BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044766
Article Type:	Original research
Date Submitted by the Author:	14-Sep-2020
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Keywords:	Stroke < NEUROLOGY, Schizophrenia & psychotic disorders < PSYCHIATRY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, MENTAL HEALTH

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Stroke Care and Case Fatality in People with and without Schizophrenia: A Retrospective Cohort Study

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Abstract word count: 296

Text word count: 2431

Tables: 4

Figures: 2

Supplemental tables: 1

Search terms: stroke, psychosis, mental illness, health services research, health disparities

ABSTRACT

Background: Schizophrenia is associated with an increased risk of death following stroke; however, the magnitude and underlying reasons for this are not well-understood.

Objective: To determine the association between schizophrenia and stroke case-fatality, adjusting for baseline characteristics, stroke severity, and processes of care.

Design: Retrospective cohort study used linked clinical and administrative databases.

Setting: All acute care institutions (N = 152) in the province of Ontario, Canada.

Participants: All patients (N = 52, 473, of whom 612 had schizophrenia) hospitalized with stroke between April 1, 2002 and March 31, 2013 and included in the Ontario Stroke Registry.

Exposure: Pre-stroke history of schizophrenia, identified using validated algorithms.

Main outcomes and measures: We compared processes of acute stroke care delivery in those with and without schizophrenia and used Cox proportional hazards models to examine the association between schizophrenia and mortality, adjusting for demographics, stroke severity, and processes of care.

Results: Compared to those without schizophrenia, people with schizophrenia were less likely to receive thrombolysis (10.1% vs. 13.4%), carotid imaging (66.3% vs. 74.0%), rehabilitation (36.6% vs. 46.6% among those with disability at discharge), or be treated with antihypertensive, lipid-lowering or anticoagulant therapies. After adjustment for age and other factors, schizophrenia was associated with death from any cause at one year [adjusted hazard ratio

(aHR) 1.34, 95% confidence interval (CI) 1.15 to 1.55]. This was mainly attributable to early deaths from stroke (aHR 1.48; 95% CI 1.20 to 1.81, with survival curves separating in the first 30 days), and the survival disadvantage was particularly marked in those aged over 70 years (one-year mortality 46.9% vs. 35.0%).

Conclusions: Schizophrenia is associated with increased stroke case fatality, which is not fully explained by stroke severity, measurable comorbid conditions, or processes of care. Future work should focus on understanding this mortality gap and on improving acute stroke and secondary preventive care in people with schizophrenia.

Strengths and limitations of this study:

1. Large, population-based sample with detailed clinical information on stroke characteristics and processes of care.
2. Complete follow-up for outcome events through administrative data.
3. Lack of information on some potential explanatory variables such as medication adherence and post-discharge care.

Introduction

Stroke is a leading cause of death and disability worldwide[1]. Schizophrenia is associated with an increased risk of stroke and other cardiovascular diseases, in part attributable to a higher prevalence of vascular risk factors including diabetes, obesity, and smoking[2-5]. Schizophrenia may also be associated with increased stroke case fatality, although the reasons for this are poorly understood[6]. Previous research shows that following myocardial infarction, people with schizophrenia are less likely than those without schizophrenia to receive recommended interventions and medications, and this may contribute to excess mortality[7-12]. It is not known whether these differences extend to stroke, and whether any differences contribute to the association between schizophrenia and stroke case fatality.

We used linked province-wide registry and administrative data to compare stroke presentation, processes of care, and case fatality after stroke in people with and without schizophrenia. We hypothesized that schizophrenia would be associated with stroke case fatality and that differences in baseline characteristics and processes of care would account for this.

Methods

Setting, data sources and study sample

Ontario is Canada's most populous province, with an estimated population of 13 million people at the time of this study[13]. All residents have coverage for hospital and physician services.

The Ontario Stroke Registry collects detailed clinical information on a simple random sample of all people with stroke or transient attack seen in the emergency department or admitted to any

acute-care hospital in the province[14]. This sampling minimizes the biases associated with data collection from selected facilities and/or patient groups[15]. Data collection is done by trained research personnel with the diagnosis of stroke confirmed by review of the chart and imaging results, and built-in data quality checks and programing ensure that there are no missing values. Validation by duplicate chart abstraction has shown excellent agreement for key variables[14].

Our study cohort consisted of all adult (age ≥ 18 years) patients hospitalized with acute stroke between April 1, 2002 and March 31, 2013 and included in the Ontario Stroke Registry. The registry provided detailed patient-level information on stroke presentation and severity, comorbid conditions, processes of care, and disability at discharge.

We linked registry data to population-based administrative databases using unique, encoded identifiers. To identify people with schizophrenia, we linked to the Canadian Institute for Health Information Discharge Abstract Database and the physician claims database. We defined schizophrenia in patients with any of 1) a primary diagnosis of schizophrenia or schizoaffective disorder during a general hospital admission [using International Classification of Diseases, 10th revision (ICD 10) codes F20 or F25], (2) a primary diagnosis of schizophrenia from a psychiatric hospital bed (DSM-IV – 295.x), or (3) three outpatient visits with a diagnosis of schizophrenia (ICD9 – 295) from outpatient physician billings within a 3-year period. Each of these criteria were applied from 1988 onward. This diagnostic algorithm has a sensitivity of 97% and a specificity of 65% for the diagnosis of schizophrenia[16].

We used the 2006 Canada Census to provide information on median neighbourhood income and the Discharge Abstract Database to identify hospitalizations for recurrent stroke or transient ischemic attack, using validated ICD-10 codes I60, I61, I63, I64, H34.0, H34.1 and G45 (excluding G45.4)[17]. We used the Ontario Registered Persons Database to identify deaths, with cause of death obtained from the provincial register that assigns cause of death based on death certificates, and with stroke deaths identified as those with ICD-10 codes I60-I69 as the primary cause of death.

Outcomes

The primary outcome was all-cause mortality within one year of stroke. Secondary outcomes were all-cause mortality at 30 days, death due to stroke at one year, disability at discharge [defined as a modified Rankin Scale (mRS) score of 3-5], and recurrent stroke hospitalization within 30 days and 1 year of discharge from the index event. We also evaluated the following processes of care: arrival by ambulance, time from "last seen normal" to hospital arrival, neuroimaging, dysphagia screening, delivery of care on a dedicated stroke unit, admission to intensive care unit (ICU), tracheostomy, placement of permanent feeding tube, a palliative approach to care, and discharge to inpatient rehabilitation.

In the subgroup of patients with ischemic stroke, we also evaluated use of carotid imaging, thrombolysis, door-to-needle time in those receiving thrombolysis and prescription of antithrombotic, antihypertensive, and lipid-lowering therapy at discharge. Among those who did not receive thrombolysis, we explored reasons why it was not given, categorized as arrival too late, contraindications, symptoms severity, delays in decision-making, other physician

decision, or no reason documented. We did not evaluate use of endovascular thrombectomy, which was not in widespread use during the study timeframe.

Analysis

We compared baseline characteristics and processes of care for people with stroke with and without schizophrenia, using standardized differences of the mean, which, unlike traditional hypothesis testing with P values, are not sensitive to large sample sizes[18]. We used a Cox proportional hazard model to estimate the effect of schizophrenia on the hazard of death. We then sequentially introduced covariates into the model as follows: (1) demographics (age, sex); (2) socioeconomic factors (neighbourhood income, rural residence); (3) clinical presentation (stroke type and severity); (4) comorbid conditions (smoking, diabetes, hyperlipidemia, hypertension); (5) processes of care (brain imaging, stroke unit care); and (6) life-sustaining interventions (ICU admission, tracheostomy, permanent feeding tube). We repeated these models in the subgroup with ischemic stroke, with the addition of the following covariates: (1) thrombolysis; (2) lipid-lowering therapy; (3) antihypertensive medications; and (4) antithrombotic therapy. We then repeated these analyses for the outcome of death due to stroke, with cumulative incidence functions used to estimate the incidence of death due to stroke over time in people with and without schizophrenia, with death from other causes treated as a competing risk.

ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of data in this project

was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported.

Results

We studied 52,473 patients hospitalized with acute stroke, of whom 612 (1.2%) had schizophrenia. Compared to those without schizophrenia, people with schizophrenia were younger at the time of stroke (median age 66 vs. 74 years), less likely to be independent prior to stroke (44.9% vs. 66.7%), and more likely to reside in long-term care facility (19.3% vs. 5.1%) or live in a low-income neighbourhood (39.2% vs. 22.9%) (Table 1). Those with schizophrenia were also less likely to have a documented pre-stroke history of hypertension (58.3% vs. 63.7%), hyperlipidemia (30.2% vs. 35.0%), atrial fibrillation (8.8% vs. 16.8%), coronary artery disease (17.3% vs. 21.6%), or cancer (4.7% vs. 7.8%), but more likely to have diabetes (31.0% vs 23.7%), cognitive impairment (17.6% vs 8.7%) or to smoke cigarettes (28.3% vs. 16.5%) [standardized difference (std. diff.) $\geq$ 0.10 for all comparisons; Table 1]. Stroke type was similar in those with and without schizophrenia, but those with schizophrenia were less likely to present with mild strokes (54.7% vs. 60.9%).

People with schizophrenia were more likely to arrive by ambulance (79.9% vs. 72.2%) but had a longer median time from symptom onset to hospital arrival (7.7 vs. 5.8 hours). Those with schizophrenia were also more likely to be screened for dysphagia (59.0% vs. 54.0%), but there were no significant differences in the use of stroke unit care, intensive care unit admission, or palliative care (Table 2).

In the subgroup with ischemic stroke, people with schizophrenia were less likely to receive thrombolysis (10.1% vs. 13.4%), carotid imaging (66.3% vs. 74.0%), antihypertensive therapy (65.8% vs. 74.2%), lipid lowering therapy (62.4% vs. 68.0%) and anticoagulation for atrial fibrillation (59.7% vs. 71.7%) (std. diff $\geq$ 0.10 for all comparisons; Table 2). The reasons for not using thrombolysis were similar between groups.

We found no differences in length of stay or death or recurrent stroke/TIA hospitalization in those with and without schizophrenia (Table 3). However, people with schizophrenia were more likely to be disabled at discharge (mRS score of 3 to 5, 54.3% vs. 46.9%) yet less likely to be discharged to inpatient rehabilitation facilities (36.6% vs. 46.6% in the disabled subgroup) (Table 3).

Crude all-cause mortality was similar in those with and without schizophrenia at 30 days (19.3% vs. 16.6%) and one year (28.1% vs. 26.8%) (Table 3). However, after adjustment for age, sex, area of residence, comorbid conditions, and processes of care, schizophrenia was associated with an increased one-year hazard of both all-cause mortality [adjusted hazard ratio (aHR) 1.34; 95% confidence interval (CI) 1.15 to 1.55; c-statistic 0.82] and mortality due to stroke (aHR 1.48; 95% CI 1.20 to 1.81), with survival curves separating in the first month after the index stroke (Table 4, Figure 1; fully adjusted models shown in Supplemental Table). There was an interaction between age and schizophrenia, with the hazard of death associated with schizophrenia mainly seen in those aged 70 years and older (Figure 2). In the subgroup aged over 70 years, people with schizophrenia had higher all-cause mortality at 30 days (31.1% vs.

20.9%; std. diff. 0.24) and one year (46.9% vs. 35.0%; std. diff 0.24) with the majority of deaths due to stroke rather than other causes (Table 3).

Discussion

In this population-based cohort study of people hospitalized with acute stroke, we found that while many processes of acute stroke care were similar between groups, schizophrenia was associated with delays in presentation and lower use of thrombolysis, vascular imaging, rehabilitation, and medications for secondary prevention. Schizophrenia was also associated with a 34% increase in the hazard of one-year post-stroke mortality, even after adjustment for age, sex, stroke severity, comorbid conditions and processes of care, and this appeared to be mainly attributable to early deaths due to stroke in older patients.

Our findings of a younger age at stroke presentation and baseline differences in the prevalence of vascular risk factors in those with and without schizophrenia are consistent with previous studies of cardiovascular disease and risk factors in people with severe mental illness[2,3,9,19,20]. Schizophrenia is associated with an increased prevalence of smoking, diabetes, obesity, and hyperlipidemia, as well as use of antipsychotic medications that increase the risk of metabolic syndrome[21,22]. Screening and management of these conditions have been promoted for the primary prevention of cardiovascular disease in people with schizophrenia, especially those on second generation antipsychotic agents; however, screening rates remain suboptimal in many populations[23-25], as do efforts to manage these risk factors among individuals with schizophrenia[26,27]. We cannot determine whether the lower prevalence of hypertension, hyperlipidemia, atrial fibrillation and cardiovascular disease among people with schizophrenia

in our cohort is due to a younger age at presentation or under-recognition of these conditions due to a lack of screening and preventive care.

It warrants mention that the prevalence of schizophrenia in our stroke cohort (1.2%) was similar to that in the general population, despite the increased risk of stroke associated with schizophrenia[6]. Our finding that people with schizophrenia were less likely than those without to present with minor strokes suggests that there may be differences in care-seeking behavior or challenges in making a diagnosis of stroke in people with less obvious stroke symptoms and concomitant schizophrenia, and that this group with minor strokes may be under-represented in our cohort. If true, this would represent a missed opportunity for care in people with schizophrenia and stroke, as minor strokes can be associated with disability, and secondary preventive care can prevent more major disabling strokes in the future[28,29].

Our findings of lower use of thrombolysis, rehabilitation, carotid imaging and medications for secondary stroke prevention are consistent with previous studies where schizophrenia has been associated with lower use of various interventions after stroke[30-33] and myocardial infarction[7,8,11]. A better understanding of the reasons behind these differences in care will be important to ensuring that people with schizophrenia have equal opportunities to receive appropriate treatment for cardiovascular disease.

We found that schizophrenia was associated with a striking 34% increase in the adjusted hazard of all-cause mortality at one year and a 48% increase in the hazard of stroke mortality, with survival curves separating in the first month after stroke. Those with schizophrenia had greater stroke severity, the most important driver of early case fatality, compared to those without

schizophrenia; however, the mortality difference persisted after adjustment for stroke severity. A similar association between schizophrenia and case fatality after myocardial infarction appears to be in part explained by differences in revascularization and other processes of care,[7-9,11,12,34-36] however, the observed association between schizophrenia and stroke case fatality in our study persisted after adjustment for processes of care, comorbid conditions, and area of residence. Of note, the survival disadvantage associated with schizophrenia was primarily seen in the older age groups, suggesting that this population requires focused study to understand the reasons for increased mortality and to identify potential interventions.

Some limitations of our study warrant emphasis. We did not have information on the severity or duration of schizophrenia, which would be helpful for identifying subgroups of people with schizophrenia at particularly high risk for adverse outcomes. We did not study exposure to antipsychotic medications, as this information was not available for our entire study cohort. This is an important limitation because antipsychotic use, particularly second-generation antipsychotics, are associated with a 2-fold increased risk of stroke among individuals with schizophrenia[37] . Our data sources did not provide information regarding the severity or control of risk factors such as diabetes or hypertension, on other vascular risk factors such as obesity and physical activity, or on factors such as medication adherence or post-discharge care. We only included people hospitalized with stroke, and thus we do not know if the higher observed stroke severity in people with schizophrenia was due to differences in care-seeking behaviour, with people with schizophrenia and minor stroke symptoms less likely to present to hospital than those without schizophrenia. Finally, our study was conducted in a province with universal access to physician and hospital services and may not be generalizable to other settings.

Despite these limitations, our large, population-based sample with detailed clinical information and complete follow-up through administrative data is likely to provide valid results on the risks and contributors to death after stroke in people with and without schizophrenia.

In summary, we found that schizophrenia is associated with deficiencies in some aspects of post-stroke care, as well as a substantial increase in stroke case fatality which is not fully explained by differences in baseline factors or processes of care. Future work should focus on collaborative efforts among psychiatrists, clinicians with expertise in cardiovascular disease, patients and other stakeholders to understand the reasons for these differences and to develop interventions to improve cardiovascular care and outcomes in people with schizophrenia and other psychotic disorders.

Acknowledgements: This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI. Parts of this report are based on Ontario Registrar General (ORG) Information on deaths, the original source of which is ServiceOntario. The views expressed therein are those of the authors and do not necessarily reflect those of ORG or Ministry of Government Services. Moira Kapral is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation of Canada and holds the Lillian Love Chair in Women's Health from the University Health Network/University of Toronto.

Funding: This study was funded by a grant-in-aid from the Heart and Stroke Foundation of Canada (HSFC G-17-0018192).

Disclosures: None.

Author contributions: MKK and KAS conceived the study and MKK drafted the manuscript. JF performed the statistical analyses. All authors contributed to the study design, interpretation of results, and revisions to the manuscript.

Patient and public involvement and dissemination plan

Patients and the public were not involved in the design or conduct of this study. Findings will be disseminated to patient organizations.

Data availability

The dataset from this study is held securely in coded form at ICES (formerly known as the Institute for Clinical Evaluative Sciences). While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Table 1: Baseline characteristics of people with stroke, with and without schizophrenia

	Schizophrenia N = 612	No schizophrenia N = 51,861	Std. diff
Age, median – years (IQR)	66 (56-77)	74 (62-82)	0.45
Female – n (%)	323 (52.8)	25552 (49.3)	0.07
Independent prior to admission – n (%)	275 (44.9)	34604 (66.7)	0.45
Long-term care – n (%)	118 (19.3)	2632 (5.1)	0.45
Lowest neighbourhood income quintile – n (%)	240 (39.2)	11860 (22.9)	0.36
Rural residence – n (%)	45 (7.4)	6599 (12.7)	0.18
Hypertension – n (%)	357 (58.3)	33051 (63.7)	0.11
Hyperlipidemia – n (%)	185 (30.2)	18129 (35.0)	0.10
Diabetes – n (%)	190 (31.0)	12304 (23.7)	0.16
Atrial fibrillation – n (%)	54 (8.8)	8714 (16.8)	0.24
Coronary artery disease – n (%)	106 (17.3)	11211 (21.6)	0.11
Cancer – n (%)	29 (4.7)	4035 (7.8)	0.13
Dementia/cognitive impairment – n (%)	108 (17.6)	4502 (8.7)	0.27
Current smoking – n (%)	173 (28.3)	8563 (16.5)	0.28
Stroke type			
Ischemic – n (%)	496 (81.0)	40734 (78.5)	0.06
Hemorrhagic – n (%)	116 (19.0)	11127 (21.5)	0.06
Stroke severity			
Mild (CNS > 8) – n (%)	335 (54.7)	31605 (60.9)	0.13
Moderate (CNS 4-8) – n (%)	128 (20.9)	8746 (16.9)	0.10
Severe (CSN < 4) – n (%)	149 (24.3)	11510 (22.2)	0.05

Std. diff = standardized difference of the mean, where values ≥ 0.10 are considered to represent a meaningful difference; IQR = interquartile range; CNS = Canadian Neurological Scale, where lower scores indicate more severe strokes.

Table 2: Presentation and processes of care in people with acute stroke with and without schizophrenia

	Schizophrenia N = 612	No schizophrenia N = 51,861	Std. diff
Arrival by ambulance – n (%)	489 (79.9)	37424 (72.2)	0.18
Time from symptom onset to ED arrival, median – hours (IQR)	7.7 (1.8-22.2)	5.8 (1.5-20.0)	0.11
Dysphagia screening – n (%)	361 (59.0)	28022 (54.0)	0.10
Stroke unit care – n (%)	281 (45.9)	23717 (45.7)	0.004
Intensive care unit admission – n (%)	126 (20.6)	11499 (22.2)	0.04
Palliative approach to care – n (%)	102 (16.7)	7398 (14.3)	0.07
Subgroup with ischemic stroke – N	***496***	***40734***	
Carotid imaging – n (%)	329 (66.3)	30157 (74.0)	0.17
Thrombolysis given -n (%)	50 (10.1)	5477 (13.4)	0.10
Reason thrombolysis not given - %			
Arrival too late	51.6	52.1	0.01
Contraindication	10.5	10.0	0.02
Symptoms too mild	21.3	28.5	0.17
Symptoms too severe	5.4	4.4	0.05
Other physician decision	11.0	8.7	0.08
Delayed decision	2.2	3.1	0.05
No reason documented	10.3	8.4	0.07
Subgroup with ischemic stroke alive at discharge – N	***433***	***36331***	
Antihypertensive therapy prescribed – n (%)	285 (65.8)	26966 (74.2)	0.18
Lipid-lowering therapy prescribed – n (%)	270 (62.4)	24690 (68.0)	0.12
Antiplatelet therapy – n (%)	344 (79.4)	28119 (77.4)	0.05
Anticoagulation (in subgroup with atrial fibrillation) – n/N (%)	40/67 (59.7)	6430/8971 (71.7)	0.25

Std. diff = standardized difference of the mean, where values $\geq$ 0.10 are considered to represent a meaningful difference; ED = emergency department; IQR = interquartile range;

Table 3: Outcomes after acute stroke in people with and without schizophrenia

	Schizophrenia N = 612	No schizophrenia N = 51,861	Std. diff
Median length of stay – days (IQR)	7 (3 – 15)	7 (3- 14)	0.06
Disabled at discharge (mRS 3 to 5) – n (%)	325 (54.3)	23856 (46.9)	0.15
In-hospital death – n (%)	95 (15.9)	7532 (14.8)	0.03
Mortality at 30 days – n (%)			
All-cause	118 (19.3)	8602 (16.6)	0.07
Due to stroke	79 (12.9)	5288 (10.2)	0.08
Non-stroke CV disease	23 (3.8)	1987 (3.8)	0.00
Other	16 (2.6)	1327 (2.6)	0.00
Mortality at 1 year – n (%)			
All-cause	172 (28.1)	13894 (26.8)	0.03
Due to stroke	93 (15.2)	6893 (13.3)	0.05
Non-stroke CV disease	41 (6.7)	3340 (6.4)	0.01
Other	38 (6.2)	3661 (7.1)	0.03
Subgroup aged ≥ 70 years - N	***228***	***30294***	
Mortality at 30 days – n (%)			
All-cause	71 (31.1)	6322 (20.9)	0.24
Due to stroke	46 (20.2)	3856 (12.7)	0.20
Non-stroke CV disease	17 (7.5)	1565 (5.2)	0.09
Other	8 (3.5)	901 (3.0)	0.03
Mortality at 1 year – n (%)			
All-cause	107 (46.9)	10604 (35.0)	0.24
Due to stroke	56 (24.6)	5196 (17.2)	0.18
Non-stroke CV disease	30 (13.2)	2725 (9.0)	0.13
Other	21 (9.2)	2683 (8.9)	0.01
Subgroup alive at discharge – N	***517***	***44330***	
Discharge to rehabilitation – n (%)	137 (26.5)	12966 (29.2)	0.17
If mRS 0 to 2 – n/N (%)	15/178 (8.4)	1658/19440 (8.5)	0.004
If mRS 3 to 5 – n/N (%)	119/325 (36.6)	11113/23856 (46.6)	0.20
Recurrent stroke/TIA within 30 days	15 (2.9)	1192 (2.7)	0.01
Recurrent stroke/TIA within 1 year	34 (6.7)	3096 (7.1)	0.02

Std. diff = standardized difference of the mean, where values > 0.10 are considered to represent a meaningful difference; IQR = interquartile range; mRS = modified Rankin Scale score, where higher scores indicate more disability; TIA = transient ischemic attack

Table 4: The effect of sequential risk adjustment on the hazard of one-year stroke case fatality associated with schizophrenia

Adjustment	All-cause mortality HR (95% CI)	Death due to stroke HR (95% CI)	Non-stroke death HR (95% CI)
-	1.08 (0.93 to 1.25)	1.16 (0.94 to 1.42)	0.98 (0.78 to 1.22)
Age and sex	1.39 (1.19 to 1.61)	1.45 (1.18 to 1.79)	1.31 (1.05 to 1.63)
Age and sex + income quintile, rural residence	1.38 (1.19 to 1.60)	1.46 (1.19 to 1.80)	1.28 (1.03 to 1.60)
Age and sex + income quintile and rural residence + stroke type and stroke severity	1.31 (1.13 to 1.52)	1.39 (1.14 to 1.71)	1.21 (0.97 to 1.52)
Age and sex + income quintile and rural residence + stroke type and stroke severity + smoking, diabetes, hyperlipidemia, hypertension	1.28 (1.11 to 1.49)	1.38 (1.12 to 1.69)	1.18 (0.95 to 1.48)
Age and sex + income quintile and rural residence + stroke type and stroke severity + smoking, diabetes, hyperlipidemia, hypertension + brain imaging within one hour of arrival, care on stroke unit	1.32 (1.14 to 1.54)	1.44 (1.18 to 1.77)	1.19 (0.96 to 1.50)
Age and sex + income quintile and rural residence + stroke type and stroke severity + smoking, diabetes, hyperlipidemia, hypertension + brain imaging within one hour of arrival, care on stroke unit + intensive care unit admission, tracheostomy, feeding tube	1.34 (1.15 to 1.55)	1.48 (1.20 to 1.81)	1.20 (0.96 to 1.50)

HR = hazard ratio for schizophrenia (N = 612) vs. no schizophrenia (N = 51,861); CI = confidence interval. Hazard of death due to stroke accounts for the competing risk of death from other causes.

Figure 1a: Cumulative incidence of death due to stroke in people with and without schizophrenia

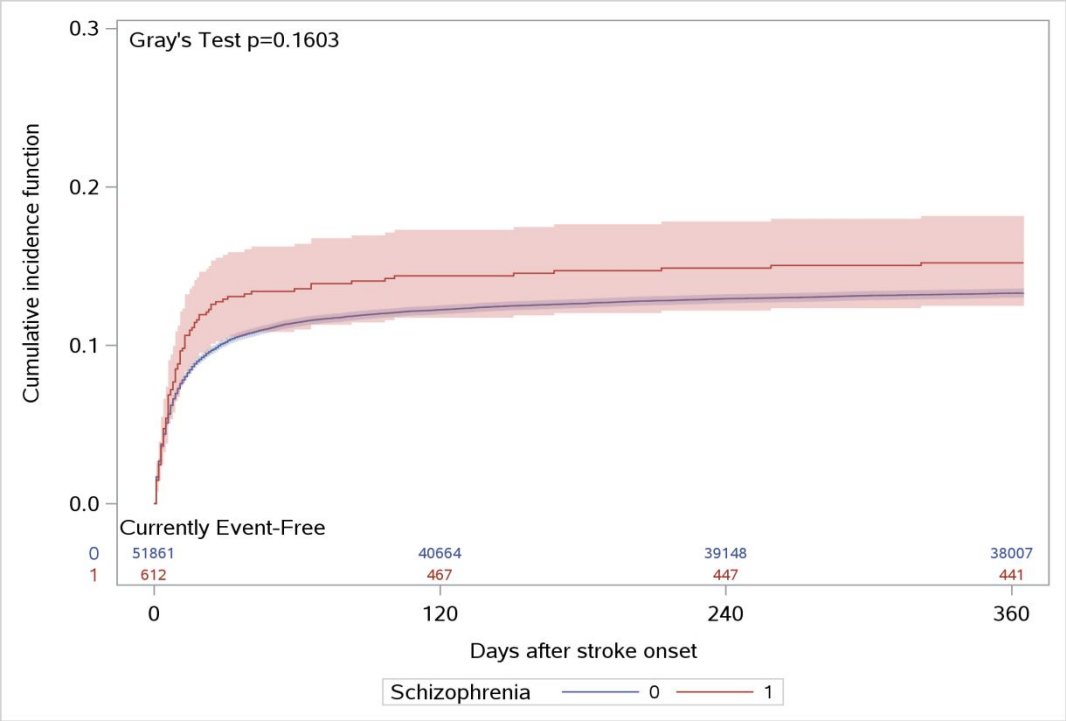


Figure 1b: Cumulative incidence of non-stroke death in people with and without schizophrenia

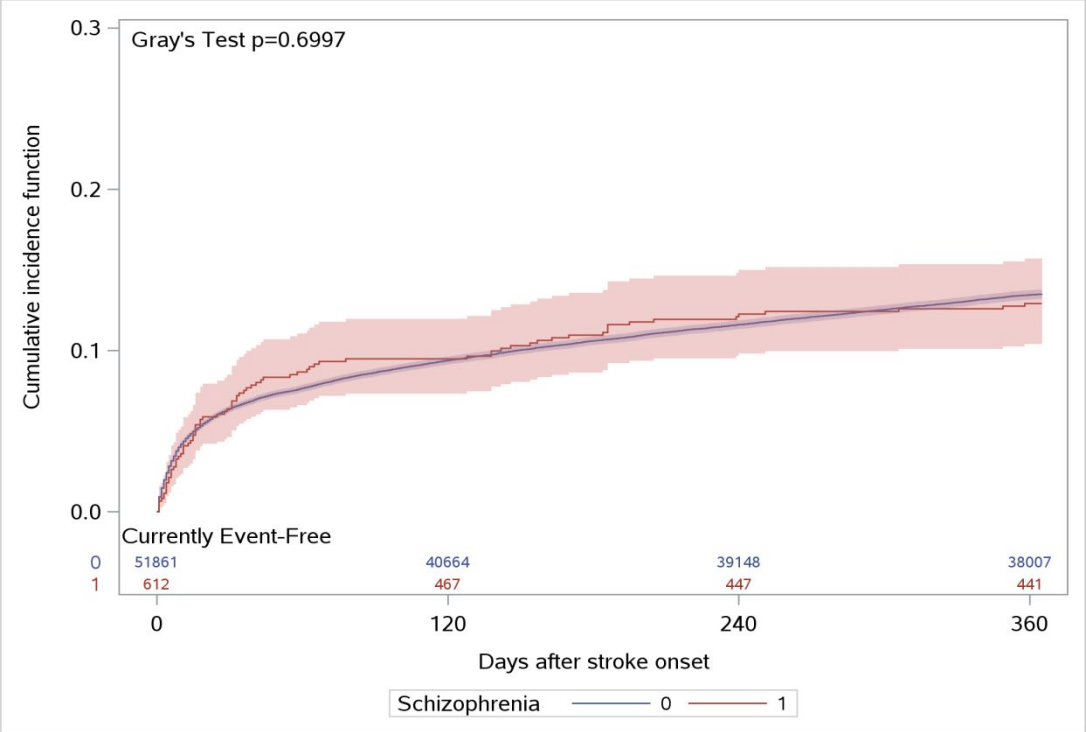
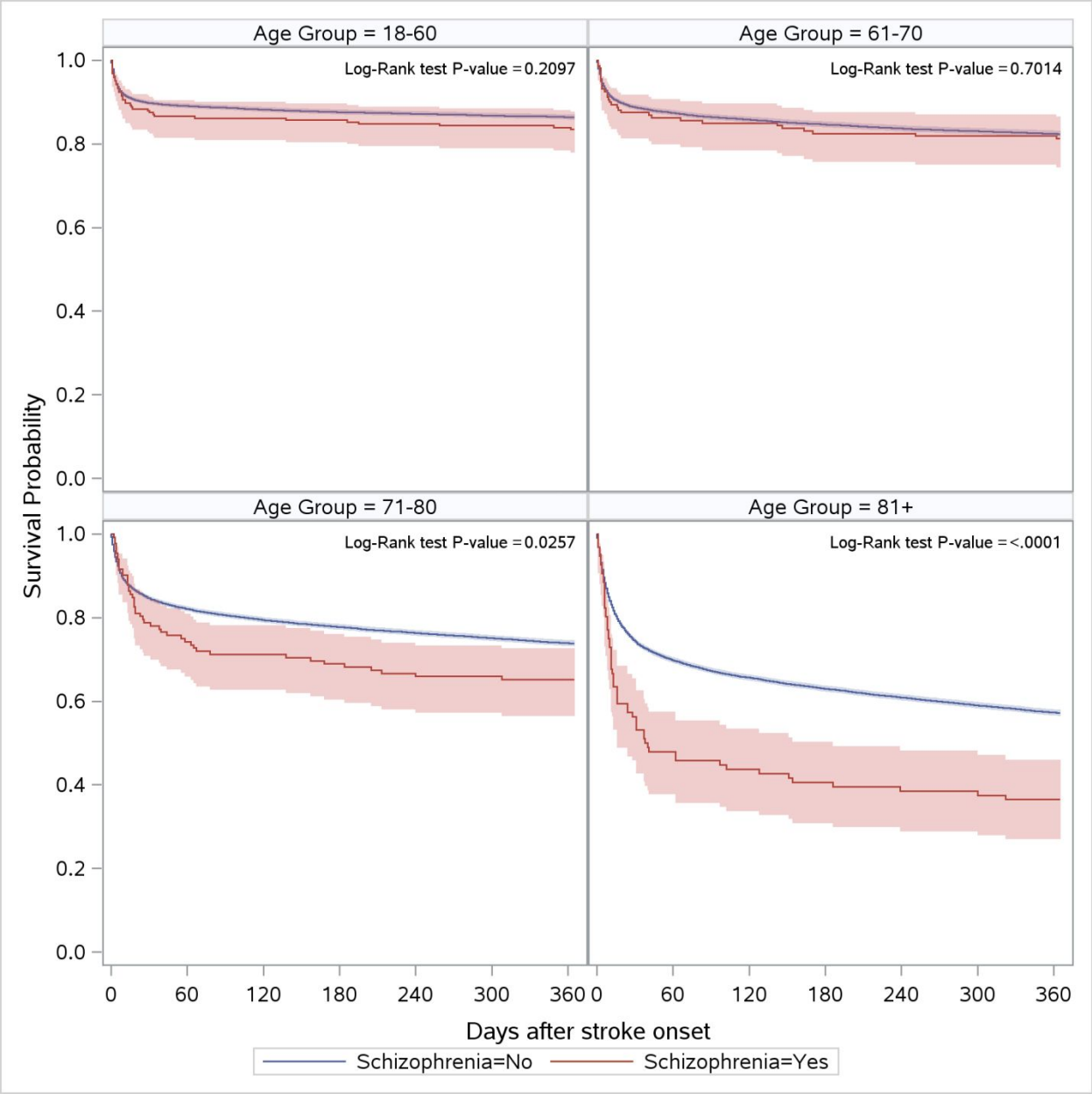


Figure 2: Survival after stroke in people with and without schizophrenia, by age group



Supplemental Table: Fully adjusted models for one-year mortality after stroke

	All-cause mortality HR (95% CI)	Death from stroke HR (95% CI)	Non-stroke death HR (95% CI)
Schizophrenia	1.34 (1.15 to 1.55)	1.48 (1.20 to 1.81)	1.20 (0.96 to 1.50)
Male sex (vs female)	1.09 (1.06 to 1.13)	1.06 (1.01 to 1.12)	1.11 (1.06 to 1.16)
Age group			
≤ 60	Reference	Reference	Reference
61-70	1.66 (1.55 to 1.78)	1.55 (1.41 to 1.71)	1.83 (1.66 to 2.02)
71-80	2.75 (2.58 to 2.92)	2.55 (2.34 to 2.78)	3.01 (2.75 to 3.30)
80+	5.00 (4.70 to 5.31)	4.85 (4.46 to 5.28)	5.34 (4.88 to 5.84)
Income quintile			
1 (lowest)	Reference	Reference	Reference
2	0.98 (0.93 to 1.03)	1.01 (0.94 to 1.08)	0.95 (0.89 to 1.02)
3	0.97 (0.92 to 1.02)	0.99 (0.92 to 1.06)	0.96 (0.90 to 1.03)
4	0.98 (0.93 to 1.03)	1.00 (0.93 to 1.08)	0.96 (0.90 to 1.04)
5 (highest)	0.94 (0.89 to 0.99)	1.03 (0.95 to 1.10)	0.86 (0.80 to 0.93)
Residence			
Large urban	Reference	Reference	Reference
Medium urban	1.02 (0.96 to 1.08)	1.10 (1.01 to 1.20)	0.95 (0.87 to 1.04)
Rural or small town	1.10 (1.05 to 1.16)	1.16 (1.08 to 1.25)	1.04 (0.97 to 1.12)
Stroke severity			
Severe	Reference	Reference	Reference
Moderate	0.48 (0.46 to 0.50)	0.45 (0.42 to 0.48)	0.52 (0.48 to 0.55)
Mild	0.18 (0.18 to 0.19)	0.13 (0.12 to 0.13)	0.25 (0.23 to 0.26)
Stroke type			
Ischemic	Reference	Reference	Reference
Hemorrhagic	1.74 (1.67 to 1.82)	2.19 (2.07 to 2.31)	1.33 (1.25 to 1.42)
Smoking	1.02 (0.96 to 1.08)	1.02 (0.94 to 1.11)	1.01 (0.94 to 1.09)
Diabetes	1.28 (1.23 to 1.33)	1.08 (1.02 to 1.15)	1.47 (1.39 to 1.55)
Hyperlipidemia	0.86 (0.82 to 0.89)	0.8 (0.79 to 0.88)	0.88 (0.84 to 0.93)
Hypertension	1.10 (1.06 to 1.15)	1.17 (1.11 to 1.24)	1.04 (0.98 to 1.10)
Neuroimaging within 1 hour	1.27 (1.23 to 1.32)	1.43 (1.37 to 1.51)	1.11 (1.06 to 1.17)
Stroke unit care	0.63 (0.61 to 0.66)	0.60 (0.57 to 0.63)	0.68 (0.65 to 0.72)
Intensive care unit admission	1.18 (1.13 to 1.22)	1.26 (1.20 to 1.34)	1.09 (1.02 to 1.16)
Tracheostomy	0.72 (0.63 to 0.83)	0.72 (0.60 to 0.86)	0.75 (0.61 to 0.92)
Feeding tube	0.82 (0.76 to 0.88)	0.74 (0.67 to 0.81)	0.93 (0.84 to 1.03)

C-statistic = 0.82 for the model of all-cause mortality

STROBE checklist of items that should be included in reports of observational studies

Article: Stroke care and outcomes in people with and without schizophrenia: a retrospective cohort study

Author: Kapral, Moira K.

	Item No	Recommendation	Location in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract, p. 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, p. 3
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Background section, p. 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Background, p.6
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, pp. 6-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, pp.6-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods (data sources and patient sample), pp. 6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, p. 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pp. 6-8
Bias	9	Describe any efforts to address potential sources of bias	1. Population-based patient sample

STROBE Checklist

			2. Complete follow up using administrative data 3. Multivariable analyses
Study size	10	Explain how the study size was arrived at	We included the entire sample of stroke patients from the study time frame.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	See methods section (statistical analysis), pp. 8-9.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	See methods section (statistical analysis), pp.8-9.
		(*b*) Describe any methods used to examine subgroups and interactions	See methods section (statistical analysis), pp.8-9.
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a. Follow up was done using administrative data
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, p. 10
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results, p.10 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results, pp. 11-12 and Tables 2-4 and Figure

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, pp. 11-12 and Tables 2-4 and Figure
		(*b*) Report category boundaries when continuous variables were categorized	Results, pp. 11-12 and Tables 2-4 and Figure
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, pp. 12-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, pp. 15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, pp. 12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, p.15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Study funding section, p. 2

BMJ Open

Stroke Care and Case Fatality in People with and without Schizophrenia: A Retrospective Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044766.R1
Article Type:	Original research
Date Submitted by the Author:	20-Dec-2020
Complete List of Authors:	Kapral, MK; University of Toronto, Medicine Kurdyak, Paul; Centre for Addiction and Mental Health, Casaubon, Leanne; Toronto Western Hospital, Fang, Jiming; ICES, Porter, Joan; Institute for Clinical Evaluative Sciences Sheehan, Kathleen; University of Toronto, Medicine
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Health services research, Mental health, Cardiovascular medicine
Keywords:	Stroke < NEUROLOGY, Schizophrenia & psychotic disorders < PSYCHIATRY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, MENTAL HEALTH

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Stroke Care and Case Fatality in People with and without Schizophrenia: A Retrospective Cohort Study

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Abstract word count: 300

Text word count: 2637

Tables: 4

Figures: 2

Supplemental tables: 1

Supplemental figures: 1

Search terms: stroke, psychosis, mental illness, health services research, health disparities

ABSTRACT

Background: Schizophrenia is associated with an increased risk of death following stroke; however, the magnitude and underlying reasons for this are not well-understood.

Objective: To determine the association between schizophrenia and stroke case-fatality, adjusting for baseline characteristics, stroke severity, and processes of care.

Design: Retrospective cohort study used linked clinical and administrative databases.

Setting: All acute care institutions (N = 152) in the province of Ontario, Canada.

Participants: All patients (N = 52,473) hospitalized with stroke between April 1, 2002 and March 31, 2013 and included in the Ontario Stroke Registry. Those with schizophrenia (N=612) were identified using validated algorithms.

Main outcomes and measures: We compared acute stroke care in those with and without schizophrenia and used Cox proportional hazards models to examine the association between schizophrenia and mortality, adjusting for demographics, comorbidity, stroke severity, and processes of care.

Results: Compared to those without schizophrenia, people with schizophrenia were less likely to receive thrombolysis (10.1% vs. 13.4%), carotid imaging (66.3% vs. 74.0%), rehabilitation (36.6% vs. 46.6% among those with disability at discharge), or be treated with antihypertensive, lipid-lowering or anticoagulant therapies. After adjustment for age and other factors,

schizophrenia was associated with death from any cause at one year [adjusted hazard ratio (aHR) 1.33, 95% confidence interval (CI) 1.14 to 1.54]. This was mainly attributable to early deaths from stroke (aHR 1.47; 95% CI 1.20 to 1.80, with survival curves separating in the first 30 days), and the survival disadvantage was particularly marked in those aged over 70 years (one-year mortality 46.9% vs. 35.0%).

Conclusions: Schizophrenia is associated with increased stroke case fatality, which is not fully explained by stroke severity, measurable comorbid conditions, or processes of care. Future work should focus on understanding this mortality gap and on improving acute stroke and secondary preventive care in people with schizophrenia.

Strengths and limitations of this study:

1. Large, population-based sample with detailed clinical information on stroke characteristics and processes of care.
2. Complete follow-up for outcome events through administrative data.
3. Lack of information on some potential explanatory variables such as medication adherence and post-discharge care.

Introduction

Stroke is a leading cause of death and disability worldwide[1]. Schizophrenia and other serious mental illnesses are associated with an increased risk of stroke,other cardiovascular diseases, and cardiovascular mortality[2-4]. This appears to be in part attributable to a higher prevalence of vascular risk factors including diabetes, obesity, and smoking[5-8]. Antipsychotic use, common in schizophrenia, is also associated with metabolic syndrome, cardiovascular disease and stroke incidence[9].

The association between schizophrenia and stroke case fatality is less well-understood, with some studies suggesting an increase[3 10 11] and others no difference[12] or a decrease[13] in post-stroke mortality in those with schizophrenia. Pre-stroke antipsychotic use has been associated with an increased risk of severe stroke which in turn could contribute to post-stroke mortality in those with schizophrenia.[14] Following myocardial infarction, the excess mortality observed in people with schizophrenia is in part explained by lower use of guideline-recommended interventions and medications[15-20]. Previous research suggests that people with schizophrenia are also less likely to receive interventions for acute stroke care and secondary prevention[12], but it is not known whether such differences in care explain variations in stroke case fatality.

We used linked province-wide registry and administrative data to answer the research question of whether stroke presentation, processes of care, and case fatality after stroke differed in people with and without schizophrenia. We hypothesized that schizophrenia would be

associated with stroke case fatality and that differences in baseline characteristics and processes of care would account for this.

Methods

Setting, data sources and study sample

Ontario is Canada's most populous province, with an estimated population of 13 million people at the time of this study[22]. All residents have coverage for hospital and physician services.

The Ontario Stroke Registry collects detailed clinical information on a simple random sample of all people with stroke or transient attack seen in the emergency department or admitted to any acute-care hospital in the province[23]. This sampling minimizes the biases associated with data collection from selected facilities and/or patient groups[24]. Data collection is done by trained research personnel with the diagnosis of stroke confirmed by review of the chart and imaging results, and built-in data quality checks and programing ensure that there are no missing values. Validation by duplicate chart abstraction has shown excellent agreement for key variables[23].

Our study cohort consisted of all adult (age $\geq$ 18 years) patients hospitalized with acute stroke between April 1, 2002 and March 31, 2013 and included in the Ontario Stroke Registry. The registry provided detailed patient-level information on stroke presentation and severity, comorbid conditions, processes of care, and disability at discharge.

We linked registry data to population-based administrative databases using unique, encoded identifiers. To identify people with schizophrenia, we linked to the Canadian Institute for Health

Information Discharge Abstract Database and the physician claims database. We defined schizophrenia in patients with any of 1) a primary diagnosis of schizophrenia or schizoaffective disorder during a general hospital admission [using International Classification of Diseases, 10th revision (ICD 10) codes F20 or F25], (2) a primary diagnosis of schizophrenia from a psychiatric hospital bed (DSM-IV – 295.x), or (3) three outpatient visits with a diagnosis of schizophrenia (ICD9 – 295) from outpatient physician billings within a 3-year period. Each of these criteria was applied from 1988 onward. This diagnostic algorithm has a sensitivity of 97% and a specificity of 65% for the diagnosis of schizophrenia[25].

We used the 2006 Canada Census to provide information on median neighbourhood income and the Discharge Abstract Database to identify hospitalizations for recurrent stroke or transient ischemic attack, using validated ICD-10 codes I60, I61, I63, I64, H34.0, H34.1 and G45 (excluding G45.4)[26]. We used the Ontario Registered Persons Database to identify deaths, with cause of death obtained from the provincial register that assigns cause of death based on death certificates, and with stroke deaths identified as those with ICD-10 codes I60-I69 as the primary cause of death.

Outcomes

The primary outcome was all-cause mortality within one year of stroke. Secondary outcomes were all-cause mortality at 30 days, death due to stroke at one year, disability at discharge [defined as a modified Rankin Scale (mRS) score of 3-5], and recurrent stroke hospitalization within 30 days and 1 year of discharge from the index event. We also evaluated the following processes of care: arrival by ambulance, time from "last seen normal" to hospital arrival,

neuroimaging, dysphagia screening, delivery of care on a dedicated stroke unit, admission to intensive care unit (ICU), tracheostomy, placement of permanent feeding tube, a palliative approach to care, and discharge to inpatient rehabilitation.

In the subgroup of patients with ischemic stroke, we also evaluated use of carotid imaging, thrombolysis, door-to-needle time in those receiving thrombolysis and prescription of antithrombotic, antihypertensive, and lipid-lowering therapy at discharge. Among those who did not receive thrombolysis, we explored reasons why it was not given, categorized as arrival too late, contraindications, symptoms severity, delays in decision-making, other physician decision, or no reason documented. We did not evaluate use of endovascular thrombectomy, which was not in widespread use during the study timeframe.

Analysis

We compared baseline characteristics and processes of care for people with stroke with and without schizophrenia, using standardized differences of the mean, which, unlike traditional hypothesis testing with P values, are not sensitive to large sample sizes[27]. We used a Cox proportional hazard model to estimate the effect of schizophrenia on the hazard of death. We then sequentially introduced covariates into the model as follows: (1) demographics (age, sex); (2) socioeconomic factors (neighbourhood income, rural residence); (3) clinical presentation (stroke type and severity); (4) comorbid conditions (smoking, diabetes, hyperlipidemia, hypertension, prior stroke); (5) processes of care (brain imaging, stroke unit care); and (6) life-sustaining interventions (ICU admission, tracheostomy, permanent feeding tube). We repeated these models in the subgroup with ischemic stroke, with the addition of the following

covariates: (1) thrombolysis; (2) lipid-lowering therapy; (3) antihypertensive medications; and (4) antithrombotic therapy. We then repeated these analyses for the outcome of death due to stroke, with cumulative incidence functions used to estimate the incidence of death due to stroke over time in people with and without schizophrenia, with death from other causes treated as a competing risk. In preliminary analyses, the proportional hazards assumption was violated for the all-cause mortality model, so in secondary analyses we estimated time-varying hazard ratios using restricted cubic splines.

ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Datasets used in this project were linked using unique encoded identifiers and analyzed at ICES. The use of data was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported.

Results

We studied 52,473 patients hospitalized with acute stroke, of whom 612 (1.2%) had schizophrenia. Compared to those without schizophrenia, people with schizophrenia were younger at the time of stroke (median age 66 vs. 74 years), less likely to be independent prior to stroke (44.9% vs. 66.7%), and more likely to reside in long-term care facility (19.3% vs. 5.1%) or live in a low-income neighbourhood (39.2% vs. 22.9%) (Table 1). Those with schizophrenia were also less likely to have a documented pre-stroke history of hypertension (58.3% vs.

63.7%), hyperlipidemia (30.2% vs. 35.0%), atrial fibrillation (8.8% vs. 16.8%), coronary artery disease (17.3% vs. 21.6%), or cancer (4.7% vs. 7.8%), but more likely to have diabetes (31.0% vs 23.7%), cognitive impairment (17.6% vs 8.7%) or to smoke cigarettes (28.3% vs. 16.5%) [standardized difference (std. diff.) $\geq$ 0.10 for all comparisons; Table 1]. Stroke type was similar in those with and without schizophrenia, but those with schizophrenia were less likely to present with mild strokes (54.7% vs. 60.9%).

People with schizophrenia were more likely to arrive by ambulance (79.9% vs. 72.2%) but had a longer median time from symptom onset to hospital arrival (7.7 vs. 5.8 hours). Those with schizophrenia were also more likely to be screened for dysphagia (59.0% vs. 54.0%), but there were no significant differences in the use of stroke unit care, intensive care unit admission, or palliative care (Table 2).

In the subgroup with ischemic stroke, people with schizophrenia were less likely to receive thrombolysis (10.1% vs. 13.4%), carotid imaging (66.3% vs. 74.0%), antihypertensive therapy (65.8% vs. 74.2%), lipid lowering therapy (62.4% vs. 68.0%) and anticoagulation for atrial fibrillation (59.7% vs. 71.7%) (std. diff $\geq$ 0.10 for all comparisons; Table 2). The reasons for not using thrombolysis were similar between groups.

We found no differences in length of stay or death or recurrent stroke/TIA hospitalization in those with and without schizophrenia (Table 3). However, people with schizophrenia were more likely to be disabled at discharge (mRS score of 3 to 5, 54.3% vs. 46.9%) yet less likely to be discharged to inpatient rehabilitation facilities (36.6% vs. 46.6% in the disabled subgroup) (Table 3).

Crude all-cause mortality was similar in those with and without schizophrenia at 30 days (19.3% vs. 16.6%) and one year (28.1% vs. 26.8%) (Table 3). However, after adjustment for age, sex, stroke severity, stroke type, area of residence, comorbid conditions, and processes of care, schizophrenia was associated with an increased one-year hazard of both all-cause mortality [adjusted hazard ratio (aHR) 1.33; 95% confidence interval (CI) 1.14 to 1.54; c-statistic 0.82] and mortality due to stroke (aHR 1.47; 95% CI 1.20 to 1.80), with survival curves separating in the first month after the index stroke (Table 4, Figure 1 and Supplemental Figure; fully adjusted models shown in Supplemental Table). There was an interaction between age and schizophrenia, with the hazard of death associated with schizophrenia mainly seen in those aged 70 years and older (Figure 2). In the subgroup aged over 70 years, people with schizophrenia had higher all-cause mortality at 30 days (31.1% vs. 20.9%; std. diff. 0.24) and one year (46.9% vs. 35.0%; std. diff 0.24) with the majority of deaths due to stroke rather than other causes (Table 3).

Discussion

In this population-based cohort study of people hospitalized with acute stroke, we found that while many processes of acute stroke care were similar between groups, schizophrenia was associated with delays in presentation and lower use of thrombolysis, vascular imaging, rehabilitation, and medications for secondary prevention. Schizophrenia was also associated with a 33% increase in the hazard of one-year post-stroke mortality, even after adjustment for age, sex, stroke type, stroke severity, comorbid conditions and processes of care, and this appeared to be mainly attributable to early deaths due to stroke in older patients.

Our findings of a younger age at stroke presentation and baseline differences in the prevalence of vascular risk factors in those with and without schizophrenia are consistent with previous studies of cardiovascular disease and risk factors in people with severe mental illness[5 6 17 28 29]. Schizophrenia is associated with an increased prevalence of smoking, diabetes, obesity, and hyperlipidemia, as well as use of antipsychotic medications that increase the risk of metabolic syndrome[30 31]. Screening and management of these conditions have been promoted for the primary prevention of cardiovascular disease in people with schizophrenia, especially those on second generation antipsychotic agents; however, screening rates remain suboptimal in many populations[31-34], as do efforts to manage these risk factors among individuals with schizophrenia[35 36]. We cannot determine whether the lower prevalence of hypertension, hyperlipidemia, atrial fibrillation and cardiovascular disease among people with schizophrenia in our cohort is due to a younger age at presentation or under-recognition of these conditions due to a lack of screening and preventive care.

It warrants mention that the prevalence of schizophrenia in our stroke cohort (1.2%) was similar to that in the general population, despite the increased risk of stroke associated with schizophrenia[21]. Our finding that people with schizophrenia were less likely than those without to present with minor strokes suggests that there may be differences in care-seeking behavior or challenges in making a diagnosis of stroke in people with less obvious stroke symptoms and concomitant schizophrenia, and that this group with minor strokes may be under-represented in our cohort. If true, this would represent a missed opportunity for care in people with schizophrenia and stroke, as minor strokes can be associated with disability, and secondary preventive care can prevent more major disabling strokes in the future[37 38].

Our findings of lower use of thrombolysis, rehabilitation, carotid imaging and medications for secondary stroke prevention are consistent with previous studies where schizophrenia has been associated with lower use of various interventions after stroke[11 39-41] and myocardial infarction[15 16 19]. A better understanding of the reasons behind these differences in care will be important to ensuring that people with schizophrenia have equal opportunities to receive appropriate treatment for cardiovascular disease.

We found that schizophrenia was associated with a striking 33% increase in the adjusted hazard of all-cause mortality at one year and a 47% increase in the hazard of stroke mortality, with survival curves separating in the first month after stroke. Those with schizophrenia had greater stroke severity, the most important driver of early case fatality, compared to those without schizophrenia; however, the mortality difference persisted after adjustment for stroke severity. A similar association between schizophrenia and case fatality after myocardial infarction appears to be in part explained by differences in revascularization and other processes of care,[15-17 19 20 42-44] however, the observed association between schizophrenia and stroke case fatality in our study persisted after adjustment for processes of care, comorbid conditions, and area of residence. Of note, the survival disadvantage associated with schizophrenia was primarily seen in the older age groups, in contrast to a study from Hong Kong which found that the association between schizophrenia and stroke case-fatality was greater in those aged under 65 years.[10] Further work is needed to understand the reasons for increased mortality in different age groups and to identify potential interventions to address this.

Some limitations of our study warrant emphasis. We did not have information on the severity or duration of schizophrenia, which would be helpful for identifying subgroups of people with schizophrenia at particularly high risk for adverse outcomes. We did not study exposure to antipsychotic medications, as this information was not available for our entire study cohort. This is an important limitation because antipsychotic use, particularly second-generation antipsychotics, are associated with a 2-fold increased risk of stroke among individuals with schizophrenia[9] . Our data sources did not provide information regarding the severity or control of risk factors such as diabetes or hypertension, on other vascular risk factors such as obesity and physical activity, or on factors such as medication adherence or post-discharge care. We only included people hospitalized with stroke, and thus we do not know if the higher observed stroke severity in people with schizophrenia was due to differences in care-seeking behaviour, with people with schizophrenia and minor stroke symptoms less likely to present to hospital than those without schizophrenia. Finally, our study was conducted in a province with universal access to physician and hospital services and may not be generalizable to other settings. Despite these limitations, our large, population-based sample with detailed clinical information and complete follow-up through administrative data is likely to provide valid results on the risks and contributors to death after stroke in people with and without schizophrenia.

In summary, we found that schizophrenia is associated with deficiencies in some aspects of post-stroke care, as well as a substantial increase in stroke case fatality which is not fully explained by differences in baseline factors or processes of care. Future work should focus on collaborative efforts among psychiatrists, clinicians with expertise in cardiovascular disease, patients and other stakeholders to understand the reasons for these differences and to develop

interventions to improve cardiovascular care and outcomes in people with schizophrenia and other psychotic disorders.

Acknowledgements: This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI. Parts of this report are based on Ontario Registrar General (ORG) Information on deaths, the original source of which is ServiceOntario. The views expressed therein are those of the authors and do not necessarily reflect those of ORG or Ministry of Government Services. Moira Kapral is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation of Canada and holds the Lillian Love Chair in Women's Health from the University Health Network/University of Toronto.

Funding: This study was funded by a grant-in-aid from the Heart and Stroke Foundation of Canada (HSFC G-17-0018192).

Disclosures: None.

Author contributions: MKK and KAS conceived the study and MKK drafted the manuscript. JF performed the statistical analyses. PK, LKC, JF, JP, and KAS contributed to the study design, interpretation of results, and revisions to the manuscript.

Patient and public involvement and dissemination plan

Patients and the public were not involved in the design or conduct of this study. Findings will be disseminated to patient organizations.

Data availability

The dataset from this study is held securely in coded form at ICES (formerly known as the Institute for Clinical Evaluative Sciences). While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Table 1: Baseline characteristics of people with stroke, with and without schizophrenia

	Schizophrenia N = 612	No schizophrenia N = 51,861	Std. diff
Age, median – years (IQR)	66 (56-77)	74 (62-82)	0.45
Female – n (%)	323 (52.8)	25552 (49.3)	0.07
Independent prior to admission – n (%)	275 (44.9)	34604 (66.7)	0.45
Long-term care – n (%)	118 (19.3)	2632 (5.1)	0.45
Lowest neighbourhood income quintile – n (%)	240 (39.2)	11860 (22.9)	0.36
Rural residence – n (%)	45 (7.4)	6599 (12.7)	0.18
Hypertension – n (%)	357 (58.3)	33051 (63.7)	0.11
Hyperlipidemia – n (%)	185 (30.2)	18129 (35.0)	0.10
Diabetes – n (%)	190 (31.0)	12304 (23.7)	0.16
Atrial fibrillation – n (%)	54 (8.8)	8714 (16.8)	0.24
Coronary artery disease – n (%)	106 (17.3)	11211 (21.6)	0.11
Prior stroke – n (%)	126 (20.6)	8992 (17.3)	0.08
Cancer – n (%)	29 (4.7)	4035 (7.8)	0.13
Dementia/cognitive impairment – n (%)	108 (17.6)	4502 (8.7)	0.27
Current smoking – n (%)	173 (28.3)	8563 (16.5)	0.28
Stroke type			
Ischemic – n (%)	496 (81.0)	40734 (78.5)	0.06
Hemorrhagic – n (%)	116 (19.0)	11127 (21.5)	0.06
Stroke severity			
Mild (CNS > 8) – n (%)	335 (54.7)	31605 (60.9)	0.13
Moderate (CNS 4-8) – n (%)	128 (20.9)	8746 (16.9)	0.10
Severe (CSN < 4) – n (%)	149 (24.3)	11510 (22.2)	0.05

Std. diff = standardized difference of the mean, where values ≥ 0.10 are considered to represent a meaningful difference; IQR = interquartile range; CNS = Canadian Neurological Scale, where lower scores indicate more severe strokes.

Table 2: Presentation and processes of care in people with acute stroke with and without schizophrenia

	Schizophrenia N = 612	No schizophrenia N = 51,861	Std. diff
Arrival by ambulance – n (%)	489 (79.9)	37424 (72.2)	0.18
Time from symptom onset to ED arrival, median – hours (IQR)	7.7 (1.8-22.2)	5.8 (1.5-20.0)	0.11
Dysphagia screening – n (%)	361 (59.0)	28022 (54.0)	0.10
Stroke unit care – n (%)	281 (45.9)	23717 (45.7)	0.004
Intensive care unit admission – n (%)	126 (20.6)	11499 (22.2)	0.04
Palliative approach to care – n (%)	102 (16.7)	7398 (14.3)	0.07
Subgroup with ischemic stroke – N	***496***	***40734***	
Carotid imaging – n (%)	329 (66.3)	30157 (74.0)	0.17
Thrombolysis given -n (%)	50 (10.1)	5477 (13.4)	0.10
Reason thrombolysis not given - %			
Arrival too late	51.6	52.1	0.01
Contraindication	10.5	10.0	0.02
Symptoms too mild	21.3	28.5	0.17
Symptoms too severe	5.4	4.4	0.05
Other physician decision	11.0	8.7	0.08
Delayed decision	2.2	3.1	0.05
No reason documented	10.3	8.4	0.07
Subgroup with ischemic stroke alive at discharge – N	***433***	***36331***	
Antihypertensive therapy prescribed – n (%)	285 (65.8)	26966 (74.2)	0.18
Lipid-lowering therapy prescribed – n (%)	270 (62.4)	24690 (68.0)	0.12
Antiplatelet therapy – n (%)	344 (79.4)	28119 (77.4)	0.05
Anticoagulation (in subgroup with atrial fibrillation) – n/N (%)	40/67 (59.7)	6430/8971 (71.7)	0.25

Std. diff = standardized difference of the mean, where values $\geq$ 0.10 are considered to represent a meaningful difference; ED = emergency department; IQR = interquartile range;

Table 3: Outcomes after acute stroke in people with and without schizophrenia

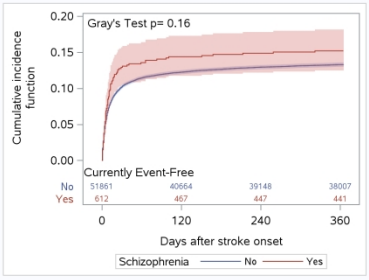
	Schizophrenia N = 612	No schizophrenia N = 51,861	Std. diff
Median length of stay – days (IQR)	7 (3 – 15)	7 (3- 14)	0.06
Disabled at discharge (mRS 3 to 5) – n (%)	325 (54.3)	23856 (46.9)	0.15
In-hospital death – n (%)	95 (15.9)	7532 (14.8)	0.03
Mortality at 30 days – n (%)			
All-cause	118 (19.3)	8602 (16.6)	0.07
Due to stroke	79 (12.9)	5288 (10.2)	0.08
Non-stroke CV disease	23 (3.8)	1987 (3.8)	0.00
Other	16 (2.6)	1327 (2.6)	0.00
Mortality at 1 year – n (%)			
All-cause	172 (28.1)	13894 (26.8)	0.03
Due to stroke	93 (15.2)	6893 (13.3)	0.05
Non-stroke CV disease	41 (6.7)	3340 (6.4)	0.01
Other	38 (6.2)	3661 (7.1)	0.03
Subgroup aged ≥ 70 years - N	***228***	***30294***	
Mortality at 30 days – n (%)			
All-cause	71 (31.1)	6322 (20.9)	0.24
Due to stroke	46 (20.2)	3856 (12.7)	0.20
Non-stroke CV disease	17 (7.5)	1565 (5.2)	0.09
Other	8 (3.5)	901 (3.0)	0.03
Mortality at 1 year – n (%)			
All-cause	107 (46.9)	10604 (35.0)	0.24
Due to stroke	56 (24.6)	5196 (17.2)	0.18
Non-stroke CV disease	30 (13.2)	2725 (9.0)	0.13
Other	21 (9.2)	2683 (8.9)	0.01
Subgroup alive at discharge – N	***517***	***44330***	
Discharge to rehabilitation – n (%)	137 (26.5)	12966 (29.2)	0.17
If mRS 0 to 2 – n/N (%)	15/178 (8.4)	1658/19440 (8.5)	0.004
If mRS 3 to 5 – n/N (%)	119/325 (36.6)	11113/23856 (46.6)	0.20
Recurrent stroke/TIA within 30 days	15 (2.9)	1192 (2.7)	0.01
Recurrent stroke/TIA within 1 year	34 (6.7)	3096 (7.1)	0.02

Std. diff = standardized difference of the mean, where values > 0.10 are considered to represent a meaningful difference; IQR = interquartile range; mRS = modified Rankin Scale score, where higher scores indicate more disability; TIA = transient ischemic attack

Table 4: The effect of sequential risk adjustment on the hazard of one-year stroke case fatality associated with schizophrenia

Adjustment	All-cause mortality HR (95% CI)	Death due to stroke HR (95% CI)	Non-stroke death HR (95% CI)
-	1.08 (0.93 to 1.25)	1.16 (0.94 to 1.42)	0.98 (0.78 to 1.22)
Age and sex	1.39 (1.19 to 1.61)	1.46 (1.19to 1.79)	1.31 (1.05 to 1.63)
Age and sex + income quintile, rural residence	1.38 (1.19 to 1.60)	1.46 (1.19 to 1.80)	1.28 (1.03 to 1.60)
Age and sex + income quintile and rural residence + stroke type and stroke severity	1.31 (1.13 to 1.52)	1.40 (1.14 to 1.72)	1.21 (0.97 to 1.52)
Age and sex + income quintile and rural residence + stroke type and stroke severity + smoking, diabetes, hyperlipidemia, hypertension, prior stroke	1.27 (1.10 to 1.48)	1.37 (1.12 to 1.68)	1.17 (0.94 to 1.46)
Age and sex + income quintile and rural residence + stroke type and stroke severity + smoking, diabetes, hyperlipidemia, hypertension, prior stroke + brain imaging within one hour of arrival, care on stroke unit	1.31 (1.13 to 1.52)	1.44 (1.17 to 1.77)	1.18 (0.95 to 1.48)
Age and sex + income quintile and rural residence + stroke type and stroke severity + smoking, diabetes, hyperlipidemia, hypertension, prior stroke + brain imaging within one hour of arrival, care on stroke unit + intensive care unit admission, tracheostomy, feeding tube	1.33 (1.14 to 1.54)	1.47 (1.20 to 1.80)	1.19 (0.95 to 1.48)

HR = hazard ratio for schizophrenia (N = 612) vs. no schizophrenia (N = 51,861); CI = confidence interval. Hazard of death due to stroke accounts for the competing risk of death from other causes.



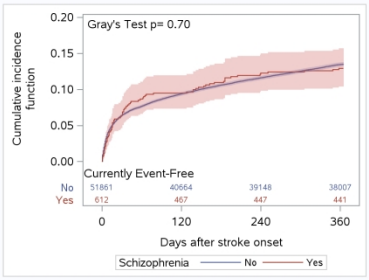


Figure 1a (top): Cumulative incidence of death due to stroke in people with and without schizophrenia
Figure 1b (bottom): Cumulative incidence of non-stroke death in people with and without schizophrenia

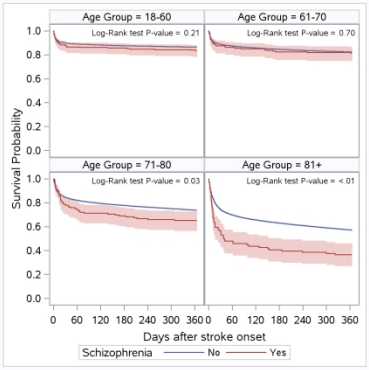
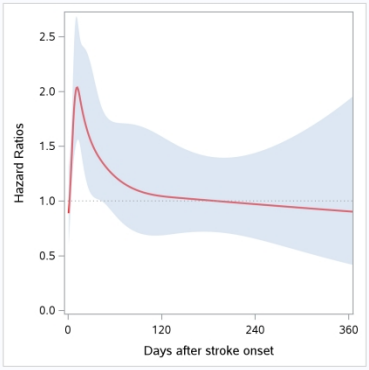


Figure 2: Survival after stroke in people with and without schizophrenia, by age group

Supplemental Table: Fully adjusted models for one-year mortality after stroke

	All-cause mortality HR (95% CI)	Death from stroke HR (95% CI)	Non-stroke death HR (95% CI)
Schizophrenia	1.33 (1.14 to 1.54)	1.47 (1.20 to 1.80)	1.19 (0.95 to 1.48)
Male sex (vs female)	1.09 (1.05 to 1.13)	1.06 (1.01 to 1.11)	1.10 (1.05 to 1.16)
Age group			
≤ 60	Reference	Reference	Reference
61-70	1.65 (1.54 to 1.77)	1.55 (1.41 to 1.71)	1.82 (1.65 to 2.01)
71-80	2.71 (2.55 to 2.89)	2.54 (2.33 to 2.77)	2.97 (2.71 to 3.26)
80+	4.91 (4.62 to 5.22)	4.83 (4.44 to 5.26)	5.24 (4.79 to 5.73)
Income quintile			
1 (lowest)	Reference	Reference	Reference
2	0.98 (0.93 to 1.03)	1.01 (0.94 to 1.09)	0.96 (0.89 to 1.03)
3	0.97 (0.92 to 1.02)	0.99 (0.92 to 1.06)	0.96 (0.90 to 1.03)
4	0.98 (0.93 to 1.03)	1.00 (0.93 to 1.08)	0.96 (0.90 to 1.04)
5 (highest)	0.94 (0.90 to 0.99)	1.03 (0.96 to 1.11)	0.87 (0.80 to 0.93)
Residence			
Large urban	Reference	Reference	Reference
Medium urban	1.02 (0.96 to 1.08)	1.10 (1.01 to 1.20)	0.95 (0.87 to 1.04)
Rural or small town	1.10 (1.05 to 1.16)	1.17 (1.09 to 1.25)	1.04 (0.97 to 1.12)
Stroke severity			
Severe	Reference	Reference	Reference
Moderate	0.48 (0.46 to 0.50)	0.45 (0.42 to 0.47)	0.52 (0.48 to 0.55)
Mild	0.18 (0.18 to 0.19)	0.12 (0.12 to 0.13)	0.25 (0.24 to 0.26)
Stroke type			
Ischemic	Reference	Reference	Reference
Hemorrhagic	1.77(1.70 to 1.84)	2.24 (2.12 to 2.37)	1.36 (1.27 to 1.44)
Smoking	1.02 (0.97 to 1.08)	1.03 (0.95 to 1.11)	1.02 (0.94 to 1.10)
Diabetes	1.27 (1.22 to 1.32)	1.07 (1.01 to 1.14)	1.45 (1.37 to 1.53)
Hyperlipidemia	0.85 (0.82 to 0.88)	0.83 (0.78 to 0.87)	0.87 (0.83 to 0.92)
Hypertension	1.09 (1.05 to 1.14)	1.16 (1.10 to 1.23)	1.03 (0.97 to 1.09)
Prior stroke	1.20 (1.15 to 1.25)	1.16 (1.09 to 1.23)	1.24 (1.18 to 1.32)
Neuroimaging within 1 hour	1.28 (1.23 to 1.32)	1.45 (1.38 to 1.52)	1.12 (1.06 to 1.18)
Stroke unit care	0.64 (0.62 to 0.66)	0.60 (0.57 to 0.63)	0.69 (0.65 to 0.72)
Intensive care unit admission	1.18 (1.14 to 1.23)	1.27 (1.20 to 1.34)	1.10 (1.03 to 1.17)
Tracheostomy	0.73 (0.64 to 0.83)	0.71 (0.60 to 0.85)	0.75 (0.61 to 0.92)
Feeding tube	0.81 (0.76 to 0.87)	0.73 (0.66 to 0.80)	0.92 (0.83 to 1.02)

C-statistic = 0.82 for the model of all-cause mortality



Supplemental Figure: Time-varying hazard ratios (and 95% confidence bands) for all-cause mortality after stroke associated with schizophrenia, estimated by a restricted cubic spline function.

STROBE checklist of items that should be included in reports of observational studies
Article: Stroke care and outcomes in people with and without schizophrenia: a retrospective cohort study
Author: Kapral, Moira K.

	Item No	Recommendation	Location in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract, p. 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, p. 3
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Background section, p. 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Background, p.6
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, pp. 6-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, pp.6-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods (data sources and patient sample), pp. 6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, p. 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pp. 6-8
Bias	9	Describe any efforts to address potential sources of bias	1. Population-based patient sample

			2. Complete follow up using administrative data 3. Multivariable analyses
Study size	10	Explain how the study size was arrived at	We included the entire sample of stroke patients from the study time frame.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	See methods section (statistical analysis), pp. 8-9.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	See methods section (statistical analysis), pp.8-9.
		(*b*) Describe any methods used to examine subgroups and interactions	See methods section (statistical analysis), pp.8-9.
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a. Follow up was done using administrative data
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, p. 10
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results, p.10 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results, pp. 11-12 and Tables 2-4 and Figure

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, pp. 11-12 and Tables 2-4 and Figure
		(*b*) Report category boundaries when continuous variables were categorized	Results, pp. 11-12 and Tables 2-4 and Figure
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, pp. 12-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, pp. 15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, pp. 12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, p.15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Study funding section, p. 2

BMJ Open

Stroke Care and Case Fatality in People with and without Schizophrenia: A Retrospective Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044766.R2
Article Type:	Original research
Date Submitted by the Author:	08-Apr-2021
Complete List of Authors:	Kapral, MK; University of Toronto, Medicine Kurdyak, Paul; Centre for Addiction and Mental Health, Casaubon, Leanne; Toronto Western Hospital, Fang, Jiming; Institute for Clinical Evaluative Sciences Porter, Joan; Institute for Clinical Evaluative Sciences Sheehan, Kathleen; University of Toronto, Medicine
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Health services research, Mental health, Cardiovascular medicine
Keywords:	Stroke < NEUROLOGY, Schizophrenia & psychotic disorders < PSYCHIATRY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, MENTAL HEALTH

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Stroke Care and Case Fatality in People with and without Schizophrenia: A Retrospective Cohort Study

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Abstract word count: 300

Text word count: 2690

Tables: 4

Figures: 2

Supplemental tables: 1

Supplemental figures: 1

Search terms: stroke, psychosis, mental illness, health services research, health disparities

ABSTRACT

Background: Schizophrenia is associated with an increased risk of death following stroke; however, the magnitude and underlying reasons for this are not well-understood.

Objective: To determine the association between schizophrenia and stroke case-fatality, adjusting for baseline characteristics, stroke severity, and processes of care.

Design: Retrospective cohort study used linked clinical and administrative databases.

Setting: All acute care institutions (N = 152) in the province of Ontario, Canada.

Participants: All patients (N = 52,473) hospitalized with stroke between April 1, 2002 and March 31, 2013 and included in the Ontario Stroke Registry. Those with schizophrenia (N=612) were identified using validated algorithms.

Main outcomes and measures: We compared acute stroke care in those with and without schizophrenia and used Cox proportional hazards models to examine the association between schizophrenia and mortality, adjusting for demographics, comorbidity, stroke severity, and processes of care.

Results: Compared to those without schizophrenia, people with schizophrenia were less likely to receive thrombolysis (10.1% vs. 13.4%), carotid imaging (66.3% vs. 74.0%), rehabilitation (36.6% vs. 46.6% among those with disability at discharge), or be treated with antihypertensive, lipid-lowering or anticoagulant therapies. After adjustment for age and other factors,

schizophrenia was associated with death from any cause at one year [adjusted hazard ratio (aHR) 1.33, 95% confidence interval (CI) 1.14 to 1.54]. This was mainly attributable to early deaths from stroke (aHR 1.47; 95% CI 1.20 to 1.80, with survival curves separating in the first 30 days), and the survival disadvantage was particularly marked in those aged over 70 years (one-year mortality 46.9% vs. 35.0%).

Conclusions: Schizophrenia is associated with increased stroke case fatality, which is not fully explained by stroke severity, measurable comorbid conditions, or processes of care. Future work should focus on understanding this mortality gap and on improving acute stroke and secondary preventive care in people with schizophrenia.

Strengths and limitations of this study:

1. Large, population-based sample with detailed clinical information on stroke characteristics and processes of care.
2. Complete follow-up for outcome events through administrative data.
3. Lack of information on some potential explanatory variables such as medication adherence and post-discharge care.

Introduction

Stroke is a leading cause of death and disability worldwide[1]. Schizophrenia and other serious mental illnesses are associated with an increased risk of stroke,other cardiovascular diseases, and cardiovascular mortality[2-4]. This appears to be in part attributable to a higher prevalence of vascular risk factors including diabetes, obesity, and smoking[5-8]. Antipsychotic use, common in schizophrenia, is also associated with metabolic syndrome, cardiovascular disease and stroke incidence[9].

The association between schizophrenia and stroke case fatality is less well-understood, with some studies suggesting an increase[3 10 11] and others no difference[12] or a decrease[13] in post-stroke mortality in those with schizophrenia. Pre-stroke antipsychotic use has been associated with an increased risk of severe stroke which in turn could contribute to post-stroke mortality in those with schizophrenia.[14] Following myocardial infarction, the excess mortality observed in people with schizophrenia is in part explained by lower use of guideline-recommended interventions and medications[15-20]. Previous research suggests that people with schizophrenia are also less likely to receive interventions for acute stroke care and secondary prevention[12], but it is not known whether such differences in care explain variations in stroke case fatality.

We used linked province-wide registry and administrative data to answer the research question of whether stroke presentation, processes of care, and case fatality after stroke differed in people with and without schizophrenia. We hypothesized that schizophrenia would be

associated with stroke case fatality and that differences in baseline characteristics and processes of care would account for this.

Methods

Setting, data sources and study sample

Ontario is Canada's most populous province, with an estimated population of 13 million people at the time of this study[21]. All residents have coverage for hospital and physician services.

The Ontario Stroke Registry collects detailed clinical information on a simple random sample of all people with stroke or transient attack seen in the emergency department or admitted to any acute-care hospital in the province[22]. This sampling minimizes the biases associated with data collection from selected facilities and/or patient groups[23]. Data collection is done by trained research personnel with the diagnosis of stroke confirmed by review of the chart and imaging results, and built-in data quality checks and programing ensure that there are no missing values. Validation by duplicate chart abstraction has shown excellent agreement for key variables[22].

Our study cohort consisted of all adult (age $\geq$ 18 years) patients hospitalized with acute stroke between April 1, 2002 and March 31, 2013 and included in the Ontario Stroke Registry. The registry provided detailed patient-level information on stroke presentation and severity, comorbid conditions, processes of care, and disability at discharge.

We linked registry data to population-based administrative databases using unique, encoded identifiers. To identify people with schizophrenia, we linked to the Canadian Institute for Health

Information Discharge Abstract Database and the physician claims database. We defined schizophrenia in patients with any of 1) a primary diagnosis of schizophrenia or schizoaffective disorder during a general hospital admission [using International Classification of Diseases, 10th revision (ICD 10) codes F20 or F25], (2) a primary diagnosis of schizophrenia from a psychiatric hospital bed (DSM-IV – 295.x), or (3) three outpatient visits with a diagnosis of schizophrenia (ICD9 – 295) from outpatient physician billings within a 3-year period. Each of these criteria was applied from 1988 onward. This diagnostic algorithm has a sensitivity of 97% and a specificity of 65% for the diagnosis of schizophrenia[24].

We used the 2006 Canada Census to provide information on median neighbourhood income and the Discharge Abstract Database to identify hospitalizations for recurrent stroke or transient ischemic attack, using validated ICD-10 codes I60, I61, I63, I64, H34.0, H34.1 and G45 (excluding G45.4)[25]. We used the Ontario Registered Persons Database to identify deaths, with cause of death obtained from the provincial register that assigns cause of death based on death certificates, and with stroke deaths identified as those with ICD-10 codes I60-I69 as the primary cause of death.

Outcomes

The primary outcome was all-cause mortality within one year of stroke. Secondary outcomes were all-cause mortality at 30 days, death due to stroke at one year, disability at discharge [defined as a modified Rankin Scale (mRS) score of 3-5], and recurrent stroke hospitalization within 30 days and 1 year of discharge from the index event. We also evaluated the following processes of care: arrival by ambulance, time from "last seen normal" to hospital arrival,

neuroimaging, dysphagia screening, delivery of care on a dedicated stroke unit, admission to intensive care unit (ICU), tracheostomy, placement of permanent feeding tube, a palliative approach to care, and discharge to inpatient rehabilitation.

In the subgroup of patients with ischemic stroke, we also evaluated use of carotid imaging, thrombolysis, door-to-needle time in those receiving thrombolysis and prescription of antithrombotic, antihypertensive, and lipid-lowering therapy at discharge. Among those who did not receive thrombolysis, we explored reasons why it was not given, categorized as arrival too late, contraindications, symptoms severity, delays in decision-making, other physician decision, or no reason documented. We did not evaluate use of endovascular thrombectomy, which was not in widespread use during the study timeframe.

Analysis

We compared baseline characteristics and processes of care for people with stroke with and without schizophrenia, using standardized differences of the mean, which, unlike traditional hypothesis testing with P values, are not sensitive to large sample sizes[26]. We used a Cox proportional hazard model to estimate the effect of schizophrenia on the hazard of death. We then sequentially introduced covariates into the model as follows: (1) demographics (age, sex); (2) socioeconomic factors (neighbourhood income, rural residence); (3) clinical presentation (stroke type and severity); (4) comorbid conditions (smoking, diabetes, hyperlipidemia, hypertension, prior stroke); (5) processes of care (brain imaging, stroke unit care); and (6) life-sustaining interventions (ICU admission, tracheostomy, permanent feeding tube). We repeated these models in the subgroup with ischemic stroke, with the addition of the following

covariates: (1) thrombolysis; (2) lipid-lowering therapy; (3) antihypertensive medications; and (4) antithrombotic therapy. We then repeated these analyses for the outcome of death due to stroke, with cumulative incidence functions used to estimate the incidence of death due to stroke over time in people with and without schizophrenia, with death from other causes treated as a competing risk. In preliminary analyses, the proportional hazards assumption was violated for the all-cause mortality models in the ischemic stroke sub-cohort and weakly violated the assumption in the main cohort. We addressed this by estimating time-varying hazard ratios using restricted cubic splines and modeling time-by-covariate interactions. [27] This allowed for an investigation of the shape of a possible covariate-time dependence without having to specify a specific functional form.

ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Datasets used in this project were linked using unique encoded identifiers and analyzed at ICES. The use of data was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported.

Results

We studied 52,473 patients hospitalized with acute stroke, of whom 612 (1.2%) had schizophrenia. Compared to those without schizophrenia, people with schizophrenia were younger at the time of stroke (median age 66 vs. 74 years), less likely to be independent prior

to stroke (44.9% vs. 66.7%), and more likely to reside in long-term care facility (19.3% vs. 5.1%) or live in a low-income neighbourhood (39.2% vs. 22.9%) (Table 1). Those with schizophrenia were also less likely to have a documented pre-stroke history of hypertension (58.3% vs. 63.7%), hyperlipidemia (30.2% vs. 35.0%), atrial fibrillation (8.8% vs. 16.8%), coronary artery disease (17.3% vs. 21.6%), or cancer (4.7% vs. 7.8%), but more likely to have diabetes (31.0% vs 23.7%), cognitive impairment (17.6% vs 8.7%) or to smoke cigarettes (28.3% vs. 16.5%) [standardized difference (std. diff.) $\geq$ 0.10 for all comparisons; Table 1]. Stroke type was similar in those with and without schizophrenia, but those with schizophrenia were less likely to present with mild strokes (54.7% vs. 60.9%).

People with schizophrenia were more likely to arrive by ambulance (79.9% vs. 72.2%) but had a longer median time from symptom onset to hospital arrival (7.7 vs. 5.8 hours). Those with schizophrenia were also more likely to be screened for dysphagia (59.0% vs. 54.0%), but there were no significant differences in the use of stroke unit care, intensive care unit admission, or palliative care (Table 2).

In the subgroup with ischemic stroke, people with schizophrenia were less likely to receive thrombolysis (10.1% vs. 13.4%), carotid imaging (66.3% vs. 74.0%), antihypertensive therapy (65.8% vs. 74.2%), lipid lowering therapy (62.4% vs. 68.0%) and anticoagulation for atrial fibrillation (59.7% vs. 71.7%) (std. diff $\geq$ 0.10 for all comparisons; Table 2). The reasons for not using thrombolysis were similar between groups.

We found no differences in length of stay or death or recurrent stroke/TIA hospitalization in those with and without schizophrenia (Table 3). However, people with schizophrenia were

more likely to be disabled at discharge (mRS score of 3 to 5, 54.3% vs. 46.9%) yet less likely to be discharged to inpatient rehabilitation facilities (36.6% vs. 46.6% in the disabled subgroup) (Table 3).

Crude all-cause mortality was similar in those with and without schizophrenia at 30 days (19.3% vs. 16.6%) and one year (28.1% vs. 26.8%) (Table 3). However, after adjustment for age, sex, stroke severity, stroke type, area of residence, comorbid conditions, and processes of care, schizophrenia was associated with an increased one-year hazard of both all-cause mortality [adjusted hazard ratio (aHR) 1.33; 95% confidence interval (CI) 1.14 to 1.54; c-statistic 0.78] and mortality due to stroke (aHR 1.47; 95% CI 1.20 to 1.80; c-statistic 0.82), with survival curves separating in the first month after the index stroke (Table 4, Figure 1 and Supplemental Figure, the latter confirming time-varying hazard ratios revealed by restricted cubic spline modeling; fully adjusted models shown in Supplemental Table). There was an interaction between age and schizophrenia, with the hazard of death associated with schizophrenia mainly seen in those aged 70 years and older (Figure 2). In the subgroup aged over 70 years, people with schizophrenia had higher all-cause mortality at 30 days (31.1% vs. 20.9%; std. diff. 0.24) and one year (46.9% vs. 35.0%; std. diff 0.24) with the majority of deaths due to stroke rather than other causes (Table 3).

Discussion

In this population-based cohort study of people hospitalized with acute stroke, we found that while many processes of acute stroke care were similar between groups, schizophrenia was associated with delays in presentation and lower use of thrombolysis, vascular imaging,

rehabilitation, and medications for secondary prevention. Schizophrenia was also associated with a 33% increase in the hazard of one-year post-stroke mortality, even after adjustment for age, sex, stroke type, stroke severity, comorbid conditions and processes of care, and this appeared to be mainly attributable to early deaths due to stroke in older patients.

Our findings of a younger age at stroke presentation and baseline differences in the prevalence of vascular risk factors in those with and without schizophrenia are consistent with previous studies of cardiovascular disease and risk factors in people with severe mental illness[5 6 17 28 29]. Schizophrenia is associated with an increased prevalence of smoking, diabetes, obesity, and hyperlipidemia, as well as use of antipsychotic medications that increase the risk of metabolic syndrome[30 31]. Screening and management of these conditions have been promoted for the primary prevention of cardiovascular disease in people with schizophrenia, especially those on second generation antipsychotic agents; however, screening rates remain suboptimal in many populations[31-34], as do efforts to manage these risk factors among individuals with schizophrenia[35 36]. We cannot determine whether the lower prevalence of hypertension, hyperlipidemia, atrial fibrillation and cardiovascular disease among people with schizophrenia in our cohort is due to a younger age at presentation or under-recognition of these conditions due to a lack of screening and preventive care.

It warrants mention that the prevalence of schizophrenia in our stroke cohort (1.2%) was similar to that in the general population, despite the increased risk of stroke associated with schizophrenia[37]. Our finding that people with schizophrenia were less likely than those without to present with minor strokes suggests that there may be differences in care-seeking behavior

or challenges in making a diagnosis of stroke in people with less obvious stroke symptoms and concomitant schizophrenia, and that this group with minor strokes may be under-represented in our cohort. If true, this would represent a missed opportunity for care in people with schizophrenia and stroke, as minor strokes can be associated with disability, and secondary preventive care can prevent more major disabling strokes in the future[38 39].

Our findings of lower use of thrombolysis, rehabilitation, carotid imaging and medications for secondary stroke prevention are consistent with previous studies where schizophrenia has been associated with lower use of various interventions after stroke[11 40-42] and myocardial infarction[15 16 19]. A better understanding of the reasons behind these differences in care will be important to ensuring that people with schizophrenia have equal opportunities to receive appropriate treatment for cardiovascular disease.

We found that schizophrenia was associated with a striking 33% increase in the adjusted hazard of all-cause mortality at one year and a 47% increase in the hazard of stroke mortality, with survival curves separating in the first month after stroke. Those with schizophrenia had greater stroke severity, the most important driver of early case fatality, compared to those without schizophrenia; however, the mortality difference persisted after adjustment for stroke severity. A similar association between schizophrenia and case fatality after myocardial infarction appears to be in part explained by differences in revascularization and other processes of care,[15-17 19 20 43-45] however, the observed association between schizophrenia and stroke case fatality in our study persisted after adjustment for processes of care, comorbid conditions, and area of residence. Of note, the survival disadvantage associated with schizophrenia was

primarily seen in the older age groups, in contrast to a study from Hong Kong which found that the association between schizophrenia and stroke case-fatality was greater in those aged under 65 years.[10] Further work is needed to understand the reasons for increased mortality in different age groups and to identify potential interventions to address this.

Some limitations of our study warrant emphasis. We did not have information on the severity or duration of schizophrenia, which would be helpful for identifying subgroups of people with schizophrenia at particularly high risk for adverse outcomes. We did not study exposure to antipsychotic medications, as this information was not available for our entire study cohort. This is an important limitation because antipsychotic use, particularly second-generation antipsychotics, are associated with a 2-fold increased risk of stroke among individuals with schizophrenia[9] . Our data sources did not provide information regarding the severity or control of risk factors such as diabetes or hypertension, on other vascular risk factors such as obesity and physical activity, or on factors such as medication adherence or post-discharge care. We only included people hospitalized with stroke, and thus we do not know if the higher observed stroke severity in people with schizophrenia was due to differences in care-seeking behaviour, with people with schizophrenia and minor stroke symptoms less likely to present to hospital than those without schizophrenia. Finally, our study was conducted in a province with universal access to physician and hospital services and may not be generalizable to other settings. Despite these limitations, our large, population-based sample with detailed clinical information and complete follow-up through administrative data is likely to provide valid results on the risks and contributors to death after stroke in people with and without schizophrenia.

In summary, we found that schizophrenia is associated with deficiencies in some aspects of post-stroke care, as well as a substantial increase in stroke case fatality which is not fully explained by differences in baseline factors or processes of care. Future work should focus on collaborative efforts among psychiatrists, clinicians with expertise in cardiovascular disease, patients and other stakeholders to understand the reasons for these differences and to develop interventions to improve cardiovascular care and outcomes in people with schizophrenia and other psychotic disorders.

Acknowledgements: This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI. Parts of this report are based on Ontario Registrar General (ORG) Information on deaths, the original source of which is ServiceOntario. The views expressed therein are those of the authors and do not necessarily reflect those of ORG or Ministry of Government Services. Moira Kapral is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation of Canada and holds the Lillian Love Chair in Women's Health from the University Health Network/University of Toronto.

Funding: This study was funded by a grant-in-aid from the Heart and Stroke Foundation of Canada (HSFC G-17-0018192).

Disclosures: None.

Author contributions: MKK and KAS conceived the study and MKK drafted the manuscript. JF performed the statistical analyses. PK, LKC, JF, JP, and KAS contributed to the study design, interpretation of results, and revisions to the manuscript.

Patient and public involvement and dissemination plan

Patients and the public were not involved in the design or conduct of this study. Findings will be disseminated to patient organizations.

Data availability

The dataset from this study is held securely in coded form at ICES (formerly known as the Institute for Clinical Evaluative Sciences). While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Figure legends:

Figure 1a (top): Cumulative incidence of death due to stroke in people with and without schizophrenia

Figure 1b (bottom): Cumulative incidence of non-stroke death in people with and without schizophrenia

Figure 2: Survival after stroke in people with and without schizophrenia, by age group

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Table 1: Baseline characteristics of people with stroke, with and without schizophrenia

	Schizophrenia N = 612	No schizophrenia N = 51,861	Std. diff
Age, median – years (IQR)	66 (56-77)	74 (62-82)	0.45
Female – n (%)	323 (52.8)	25552 (49.3)	0.07
Independent prior to admission – n (%)	275 (44.9)	34604 (66.7)	0.45
Long-term care – n (%)	118 (19.3)	2632 (5.1)	0.45
Lowest neighbourhood income quintile – n (%)	240 (39.2)	11860 (22.9)	0.36
Rural residence – n (%)	45 (7.4)	6599 (12.7)	0.18
Hypertension – n (%)	357 (58.3)	33051 (63.7)	0.11
Hyperlipidemia – n (%)	185 (30.2)	18129 (35.0)	0.10
Diabetes – n (%)	190 (31.0)	12304 (23.7)	0.16
Atrial fibrillation – n (%)	54 (8.8)	8714 (16.8)	0.24
Coronary artery disease – n (%)	106 (17.3)	11211 (21.6)	0.11
Prior stroke – n (%)	126 (20.6)	8992 (17.3)	0.08
Cancer – n (%)	29 (4.7)	4035 (7.8)	0.13
Dementia/cognitive impairment – n (%)	108 (17.6)	4502 (8.7)	0.27
Current smoking – n (%)	173 (28.3)	8563 (16.5)	0.28
Stroke type			
Ischemic – n (%)	496 (81.0)	40734 (78.5)	0.06
Hemorrhagic – n (%)	116 (19.0)	11127 (21.5)	0.06
Stroke severity			
Mild (CNS > 8) – n (%)	335 (54.7)	31605 (60.9)	0.13
Moderate (CNS 4-8) – n (%)	128 (20.9)	8746 (16.9)	0.10
Severe (CSN < 4) – n (%)	149 (24.3)	11510 (22.2)	0.05

Std. diff = standardized difference of the mean, where values ≥ 0.10 are considered to represent a meaningful difference; IQR = interquartile range; CNS = Canadian Neurological Scale, where lower scores indicate more severe strokes.

Table 2: Presentation and processes of care in people with acute stroke with and without schizophrenia

	Schizophrenia N = 612	No schizophrenia N = 51,861	Std. diff
Arrival by ambulance – n (%)	489 (79.9)	37424 (72.2)	0.18
Time from symptom onset to ED arrival, median – hours (IQR)	7.7 (1.8-22.2)	5.8 (1.5-20.0)	0.11
Dysphagia screening – n (%)	361 (59.0)	28022 (54.0)	0.10
Stroke unit care – n (%)	281 (45.9)	23717 (45.7)	0.004
Intensive care unit admission – n (%)	126 (20.6)	11499 (22.2)	0.04
Palliative approach to care – n (%)	102 (16.7)	7398 (14.3)	0.07
Subgroup with ischemic stroke – N	***496***	***40734***	
Carotid imaging – n (%)	329 (66.3)	30157 (74.0)	0.17
Thrombolysis given -n (%)	50 (10.1)	5477 (13.4)	0.10
Reason thrombolysis not given - %			
Arrival too late	51.6	52.1	0.01
Contraindication	10.5	10.0	0.02
Symptoms too mild	21.3	28.5	0.17
Symptoms too severe	5.4	4.4	0.05
Other physician decision	11.0	8.7	0.08
Delayed decision	2.2	3.1	0.05
No reason documented	10.3	8.4	0.07
Subgroup with ischemic stroke alive at discharge – N	***433***	***36331***	
Antihypertensive therapy prescribed – n (%)	285 (65.8)	26966 (74.2)	0.18
Lipid-lowering therapy prescribed – n (%)	270 (62.4)	24690 (68.0)	0.12
Antiplatelet therapy – n (%)	344 (79.4)	28119 (77.4)	0.05
Anticoagulation (in subgroup with atrial fibrillation) – n/N (%)	40/67 (59.7)	6430/8971 (71.7)	0.25

Std. diff = standardized difference of the mean, where values $\geq$ 0.10 are considered to represent a meaningful difference; ED = emergency department; IQR = interquartile range;

Table 3: Outcomes after acute stroke in people with and without schizophrenia

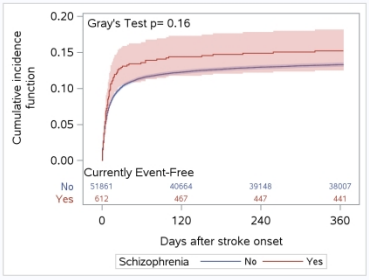
	Schizophrenia N = 612	No schizophrenia N = 51,861	Std. diff
Median length of stay – days (IQR)	7 (3 – 15)	7 (3- 14)	0.06
Disabled at discharge (mRS 3 to 5) – n (%)	325 (54.3)	23856 (46.9)	0.15
In-hospital death – n (%)	95 (15.9)	7532 (14.8)	0.03
Mortality at 30 days – n (%)			
All-cause	118 (19.3)	8602 (16.6)	0.07
Due to stroke	79 (12.9)	5288 (10.2)	0.08
Non-stroke CV disease	23 (3.8)	1987 (3.8)	0.00
Other	16 (2.6)	1327 (2.6)	0.00
Mortality at 1 year – n (%)			
All-cause	172 (28.1)	13894 (26.8)	0.03
Due to stroke	93 (15.2)	6893 (13.3)	0.05
Non-stroke CV disease	41 (6.7)	3340 (6.4)	0.01
Other	38 (6.2)	3661 (7.1)	0.03
Subgroup aged ≥ 70 years - N	***228***	***30294***	
Mortality at 30 days – n (%)			
All-cause	71 (31.1)	6322 (20.9)	0.24
Due to stroke	46 (20.2)	3856 (12.7)	0.20
Non-stroke CV disease	17 (7.5)	1565 (5.2)	0.09
Other	8 (3.5)	901 (3.0)	0.03
Mortality at 1 year – n (%)			
All-cause	107 (46.9)	10604 (35.0)	0.24
Due to stroke	56 (24.6)	5196 (17.2)	0.18
Non-stroke CV disease	30 (13.2)	2725 (9.0)	0.13
Other	21 (9.2)	2683 (8.9)	0.01
Subgroup alive at discharge – N	***517***	***44330***	
Discharge to rehabilitation – n (%)	137 (26.5)	12966 (29.2)	0.17
If mRS 0 to 2 – n/N (%)	15/178 (8.4)	1658/19440 (8.5)	0.004
If mRS 3 to 5 – n/N (%)	119/325 (36.6)	11113/23856 (46.6)	0.20
Recurrent stroke/TIA within 30 days	15 (2.9)	1192 (2.7)	0.01
Recurrent stroke/TIA within 1 year	34 (6.7)	3096 (7.1)	0.02

Std. diff = standardized difference of the mean, where values > 0.10 are considered to represent a meaningful difference; IQR = interquartile range; mRS = modified Rankin Scale score, where higher scores indicate more disability; TIA = transient ischemic attack

Table 4: The effect of sequential risk adjustment on the hazard of one-year stroke case fatality associated with schizophrenia

Adjustment	All-cause mortality HR (95% CI)	Death due to stroke HR (95% CI)	Non-stroke death HR (95% CI)
-	1.08 (0.93 to 1.25)	1.16 (0.94 to 1.42)	0.98 (0.78 to 1.22)
Age and sex	1.39 (1.19 to 1.61)	1.46 (1.19to 1.79)	1.31 (1.05 to 1.63)
Age and sex + income quintile, rural residence	1.38 (1.19 to 1.60)	1.46 (1.19 to 1.80)	1.28 (1.03 to 1.60)
Age and sex + income quintile and rural residence + stroke type and stroke severity	1.31 (1.13 to 1.52)	1.40 (1.14 to 1.72)	1.21 (0.97 to 1.52)
Age and sex + income quintile and rural residence + stroke type and stroke severity + smoking, diabetes, hyperlipidemia, hypertension, prior stroke	1.27 (1.10 to 1.48)	1.37 (1.12 to 1.68)	1.17 (0.94 to 1.46)
Age and sex + income quintile and rural residence + stroke type and stroke severity + smoking, diabetes, hyperlipidemia, hypertension, prior stroke + brain imaging within one hour of arrival, care on stroke unit	1.31 (1.13 to 1.52)	1.44 (1.17 to 1.77)	1.18 (0.95 to 1.48)
Age and sex + income quintile and rural residence + stroke type and stroke severity + smoking, diabetes, hyperlipidemia, hypertension, prior stroke + brain imaging within one hour of arrival, care on stroke unit + intensive care unit admission, tracheostomy, feeding tube	1.33 (1.14 to 1.54)	1.47 (1.20 to 1.80)	1.19 (0.95 to 1.48)

HR = hazard ratio for schizophrenia (N = 612) vs. no schizophrenia (N = 51,861); CI = confidence interval. Hazard of death due to stroke accounts for the competing risk of death from other causes.



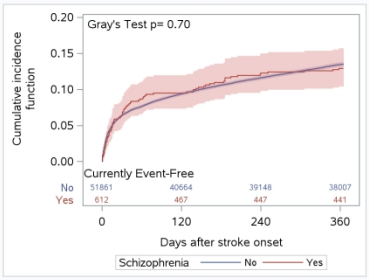


Figure 1a (top): Cumulative incidence of death due to stroke in people with and without schizophrenia
Figure 1b (bottom): Cumulative incidence of non-stroke death in people with and without schizophrenia

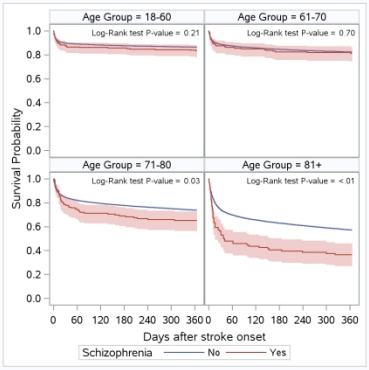
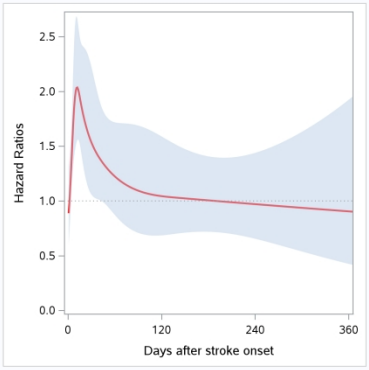


Figure 2: Survival after stroke in people with and without schizophrenia, by age group



Supplemental Figure: Time-varying hazard ratios (and 95% confidence bands) for all-cause mortality after stroke associated with schizophrenia, estimated by a restricted cubic spline function.

Supplemental Table: Fully adjusted models for one-year mortality after stroke

	All-cause mortality HR (95% CI)	Death from stroke HR (95% CI)	Non-stroke death HR (95% CI)
Schizophrenia	1.33 (1.14 to 1.54)	1.47 (1.20 to 1.80)	1.19 (0.95 to 1.48)
Male sex (vs female)	1.09 (1.05 to 1.13)	1.06 (1.01 to 1.11)	1.10 (1.05 to 1.16)
Age group			
≤ 60	Reference	Reference	Reference
61-70	1.65 (1.54 to 1.77)	1.55 (1.41 to 1.71)	1.82 (1.65 to 2.01)
71-80	2.71 (2.55 to 2.89)	2.54 (2.33 to 2.77)	2.97 (2.71 to 3.26)
80+	4.91 (4.62 to 5.22)	4.83 (4.44 to 5.26)	5.24 (4.79 to 5.73)
Income quintile			
1 (lowest)	Reference	Reference	Reference
2	0.98 (0.93 to 1.03)	1.01 (0.94 to 1.09)	0.96 (0.89 to 1.03)
3	0.97 (0.92 to 1.02)	0.99 (0.92 to 1.06)	0.96 (0.90 to 1.03)
4	0.98 (0.93 to 1.03)	1.00 (0.93 to 1.08)	0.96 (0.90 to 1.04)
5 (highest)	0.94 (0.90 to 0.99)	1.03 (0.96 to 1.11)	0.87 (0.80 to 0.93)
Residence			
Large urban	Reference	Reference	Reference
Medium urban	1.02 (0.96 to 1.08)	1.10 (1.01 to 1.20)	0.95 (0.87 to 1.04)
Rural or small town	1.10 (1.05 to 1.16)	1.17 (1.09 to 1.25)	1.04 (0.97 to 1.12)
Stroke severity			
Severe	Reference	Reference	Reference
Moderate	0.48 (0.46 to 0.50)	0.45 (0.42 to 0.47)	0.52 (0.48 to 0.55)
Mild	0.18 (0.18 to 0.19)	0.12 (0.12 to 0.13)	0.25 (0.24 to 0.26)
Stroke type			
Ischemic	Reference	Reference	Reference
Hemorrhagic	1.77(1.70 to 1.84)	2.24 (2.12 to 2.37)	1.36 (1.27 to 1.44)
Smoking	1.02 (0.97 to 1.08)	1.03 (0.95 to 1.11)	1.02 (0.94 to 1.10)
Diabetes	1.27 (1.22 to 1.32)	1.07 (1.01 to 1.14)	1.45 (1.37 to 1.53)
Hyperlipidemia	0.85 (0.82 to 0.88)	0.83 (0.78 to 0.87)	0.87 (0.83 to 0.92)
Hypertension	1.09 (1.05 to 1.14)	1.16 (1.10 to 1.23)	1.03 (0.97 to 1.09)
Prior stroke	1.20 (1.15 to 1.25)	1.16 (1.09 to 1.23)	1.24 (1.18 to 1.32)
Neuroimaging within 1 hour	1.28 (1.23 to 1.32)	1.45 (1.38 to 1.52)	1.12 (1.06 to 1.18)
Stroke unit care	0.64 (0.62 to 0.66)	0.60 (0.57 to 0.63)	0.69 (0.65 to 0.72)
Intensive care unit admission	1.18 (1.14 to 1.23)	1.27 (1.20 to 1.34)	1.10 (1.03 to 1.17)
Tracheostomy	0.73 (0.64 to 0.83)	0.71 (0.60 to 0.85)	0.75 (0.61 to 0.92)
Feeding tube	0.81 (0.76 to 0.87)	0.73 (0.66 to 0.80)	0.92 (0.83 to 1.02)

Cox proportional hazard model for the hazard of mortality within 1-year of stroke adjusted for demographics, comorbid conditions, stroke severity, stroke type, and in-hospital care, with factors entered sequentially to the model

C-statistic = 0.78 for the model of all-cause mortality; 0.82 for death from stroke and 0.74 for non-stroke death

STROBE checklist of items that should be included in reports of observational studies
Article: Stroke care and outcomes in people with and without schizophrenia: a retrospective cohort study
Author: Kapral, Moira K.

	Item No	Recommendation	Location in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract, p. 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, p. 3
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Background section, p. 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Background, p.6
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, pp. 6-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, pp.6-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods (data sources and patient sample), pp. 6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, p. 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, pp. 6-8
Bias	9	Describe any efforts to address potential sources of bias	1. Population-based patient sample

			2. Complete follow up using administrative data 3. Multivariable analyses
Study size	10	Explain how the study size was arrived at	We included the entire sample of stroke patients from the study time frame.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	See methods section (statistical analysis), pp. 8-9.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	See methods section (statistical analysis), pp.8-9.
		(*b*) Describe any methods used to examine subgroups and interactions	See methods section (statistical analysis), pp.8-9.
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a. Follow up was done using administrative data
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, p. 10
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results, p.10 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results, pp. 11-12 and Tables 2-4 and Figure

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, pp. 11-12 and Tables 2-4 and Figure
		(*b*) Report category boundaries when continuous variables were categorized	Results, pp. 11-12 and Tables 2-4 and Figure
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, pp. 12-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, pp. 15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, pp. 12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, p.15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Study funding section, p. 2