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An increased risk of stroke among young schizophrenia patients

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Abstract

Objective: This study sets out to estimate the risk of stroke developing among young schizophrenia patients during a five-year follow-up period after hospitalization for episodes of acute exacerbation.
Methods: Hospitalized schizophrenia patients under 45 years of age were identified from the Taiwan National Health Insurance Research Database for the year 1998 ($n=5001$). Two age-matched cases were randomly selected for each schizophrenia patient from among patients who underwent appendectomies in the same year ($n=10{,}002$). Each individual patient was retrospectively followed up from 1998 until the end of 2003 to determine whether any had developed strokes. Cox proportional hazard regressions were carried out to compute the adjusted five-year survival rate.
Results: A total of 219 patients (1.46%) developed strokes during the five-year follow-up period, with the attacks occurring among 2.46% of schizophrenia patients and 0.94% of the comparison cohort. Following adjustment for patients' demographic characteristics, select comorbid medical disorders and substance abuse, schizophrenia patients were found to be 2.02 times ($p<0.001$) more likely to develop strokes during the follow-up period than age-matched appendectomy patients. The adjusted hazard ratios of developing stroke for male and female schizophrenia patients were, respectively, 1.64 ($p<0.001$) and 2.87 ($p<0.001$) times greater than their counterparts in the comparison group.
Conclusions: As compared with the comparison group, young schizophrenia patients demonstrated a two-fold increased risk of developing stroke during the five-year period after hospitalization. The risk of developing stroke among schizophrenia patients was found to be much higher for females than males.

Keywords: Schizophrenia; Stroke; Young stroke

1. Introduction

Higher medical morbidity and mortality rates have been reported in a number of studies on schizophrenia patients (Brown, 1997; Osby et al., 2000; Brown et al.,

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2000; Auquier et al., 2006), with the lines of evidence suggesting that, compared to the general population, all causes of mortality among this particular group of patients are two to three times higher. In addition to unnatural deaths (including both accidents and suicides), the leading causes of excessive mortality in schizophrenia patients are cardiovascular, cerebrovascular and respiratory diseases.

Although numerous studies have examined the incidence or prevalence of mortality from cardiovascular and respiratory diseases among schizophrenia patients over the past decade (Hennekens et al., 2005; McCreadie and Scottish Schizophrenia Lifestyle Group, 2003; Davidson, 2002; Filik et al., 2006), little attention has been given to any investigation of the incidence or risk of developing cerebrovascular diseases within this particular population. Curkendall et al. (2004) reported that the adjusted risk of developing stroke was significantly higher among schizophrenia patients (odds ratio 2.1) than among comparable age- and sex-matched individuals. Nevertheless, their study was heavily reliant upon data from a single province, such that the findings may not be generalized to the population as a whole.

Clearly, the lack of studies on the association between schizophrenia and the risk of developing cerebrovascular diseases prevents mental healthcare and related healthcare professionals from identifying further the simultaneous contributions of biochemical, metabolic and immune factors to the excessive morbidity and mortality rates among schizophrenia patients. This study therefore sets out to estimate the risk of stroke developing among young schizophrenia patients during a five-year follow-up period after hospitalization for episodes of acute exacerbation. Estimation of the risk of developing stroke is also undertaken for another cohort of patients who underwent appendectomies during the same period. The risks for these two cohorts are subsequently calculated and compared after adjusting for demographic characteristics, select comorbid medical conditions, and substance abuse.

2. Methods

2.1. Database

This study used data from the National Health Insurance Research Dataset (NHIRD), published by the National Health Research Institute in Taiwan, covering the years 1996 to 2003. The dataset includes all claims data from Taiwan's National Health Insurance (NHI) program, which was implemented as a means of financing healthcare for all Taiwanese citizens. The NHI program currently has over 21 million enrollees, representing around 96% of the island's population, and is characterized by a single-payer payment system with unrestricted access to any mental healthcare provider of the patient's choice. Thus, the NHRID offers a unique opportunity to identify the risk of stroke development among young schizophrenia patients. Since the NHIRD consisted of de-identified secondary data released for public access for research purposes, the study was exempt from full review by the Internal Review Board (IRB).

2.2. Study sample

Our study design features a study cohort and a comparison cohort. The study cohort comprised all patients under 45 years old who were hospitalized for schizophrenia between January and December 1998 (any ICD-9-CM 295 code other than 295.7-schizoaffective disorder). In order to avoid the potential confounding factors of institutionalization and chronicity, those who had been hospitalized for schizophrenia or who received any psychiatric treatment for schizophrenia during the previous two-year period were excluded from the study cohort, as were patients previously diagnosed with stroke (ICD-9-CM codes 430–438). To ensure the validity of psychiatric diagnoses, all patients selected had at least two consensus schizophrenia diagnoses during the follow-up period after the index hospitalization.

The comparison cohort was chosen from among patients younger than 45 years old who were hospitalized for an appendectomy (ICD-OP code 47.0) between January and December 1998. The reason for the selection of appendectomy patients as the comparison group was that patients undergoing appendectomies were relatively indistinguishable from the general population.

There were no statistically significant differences found between the comparison population and the general population in Taiwan with regard to either gender ($p>0.05$) or age ($p>0.05$). Furthermore, the procedures involved in an appendectomy have no known long-term impact on brain functioning, and indeed, there has never been any study reporting any increased risk of schizophrenia among patients undergoing an appendectomy. Appendectomy patients were, however, excluded if they had ever been diagnosed with any major psychiatric disorder in the two years preceding appendectomy (ICD-9-CM codes 290, 294, 295, 296 or 297). Again, patients with a previous diagnosis of stroke were also excluded.

A total of 5001 patients suffered from schizophrenia and 18,754 patients underwent appendectomies during the study period. Since there is a significant difference in the mean age between schizophrenia and appendectomy

patients (31.1 years for schizophrenia and 24.1 years for appendectomies), we further refined our criteria for the comparison group by randomly selecting 10,002 appendectomy patients (two for every schizophrenia patient) matched with the study group in terms of age (<18, 18–24, 25–34 and ≥35 years). Tracking of each patient was subsequently undertaken, from their hospitalization in 1998 until the end of 2003, using administrative data to identify all patients who developed strokes. The data was also linked to mortality data in Taiwan to calculate the stroke-free survival time after hospitalization for a five-year period, with cases censored if individuals died from non-stroke causes during that time (440 patients had already died from non-stroke causes, comprising of 316 from the study cohort and 124 from the comparison cohort).

The regression modeling also adjusted for socio-demographic characteristic variables including gender, income-related insurance payment amount as a proxy for income (0, NT$1–NT15,840, NT15,841–NT25,000, ≥NT25,001), level of urbanization and the geographical location of the community in which the patient resided (Northern, Central, Eastern and Southern Taiwan). The reason for selecting NT$15,840 as the cutoff point was that this value is stipulated by the government as the minimum wage for full-time employees in Taiwan.

Prior studies have reported that the occurrence of stroke is associated with both geographical regions and levels of urbanization; these two variables are therefore also taken into account in the regression modeling. In accordance with the standards published by the Taiwanese National Health Research Institute, urbanization levels in Taiwan comprise seven strata, with level 1 referring to the 'most urbanized' communities and level 7 referring to the 'least urbanized' communities. However, given that there were only very small numbers of schizophrenia cases in levels 5, 6 and 7, these three levels were combined into one single group, which was thereafter referred to as level 5. Details on select comorbid medical disorders including hypertension, diabetes, hyperlipidemia and substance abuse were also extracted from the claims data at the time of the index discharge, essentially because these conditions may exacerbate the risk of stroke.

2.3. Statistical analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform the statistical analyses in this study, with descriptive analyses being carried out on all of the identified variables, including the frequency and percentage. Pearson χ^2 tests were used to examine the differences between the two cohorts, in terms of socio-demographic characteristics, select comorbid medical disorders, substance abuse and the risk of stroke development. The five-year stroke-free survival rate was then estimated under the Kaplan–Meier method, with the log-rank test being used to examine the differences

Table 1
Demographic characteristics and comorbid medical disorders of schizophrenia and appendectomy patient samples in Taiwan, 1998 (n=15,003)

Variable	Schizophrenia patients		Appendectomy patients		p value
	Total no.	%	Total no.	%	
Gender					<0.001
Male	2926	58.5	5071	50.7	
Female	2075	41.5	4931	49.3	
Age					0.995
<18	152	3.0	310	3.1	
18–24	931	18.6	1850	18.5	
25–34	2133	42.7	4281	42.8	
>34	1785	35.7	3561	35.6	
Hypertension					<0.001
Yes	55	1.1	70	0.7	
No	4946	98.9	9932	99.3	
Diabetes					<0.001
Yes	75	1.5	90	0.9	
No	4926	98.5	9912	99.1	
Hyperlipidemia					<0.001
Yes	27	0.5	30	0.3	
No	4974	99.5	9971	99.7	
Substance abuse					<0.001
Yes	71	1.6	32	0.3	
No	4930	98.6	9969	99.7	
Income-related insured amount					<0.001
0	911	18.2	3631	36.3	
NT–15,840	2591	51.8	1270	12.7	
NT5,841–25,000	1339	26.8	3201	32.0	
≥NT$25,001	160	3.2	1900	19.0	
Urbanization level					<0.001
1	5576	29.7	2441	24.4	
2	5036	26.9	2821	28.2	
3	3160	16.9	1640	16.4	
4	2343	12.5	1480	14.8	
5	2639	14.1	1620	16.2	
Geographical region					<0.001
Northern	2139	42.8	5021	50.2	
Central	1164	23.3	2110	21.1	
Southern	1473	29.5	2631	26.3	
Eastern	225	4.5	240	2.4	

between the two cohorts. Cox proportional hazard regressions were also carried out as a means of computing the adjusted five-year survival rate following adjustment for the abovementioned variables. Finally, hazard ratios (HR) are presented along with the 95% confidence intervals (95%CI), with a significance level of 0.05 having been adopted for this study.

3. Results

Of the total sample of 15,003 patients under the age of 45 years, 219 patients (1.46%) had developed strokes during the five-year follow-up period. The details of the distribution of the demographic characteristics, select comorbid medical disorders, and substance abuse for these two cohorts are provided in Table 1.

Table 2
Stroke development among schizophrenia and appendectomy patient samples in Taiwan during the five-year follow-up period

Variable	Stroke development								*p* value
	Schizophrenia patients				Appendectomy patients				
	Yes		No		Yes		No		
	N	%	*N*	%	*N*	%	*N*	%	
Gender									
Male	66	2.3	2860	97.7	56	1.1	5015	98.9	<0.001
Female	57	2.8	2018	97.3	40	0.8	4891	99.2	<0.001
Age									
<18	1	0.7	152	99.3	2	0.6	308	99.4	0.381
18–24	14	1.5	917	98.5	13	0.7	1837	99.3	0.017
25–34	44	2.1	2089	97.9	34	0.8	4247	99.2	<0.001
>34	64	3.6	1720	96.4	75	2.1	3486	97.9	<0.001
Income-related insured amount									
0	21	2.3	890	97.7	14	0.4	3617	99.6	<0.001
NT–15,840	69	2.7	2521	97.3	22	1.7	1248	98.3	0.014
NT5,841–25,000	32	2.4	1307	97.6	35	1.1	3166	98.9	<0.001
≥NT$25,001	1	0.6	160	99.4	21	1.1	1879	98.9	0.185
Urbanization level									
1	27	2.2	1192	97.8	22	0.9	2419	99.1	<0.001
2	32	2.3	1378	97.7	25	0.9	2796	99.1	<0.001
3	13	1.6	808	98.4	13	0.8	1627	99.2	0.038
4	15	2.0	736	98.0	22	1.5	1458	98.5	0.388
5	36	4.5	764	95.5	10	0.6	1610	99.4	<0.001
Geographical region									
Northern	50	2.3	2089	97.7	35	0.7	4986	99.3	<0.001
Central	41	3.5	1123	96.5	25	1.2	2085	98.8	<0.001
Southern	27	1.8	1446	98.2	26	1.0	2605	99.0	0.009
Eastern	5	2.2	220	97.8	4	1.8	236	98.2	0.678

Note: Total sample number=15,003.

Table 3
Crude hazard ratios of stroke development during the five-year follow-up period for schizophrenia and appendectomy patient samples in Taiwan

	Stroke development				Crude hazard ratio	95% CI
	Yes		No			
	N	%	*N*	%		
Schizophrenia patients						
Male	66	2.30	2860	97.30	2.123	1.544–2.923
Female	157	2.80	2108	97.30	4.078	2.857–5.727
Total	123	2.46	4878	97.54	2.721	2.142–3.517
Appendectomy patients						
Male	56	1.10	5015	98.90	1.000	–
Female	40	0.81	4891	99.19	1.000	–
Total	96	0.94	9906	99.06	1.000	–

Note: Total sample number=15,003.

The mean age of the sampled patients was 31.1 years. As compared to the appendectomy patients, the schizophrenia patients were more likely to be male, cormobid with hypertension, diabetes or hyperlipidemia, and residing in the less urbanized areas or in the southern part of Taiwan at the time of the index discharge (all $p<0.001$).

The distribution of stroke for the two cohorts during the five-year follow-up period, by demographic characteristics, is provided in Table 2. The Pearson χ^2 tests reveal that, as compared to the appendectomy patients, with the exception of those residing in eastern Taiwan, schizophrenia patients were more likely to develop stroke during the follow-up period in every segment, whether in terms of gender, age, income-related insured amount, urbanization level or geographical region ($p<0.001$).

The crude hazard ratios of stroke development for the two cohorts are presented in Table 3, which reveals that 2.46% of the schizophrenia patients and 0.94% of the appendectomy patients suffered from strokes between 1998 and 2003 ($p<0.001$).

For schizophrenia patients, the risk of stroke development during the follow-up period was 2.721 times (95% CI=2.142–3.517, $p<0.001$) that for appendectomy patients. Rather surprisingly, the risk of stroke development among female schizophrenia patients was significantly higher than that for female appendectomy patients, by a multiple of 4.078 (95% CI=2.857–5.727, $p<0.001$).

The log-rank test indicating that schizophrenia patients had significantly lower five-year survival rates ($p<0.001$). Details of the adjusted hazard ratios of

stroke development, by cohort, are provided in Table 4. As the table shows, following adjustment for the patients' gender, income, level of urbanization, geographical location and comorbid medical disorders, schizophrenia patients were found to be 2.02 times more likely to develop strokes during the follow-up period than their counterparts in the appendectomy comparison group (95% CI = 1.53–2.54, $p < 0.001$).

The adjusted hazard ratios of stroke development during the five-year follow-up period were 1.64 (95% CI = 1.24–2.43, $p < 0.001$) times more for male schizophrenia patients than those for male appendectomy patients and 2.87 (95% CI = 1.82–4.36, $p < 0.001$) times more for female schizophrenia patients than those for female appendectomy patients. Furthermore, as expected, patients complicated with hypertension (hazard ratios

Table 4
Adjusted hazard ratio of stroke development during the five-year follow-up period for schizophrenia and appendectomy patient samples in Taiwan

Variables	Stroke development					
	Total		Male		Female	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Cohort						
Schizophrenia	2.02	1.53–2.54	1.64	1.24–2.43	2.87	1.82–4.36
Appendectomy (reference group)	1.00	–	1.00	–	1.00	–
Gender						
Male	1.43	0.89–2.29	–	–	–	–
Female (reference group)	1.00	–	–	–	–	–
Hypertension						
Yes	10.72	6.95–17.82	10.66	5.98–18.76	13.98	6.34–30.71
No (reference group)	1.00	–	1.00	–	1.00	–
Diabetes						
Yes	3.97	2.23–7.14	4.01	1.86–8.58	4.05	1.54–10.62
No (reference group)	1.00	–	1.00	–	1.00	–
Hyperlipidemia						
Yes	2.31	0.94–6.25	3.56	1.24–9.10	2.36	0.92–5.38
No (reference group)	1.00	–	1.00	–	1.00	–
Substance abuse						
Yes	0.62	0.29–4.51	0.74	0.11–5.48	0.55	0.23–3.26
No (reference group)	1.00		1.00		1.00	
Income-related insured amount						
0 (reference group)	1.00	–	1.00	–	1.00	–
NT–15,840	1.67	1.32–2.61	1.38	0.78–2.46	2.36	1.34–4.16
NT5,841–25,000	1.25	0.96–1.99	0.93	0.52–1.68	2.17	1.25–3.76
≥NT$25,001	1.45	0.73–1.14	1.21	0.63–2.35	1.26	0.57–2.82
Urbanization level						
1 (reference group)	1.00	–	1.00	–	1.00	–
2	1.12	0.80–1.56	1.33	0.84–2.09	0.76	0.46–1.24
3	0.86	0.57–1.30	0.87	0.49–1.54	0.71	0.39–1.29
4	1.31	0.89–1.94	1.37	0.79–2.37	1.04	0.59–1.83
5	1.16	0.78–1.72	1.30	0.76–2.21	0.88	0.48–1.61
Geographic region						
Northern (reference group)	1.00	–	1.00	–	1.00	–
Central	1.64	1.21–2.22	1.64	1.08–2.48	1.80	1.14–2.85
Southern	0.99	0.73–1.35	1.06	0.70–1.59	1.03	0.63–1.67
Eastern	1.20	0.66–2.20	0.75	0.26–2.14	1.55	0.70–3.43

Note: Total sample number = 15,003.

ranging between 10.66 and 13.98) and diabetes (hazard ratios ranging between 3.97 and 4.05) had a greater likelihood of the development of a stroke.

4. Discussion

After adjusting for demographic characteristics, select comorbid medical disorders and substance abuse, the results of this study indicate that, as compared with the comparison group of appendectomy patients, young schizophrenia patients have a two-fold higher risk of developing stroke within 5 years of their hospitalization for acute exacerbation of schizophrenia. For schizophrenia patients, the risk of developing stroke was, rather surprisingly, much greater among females than males.

Curkendall et al. (2004) reported a 2.1 adjusted hazard ratio for stroke between schizophrenia patients and a comparison group. Given that their study selected patients from all age groups, the similarity with the figures presented in this study reveal an urgent need for medical care aimed at improved prevention, evaluation and treatment options for young schizophrenia patients. Furthermore, a recent study by Osborn et al. showed that there was a significant increase in the risk of death from stroke for patients over the age of 50 years who had severe mental illnesses, but no increased risk for mentally ill patients who were younger (Osborn et al., 2007). Although mortality rates may reflect both the occurrence of disease and its outcome, the increased risk of stroke mortality for older patients with severe mental illness could possibly indicate a higher morbidity rate for stroke during their earlier years. Stroke in young adults can be devastating for both the victims and their families. For schizophrenia patients who have strokes, the emotional, social, or physical sequelae after surviving a stroke could exacerbate their psychiatric condition and further compromise the quality of life for both the patients and their caregivers.

Unhealthy lifestyles including poor diet, a lack of exercise, smoking and obesity are considered to be major causes of the excess morbidity and mortality rates for schizophrenia patients (Brown et al., 2000). Indeed, schizophrenia patients have a reported tendency to make poor dietary choices, largely attributable to their social disadvantages and schizophrenic symptoms (McCreadie, 2003). Inappropriate dietary habits, namely a low intake of fruit and vegetables, together with a lack of exercise, may adversely affect the wellbeing of patients, which may predispose them to stroke in the long run.

Despite the lack of information about diet within our dataset, given that older patients and those who received psychiatric treatment over the previous 2 years were excluded from this study in order to avoid the confounding factors of institutionalization and chronicity, the increased risk of developing stroke is unlikely to be explained solely by the impact of unhealthy lifestyles. In fact, as compared with the lifestyle study of community-dwelling schizophrenia patients undertaken by McCreadie (2003), our study cohort had a much lower unemployment rate (18.2% versus 98.0%), making their lifestyles more similar to those of other individuals in their communities.

Cigarette smoking is frequently seen as an important risk factor for cardiovascular and cerebrovascular events among schizophrenia patients (Brown et al., 2000; Hennekens et al., 2005; Goff et al., 2005). However, a prior study in Taiwan demonstrated only a slight increase in the prevalence of tobacco use among schizophrenia inpatients, compared to the high smoking rate among the general population (Liao et al., 2002). Therefore, smoking may *not* be a major reason contributing to increased stroke rates found by our study among young, community-dwelling schizophrenia patients. Obesity—in particular the weight gain induced by the use of antipsychotics—has been seen as contributing significantly to the risk for numerous diseases, including insulin resistance, lipid abnormalities and hypertension (Newcomer et al., 2007), all of which can result in vascular events such as stroke.

The lack of general healthcare among schizophrenia patients, including recognition and treatment of rapidly developing health conditions, may place this patient population at greater risk for stroke; indeed, our prior study found that only a small proportion of schizophrenia patients with diabetes in Taiwan received appropriate medical care (Lin et al., 2007). Another recent study also indicated that inequalities remained in primary care for coronary heart disease for patients with serious mental illness, particularly in terms of identifying and treating higher cholesterol levels among schizophrenia patients (Hippisley-Cox et al., 2007). Although we did find higher comorbidity rates for hypertension, diabetes and hyperlipidemia among schizophrenia patients, the actual need for medical care for such conditions far exceeds the number of patients currently being treated.

The significantly higher risk of developing stroke among young female schizophrenia patients represents a significant departure from widely-held beliefs about the relationship between gender and stroke occurrence. Stroke incidence is reportedly higher in men than in women, and women are, on average, several years older than men at the time of their first stroke (Wyller, 1999). However, it has been found that in schizophrenia patients, obesity is more common among females than males (Homel et al., 2002). Young female schizophrenia

patients may exhibit disproportionate weight gain from the use of psychotropic agents, especially atypical antipsychotics. It is therefore suggested that a further large-scale clinical follow-up study should be initiated in order to clarify the mechanisms involved in the high risk of developing stroke among young female schizophrenia patients.

The fact that the sampled schizophrenia patients in this study had not taken any psychotropic agents in the two-year period prior to their recruitment suggests that adverse drug effects on the cerebrovascular system may develop in a relatively short period of time. The possibility of rapid development of cerebrovascular disease after starting psychotropic medications could be a cause of worry for both patients and clinicians alike.

By using a five-year baseline, starting from the first diagnosed episode of schizophrenia, we have probably excluded patients who have used such medications long term, Because the chronic and socially disruptive nature of the disease generally brings schizophrenia patients into frequent contact with medical professionals (especially true in Taiwan, where younger people are likely to have parents involved in such situations), we feel that by excluding those who saw a doctor in the preceding two-year period and those over age 45, it is very unlikely that the patients in our study had previously received treatment (i.e., medication), even if they had previous (probably untreated) episodes of the disease.

The findings of this study need to be interpreted within the context of three limitations. First of all, schizophrenia, stroke or any secondary diagnoses that are totally reliant upon administrative claims data may be less accurate than those undertaken in person through a standardized procedure. However, the NHI Bureau randomly samples a fixed percentage of claims from every hospital each year, so as to verify the diagnosis validity and the quality of care through chart review by an independent peer group. Any hospital with outlier charges or outlier patterns for any diagnosis group faces the risk of audit and subsequent heavy penalties by the NHI Bureau when discrepancies or overcharging are discovered. In order to ensure the validity of the schizophrenia diagnoses in this study, we ensured that all of the study cohort patients had at least two consensus schizophrenia diagnoses after the index hospitalization. Furthermore, virtually all hospitals in Taiwan capable of admitting stroke patients are equipped with CT or MRI scanners which can considerably increase the validity of stroke diagnosis.

Our second limitation is that some variables such as dietary habits, cigarette smoking and body mass index, which may contribute to stroke development, were not available in the dataset, which could compromise our findings. Thirdly, because the database starts in 1995, we cannot definitively identify and exclude the schizophrenia patients who were chronically disabled or even institutionalized before 1995. The NHIRD contains no information regarding the patient's duration of illness and number of episodes. Those variables may make certain contributions to the development of stroke.

However, we specifically selected younger schizophrenia patients who are less likely to have been institutionalized or have had the disease for an extended time for the study. This approach may result in problems of representativeness, but it minimizes some confounding factors. Though sampled patients were free from psychotropic agents for at least 2 years before their index admission, no information is available on their medication use before the two-year period.

The five-year baseline used in our study has one particular advantage; the association we have identified between schizophrenia and stroke suggests physicians should attend to this possibility starting from a patient's first known episode of the disease. Further studies therefore need to be initiated to verify whether schizophrenia patients are at an higher risk for stroke. The increased burden of stroke among young schizophrenia patients may elevate the importance of developing early intervention and prevention programs to reduce the morbidity and mortality from stroke. Our findings stress the urgent need for more active monitoring and treatment for schizophrenia patients of the well-recognized risk factors associated with stroke, including hypertension, diabetes and hyperlipidemia; furthermore, this may need to be undertaken at an earlier age in order to get the maximum possible benefit.

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Contributors

Author Herng-Ching Lin designed the study and wrote the draft. Authors Fei-Hsiu Hsiao and Hsin-Chien Lee managed the literature searches and analyses. Authors Senyeong Kao and Yi-Ting Hwang undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Conflict of interest

None.

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