

Risk of premature stroke in recent immigrants (PRESARIO)

Population-based matched cohort study



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ABSTRACT

Background: New immigrants to North America, most of whom are under age 50 years, exhibit fewer risk factors for cardiovascular disease than their native-born counterparts, yet the stress of resettlement may conceivably place them at higher risk of stroke. We determined the risk of acute stroke associated with recency of immigration.

Methods: We completed a population-based matched cohort study in Ontario, the largest province in Canada, from April 1, 1995, to March 31, 2007. Overall, 965,829 new immigrants were matched to 3,272,393 long-term residents by year of birth, sex, and location. New immigrants were identified as new recipients of universally available public health insurance, and long-term residents were those insured for 5 years or longer.

Results: The mean age of the participants at study entry was about 34 years and the total number of observed strokes was 6,216 after a median duration of follow-up of about 6 years. The incidence rate of acute stroke was 1.69 per 10,000 person-years among new immigrants and 2.56 per 10,000 person-years among long-term residents (crude hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.62–0.71). After adjusting for age, income quintile, urban vs rural residence, history of hypertension, diabetes mellitus and smoking, and number of health insurance claims, the HR for stroke was 0.69 (95% CI 0.64–0.74). Similar risk estimates were seen for both ischemic and hemorrhagic stroke subtypes.

Conclusion: New immigrants appear to be at lower risk of premature acute stroke than long-term residents. This finding does not appear to be explained by the availability of health care services or income level. *Neurology*® 2010;74:451–457

GLOSSARY

CI = confidence interval; DAD = Discharge Abstract Database; HR = hazard ratio; ICD = International Classification of Diseases; OHIP = Ontario Health Insurance Plan; OR = odds ratio; PRESARIO = Premature Stroke Associated with Recency of Immigration to Ontario; RPDB = Registered Persons Database.

Large-scale immigration remains one of the great human activities of the past 100 years. Immigrants play an essential role in the new economy, social development, and the arts. According to the United Nations, there are more than 200 million migrants globally (<http://esa.un.org/migration>). About 75% of all immigrants are found within just 12% of all countries, Canada being one of them. In 2005, Canada received 262,200 immigrants, of which more than half settled in Ontario, the country's most populated province. Overall, approximately one-quarter of all Ontarians were born in another country.¹

Recent immigrants to Canada and the United States, most of whom are under age 50 years, tend to exhibit lower rates of chronic diseases like hypertension compared to native-born citizens.² This decreased prevalence of disease is called “the healthy immigrant effect.”³ There

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From the Division of Neurology (G.S.), Department of Medicine (G.S., D.A.R., J.G.R.), Department of Health Policy Management and Evaluation (G.S., D.A.R., J.G.R.), Institute of Clinical Evaluative Sciences (G.S., D.A.R., H.L., J.G.R.), and Obstetrics and Gynecology (J.G.R.), St. Michael's Hospital, Sunnybrook and Women's College Health Sciences Centre (D.A.R.), and Faculty of Social Work and Department of Family & Community Medicine (E.F.-T.), University of Toronto, Toronto, Ontario; and Population Health Research Institute and the Department of Medicine, Division of Cardiology (E.L.), McMaster University, Hamilton, Ontario, Canada.

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are 3 hypothesized reasons for this effect. Individuals willing and able to undergo the stress and difficulties of immigration are usually in excellent physical and mental health prior to immigration (i.e., self-selection effect). Furthermore, the medical examination required of all potential immigrants screens out unhealthy candidates. The “salmon effect” suggests that immigrants who experience ill health and/or long-term unemployment return to their country of origin, thereby enhancing the health profile of the immigrant cohort.⁴

Upon arrival, however, new immigrants are exposed to persistent stressors as they adapt to changes in diet, employment, housing, and social relationships.^{3,5} These stressors may theoretically place them at higher risk of stroke and other forms of cardiovascular disease,^{6,7} but whether this is so is not known.

We determined the risk of premature stroke among new immigrants to Ontario, where universal health care is available to all its residents, and detailed computerized medical records are also maintained. We also evaluated whether new immigrants have higher rates of stroke-related mortality and institutionalization compared to long-term or native-born residents (hereafter called “long-term residents”).

METHODS Risk of Premature Stroke Associated with Recency of Immigration to Ontario (PRESARIO) was a population-based matched retrospective cohort study. All participants had to be enrolled in the Ontario Health Insurance Plan (OHIP), which covers most aspects of health care and for which there is no user fee.

Participants. We included adults aged 16 to 65 years at study entry. New immigrants were defined as those who received a new OHIP number at any time between April 1, 1995, and March 31, 2006. Long-term residents were defined as those aged 16 to 65 years who had an active OHIP number for 5 years or more during this same time period.

We attempted to match each immigrant to 5 randomly selected long-term residents by year of birth (i.e., within 365 days), sex, and Local Health Integration Network, the latter representing 1 of 14 geographic entities designed to plan, integrate, and fund local health services; however, a minimum match of one long-term resident per new immigrant was permitted. Each long-term resident was assessed in the 60-month period before study entry date to ensure that the OHIP number was active during that time, with at least one OHIP claim (to ensure that the person was living in Ontario). Hence, a long-term resident may have been born in Ontario or emigrated to the province at least 5 years earlier. Persons with more than one OHIP eligibility record were excluded, as described below.

Outcomes. The main study outcome was a hospitalization with a most responsible diagnosis (i.e., primary discharge diagnosis) of acute stroke determined through the International Classification of Diseases, 9th (ICD-9) and 10th (ICD-10) revisions. A premature stroke was defined as that arising before age 65 years. Though somewhat arbitrary, this upper age cutoff avoids the term “stroke in the young,” which usually applies to individuals under age 45 or 50 years. Second, approximately 40% of strokes in Canada arise after age 80 years; yet fewer than 0.1% of immigrants are over age 65 years.

We also evaluated the specific risk of ischemic stroke (ICD-9 433 and 434, ICD-10 I63), hemorrhagic stroke (ICD-9 430 and 431, ICD-10 I60 and I61), and stroke of undetermined cause (ICD-9 436, ICD-10 I64). Secondary study outcomes following an incident stroke included mean length of hospital stay, discharge to a long-term care facility, and both 30-day and 1-year mortality.

Data sources. PRESARIO was completed using 3 deterministically linked provincial health care administrative databases. Hospitalization records were obtained from the Canadian Institute for Health Information Discharge Abstract Database (DAD), which was used to identify a hospitalization for acute stroke, as well as related hospital length of stay and disposition (discharged alive or dead, as well as to a long-term care facility) thereafter. The anonymized discharge abstracts contain the unique encrypted healthcare number, age and sex of the individual, date of admission, and up to 25 diagnoses in ICD-9 (before 2002) and ICD-10 (from 2002 onward). Date of issue of a health insurance number, used as a proxy for the date of arriving in Ontario, was retrieved from the Registered Persons Database (RPDB). This database contains health care identifiers and demographic and vital information for all eligible individuals. The RPDB was linked with the DAD to ascertain deaths arising after hospital discharge. The OHIP database contains records of all physicians' billing information for outpatient and inpatient services, including a service date and a single diagnosis. Since some conditions (e.g., preexisting hypertension, diabetes mellitus, and smoking) may be diagnosed on an outpatient basis, we used the OHIP database to identify comorbidities arising between the study entry date and either the day before hospitalization for an acute stroke or the date of censoring, whichever came first. To avoid counting people who emigrated from and then returned to Ontario, we excluded those with more than one OHIP eligibility record, defined as the presence of multiple start dates in the RPDB eligibility file after April 1, 1990. Income quintile was based on the 2001 Statistics Canada Census, which assigns income quintiles to each neighborhood community, with 1 representing the lowest and 5 representing the highest income quintile.⁸

The health care databases were linked anonymously using encrypted individual health card numbers to safeguard patient confidentiality.

Standard protocol approvals. PRESARIO was approved by the Research Ethics Boards at our local institutions (Sunnybrook and St. Michael's Hospitals).

Analyses. The period of observation for each new immigrant began on the date of the new OHIP number (which is typically 3 months after achieving residency in Ontario⁹). The period of observation for each long-term resident began on the same date as the new immigrant that the person was matched to. Time-to-event analysis was performed up to March 31, 2007. An individual was

Table 1 Characteristics of study participants^a

Characteristics	New immigrants (n = 965,829)	Long-term residents (n = 3,272,393)
Measured at study entry		
Mean (SD) age, y	33.2 (10.1)	34.3 (10.9)
Age groups, y		
16-30	420,044 (43.5)	1,293,001 (39.5)
31-44	420,288 (43.5)	1,399,720 (42.8)
45-64	125,497 (13.0)	579,672 (17.7)
Females	480,719 (49.8)	1,625,688 (49.6)
Income quintile (Q)		
Q1 (lowest)	291,982 (30.8)	550,356 (16.9)
Q2	214,043 (22.6)	639,480 (19.6)
Q3	172,263 (18.2)	679,387 (20.8)
Q4	144,675 (15.2)	705,441 (21.6)
Q5 (highest)	126,241 (13.3)	690,706 (21.2)
Unknown	16,723 (1.7)	7,126 (0.2)
Urban residence	923,158 (95.6)	2,916,033 (89.1)
At study entry		
Hypertension	130,718 (13.5)	601,921 (18.4)
Dyslipidemia	155,112 (16.1)	532,418 (16.3)
Diabetes mellitus	74,273 (7.7)	257,625 (7.9)
Current smoking	1,146 (0.12)	8,920 (0.27)
Mean (SD) no. of physician claims	35.7 (48.2)	46.5 (60.6)
Median (IQR) duration of follow-up, y	5.5 (2.8-8.5)	6.2 (3.6-9.0)

Abbreviation: IQR = interquartile range.

^aData are presented as n (%) unless otherwise indicated.

censored when hospitalized for an acute stroke, if he or she left the province, died, or reached the end of the study period.

The incidence rate of acute stroke was determined for both new immigrants and long-term residents. A survival curve was generated using the Kaplan-Meier procedure, with disease-free survival compared between new immigrants and long-term residents using a log-rank test. Crude and adjusted hazard ratios

(HR) and 95% confidence intervals (CI) were derived by multivariable Cox proportional hazards models, with long-term residents serving as the referent category. Adjustment variables included age (continuous in years), income quintile (quintiles 1 to 5), and urban vs rural residence, each at study entry, as well as diagnosed hypertension, diabetes mellitus or smoking, and number of physician OHIP claims, each after study entry. A sensitivity analysis was for the above after excluding all long-term residents hospitalized for stroke within the 60-month period before study entry. Stratified analyses were also performed for the following participant characteristics at study entry: age (16 to 30, 31 to 44, and 45 to 64 years), sex, rural and urban residence, and income quintile.

Among those hospitalized for an acute stroke during the study period, hospital length of stay was compared between immigrants and long-term residents using an unpaired *t* test. We also evaluated their risk of in-hospital, 30-day, and 1-year mortality, the risk of being admitted to a long-term care facility directly from hospital, as well as the risk of either in-hospital mortality or admission to a long-term care facility. Crude and adjusted odds ratios (OR) and 95% CI were derived using conditional logistic regression analysis to express this risk, using the same variables as in the Cox proportional hazards model above.

All *p* values were 2-sided, at a significance level of 0.05. Analyses were performed using SAS for UNIX (SAS Institute Inc., Cary, NC).

RESULTS We excluded 201 individuals aged over 65 years (98 immigrants and 103 long-term residents). Of the 4,238,222 individuals less than 65 years included in the study, 965,829 participants were classified as new immigrants and 3,272,393 as matched long-term residents.

The mean ages of the immigrant and long-term residents at study entry were 33 and 34 years, respectively; more than 85% were under age 45 years (table 1). About half of all participants were female, and 96% of immigrants and 89% of long-term residents dwelled in an urban area. There were more immigrants residing the lowest income quintile area (31% vs 17%). After study entry, the prevalence of hypertension was lower among new immigrants than long-term residents (14% vs 18%). Fewer physician OHIP claims were submitted for new immigrants (36%) than for long-term residents (47%) (table 1). The median duration of follow-up was 5.5 years for new immigrants and 6.2 years for long-term residents.

Study outcomes. There were 933 premature strokes among the new immigrants and 5,283 events among the long-term residents, corresponding to incidence rates of 1.7 and 2.6 per 10,000 person-years (crude HR 0.66, 95% CI 0.62–0.71) (figure 1, table 2). After adjustment for potential confounders, the HR for acute stroke changed minimally (0.69, 95% CI 0.64–0.74). Upon excluding 148 long-term residents with a known history of stroke up to 60 months before study entry, new immigrants re-

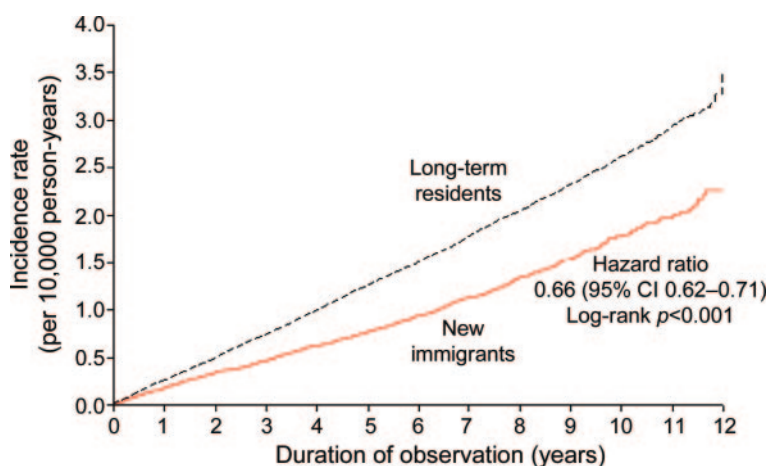
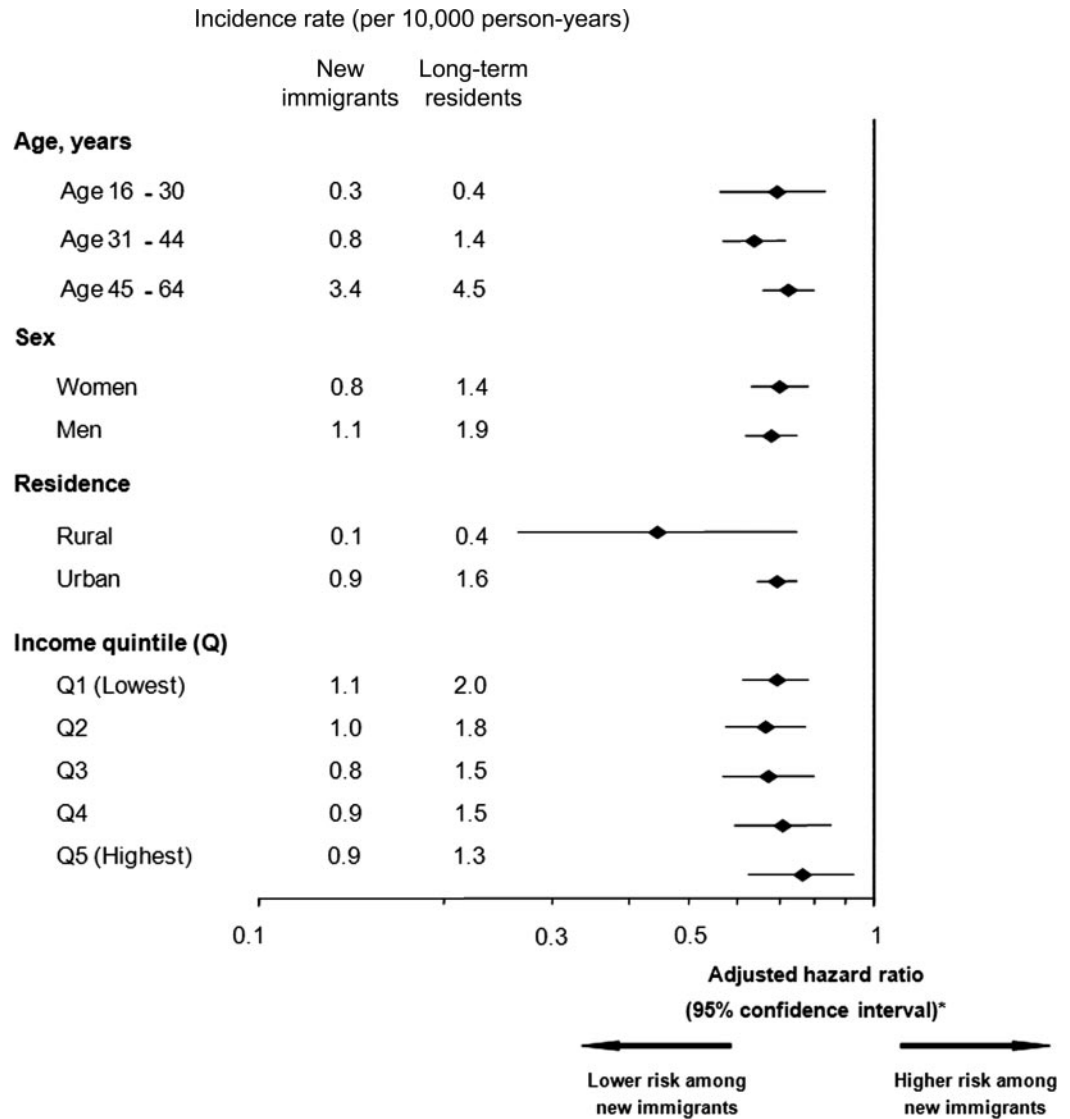
Figure 1 Risk of premature acute stroke, comparing 965,829 new immigrants and 3,272,393 long-term residents in Ontario

Figure 2 Risk of premature acute stroke according to participant characteristics at study entry, comparing new immigrants and long-term residents



*Adjusted for age (continuous in years), income quintile, and urban vs rural residence, each at study entry, as well as diagnosed hypertension, diabetes mellitus or smoking, and number of physician claims, each after study entry.

Table 2 Risk of premature acute stroke comparing new immigrants and long-term residents

Study outcome	No. (incidence rate per 10,000 person-years)		Hazard ratio (95% confidence interval)	
	New immigrants (n = 965,829)	Long-term residents (n = 3,272,393)	Unadjusted	Adjusted ^a
All strokes	933 (1.7)	5,283 (2.6)	0.66 (0.62–0.71)	0.69 (0.64–0.74)
Ischemic stroke	411 (0.74)	2,319 (1.1)	0.66 (0.60–0.74)	0.71 (0.64–0.79)
Hemorrhagic stroke	326 (0.59)	1,789 (0.87)	0.68 (0.60–0.77)	0.69 (0.61–0.78)
Undetermined stroke	195 (0.35)	1,170 (0.57)	0.62 (0.54–0.73)	0.65 (0.56–0.76)

^aAdjusted for age (continuous in years), income quintile, and urban vs. rural residence, each at study entry, as well as diagnosed hypertension, diabetes mellitus, or smoking, and number of physician claims, each after study entry.

maintained at a lower associated risk of new-onset acute stroke (crude HR 0.72, 95% CI 0.67–0.77). Comparable adjusted HRs were observed for ischemic, hemorrhagic, and undetermined premature stroke subtypes (table 2). The risk of stroke was also significantly lower among new immigrants across age, sex, residence, and income strata (figure 2).

Among those who developed an acute stroke during the study period, hospital length of stay was longer for new immigrants than long-term residents (12.5 vs 11.2 days; $p < 0.0001$). While no significant difference was observed for in-hospital, 30-day, or 1-year mortality, new immigrants were more likely discharged to be transferred from hospital to a long-term care facility than long-term residents (adjusted OR 1.4, 95% CI 1.0–1.9) (table 3).

Table 3 Risk of death or institutionalization comparing new immigrants and long-term residents who developed a premature acute stroke during the study period

Study outcome	No. (%)		Odds ratio (95% confidence interval)	
	Recent immigrants (n = 933)	Long-term residents (n = 5,283)	Unadjusted	Adjusted ^a
Mortality				
In-hospital	90 (9.7)	589 (11.2)	0.85 (0.67-1.1)	0.91 (0.71-1.2)
30-day	94 (10.1)	629 (11.9)	0.83 (0.66-1.0)	0.89 (0.70-1.1)
1-year	125 (13.4)	837 (15.8)	0.82 (0.67-1.0)	0.88 (0.71-1.1)
Institutionalization at the time of hospital discharge				
In-hospital mortality or institutionalization at the time of hospital discharge	141 (15.1)	797 (15.1)	1.0 (0.83-1.2)	1.1 (0.86-1.3)

^aAdjusted for age (continuous in years), income quintile, and urban vs rural residence, each at study entry, as well as diagnosed hypertension, diabetes mellitus, or smoking, and number of physician claims, each after study entry.

DISCUSSION In this large population-based cohort study, new immigrants had about a 30% lower relative risk of premature acute stroke than matched long-term residents. This was so for all stroke subtypes, across various age, sex, residence, and income strata, and upon adjusting for conventional stroke risk factors and physician visits. On the other hand, when a new immigrant sustained an acute stroke, they had a slightly longer hospital length of stay and a marginally higher likelihood of transfer to a long-term care facility.

Our study has several limitations. First, we used the date of enrollment in universal health insurance (OHIP) to approximate of the time of arrival to Ontario. Since most immigrants become eligible for OHIP after 3 months of achieving residency, this may not be a critical issue. Although we attempted to capture all immigrants, refugees and those who had not yet received OHIP were missed. Had we misclassified the time of new receipt of OHIP, or had confused new immigrants with long-term residents, then our effect sizes would likely have been attenuated. We did not have access to information on the study participants' educational attainment or lifestyle, nor did we possess measures of blood pressure, blood glucose, serum lipids, or stroke severity. While the majority of immigrants to Ontario are from Asia (see appendix e-1 on the *Neurology*[®] Web site at www.neurology.org), we lacked information on ethnic background or country of birth of individual study participants, which may limit the generalizability of our results to other countries. We also lacked details about the preexisting health of the new immigrants in our study, even though we had at least

5 years of administrative health data for the long-term residents. Although a rare event, participants who left the province were censored in our study, yet we have no information about their subsequent health status. Finally, our findings do not address the risk of stroke among immigrants aged 65 years and older, since they comprised a tiny proportion (0.01%) of all new immigrants, and were excluded from our study. Despite these limitations, PRESARIO provides new and precise information about the risk of premature stroke among recent immigrants. New immigrants were carefully matched to long-term residents, and risk estimates were adjusted for other relevant predictors of stroke.

Canada has one of the highest rates of immigration. According to the 2006 Census, there were 3,398,725 foreign-born individuals in Ontario, representing 28.3% of the total population, the highest proportion among all Canadian provinces. Ontario is also one of the most ethnically diverse areas in the world (see appendix e-1 for details). The results of our study constitute the first step in understanding the stroke risk and associated factors in recent immigrants. At least 3 major determinants have been ascribed to the health of immigrants after their resettlement.¹⁰ The first is presence of a preexisting illness.^{3,11} The second is the process of convergence, in which health patterns or habits in the destination country are adopted.^{3,12} The third is resettlement stress, related to new physical, psychosocial, and environmental factors.^{3,12} In our study, new immigrants had a lower rate of hypertension, a finding supported by others.^{13,14} The tendency for young immigrants to have lower rates of chronic diseases than their host country counterparts may reflect the fact that the most robust individuals choose to immigrate. Furthermore, required medical examinations of all prospective immigrants screen out many unhealthy applicants.¹⁵ It seems unlikely that the salmon effect played a substantial role in this prospective study. The salmon effect suggests that those with a chronic and debilitating illness return to their country of origin, thereby lowering morbidity and mortality rates among immigrants. The outcome investigated in this study—premature acute stroke—is a sudden onset condition, however. Finally, it is possible that we may have missed some fatal out-of-hospital strokes, but this minor bias would not have weighed more on recent immigrants than long-term residents, all of whom were eligible for OHIP.

Not all studies support a healthy immigrant effect. In one Israeli study, recent immigrants had higher rates of hypertension and coronary angina than their Israeli-born counterparts, but many immigrants had originated from the former Soviet

Union.¹⁶ In another study, the prevalence of cardiac disease was 3 to 5 times higher among Japanese Americans than their compatriots who had retained a traditionally Japanese lifestyle.¹⁷ In a Swedish study in Stockholm County, foreign-born individuals aged 30 to 74 years had a higher adjusted risk of myocardial infarction than those born in Sweden.¹⁸ In Canada, the United States, and other Western nations, many recent immigrants originate from South and East Asia, where the rates of obesity, hypertension, and diabetes mellitus are typically lower.^{19,20} For other medical conditions, such as cancer, large Swedish epidemiologic studies showed more inconsistent results.^{21,22}

The finding that new immigrants who sustain a stroke may have a longer hospitalization stay and need for long-term care raises important questions. Is this a reflection of differences in stroke severity or acute stroke care? The lack of difference in in-hospital mortality makes the latter less likely. On the other hand, Canada's universal health care system offers equal access to emergency care, especially for an acute and time-sensitive medical condition like an acute stroke. So, are new immigrants with stroke less able to mobilize resources to return home? Given that our study participants were so young, it may be that the new immigrants were more apt to be single and without supportive care from family members compared to long-term residents. Clearly, having detailed information of the country of birth and some basic physical and social measures of new immigrants (and their non-immigrant counterparts) could help explain why new immigrants have fewer strokes than long-term residents, but may do worse after having a stroke.

Our findings verify the presence of a healthy immigrant effect in relation to stroke risk.³ Accordingly, policies are needed that aim to preserve the healthier state of new immigrants, while continuing to focus on lowering stroke risk among all adults.²³ What we learn could translate into long-term health benefits for the whole population, irrespective of their immigrant status.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Hong Lu, Dr. Gustavo Saposnik, and Dr. Joel Ray. The statistical analysis was completed at the Institute of Clinical Evaluative Sciences (ICES), University of Toronto.

DISCLOSURE

Dr. Saposnik receives research support from the Ontario Stroke System and the SE Toronto Stroke Program (operational grants) and from the Heart and Stroke Foundation Ontario (Clinician Scientist Award). Dr. Redelmeier serves as Canada Research Chair in Medical Decision Sciences. Dr. Lu reports no disclosures. Dr. Fuller-Thomson serves on an editorial advisory board of the *Journal of Gerontological Social Work* and receives research support from the Social Science and Humanities Research Council, Canada. Dr. Lonn serves on scientific advisory boards for

AstraZeneca, GlaxoSmithKline, Merck Serono, Novartis, Sanofi-Aventis, and Abbott; and receives research support from AstraZeneca, Glaxo-SmithKline, Roche, Canadian Institutes of Health Research, and the Heart and Stroke Foundation of Canada. Dr. Ray reports no disclosures.

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.