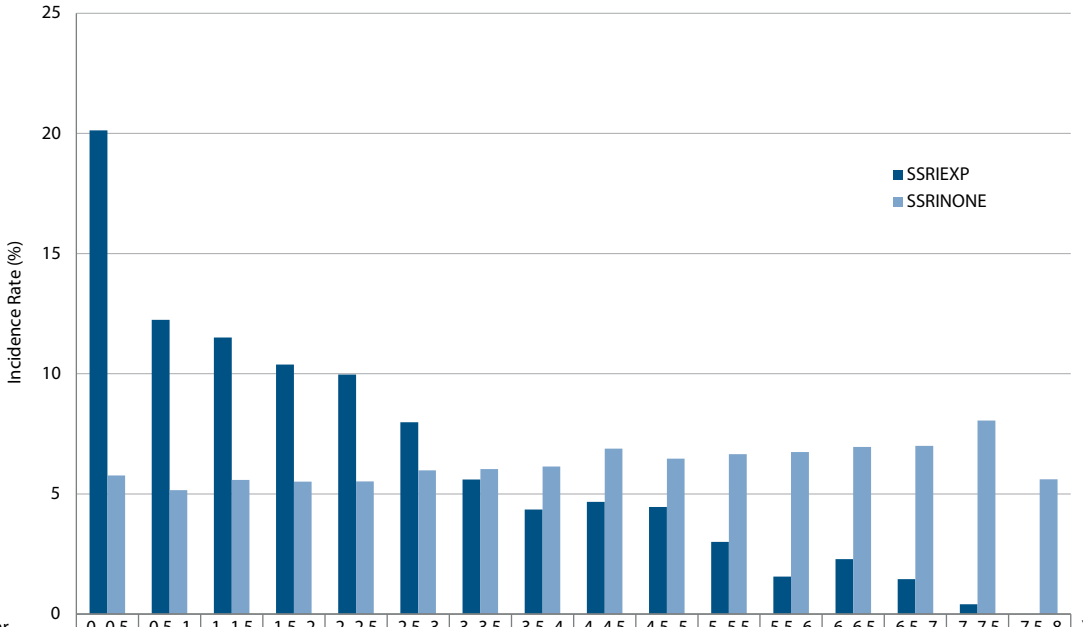
A reasonable statistical approach is to include information available in the NHIRD on nonpsychiatric diseases that might contribute to the risk of stroke. On the basis of this principle, angina pectoris (AP), myocardial infarction (MI), atrial fibrillation (AF), congestive heart failure (CHF) and peripheral artery disease (PAD), diabetes mellitus (DM), hypertension and hyperlipidemia, and renal diseases (ie, end-stage renal disease [ESRD] and chronic kidney disease) were included in our regression analysis. DM, hypertension, and hyperlipidemia were confirmed by the records of 1 or more prescriptions for the diagnoses. For concomitant use of drugs that may affect the risk of stroke, aspirin (ATC code: A01AD05, B01AC06, and N02BA01), heparin (ATC code: B01AB01), warfarin (ATC code: B01AA03), and nonsteroidal anti-inflammatory drugs (NSAIDs) (ATC code: M01A, M02A, and N02BA) were included.

For subjects who did not use SSRIs, information on diseases that might increase the risk of stroke in the previous 12 months from January 1, 2001, was retrieved from the database. Subjects were excluded if they had any inpatient diagnosis of stroke or 3 outpatient records of stroke before January 1, 2001. Subjects with no SSRI exposure but with any diagnosis of mental disorder (*ICD-9* code: 290–319) between January 1, 2001, and December 31, 2007, were also excluded. Finally, a total of 408,932 adult subjects were included in the statistical analysis.

Statistical Analysis

Distributions of SSRIEXP and SSRINONE subjects in age, gender, and comorbidity were examined using χ^2 tests. Kaplan-Meier curve and log rank test were used to examine the difference in stroke occurrence between SSRIEXP and SSRINONE subjects. Multivariable Cox proportional-hazards model was used to explore the relation between SSRI exposure and occurrence of stroke, adjusted for age, gender, and comorbidity. The proportional hazard assumption was tested graphically and by including the interaction of time with each covariate. All statistical tests were 2 sided, conducted at the

Figure 2. Incidence of First Onset Stroke Events in SSRIEXP and SSRINONE Subjects in the Follow-Up Period



Year	0–0.5	0.5–1	1–1.5	1.5–2	2–2.5	2.5–3	3–3.5	3.5–4	4–4.5	4.5–5	5–5.5	5.5–6	6–6.5	6.5–7	7–7.5	7.5–8
SSRIEXP	20.13	12.24	11.51	10.38	9.97	7.98	5.6	4.35	4.67	4.46	3.00	1.56	2.29	1.45	0.41	0
SSRINONE	5.77	5.16	5.58	5.51	5.52	5.98	6.03	6.14	6.88	6.47	6.65	6.74	6.95	7.00	8.05	5.61

Abbreviations: SSRIEXP = selective serotonin reuptake inhibitor–exposed, SSRINONE = selective serotonin reuptake inhibitor–nonexposed.

significance level of .05, and reported using *P* values and/or 95% confidence intervals (CIs). All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, North Carolina). Because ischemic stroke may be different (or at least partly different) from hemorrhagic stroke etiologically, we analyzed the risk of stroke together and separately.

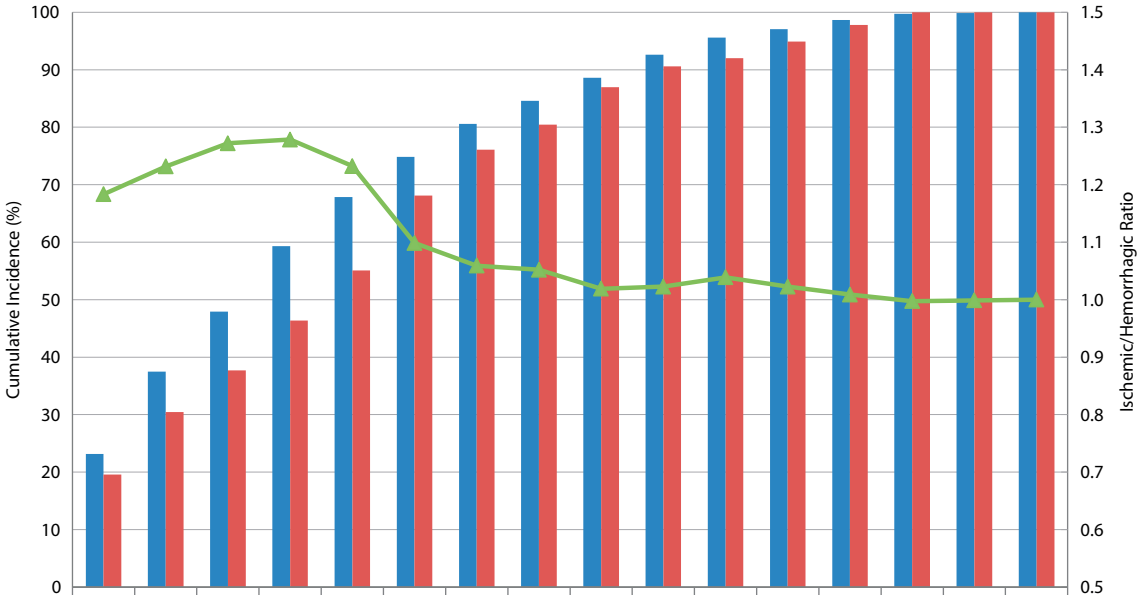
RESULTS

The incidence rates of first onset stroke in the 20–29, 30–39, 40–49, 50–59, 60–69, and 70+ years age strata were 0.33%, 1.00%, 3.25%, 8.40%, 15.10%, and 17.78%, respectively. χ^2 statistics for age, sex, use of drugs that affect the risk of stroke (ie, aspirin, heparin, warfarin, and NSAID), comorbid diseases, and stroke are summarized in Supplementary eTables 1, 2, and 3. Compared with SSRINONE subjects, the SSRIEXP subjects were significantly older ($P < .001$) and more likely to be female ($P < .001$). The proportion of SSRIEXP subjects experiencing stroke was 6.7%, while the proportion in SSRINONE subjects was 2.8% ($P < .001$). For comorbidity, AF, MI, CHF, AP, PAD, DM, hyperlipidemia, hypertension, or renal diseases (*P* values < .001) were significantly more prevalent in SSRIEXP subjects than in SSRINONE subjects; use of aspirin, heparin, warfarin, and NSAIDs was also more frequent in SSRIEXP subjects ($P < .001$). All of the above mentioned variables demonstrated significant differences when stratified into ischemic stroke and hemorrhagic stroke.

The average length of follow-up for all subjects was 7.5 years. Kaplan-Meier survival analysis demonstrated a greater probability of first onset stroke events in SSRIEXP subjects than in SSRINONE subjects (Figure 1, *P* value of log rank test < .001). At the end of the follow-up period, nearly 10% of the SSRIEXP subjects had experienced stroke, while this occurred in only 2%–3% of the SSRINONE subjects. Incidence rates of first onset stroke events of SSRIEXP and SSRINONE subjects during the follow-up period are shown in Figure 2. About 20% of the stroke events in SSRIEXP subjects occurred during the first 6 months. The higher incidence rates of stroke event in SSRIEXP subjects compared with SSRINONE subjects persisted to the 3 year time point. While the incidence rate trend in SSRIEXP subjects subsequently gradually decreased, that of SSRINONE subjects remained between 5%–8% during the research period. While no new stroke events occurred in SSRIEXP subjects during the final 6 months, an incidence rate of 5.61% was found in SSRINONE subjects. In other words, the average stroke risk in SSRINONE subjects was relatively stable along with time as compared with SSRIEXP subjects.

The proportion of ischemic stroke is generally higher than that of hemorrhagic stroke across populations.[2] Theoretically, the ischemic/hemorrhagic stroke cumulative incidence rate ratios in SSRIEXP subjects should always be larger than 1 and persist on a stable trend along with time if no major interfering factors exist in disease development. As expected, the cumulative incidence rate ratio in our study was larger than 1 at each time point. Worth noting is that the ratios were higher during the 0 to 2.5 years time period but gradually approached an equal level in the following period,

Figure 3. Cumulative Incidence of Ischemic and Hemorrhagic Stroke and Ratio of Cumulative Incidence (Ischemic/Hemorrhagic) in SSRIEXP and SSRINONE Subjects



Year	0–0.5	0.5–1	1–1.5	1.5–2	2–2.5	2.5–3	3–3.5	3.5–4	4–4.5	4.5–5	5–5.5	5.5–6	6–6.5	6.5–7	7–7.5	7.5–8
Ischemic	23.16	37.48	47.93	59.3	67.87	74.83	80.59	84.61	88.62	92.63	95.59	97.06	98.66	99.72	99.85	99.98
Hemorrhagic	19.57	30.43	37.68	46.38	55.07	68.12	76.09	80.43	86.96	90.57	92.01	94.91	97.8	99.97	99.97	99.97
Ischemic/ hemorrhagic ratio	1.183	1.232	1.272	1.279	1.232	1.099	1.059	1.052	1.019	1.023	1.039	1.023	1.009	0.997	0.999	1

Abbreviations: SSRIEXP = selective serotonin reuptake inhibitor–exposed, SSRINONE = selective serotonin reuptake inhibitor–nonexposed.

Table 1. Cox Proportion-Hazard Regressions for All Stroke Events (n = 12,148), Ischemic Stroke (n = 10,472), and Hemorrhagic Stroke (n = 2,201)

	All Stroke Events				Ischemic Stroke				Hemorrhagic Stroke			
Group	Hazard	95% CI			Hazard	95% CI			Hazard	95% CI		
Variable	Ratio	Lower	Upper	Sig	Ratio	Lower	Upper	Sig	Ratio	Lower	Upper	Sig
SSRI exposure (vs nonexposure)	2.55	2.38	2.73	***	2.40	2.23	2.58	***	2.19	1.85	2.59	***
Demographic factors												
Age (10-year increments)	2.09	2.06	2.12	***	2.12	2.09	2.15	***	1.70	1.65	1.74	***
Sex	1.42	1.37	1.47	***	1.41	1.35	1.47	***	1.67	1.53	1.82	***
Comorbidity												
Atrial fibrillation	1.10	0.89	1.35	NS	1.08	0.87	1.34	NS	1.13	0.69	1.84	NS
Myocardial infarction	1.30	1.13	1.50	***	1.27	1.10	1.47	**	1.00	0.68	1.47	NS
Congestive heart failure	1.04	0.93	1.18	NS	1.05	0.93	1.19	NS	0.96	0.70	1.32	NS
Angina pectoris	1.02	0.95	1.09	NS	1.03	0.96	1.11	NS	0.83	0.69	0.98	*
Peripheral artery disease	1.44	0.85	2.43	NS	1.44	0.87	2.40	NS	2.38	0.98	5.74	NS
Diabetes mellitus	1.99	1.89	2.10	***	2.01	1.90	2.12	***	1.32	1.14	1.54	***
Hyperlipidemia	1.08	1.01	1.14	*	1.13	1.06	1.20	***	0.77	0.65	0.91	**
Hypertension	1.85	1.77	1.94	***	1.87	1.78	1.96	***	2.14	1.91	2.40	***
Renal disease												
Chronic kidney disease	1.18	0.94	1.48	NS	1.06	0.83	1.36	NS	1.11	0.61	2.01	NS
End-stage renal disease	2.13	1.65	2.75	***	1.94	1.47	2.56	***	2.61	1.52	4.47	***
Drugs												
Aspirin	1.16	1.09	1.24	***	1.20	1.12	1.28	***	1.25	1.08	1.45	**
Heparin	1.15	0.92	1.43	NS	1.22	0.98	1.52	NS	1.60	1.02	2.51	*
Warfarin	1.74	1.38	2.19	***	1.70	1.34	2.17	***	1.87	1.16	3.01	**
NSAIDs	1.11	1.07	1.15	***	1.15	1.11	1.20	***	0.93	0.86	1.02	NS

*$P < .01$.
**$P < .001$.
***$P < .0001$.
Abbreviations: NS = nonsignificant, NSAID = nonsteroidal antiinflammatory drug, sig = significance level, SSRI = selective serotonin reuptake inhibitor.

Table 2. Adjusted Hazard Ratios of Stroke for SSRI Exposure by Age and Stroke Type[a]

	All Stroke Events			Ischemic Stroke			Hemorrhagic Stroke		
Age Stratum	Hazard Ratio	95% CI Lower	95% CI Upper	Hazard Ratio	95% CI Lower	95% CI Upper	Hazard Ratio	95% CI Lower	95% CI Upper
20–39 y	5.15	3.89	5.15	4.83	3.44	6.78	3.40	1.96	5.91
40–54 y	2.96	2.56	2.96	2.78	2.37	3.26	2.26	1.59	3.23
55–64 y	2.05	1.75	2.05	2.17	1.84	2.55	2.01	1.38	2.93
65+ y	2.51	2.28	2.51	2.38	2.16	2.63	2.21	1.72	2.83

[a]Each age stratum was adjusted by age, sex, diabetes, hypertension, hyperlipidemia, and renal diseases. All results shown are statistically significant.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

indicating an excess of ischemic stroke events in SSRIEXP subjects during the early follow-up period (Figure 3).

Independent Contributions by Multivariate Cox Proportional-Hazards Regressions

Because the distributions of age, sex, use of stroke prevention medicines, diseases comorbid with stroke, and stroke were significantly different between SSRIEXP and SSRINONE subjects, we built a Cox proportional-hazards regression adjusting for all these variables (Table 1). Independent hazard ratio (HR) of all stroke events after accounting for all other variables was 2.55 (95% CI, 2.38–2.73) for SSRIEXP subjects. The independent HR increased by 2.09 (95% CI, 2.06–2.12) for every 10-year increment in age. Being male increased the HR by 1.42 (95% CI, 1.37–1.47). Existence of MI, DM, hyperlipidemia, hypertension, and ESRD increased the independent HRs of stroke by 1.30 (95% CI, 1.13–1.50), 1.99 (95% CI, 1.89–2.10), 1.08 (95% CI, 1.01–1.14), 1.85 (95% CI, 1.77–1.94), and 2.13 (1.65–2.75), respectively. AF, CHF, AP, and PAD were not statistically significant in the model. Hyperlipidemia had a relatively small contribution while ESRD had the largest independent contribution to stroke among the variables. While use of aspirin, warfarin, and NSAIDs had independent HRs of 1.16 (95% CI, 1.09–1.24), 1.74 (95% CI, 1.38–2.19), and 1.11 (95% CI, 1.07–1.15) in stroke, use of heparin was not significant in the model. Analysis of propensity score matching for possible bias selection showed no evidence of bias selection in our analysis (data not shown).

The independent HR for ischemic stroke in SSRIEXP subjects after accounting for all other variables was 2.40 (95% CI, 2.23–2.58), while that of hemorrhagic stroke was 2.19 (95% CI, 1.85–2.59). Apparently, SSRI exposure had a stronger effect on ischemic stroke than hemorrhagic stroke. Some variables had similar trends of independent contribution to ischemic and hemorrhagic stroke. These include age, sex, AF, DM, hypertension, ESRD, use of aspirin, and use of warfarin. Chronic kidney disease showed no role in both types of stroke. Some variables contributed to 1 type of stroke only: subjects with MI had an increased risk of ischemic stroke (HR = 1.27; 95% CI, 1.10–1.47) but not hemorrhagic stroke; subjects with AP had a lower risk of hemorrhagic stroke (HR = 0.83; 95% CI, 0.69–0.98) but not ischemic stroke. For the effects of stroke prevention medicines, subjects who used heparin had an increased risk of hemorrhagic stroke (HR = 1.60; 95% CI, 1.02–2.51) but not ischemic stroke, and subjects who used NSAIDs had an increased risk of ischemic stroke (HR = 1.15; 95% CI, 1.11–1.20) but not hemorrhagic stroke. Also, subjects with hyperlipidemia had an increased risk of ischemic stroke (HR = 1.13; 95% CI, 1.06–1.20) but a reduced risk of hemorrhagic stroke (HR = 0.77; 95% CI, 0.65–0.91). The question of whether indication of SSRI use (diagnosis of major depression) affected the risk of stroke and therefore confounded the statistical outcome was also examined. The analysis showed only a borderline trend toward significance ($P = .0589$), and thus a role of indication of SSRI use in increasing the risk of stroke cannot be concluded (Supplementary eTable 4).

HRs in Different Age Strata

Adjusted HRs for all stroke, ischemic stroke, and hemorrhagic stroke in SSRIEXP subjects compared with SSRINONE subjects at different age strata are summarized in Table 2. The HR for all stroke events was 5.15 (95% CI, 3.89–5.15) for SSRIEXP subjects at the age of 20–39 years. The ratios decreased to 2.96 (95% CI, 2.56–2.96) at the age of 40–54 and 2.05 (95% CI, 1.75–2.05) at the age of 55–64, with a slight increase to 2.51 (95% CI, 2.28–2.51) for subjects 65 years or older. Stratified analysis of ischemic stroke and hemorrhagic stroke resulted in a similar trend of hazard ratio. The HRs for ischemic stroke were 4.83 (95% CI, 3.44–6.78), 2.78 (95% CI, 2.37–3.26), 2.17 (95% CI, 1.84–2.55), and 2.38 (95% CI, 2.16–2.63), and those of hemorrhagic stroke were 3.40 (95% CI, 1.96–5.96), 2.26 (95% CI, 1.59–3.23), 2.01 (95% CI, 1.38–2.93), and 2.21 (95% CI, 1.72–2.83).

DISCUSSION

The increased risk of stroke in our SSRIEXP subjects was not merely invoked by SSRIs, but also involved contribution from multiple factors. The higher risk of ischemic stroke in male SSRIEXP subjects was in accordance with previous findings.[16] While specific gender difference in primary hemorrhagic stroke varies across populations,[17] we found that male SSRIEXP subjects were more likely to have hemorrhagic stroke. It should be emphasized that the independent HR of stroke that increased with age (2.09 [95% CI, 2.06–2.12] for every 10-year increment, based on all age strata) is not inconsistent with the younger risk of stroke in age-stratified analysis or the earlier occurrence of stroke in the follow-up period. The results indicate an overall positive effect of age on stroke risk; the earlier occurrence of stroke indicates the risky time window, and the HR of stroke in younger SSRIEXP subjects represents their relative risk compared with SSRINONE subjects of the same age stratum. There are 2 possible explanations for the higher risk of stroke in SSRIEXP subjects in the early stage of the 8-year follow-up: (1) SSRIs potentially invoked stroke in vulnerable subjects and (2) the stroke effects of SSRIs were shorter term (0–3 years) and decreased with time. Other issues worth looking into further are the effects of nonpsychiatric

medications used by the SSEIEXP subjects. Heparin, for example, showed contribution to hemorrhagic stroke but not ischemic stroke, and NSAIDs showed contribution to ischemic stroke but not hemorrhagic stroke. It is difficult to judge from the current analysis the implications of the statistical results. Additional investigations into this question are required to gain further insight.

How SSRIs invoke the early occurrence of stroke in the SSRIEXP subjects is unclear. Neuroimaging and genetic studies link depression to a complex neuronal circuitry regulated by different neurotransmitters and neuropeptides, including an abnormal regulation of serotonin, which is also a peripheral hormone mostly transported by platelets in blood circulation.[18] SSRIs bind on serotonin transporter (SERT), inhibit recycling of serotonin to presynaptic cell membrane, increase the concentration of synaptic serotonin,[19] and thus correct serotonergic transmission toward normal. SERT is expressed in platelets, and inhibition of serotonin also occurs in platelets in the presence of an SSRI. Previous research demonstrated a reduction of platelet serotonin in drug-naive depressed patients compared with controls.[20] The reduction was even more obvious in patients who were paroxetine responders compared with nonresponders.[21] SSRIs produced a drastic decrease of 80%–90% in platelet serotonin content after several weeks of treatment in either depressive patients[22–24] or normal subjects.[25] These findings indicate that patients with depression are likely to have lower platelet serotonin, and SSRI treatment further reduces the levels. While SSRIs enhance serotonergic transmission in brain, hemostasis function in which the activated platelets release serotonin and induce vasoconstriction, further amplifying platelet activation at the site of vessel wall injury, is reduced.[26] Interestingly, Akoudad et al found that both SSRIs and non-SSRIs increased the risk of cerebral microbleeding, with yet unidentified mechanisms other than platelet impairment,[27] which also increased the risk of stroke.[28] Moreover, platelets may not behave normally under specific pathological conditions. As shown in a number of animal hypertension models, the platelet is activated with a lower amount of serotonin,[29] and therefore there is increased sensitivity in the activation of hemostasis function in the platelets of the hypertension animals. We suspect that SSRIs are more likely to induce cerebral microbleeding among younger SSRIEXP subjects, and a drastic drop of serotonin storage in platelets with certain comorbidity (eg, hypertension) may initiate alternative pathways to overcorrection of hemostasis function and lead to higher risk of stroke in these subjects. The SSRIEXP subjects with cardiovascular and renal diseases may represent a part of this vulnerable group. It is also possible that continuous use of SSRIs over a longer term may be required to exert the desired antidepressant effect or, otherwise, only disadvantages are seen. Further investigation of both possibilities is warranted.

A key strength of this study was the use of a large database. However, there are several potential limitations. First, drug dosage data were not available, and thus the effects cannot be evaluated. Second, only a few confounders that can be explained by current knowledge were accounted for in our statistical analysis. Nevertheless, a statistical model should not include an unlimited number of possible confounders or it will be overadjusted. Third, we required SSRI treatment for 2 consecutive months to define exposure, but follow-up began at the date of the first prescription; this could have introduced an immortal time bias. The time between the date of the first and second prescriptions is immortal; that is, by definition, all SSRIEXP subjects must have survived until their second SSRI prescription, yet in the analysis they were given credit, in the form of person-time, for this immortal period. To resolve this possible bias, we conducted an analysis in which SSRI exposure was defined as ever using SSRIs, but the results did not differ from those of the main analysis (data not shown).

CONCLUSIONS

We conclude that use of SSRIs increases the risk of stroke, especially ischemic stroke, across age strata and that the risk is higher in younger adult subjects. Possible contributions of physical and mental disorders to risk of stroke remain to be analyzed. The risk of stroke appeared higher in the first 3 years of SSRI exposure but became lower afterward. Whether this represents a bring-forward phenomenon of susceptible stroke events or a protective outcome remains to be investigated. Provided that precautions are taken in the first 3 years of treatment, SSRIs are still generally safe to use in treating people who suffer from depression and related symptoms.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Risk of First Onset Stroke in SSRI-Exposed Adult Subjects: Survival Analysis and Examination of Age and Time Effects

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List of Supplementary Material for the article

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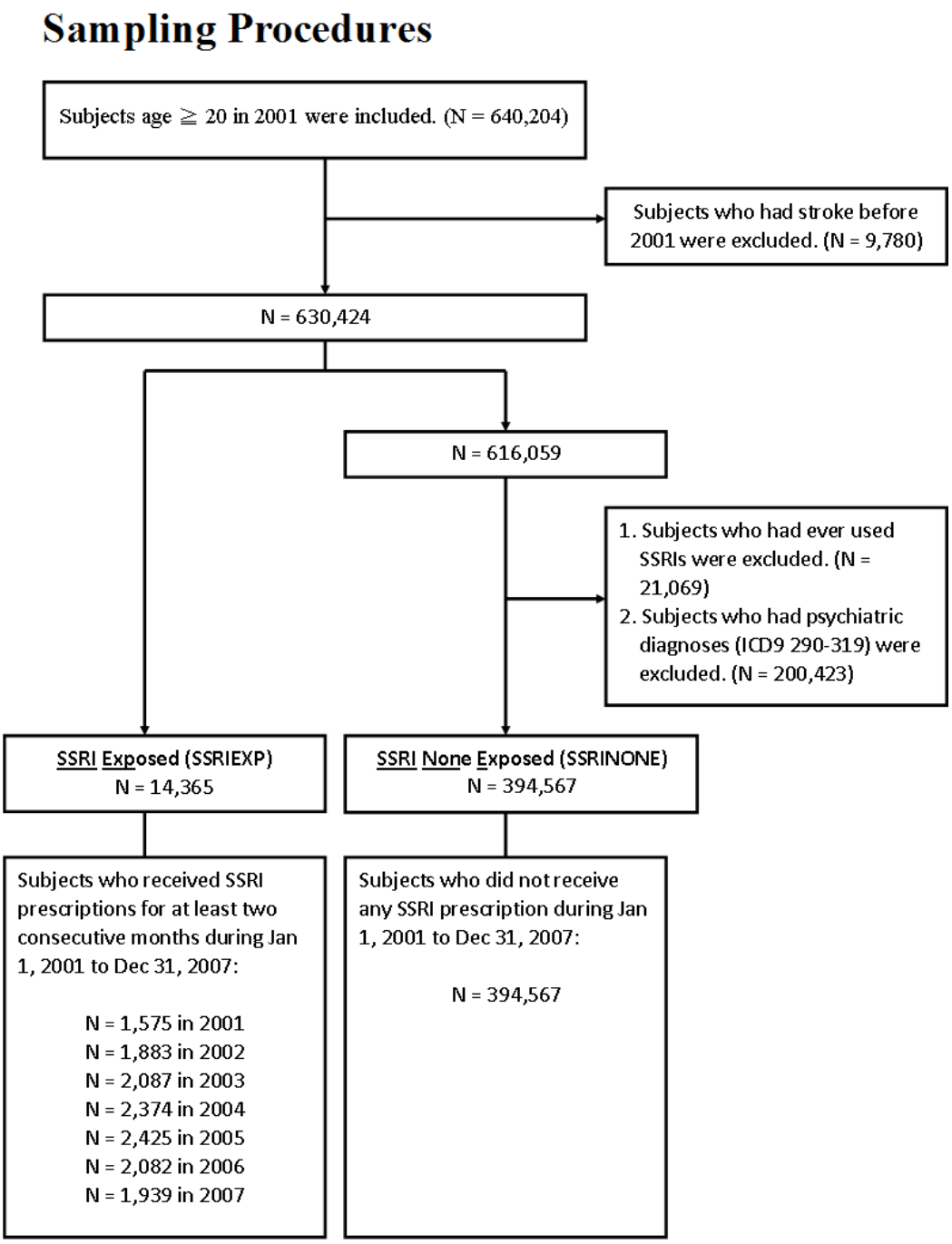
eFigure 1



eTable 1. Proportion of stroke event between SSRIEXP and SSRINONE subjects, as compared by age, sex, medication and diseases contributing to the risk of all stroke events. P values for the χ^2 tests are shown at right column. Significant values are in bold.

Variable	Total n = 408,932		SSRINONE n=394,567		SSRIEXP n = 14,365		P value
	n	%	n	%	n	%	
Age (year)							
20-29	116,851	28.6	114,880	29.1	1,971	13.7	**<0.001**
30-39	111,457	27.3	107,943	27.4	3,514	24.5	
40-49	91,066	22.3	87,710	22.2	3,356	23.4	
50-59	44,312	10.8	41,856	10.6	2,456	17.1	
60-69	27,536	6.7	26,020	6.6	1,516	10.6	
70+	17,710	4.3	16,158	4.1	1,552	10.8	
Sex							
Female	190,078	46.5	181,018	45.9	9,060	63.1	**<0.001**
Male	218,854	53.5	213,549	54.1	5,305	36.9	
Stroke							
No	396,784	97.0	383,376	97.2	13,408	93.3	**<0.001**
Yes	12,148	3.0	11,191	2.8	957	6.7	
AF							
No	408,506	99.9	394,212	99.91	14,294	99.51	**<0.001**
Yes	426	0.1	355	0.09	71	0.49	
MI							
No	407,883	99.7	393,689	99.8	14,194	98.8	**<0.001**
Yes	1,049	0.3	878	0.2	171	1.2	
CHF							
No	407,355	99.6	393,228	99.7	14,127	98.3	**<0.001**
Yes	1,577	0.4	1,339	0.3	238	1.7	
AP							
No	400,774	98.0	387,695	98.3	13,079	91.1	**<0.001**
Yes	8,158	2.0	6,872	1.7	1,286	9.0	

PAD								
No		408,872	99.99	394,519	99.99	14,353	99.92	<**0.001**
Yes		60	0.01	48	0.01	12	0.08	
DM								
No		399,012	97.6	385,565	97.7	13,447	93.6	<**0.001**
Yes		9,920	2.4	9,002	2.3	918	6.4	
Hyperlipidemia								
No		394,781	96.5	382,027	96.8	12,754	88.8	<**0.001**
Yes		14,151	3.5	12,540	3.2	1,611	11.2	
Hypertension								
No		382,815	93.6	371,247	94.1	11,568	80.5	<**0.001**
Yes		26,117	6.4	23,320	5.9	2,797	19.5	
Renal diseases								
No		408,088	99.80	393,847	99.82	14,241	99.14	<**0.001**
Yes	CKD	422	0.10	359	0.09	63	0.44	
	ESRD	422	0.10	361	0.09	61	0.42	
Aspirin								
No		394,400	96.5	381,244	96.6	13,156	91.6	<**0.001**
Yes		14,532	3.6	13,323	3.4	1,209	8.4	
Heparin								
No		408,384	99.87	394,160	99.90	14,224	99.02	<**0.001**
Yes		548	0.13	407	0.10	141	0.98	
Warfarin								
No		408,526	99.9	394,216	99.91	14,310	99.62	<**0.001**
Yes		406	0.1	351	0.09	55	0.38	
NSAIDs								
No		182,808	44.7	179,258	45.4	3,550	24.7	<**0.001**
Yes		226,124	55.3	215,309	54.6	10,815	75.3	

Abbreviations: AF = atrial fibrillation, AP = angina pectoris, CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, ESRD = end-stage

renal disease, MI = myocardial infarction, NSAIDs = nonsteroidal anti-inflammatory drugs, PAD = peripheral artery disease, SSRI = selective serotonin reuptake inhibitor, SSRIEXP = SSRI exposed, SSRINONE = SSRI none exposed.

eTable 2. Ischemic stroke.

Variable	Total n = 409,819		SSRINONE n=395,164		SSRIEXP n = 14,655		P value
	N	%	n	%	n	%	
Age (year)							
20-29	116,872	28.52	114,896	29.08	1,976	13.48	**<0.001**
30-39	111,499	27.21	107,965	27.32	3,534	24.11	
40-49	91,177	22.25	87,785	22.21	3,392	23.15	
50-59	44,484	10.85	41,977	10.62	2,507	17.11	
60-69	27,783	6.78	26,201	6.63	1,582	10.79	
70+	18,004	4.39	16,340	4.13	1,664	11.35	
Sex							
Female	190,420	46.46	181,222	45.86	9,198	62.76	**<0.001**
Male	219,399	53.54	213,942	54.14	5,457	37.24	
Stroke							
No	399,347	97.44	385,554	97.57	13,793	94.12	**<0.001**
Yes	10,472	2.56	9,610	2.43	862	5.88	
AF							
No	409,380	99.89	394,801	99.91	14,579	99.48	**<0.001**
Yes	439	0.11	363	0.09	76	0.52	
MI							
No	408,745	99.74	394,268	99.77	14,477	98.79	**<0.001**
Yes	1,074	0.26	896	0.23	178	1.21	
CHF							
No	408,200	99.6	393,799	99.65	14,401	98.27	**<0.001**
Yes	1,619	0.4	1,365	0.35	254	1.73	
AP							
No	401,521	97.98	388,202	98.24	13,319	90.88	**<0.001**
Yes	8,298	2.02	6,962	1.76	1,336	9.12	
PAD							
No	409,755	99.98	395,114	99.99	14,641	99.9	**<0.001**

Yes		64	0.02	50	0.01	14	0.1	
DM								
No		399,733	97.54	386,050	97.69	13,683	93.37	<**0.001**
Yes		10,086	2.46	9,114	2.31	972	6.63	
Hyperlipidemia								
No		395,540	96.52	382,548	96.81	12,992	88.65	<**0.001**
Yes		14,279	3.48	12,616	3.19	1,663	11.35	
Hypertension								
No		383,154	93.49	371,444	94	11,710	79.9	<**0.001**
Yes		26,665	6.51	23,720	6	2,945	20.1	
Renal disease								
No		408,960	99.79	394,436	99.82	14,524	99.11	<**0.001**
Yes	CKD	431	0.11	365	0.09	66	0.45	
	ESRD	428	0.1	363	0.09	65	0.44	
Aspirin								
No		395,030	96.39	381,656	96.58	13,374	91.26	<**0.001**
Yes		14,789	3.61	13,508	3.42	1,281	8.74	
Heparin								
No		409,246	99.86	394,745	99.89	14,501	98.95	<**0.001**
Yes		573	0.14	419	0.11	154	1.05	
Warfarin								
No		409,393	99.9	394,797	99.91	14,596	99.6	<**0.001**
Yes		426	0.1	367	0.09	59	0.4	
NSAIDs								
No		183,113	44.68	179,487	45.42	3,626	24.74	<**0.001**
Yes		226,706	55.32	215,677	54.58	11,029	75.26	

Abbreviations: AF = atrial fibrillation, AP = angina pectoris, CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, ESRD = end-stage renal disease, MI = myocardial infarction, NSAIDs = nonsteroidal anti-inflammatory

drugs, PAD = peripheral artery disease, SSRIEXP = selective serotonin reuptake inhibitor exposed, SSRINONE = selective serotonin reuptake inhibitor none exposed.

eTable 3. Hemorrhagic stroke.

Variable	Total n = 413,485		SSRINONE n=395,164		SSRIEXP n = 16,543		P value
	N	%	n	%	n	%	
Age (year)							
20-29	116879	28.27	114892	28.94	1987	12.01	**<0.001**
30-39	111541	26.98	107984	27.2	3557	21.5	
40-49	91403	22.11	87890	22.14	3513	21.24	
50-59	45057	10.9	42268	10.65	2789	16.86	
60-69	28818	6.97	26779	6.75	2039	12.33	
70+	19787	4.79	17129	4.32	2658	16.07	
Sex							
Female	192154	46.47	181942	45.84	10212	61.73	**<0.001**
Male	221331	53.53	215000	54.16	6331	38.27	
Stroke							
No	411284	99.47	394903	99.49	16381	99.02	**<0.001**
Yes	2201	0.53	2039	0.51	162	0.98	
AF							
No	412921	99.86	396536	99.9	16385	99.04	**<0.001**
Yes	564	0.14	406	0.1	158	0.96	
MI							
No	412277	99.71	395998	99.76	16279	98.4	**<0.001**
Yes	1208	0.29	944	0.24	264	1.6	
CHF							
No	411620	99.55	395495	99.64	16125	97.47	**<0.001**
Yes	1865	0.45	1447	0.36	418	2.53	
AP							
No	404221	97.76	389591	98.15	14630	88.44	**<0.001**
Yes	9264	2.24	7351	1.85	1913	11.56	
PAD							
No	413399	99.98	396882	99.98	16517	99.84	**<0.001**

Yes		86	0.02	60	0.02	26	0.16	
DM								
No		402417	97.32	387328	97.58	15089	91.21	<**0.001**
Yes		11068	2.68	9614	2.42	1454	8.79	
Hyperlipidemia								
No		398267	96.32	383896	96.71	14371	86.87	<**0.001**
Yes		15218	3.68	13046	3.29	2172	13.13	
Hypertension								
No		384269	92.93	371922	93.7	12347	74.64	<**0.001**
Yes		29216	7.07	25020	6.3	4196	25.36	
Renal disease								
No		412537	99.77	396195	99.81	16342	98.78	<**0.001**
Yes	CKD	481	0.12	379	0.10	102	0.62	
	ESRD	467	0.11	368	0.09	99	0.60	
Aspirin								
No		396797	95.96	382381	96.33	14416	87.14	<**0.001**
Yes		16688	4.04	14561	3.67	2127	12.86	
Heparin								
No		412790	99.83	396485	99.88	16305	98.56	<**0.001**
Yes		695	0.17	457	0.12	238	1.44	
Warfarin								
No		412909	99.86	396494	99.89	16415	99.23	<**0.001**
Yes		576	0.14	448	0.11	128	0.77	
NSAID								
No		184079	44.52	180079	45.37	4000	24.18	<**0.001**
Yes		229406	55.48	216863	54.63	12543	75.82	

Abbreviations: AF = atrial fibrillation, AP = angina pectoris, CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes mellitus, ESRD = end-stage renal disease, MI = myocardial infarction, NSAIDs = nonsteroidal anti-inflammatory

drugs, PAD = peripheral artery disease, SSRIEXP = selective serotonin reuptake inhibitor exposed, SSRINONE = selective serotonin reuptake inhibitor none exposed.

eTable 4. Cox proportion hazard regression model of stroke controlling for major depression and other variables (n = 609,355).

variable	Hazard Ratio	95% CI		*P* value
		Lower	Upper	
SSRIs (Use/ Non-use)	1.48	1.38	1.60	**<0.001**
Age (10 years)	1.08	1.07	1.08	**<0.001**
Sex (Male/ Female)	1.24	1.21	1.26	**<0.001**
Major depression (Yes/ No)	1.13	1.00	1.29	0.0589
Diabetes (Yes/ No)	1.77	1.72	1.83	**<0.001**
Hypertension (Yes/ No)	1.81	1.77	1.86	**<0.001**
Hyperlipidemia (Yes/ No)	1.19	1.15	1.23	**<0.001**
Renal disease				
CKD (Yes/ No)	1.23	1.08	1.40	**0.0022**
ESRD (Yes/ No)	2.04	1.73	2.41	**<0.001**

This dataset included patients with major depression before January 1, 2001 to account its effect from the beginning of the follow-up period so that a possible bias by indication of selective serotonin reuptake inhibitors can be examined.
Abbreviations: SSRIs = selective serotonin reuptake inhibitors, CKD = chronic kidney disease, ESRD = end-stage renal disease.