THE ASSOCIATION BETWEEN IMMIGRATION STATUS AND STROKE INCIDENCE, CARE AND OUTCOMES

(Spine title: Immigration status and stroke)

by

Manav Virat Vyas

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The association between immigration status and stroke incidence, care and outcomes

Manav V. Vyas

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ABSTRACT

Immigrants to high-income countries have a lower cardiovascular disease incidence and mortality compared to host populations, a phenomenon termed the *healthy immigrant effect*. However, differences in stroke incidence, care and outcomes between immigrants and host populations have not been well-characterized. We studied the incidence, acute care, and short-term and long-term outcomes of stroke in immigrants compared to long-term residents in Ontario, Canada. People born outside of Canada who immigrated after 1985 were considered immigrants. Compared to long-term residents, immigrants had stroke at a younger age and had a lower adjusted hazard of stroke (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.66-0.68). Compared to long-term residents, immigrants were less likely to seek care for transient ischemic attacks, and among patients with ischemic stroke, immigrants received equal or better acute stroke care, had higher disability on discharge (adjusted risk ratio 1.18, 95% CI 1.13-1.22), and marginally lower long-term (15 years) mortality (adjusted HR 0.94, 95% CI 0.88-1.00). These associations varied with age at the time of stroke, stroke

subtype, ethnicity, country of origin, and immigration class, highlighting heterogeneity in the observed healthy immigrant effect. While the lower incidence of stroke and the lower mortality following stroke in immigrants compared to long-term residents may suggest a healthy immigrant effect, the younger age at the time of stroke and the higher disability on discharge in immigrants compared to long-term residents highlights a higher risk of premature and disabling stroke in immigrants. Further research should evaluate the reasons for the observed differences, which could then inform the design of effective interventions to improve stroke outcomes for both immigrants and long-term residents.

Keywords immigration status, stroke, incidence, care, outcomes, and ethnicity

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1 Overview of objectives

a. To compare the incidence of stroke in immigrants and long-term residents.

b. To study the quality of acute stroke care and short-term outcomes after ischemic stroke in immigrants and long-term residents.

c. To evaluate long-term outcomes and secondary stroke preventive care in immigrants and long-term residents with ischemic stroke.

d. For all of the above, to evaluate the effect of immigration-related factors such as country of origin, time since immigration, age at arrival, and immigration class.

2 Scope of the problem

Migration is a universal phenomenon. Animals and birds migrate long distances, integrating external and internal factors, to avoid adverse seasonal climates, avoid predators at vulnerable life stages, and reach final destinations that provide food.[1] There is evidence that supports that human migration began about 1.8 million years ago as the genus *Homo* moved out of the continent now known as Africa to other parts of the world.[2] Over the years, human beings have migrated for a variety of reasons, and the factors associated with this migration have changed over time. Figure 1.1 shows some factors associated with human migration in modern times.

In recent years, human migration has increased due to socio-economic reasons, as well as war, persecution and climate change.[3] In 2019, over 200 million people worldwide were considered immigrants.[4] While most migration occurs from one low- or middle-income country to a neighbouring low- or middle-income country, the second most common type of migration is from a low- or middle-income country to a high-income country, and this is the focus of this dissertation.[5] In 2018, approximately 10 million people migrated permanently or temporarily to one of the G20 countries.[5] Many of these immigrants now reside in North America and Europe.[4] In addition to providing immigrants with a safe living environment (in most high-income countries), such migration has allowed populations of the host countries to grow, which has been associated with an economic advantage.[6] In the absence of immigrants from low- and middle-income countries, it is anticipated that by 2070 the population of North

America would decrease by 21%.[7] Thus, in addition to contributing to growing economies, immigrants lead to demographic shifts in the host populations. These demographic shifts affect population-level health in host populations, making it important for healthcare providers and policy makers to understand the health of immigrants.[3]

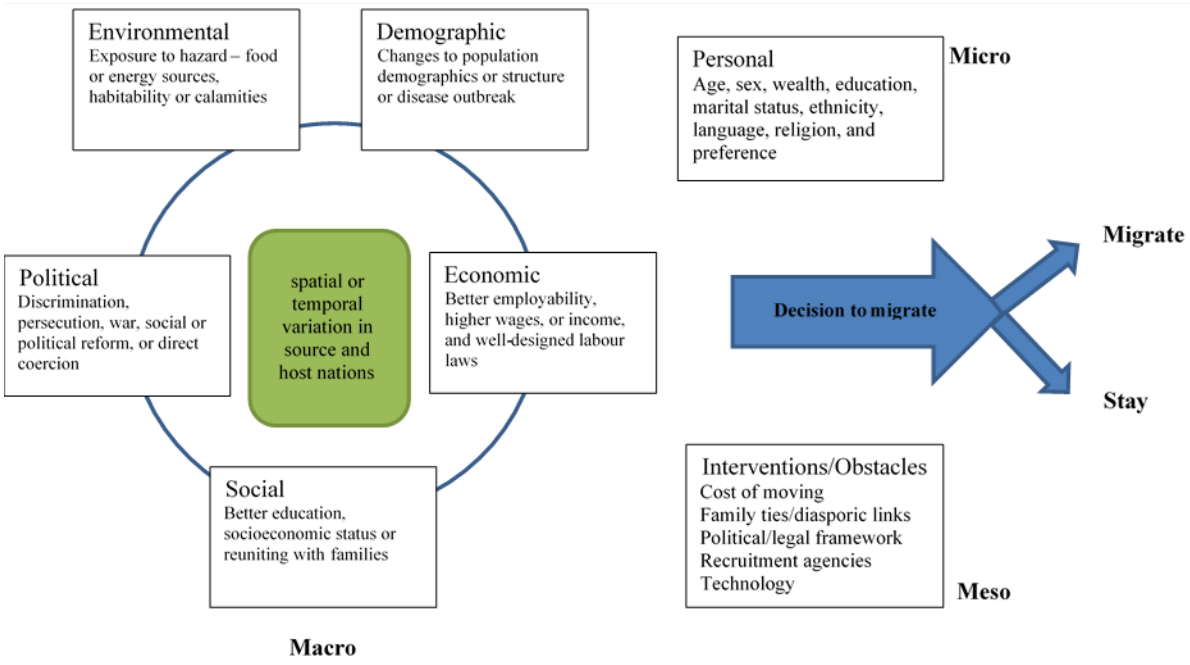


Figure 1.1. Factors related to human migration.

(Adapted from Foresight: Migration and Global Environmental Change (2011) Final Project Report. The Government Office of Science, London)

3 Immigrants in Canada

Prior to "European contact", Canada was inhabited by people of different cultural backgrounds who settled in the North Americas for agriculture and fishing.[8] First Nations, Inuit and Métis people are jointly recognized as the Aboriginal peoples of Canada, hereafter referred to as Indigenous peoples of Canada. British and French colonization during the 17th and 18th centuries led to a shift in the demographics of Canada's population. This colonization of the Canadian lands led to significant changes in lives of Indigenous peoples of Canada, and reconciliation efforts are still underway for the wrong done to the rightful owners of Canadian lands. Indigenous peoples of Canada, who are considered the owners of

the Canadian lands, are the only non-immigrants to Canada. However, this dissertation will focus on immigrants who arrived in Canada after 1985 (because of limitations in our data – *vide infra*). This dissertation also does not identify Indigenous people as a separate group for analyses, as such work must be undertaken in partnership with Indigenous communities or organizations and is beyond the scope of this body of work.

Since Confederation in 1867, more than 17 million immigrants have come to Canada[9] and Canada is considered a "mosaic" country because of its history of accepting immigrants over the years. According to the 2016 Census report, approximately 1 in 5 Canadians identified themselves as foreign-born or immigrant.[10] Most immigrants to Canada after the World Wars came from Europe and North America based on the then present nationality- and ethnicity-based immigration policies. However, in 1967, Canada became the first country to introduce a points-based system for economic migration (Order-in-Council, October 1st, 1967, PC 1616) that facilitated immigration of people of non-European and non-American backgrounds. Some version of this scoring system has been employed to the present date. The points are accumulated based on education, work experience, proficiency in either the English or French language, and family ties in Canada. A higher score suggests a higher likelihood of immigration, and the cut-off values have varied over the years. As a result of this policy, recent Canadian immigrants have been younger and more educated compared to immigrants who arrived in prior years, and compared to the host populations.[10] The country of origin of immigrants has changed over time, with the majority of the most recent immigrants to Canada arriving from South Asia, East Asia, and Africa.[11]

4 Immigrants in Ontario

Ontario is Canada's most populous province. Of the total Ontario population of 14 million people, approximately 21% are considered immigrants.[10] Permanent residents and citizens and those on valid work visas are covered by the provincial health plan which includes coverage for physician services, hospital and emergency room care, and investigations ordered by physicians. Prescription medications are also covered for those who are 65 years or older and for younger people if they spend a part (approximately 4% or more) of their net income on prescription drug costs. The vast majority of immigrants to Ontario have public

healthcare coverage which is identical to that of long-term residents. This is in contrast to some high-income countries where the quality of healthcare is closely related to health insurance coverage.[12] Those not covered under Ontario's health insurance plan include asylum seekers, migratory farm workers and undocumented immigrants, and the findings from this dissertation will not apply to these groups. This is a limitation of this dissertation.

5 Immigration and health

5.1 Healthy immigrant effect

Previous research suggests that immigrants are generally healthier than host populations. This is called a *healthy immigrant effect*.[13,14] It is due a selection bias whereby only those with a certain human capital and health can immigrate.[15] Such selection bias is amplified by the points-based system which favours immigrants with knowledge of Canadian languages, as well as certain education and work experience.[16] Furthermore, pre-immigration health assessments aim to select those who are healthy and can contribute to the Canadian economy.[17]

The effect of such selective migration and its impact on health has been studied previously. Compared to the host populations, immigrants have been found to have a lower all-cause mortality[18], lower incidence of cancer[19], schizophrenia[20], and cardiovascular disease[21], and lower mortality following these conditions[22,23]. However, this healthy immigrant advantage varies based on various factors, including immigration class (refugee vs. economic) and country of origin.[21] It has also been shown to vary based on measures of acculturation as the immigrants accrue risk factors similar to that of host populations, known as the *acculturation effect*.

5.2 Acculturation effect

Multiple reasons have been proposed for the acculturation effect. Immigrants from low- and middle-income countries typically have lower rates of unhealthy behaviours compared to host populations in high income countries. When this is a consequence of delayed industrialization and its attendant side effects, it has been described as a *time traveller effect*.[24] However, with time, health behaviours including smoking[25], alcohol use[26], sedentary

behaviour[27], and diet[28] may change in immigrants such that the rates in immigrants become similar to those of the host populations. In addition to lifestyle changes, immigrants may also face psychosocial problems that include stress of living in new environment and living away from their families, which could influence the risk of chronic disease over time.[29,30] Furthermore, immigrants may face discrimination and racism and this too has been linked to poor health outcomes, including cancer and cardiovascular disease.[31–33] Lastly, immigrants are often underemployed – working in a career or a job that is not representative of the education level attained – because their education from home countries is not transferrable, or not easily transferrable.[31] Many immigrants work in precarious work environments, including doing shift work, which has been linked to development of cardiovascular disease and cancer.[34,35]

The most commonly used proxy of acculturation is time since immigration because over time immigrants accrue risks similar to that of host nations. However, age at which immigrants arrive in host nations also makes a difference because younger immigrants are more likely to assimilate than older immigrants.[36] Furthermore, immigration class could modify this association, as those who migrate on economic basis are more likely to adapt when compared to immigrants who arrive as refugees (forced migration).[37]

5.3 Return migration (salmon effect)

Much like the salmon and other species that return to their spawning grounds or birth place at the end of life, humans may also return to their regions of origin closer to the time of their death.[38,39] The reasons for such return migration are not clearly understood, but one hypothesis is that there is a sense of stability and comfort in being close to one's place of origin.[24] Other factors may include being closer to friends and family, and patriotic sentiments. This return migration can affect studies of mortality in immigrants compared to long-term residents because eventual deaths in those who return to their home regions will not be counted in the country under study. Such unbalanced follow-up between two comparison groups has been shown to lead to biased estimates in both observational and experimental studies.[40,41] This bias, called the *salmon bias*, has been well-studied in Hispanic

and Asian Americans returning to their home regions in older ages and eventually being lost to follow-up.[42,43]

6 Why study stroke?

6.1 Stroke is a leading cause of death and disability

Stroke is a leading cause of death and disability worldwide.[44] Stroke is also a common cardiovascular condition. The lifetime risk of stroke in people over 25 years as per the Global Burden of Disease study was about 24.9% in 2016, with no difference in the lifetime risk of stroke between men and women (24.7% vs. 25.1%).[45] This suggests that there is a 1 in 4 chance of developing stroke over one's lifetime. The worldwide age-standardized incidence of stroke in 2016 was 203 per 100,000 people, which was lower than estimates from previous years, yet higher than that of most other neurological conditions.[46] Stroke is among the most common causes of hospital admissions in Canada, and in 2013, about 405,000 people in Canada were living with the effects of stroke.[47,48]

In addition to being common, stroke is associated with significant morbidity and mortality. In 2016, about 5.5 million deaths worldwide were attributed to stroke and 116.4 million disability adjusted life-years were lost due to stroke, the highest among all neurological conditions.[46] The estimated weighted-mean cost per patient per month of outpatient and inpatient stroke care from a healthcare perspective was about US dollars (USD) 1,515 (standard deviation USD 1,396) based on a study of 60 different stroke programs across various countries.[49] These costs did not include costs from informal caregiving or lost productivity[50]. In Canada, the average annual costs of stroke based on a single centre study was Canadian dollar (CAD) 74,353, with higher costs for disabling stroke (CAD 107,833).[51] Because of its high cost and the high incidence and prevalence, stroke is one of the most expensive health conditions in Canada, with an estimated CAD 3.6 billion a year in both direct and indirect costs.[52] Thus, studying stroke incidence and outcomes is valuable from a public health perspective, and for the planning of healthcare services and spending. Given the increasing population of immigrants worldwide, it is important to study the association of immigration status with stroke incidence and outcomes.

6.2 Unique characteristics of stroke

Unlike other medical conditions such as cancer or mental health conditions that have an insidious onset of symptoms, stroke by definition involves the rapid or sudden onset of focal neurological symptoms, often characterized by weakness or language difficulties that last for more than 24 hours.[53] Thus, most patients with symptoms of stroke end up seeking some form of health care either at the onset of the symptoms or shortly thereafter. Therefore, this avoids *length-time bias* which is common when studying other medical conditions such as cancer.[54] Furthermore, contrary to mental health conditions where stigma and patient preferences influence health seeking behaviour and eventual diagnosis[55], the physical symptoms of stroke are usually sufficiently noticeable to permit a prompt diagnosis.[56] One exception may be patients with minor stroke or transient ischemic attack (TIA) who may not seek urgent medical attention, or may seek attention outside of an acute care hospital.[57] According to the Canadian Stroke Best Practice Guidelines and other international guidelines, people with suspected or confirmed stroke should be admitted to an acute care hospital for urgent evaluation.[58,59] This allows one to use hospitalizations or emergency department visits, typically captured in administrative health data, as a proxy for stroke incidence. Because evidence-based measures of quality of care are well-developed for stroke care, these can be used as a proxy for the overall quality of health care in immigrants compared to long-term residents.[58,59] Lastly, most patients with stroke require regular medical follow-up for management of vascular risk factors and secondary prevention, and thus one can study quality of secondary stroke preventive care and long-term outcomes following stroke.[60,61] Therefore, from a public health perspective, studying the association between immigration status and stroke incidence, care and outcomes can provide important information on immigrant health that is not confounded by disease-specific diagnostic or care-seeking biases.

7 Immigration and stroke

The following section is a narrative summary of the literature on immigration status and stroke. The literature search was done in Medline using subject heading [exp Cerebrovascular Disorders/ and exp human migration/] and free text words (‘cerebral’ or

'cva' or 'cve' or 'cerebro' or 'ICH' or 'TIA' or 'SAH' or 'subarachnoid' or 'stroke' or 'infarct' or 'transient ischemic attack' or 'parenchymal' or 'intracerebral hemorrhage' or 'bleed', and 'immigrant' or 'migrant' or 'immigration' or 'emigrant' or 'emigration' or 'refugee' or 'expat' or 'asylum'), and only including studies published in English language.

7.1 Stroke incidence

Estimates of stroke incidence in immigrants compared to the host populations have generated variable findings. In a Danish study of over 45,000 people hospitalized due to cardiovascular disease, the adjusted incidence of stroke was similar in immigrants who arrived as refugees and the host population (incidence rate ratio [IRR] 1.07, 95% confidence interval [CI], 0.97-1.18), but it was lower in immigrants who arrived in the family-reunified category (IRR 0.56, 95% CI 0.48-0.66).[62] In Sweden, the adjusted relative risk of a first-ever stroke in a cohort of people living in the city of Malmö was higher in those born in Hungary or Yugoslavia (immigrants) compared to those born in Sweden, and lower in immigrants born in China or Vietnam compared to those born in Sweden.[63] In comparison, the rate of stroke-related hospitalization in Italy was higher in immigrant men and women compared to the Italian population.[64] In the United States of America (US), the Health and Retirement Study, including adults (50 years and older) reported a lower odds ratio (OR) of incident stroke (OR 0.58, 95% CI 0.41-0.81) in foreign-born Hispanics compared to non-Hispanic Whites, in comparison to stroke incidence in US-born Hispanics compared to non-Hispanic Whites (OR 1.07, 95% CI 0.80-1.42) .[65] A Canadian study of young adults (aged 18 to 65 years) found that the incidence of stroke in immigrants was lower than in non-immigrants, despite adjusting for various baseline differences, but it did not evaluate the risk based on country of origin or immigration class.[66] Another Canadian study found that the age-standardized incidence of stroke was lower in immigrants (1 per 1000 person-years) compared to long-term residents (1.3 per 1000 person-years), with variation in the risk based on the region of origin of immigrants.[21] These findings highlight the need to consider both the country of origin and the immigration class of immigrants when studying the influence of immigration status on stroke incidence. Of note, little is known about potential differences in the incidence of stroke subtypes (ischemic vs. hemorrhagic) in immigrants compared to non-

immigrants, or about the effect of measures of acculturation such as time since immigration or age at immigration.

7.2 Acute care and short-term outcomes

One prior study has reported on short-term stroke outcomes in immigrants compared to long-term residents. The Brain Attack Surveillance in Corpus Christi project included 935 Mexican Americans with stroke of whom 83 (8.9%) were immigrants with an average length of stay in the US of 47 years.[67] While there were no major differences in baseline vascular risk factors, at 90 days post-stroke immigrants had a better functional outcome (activities of daily living/instrumental activities of daily living; mean difference, -0.22; P=0.02; 1-4, higher scores worse) and no difference in neurological outcomes (log-National Institutes of Health Stroke Scale [NIHSS]; mean difference, -0.15; P=0.15; 0-44, higher scores worse) compared to non-immigrants.[67] In Florida, a small case series (n = 216) comparing acute stroke care of Haitian (immigrants from Haiti) to non-Haitian stroke patients found no significant differences in stroke severity or rates of thrombolysis administration[68] To our knowledge, there have been no other published studies comparing acute stroke care in immigrants and non-immigrants.

7.3 Long-term outcomes

All-cause mortality at one-year following a diagnosis of stroke was lower, although the confidence interval crossed 1.0, in immigrants compared to non-immigrants in Ontario, Canada (OR 0.88, 95% CI 0.71-1.1).[60] In Denmark, all-cause mortality (average follow-up time 5.4 years) following stroke was lower in refugees (HR 0.72, 95% CI 0.60-0.87) and family-reunified immigrants (HR 0.64, 95% CI 0.48-0.86) compared to the general population.[62] However, in the same study, there was no difference in cardiovascular disease-related mortality following stroke in immigrants compared to the general population, irrespective of immigration class.[62] To our knowledge, the long-term rates of vascular event recurrence or stroke recurrence based on immigration status have not been reported.

8 Ethnicity and stroke

The association between immigration status and stroke incidence, care and outcomes cannot be studied without considering the ethnicity of immigrants. Ethnicity refers to shared culture, such as language, ancestry, practices, and beliefs whereas race refers to physical differences that groups and cultures consider socially significant.[69] For the purposes of this dissertation, we will mainly focus on ethnicity; however, when reviewing the literature in the US, we will describe race-related disparities in care (especially concerning Black Americans).

8.1 Ethnicity and stroke incidence

Previous research has shown variation in the incidence of stroke and subtypes based on ethnicity. Compared to the Dutch ethnic group in the Netherlands, the risk of overall stroke and each stroke subtype was higher in the Surinamese ethnic group, and lower in the Moroccan ethnic group.[70] In South London, people of African and Caribbean origin had a higher rate of stroke and its subtypes compared to the White British.[71] In the US, a higher of risk of overall stroke was found among Blacks[72] and Hispanics[73] compared to White Americans, whereas the risk was lower for ischemic stroke and higher for intracerebral hemorrhage in Asian Americans[74]. In Canada, South Asian ethnicity was associated with a lower risk of ischemic stroke and hemorrhagic stroke; whereas Chinese ethnicity was associated with a lower risk of ischemic stroke, but a higher risk of hemorrhagic stroke.[75] Therefore, when evaluating the incidence of stroke, one should assess for ethnic differences in the incidence of stroke subtypes as well as overall stroke incidence.

8.2 Ethnicity and stroke care and short-term outcomes

In Amsterdam, a hospital-based study of 510 patients with acute stroke found that non-White patients were less likely to receive thrombolysis than White patients (odds ratio [OR] 0.34, 95% CI 0.17-0.71), and this was partly explained by a later arrival at the hospital.[76] Similarly, in the US, compared to White patients, Black and Hispanic patients with stroke were less likely to receive thrombolysis, deep vein thrombosis prophylaxis, and antithrombotics and lipid-lowering therapy on discharge.[77] In a cohort of patients with ischemic stroke over the age of 65 years (i.e., Medicare beneficiaries) in the US, non-White ethnic groups (Black, Hispanic, and Asian) had lower unadjusted and adjusted odds of being independently

ambulatory at discharge than their White counterparts.[78] Another study found that Asian Americans had a lower adjusted odds of being independently ambulatory at discharge after stroke than White Americans (OR 0.84, 95% CI 0.79-0.99) and a lower odds of achieving a modified Rankin score of 0 or 1 (OR 0.80, 95% CI 0.76-0.83).[79] In one Canadian study, the odds of institutionalization (being admitted to a long-term care facility) after stroke were higher in immigrants than non-immigrants, in both unadjusted and adjusted analyses; however, the confidence intervals were wide and included null values.[66]

8.3 Ethnicity and long-term outcomes

In England, Black Caribbeans and Black Africans have been found to have better long-term survival at 15 years compared to Whites after a diagnosis of stroke.[80,81] In contrast, long-term mortality following stroke in a US study did not vary based on race in one study.[82] The South London Stroke Registry in the UK did not find an association between Black ethnicity and risk of stroke recurrence at 10 years[83,84]; whereas, the multivariable-adjusted hazard ratio of recurrent stroke among Black Americans was 1.36 (95% CI 1.29-1.44) compared to White Americans in one US study.

Thus, ethnicity is an important consideration when evaluating stroke incidence, care and outcomes of immigrants.

9 Potential confounders

9.1 Age

Age is the most important risk factor for stroke incidence, and older age is associated with increased disability and mortality after stroke.[85,86] As previously discussed, due to selective migration patterns, immigrants are generally younger than host populations. In addition, Black, Hispanic or Asian ethnic groups have stroke at a younger age than White populations.[79,87,88] Thus, it is important to consider the differential effect of age on the association between immigration and stroke incidence and case-fatality.

9.2 Socioeconomic status

Low socioeconomic status has been associated with a higher risk of stroke incidence and worse outcomes following stroke.[89–93] Therefore, when studying the association between

immigration status and stroke incidence and outcomes, it is important to account for differences in socioeconomic status between immigrant and host populations.

Socioeconomic status generally incorporates some measure of income and/or education. Because of points-based immigration policies, immigrants in Canada are generally well-educated (especially those who arrived as economic migrants), yet have a higher likelihood of having chronic low-income (defined as family income below the low-income cut-off for 5 consecutive years or more) than those who are Canadian-born..[94] Chronic low-income was observed in immigrants irrespective of education attainment and duration of stay in Canada, and unobserved factors other than economic policy and immigrant background characteristics were felt to be contributing to these differences.[94]

9.3 Lifestyle and vascular risk factors

In an international case-control study that included people from 32 different countries around the world, a large proportion of the variation in the risk of stroke was explained by the presence of vascular risk factors that included: hypertension, diabetes, dyslipidemia, waist-to-hip ratio, smoking, physical activity, dietary habits, alcohol intake and psychosocial factors.[95] These risk factors (collectively known as vascular risk factors) have been associated with stroke incidence and stroke outcomes.[95] Prevalence of these risk factors can change upon immigration and with acculturation[27,28,96], and can vary based on immigration class.[97]

Previous research suggests that immigrants to Sweden and the US have lower rates of smoking and alcohol use than the host populations.[98,99] These differences could be related to lower access to these substances in some countries of origin or due to differences in cultural practices and societal norms regarding substance use.[99] Similarly, the dietary habits of immigrants depend on ethnocultural factors and tend to differ from those of the host populations.[28,100,101] Availability and access to fruits and vegetables is different in source countries and host countries which could partly be responsible for the differences in dietary habits.[100] While most dietary choices of immigrants are considered healthier in regards to cardiovascular disease incidence than the western diet, the dietary habits of South Asians have been associated with a higher risk of cardiovascular disease.[28] The rates of active or

sedentary behaviours also vary based on immigration status.[102,103] Differences in physical activity and diet coupled with ethnicity influence rates of obesity and waist-hip ratio, and vary with immigration status.[104,105]

Immigrants have been found to have lower rates of hypertension than host populations in the US and Canada.[104,106] However, in a population-based survey in the US, South Asian immigrants developed hypertension at a younger age than non-immigrants (non-Hispanic Whites),[107] and studies from the US and the UK suggest that immigrants are less likely than the host populations to achieve control of hypertension.[108,109] Furthermore, rates of hypertension vary with ethnicity, with those arriving from Africa and the Caribbean more likely to have hypertension than other immigrant groups in the UK, and by race, as Black Americans have a higher population attributable risk of hypertension for cardiovascular disease than White Americans.[110,111] Similarly, the prevalence of diabetes in immigrants varies based on country of origin, with those from the Indian subcontinent (which includes India, Pakistan, Afghanistan, Sri Lanka) having a higher prevalence than immigrants from other world regions.[104,112,113] Furthermore, the influence of diabetes on the incidence and outcomes of stroke is different in South Asians compared to non-South Asian ethnic groups, suggesting an additive interaction of diabetes with South Asian ethnicity.[114] Lastly, based on a systematic review of the literature on the incidence and care of diabetes among immigrants around the world, it was noted that that control of diabetes in immigrants was on average worse than that of host populations, with access to primary preventative care, access to affordable medications, and lack of knowledge and language barriers identified as possible explainations.[115] In the US, Hispanic immigrants were found to have higher rates of hyperlipidemia (above normal total cholesterol) and among those treated for high cholesterol, only 64.3% had achieved appropriate cholesterol control.[96]

Therefore, it is important to evaluate vascular risk factors when studying the association between immigration status and stroke incidence and outcomes.

10 Confounders vs. mediators

When considering the pathways through which immigration status could be associated with stroke incidence and outcomes, it is important to recognize that traditional vascular risk

factors such as smoking, alcohol use, sedentary behaviour, diet, hypertension, diabetes, and dyslipidemia, and ethnicity can also be considered mediators, and not mere confounders.[116] This is the case because these risk factors may be in the causal pathway of the association between immigration status and stroke incidence and outcomes (mediator), for example, diet has been shown to mediate the association between immigration and acculturation and prevalence of diabetes[117], and are also independently associated with both immigration status and stroke incidence and outcomes (confounder). However, in the US, such traditional risk factors only accounted for half of the excess stroke risk in Blacks compared to Whites[118], and similarly in Canada, traditional risk factors did not fully explain the observed variation in the incidence of cardiovascular disease between different immigrants based on region of origin.[21] Therefore, to understand the contribution of various risk factors on the observed associations between immigrations status and outcomes of interest, this dissertation will report unadjusted, age- and sex-adjusted, and fully adjusted associations between immigration status and stroke incidence and outcomes. The fully adjusted outcomes will include traditional vascular risk factors, when available. This dissertation will not attempt to address whether the latter are mediators, confounders or both. Furthermore, interactions between immigration status and vascular risk factors are also beyond the scope of this dissertation, but will be considered in future research projects.

11 Why is it difficult to study immigrants?

11.1 Selection bias when studying immigrants

In an experimental study of new butterflies that were released into different habitat patches, about 40% of the butterflies settled in a new patch during their lifetime (immigrated from original patch), and the factors associated with lower rates of emigration included higher density of butterflies, abundance of flowers, and large patch area. Female butterflies emigrated earlier in their life and moved farther away than male butterflies, and the emigrating butterflies were larger than those who stayed.[119] Similar to animal studies, many factors are responsible for human migration and vary based on factors related to individuals, home countries, and host countries. While most human migration can be considered

controlled or planned, it can occur due to natural calamities (earthquakes, tsunami and floods) or human-made calamities (war and persecution).

Furthermore, as previously mentioned, observational studies are often only able to study a select group of immigrants because of difficulties in identifying these individuals in host nations, or because some return to their home countries closer to the end of the life and are lost to follow-up. Figure 1.2 highlights the selection biases at play when studying the health of immigrants in host nations.

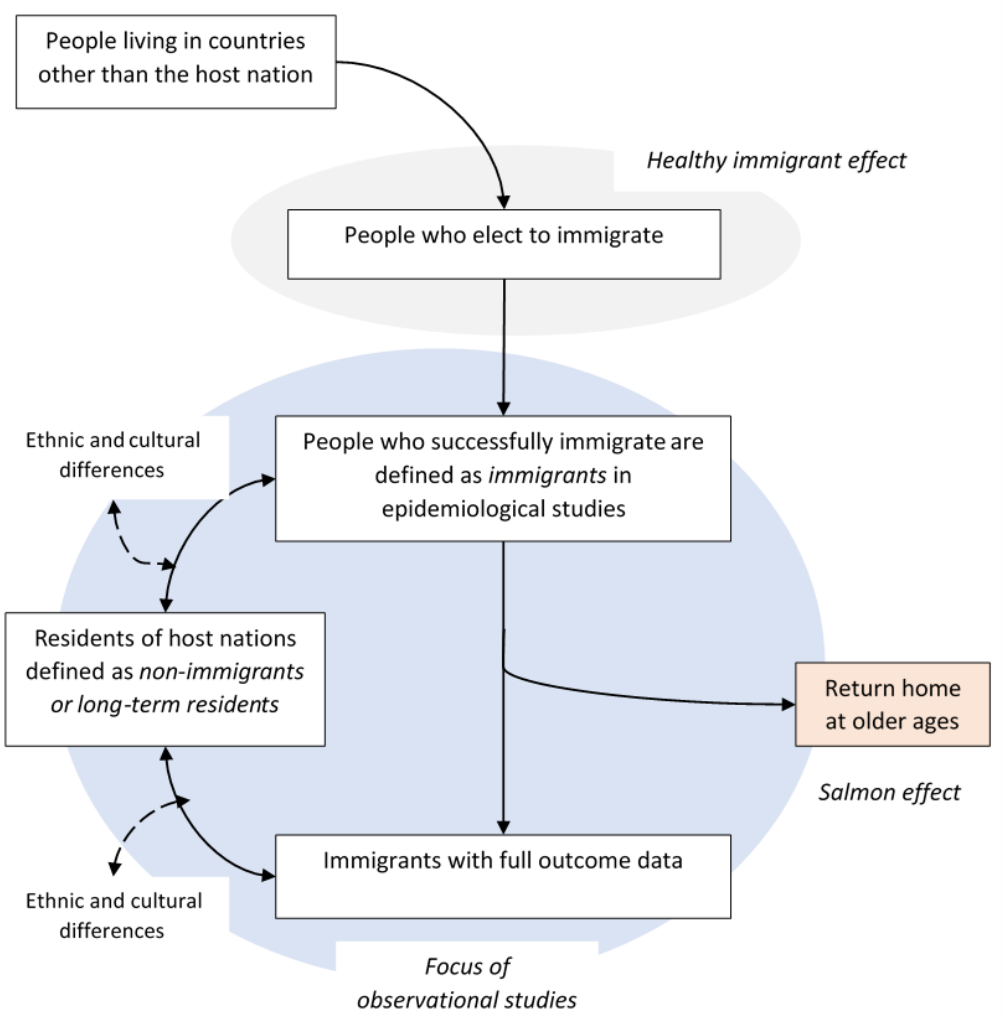


Figure 1.2. Selection bias in observational studies of immigrants in host nations.

11.2 Lack of randomized controlled trials

A natural experiment study of immigration via a random selection process (a lottery system) found that the Tongan people who immigrated (randomly selected) to New Zealand had higher rates of hypertension that persisted over time compared to those living in Tonga who applied but were not randomized to immigrate to New Zealand.[120] However, such natural experiment studies in humans are rarely possible.

Thus, one has to rely on well-designed observational studies to evaluate the health effects of immigration.

11.3 Lack of animal models

Studies on migratory birds found biological changes of pre-migratory hyperphagia and obesity to act as an energy source for short- or long-range flights and support pre-migration preparation in animals.[121] However, unlike animals, migration in humans is not a biological process alone, as many socioeconomic factors dictate who elects to migrate. Furthermore, the lived experience of immigrants before and immediately after immigration is unique and varies based on individual, environmental and social factors. This psychosocial impact of immigration is difficult to evaluate using animal models.

12 Rationale for the research

For the reasons described above it is challenging to study the health of immigrants, yet it is important to study the association between immigration status and stroke incidence, care and outcomes because the number of immigrants will likely continue to increase world-wide and the knowledge of this association will be helpful for host nations to plan allocation of health care resources. This is especially important as immigrants are generally younger than the host populations, and will contribute to the ageing population of host nations over time. Further, immigration is both a consequence of the social determinants of health and a social determinant of health in its own right. Thus, studying immigrant health in high-income countries allows one to evaluate the impact of socioeconomic factors associated with being an immigrant (for example age, sex, ethnicity, education) on maintaining or degrading health upon immigration such that the observed associations can be applicable to broader

populations beyond immigrants.[122] Finally, if ethnic differences in stroke incidence or outcomes based on the country of origin of immigrants are identified, future work can focus on understanding the social and biological factors driving these differences which can in turn guide the development of targeted primary and secondary prevention measures.

13 Data sources

13.1 Administrative databases

Health administrative data are routinely collected health information, which include information on acute care hospital admissions (Canadian Institutes of Health Information Discharge Abstract Database) and same day surgery or emergency department (ED) visits (National Ambulatory Care Reporting Systems). Diagnoses, including the main diagnosis – the most resource intensive diagnosis – are included in these databases using International Statistical Classification of Diseases and Related Health Problems 9th revision (ICD-9) and 10th revision (ICD-10) codes. These databases will be the primary source to identify incident events of stroke or transient ischemic attack (TIA) (chapter 2).[123] Using information from hospitalizations alone to identify incident stroke or TIA has been shown to be excellent with over 92% (95% CI 88-95) correct diagnoses, with kappa statistic of 0.89 (95% CI 0.82-0.96).[123] While this study did not report sensitivity or positive predictive value, another study, using similar inpatient hospitalizations codes for incident stroke or TIA, reported a sensitivity of 82.2% (95% CI 81.0-83.3) and a positive predictive value of 68.8% (95% CI 67.5-70.0).[124] For prevalent cases, different from incident cases, we will further include primary care or specialist physician visits where the final diagnosis code was in keeping with a stroke or TIA. A combination of acute care, emergency department, and outpatient care (one hospitalization or emergency department visit for stroke or TIA **OR** two (2) outpatient physician claims of stroke or TIA within 365 days) has been shown to have moderate sensitivity (68.0%; 95% confidence interval [CI] 60.5-75.5) and very high specificity (98.9%; 95% CI 98.6-99.2) for the identification of prevalent stroke or TIA.[125]

We will also include the following databases, where relevant, to determine prevalence of risk factors, receipt of outpatient or ambulatory care, or loss to follow-up: Registered Persons Database (RPDB) to obtain demographic (date of birth, sex, date of death and date of last

health system contact) information on people who have ever received provincial health coverage; National Rehabilitation Reporting System (NRRS) to capture outpatient or inpatient rehabilitation received at a designated rehabilitation centre; Ontario Drug Benefit database (ODB) to identify prescription claims; Ontario Health Insurance Plan (OHIP) Claims database to determine eligibility of receipt of provincial health insurance plan and to identify outpatient physician visits; Ontario Laboratories Information System (OLIS) for laboratory results; the Postal Code Conversion File (PCCF) to permit linkage to the Canada Census database to determine neighbourhood-level income; and the death registry and the Office of the Registral General Database (ORGD) to provide information on deaths and cause of death.

These databases are held securely at ICES (formerly the Institute for Clinical Evaluative Sciences) and are linked using unique encoded identifiers. ICES has developed its own validated cohort algorithms to identify people with hypertension[126], diabetes[127], chronic obstructive pulmonary artery disease[128], and congestive heart failure[129]. We will use these algorithms to identify the prevalence of these conditions in our cohorts, as well as similar validated algorithms for dyslipidemia[130] and atrial fibrillation[131]. Please see Table 1.1 for details on definitions of various outcomes and covariates.

13.2 Ontario Stroke Registry

The Ontario Stroke Registry (OSR) is a province-wide registry that includes data on all consecutive stroke patients seen at regional stroke centres in Ontario between 2003 to 2013, as well as on a population-based simple random sample of patients seen at all other institutions across the province of Ontario.[132] Data collection was performed by chart abstractors with neurological expertise, with the final diagnosis and other data elements obtained through review of clinical and neuroimaging data. Validation by duplicate chart abstraction has shown excellent agreement for key variables in the OSR.[132] The registry collected information on pre-hospital care (arrival by ambulance, time from symptom onset to hospital arrival, care received at a regional stroke centre), hyperacute stroke care (hospital arrival to brain imaging, results of brain imaging, receipt of thrombolysis, door-to-needle time, admission to intensive care unit, admission to stroke unit) and in-hospital care (vessel

imaging and results, whether a swallowing assessment was performed, prescription of antihypertensive, antiplatelet or anticoagulants on discharge in patients with ischemic stroke, duration of hospitalization, and in-hospital complications, including pneumonia and deep vein thrombosis). It also included clinical information such as the National Institutes of Health Stroke Scale (NIHSS), side of stroke, type of stroke, and modified Rankin Scale (mRS) on discharge. The registry has been used previously to identify sex differences in care and outcomes following stroke[133], to evaluate the effect of socioeconomic status on stroke[92], and to evaluate factors associated with in-hospital complications such as pneumonia[134], and percutaneous endoscopic gastrostomy (PEG)[135]. We will use data from the registry to evaluate acute stroke care, disability on discharge, and long-term outcomes following ischemic stroke (chapters 3 and 4).

13.3 Surname algorithm

Unlike the United Kingdom[136] and the United States[84] where data on ethnicity or race are collected in hospital-based records, Canada does not collect these data at the time of hospitalization or at the time of application of provincial health insurance coverage. Thus, we will use a surname algorithm developed by ICES to classify the Ontario population (both immigrants and long-term residents) into three ethnic groups: South Asian, Chinese and other.[137] Among long-term residents, the "other" category is mainly comprised of Caucasians. As per the 2016 Census Report, of the 3.8 million (29.3% of Ontario's population) people residing in Ontario who self-identified as visible minority, 29.6% were of South Asian ethnicity (Indian, Pakistani, Sri Lankan, or Bangladeshi) and 19.4% were of Chinese ethnicity (people from China, Taiwan, Hong Kong or Macau). These two ethnic groups constituted the most common non-Caucasian ethnic groups in Ontario followed by Black (16.2%), Filipino (8.6%), and Arab (5.4%) ethnicity.[10] Indigenous peoples constituted 2.8% of Ontario's population. The positive predictive value using the surname algorithm compared to the self-reported ethnicity on survey data was 89.3% for South Asian ethnicity and 91.9% for Chinese ethnicity. The algorithm has low sensitivity (50.4% for South Asian and 80.2% for Chinese), and thus, should be used with caution when evaluating the proportion of people with a certain ethnicity in a disease cohort.[137]

13.4 Immigration Refugee and Citizenship Canada database

Immigration Refugee and Citizenship Canada (IRCC) is a federal agency overseen by the Ministry of Immigration that reviews immigration applications and selects the immigrants that meet Canadian immigration requirements. The IRCC's permanent resident database containing the Ontario portion is available for use at ICES. This includes records of people who landed in Ontario; immigrants who initially landed in another province, but eventually resided in Ontario are not included in the IRCC. The start date for these records is January 1, 1985. The database contains information on country of citizenship at the time of immigration application, immigration class (economic, family class, or refugee class), age at the time of arrival, and year of arrival. Economic immigrants are those who arrived through the points-based scoring system, family class immigrants are those who arrived based on family reunification procedures, and refugee class immigrants are those who arrived as refugees.

Overall, 85% of records in the IRCC can be matched to ICES administrative databases, either using deterministic, or, when not possible, probabilistic linkage. There is no variation in the success of this match based on age or sex.

14 Defining immigration status in Ontario

We will obtain records of immigrants arriving to Ontario from the IRCC's permanent resident database. We will define *immigrants* as those born of outside of Canada who became permanent residents after January 1, 1985, whereas those born in Canada or those who arrived in Ontario prior to January 1, 1985 will be considered *long-term residents.* Thus, the latter group will include both Canadian born and, because the cohort start date for this dissertation was 2003, those immigrants who have lived in Ontario for 18 years or more. Our data sources do not allow us to identify those immigrants not included in the IRCC database (asylum seekers, migratory workers, and people awaiting refugee hearings). If eligible for provincial health insurance, some of these immigrants will be misclassified as long-term residents; however, we assume that they will represent a small proportion of long-term residents.

Because we are interested in the ethnic origin of immigrants, we will use the country of citizenship at the time of immigration and classify the immigrant group into the following

categories to group them in world regions that could represent similar ethnicities: Western countries, Africa, Caribbean, East Asia, Latin America, Middle East, and South Asia (see Table 1.2 for list of countries included in each region).

Table 1.1. Definitions of variables included in this dissertation.

Variable	Type	Definition	Data source	Chapters that used this variable
Exposures of interest				
Immigration status	Binary	*Immigrants* – born outside of Canada and moved after January 1, 1985 *Long-term residents* – Canadian born or those who moved to Canada before January 1, 1985	IRCC	All chapters
Among immigrants only				
Time since immigration	Categorical	<5, 5 to 10 years, and > 10 years	IRCC	All chapters
Age at arrival	Categorical	< 25, 25 to 50 years, and > 50 years	IRCC	All chapters
Immigration class	Categorical	*Family or other* – people who immigrated under the family reunification program of immigration *Economic* – people who immigrated based on points-based system of immigration	IRCC	All chapters

		Refugee – people who immigrated based on humanitarian grounds of immigration		
Region of origin	Categorical	See details in Table 1.2	IRCC	All chapters
Ethnicity	Categorical	*Chinese* – people from or having ancestry in China, Hong Kong, Macau, or Taiwan *South Asian* – people from or having ancestry in India, Pakistan, Sri Lanka or Bangladesh *Other* – not belonging to either of above two categories	Surname algorithm	4
Outcomes of interest				
Incident stroke or transient ischemic attack (TIA)	Binary	Hospitalization or emergency department with a corresponding ICD-10 code in the main diagnostic field: H34.1, G45.x excluding G45.4, I60.x excluding I60.8, I61, I63, I64.	CIHI-DAD or NACRS	2
Incident ischemic stroke	Binary	Hospitalization or emergency department with a corresponding ICD-10 code in the main diagnostic field: H34.1, I63, I64	CIHI-DAD or NACRS	2 & 4
Incident intracerebral hemorrhage	Binary	Hospitalization or emergency department with a corresponding ICD-10 code in the main diagnostic field: I61	CIHI-DAD or NACRS	2 & 4
Incident subarachnoid hemorrhage	Binary	Hospitalization or emergency department with a corresponding ICD-10 code in the main diagnostic field: I60 excluding I60.8	CIHI-DAD or NACRS	2

modified Rankin scale	Categorical	Based on chart review 0 = no disability 1 = No significant disability despite symptoms; able to carry out all usual duties and activities 2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 = Moderate disability; requiring some help, but able to walk without assistance 4 = Moderately severe disability; unable to walk and attend to bodily needs without assistance 5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 = dead	OSR	3
Disabled on discharge	Binary	mRS between 3 and 5 – measured on the day of discharge	OSR	3
Death	Binary	Along with date of death	RPBD	All chapters
Vascular event recurrence	Binary	Incident stroke (composite of ischemic stroke or intracerebral hemorrhage) identified based on the code reported above **OR** Incident MI (ICD 10: I21 or I22)	CIHI-DAD or NACRS	4
Stroke recurrence	Binary	Incident stroke (composite of ischemic stroke or intracerebral hemorrhage) identified based on the code reported above	CIHI-DAD or NACRS	4

Cardiovascular mortality	Binary	Death in patients with the following ICD code as the most likely cause of death: I20-25or I60-69 (cardio) or I63, I64, H34.1	OGRD	4
Process measures				
Arrival by ambulance	Binary	Chart review	OSR	3
Times from last seen normal to arrival in hospital (in hours)	Continuous			
Type of cerebrovascular event – ischemic stroke vs. TIA	Categorical			
Patients with TIA admitted to an inpatient unit	Binary			
Received thrombolysis	Binary			
Reason for no thrombolysis – too late	Binary			
Palliative status	Binary			
Length of stay	Continuous			

National Institutes of Health Stroke Scale (NIHSS)	Continuous			
Carotid imaging	Binary			
Dysphagia screening				
Stroke unit care				
Echocardiography				
Holter monitor				
Anti-platelet or anti-coagulant agent on discharge				
Anti-hypertensive agent on discharge				
Lipid-lowering agent on discharge				
Secondary stroke preventive care				
Receipt of test for HbA1 or LDL	Binary	Test results included in provincial laboratory database	OLIS	4
Met target for HbA1c or LDL	Binary	If they reach the target as defined in the text	OLIS	4

Medication prescription filled	Binary	Based on data available in provincial drug coverage database using drug identification number (DIN) which is an 8-digit number assigned to each drug approved by Food and Drugs Act	ODB	4
Proportion days covered	Continuous	$\left(\frac{number\ of\ days \text{ covered } in\ a\ period}{number\ of\ days\ in\ a\ period}\right) * 100$	ODB	4
Adherent to medication	Binary	If PDC > 80%	ODB	4
Covariates of interest				
Age	Continuous	Based on date of birth of participants	RPDB	All chapters
Sex	Binary	Women or men, men used as the comparison group	RPDB	All chapters
Neighbourhood-level income	Quintiles	Obtained by linking census information from 2006 and 2011 to postal-code files	PCCF and Census	All chapters
Date of last contact	Continuous, date	Obtained from a variety of databases at ICES (see details in Table 4.1)	Multiple sources	All chapters
Hypertension	Binary	≥ 1 Hospitalization for hypertension **OR** ≥ 2 physician claims in a two-year period **OR** 1 physician claim followed by another physician claim or hospitalization within two years.	Multiple sources	All chapters

Diabetes	Binary	≥ 3 physician diagnostic code (250) in a one-year period	Multiple sources	All chapters
Chronic obstructive pulmonary disease (COPD)	Binary	≥1 Hospitalization for COPD **OR** ≥ 3 physician claims in a two-year period	Multiple sources	2
Charlson comorbidity index	Continuous	ICES-derived scale (described in detail in the text section 6.1 in Chapter 3)	Multiple sources	All chapters
Congestive heart failure (CHF)	Binary	≥ 1 Hospitalization **OR** 1 physician claim in emergency visit or outpatient clinic, followed by ≥ 1 Hospitalization, ER visit, or physician claim within one year.	Multiple sources	2
	Binary	Based on chart review	OSR	3, 4
Dyslipidemia	Binary	Based on OLIS database: Levels above the threshold (2.5 mg/dL) will be considered to have hyperlipidemia **OR** ODB claims for one of the statins (using DIN list)	Multiple sources	2
		Based on chart review	OSR	3, 4
Atrial fibrillation	Binary	1 hospitalization (CIHI-DAD) or 1 emergency room visit (NACRS/SDS), ICD-10 (2002 onwards) – I48; ICD-9 (pre-2002) – 427.31 or 427.32 **OR** cardioversion (without physician billing codes) – using billing code Z437	Multiple sources	2
	Binary	Based on chart review	OSR	3, 4
Stroke or TIA prevalence	Binary	one hospitalization or emergency department visit for stroke or TIA (using ICD-9 or ICD-10 codes) **OR**	CIHI-DAD,	2

		two outpatient physician claims of stroke or TIA within 365 days (OHIP specific diagnostic codes)	NACRS or OHIP	
Prior stroke or TIA	Binary	Based on chart review	OSR	3, 4
Dementia	Binary	Chart review	OSR	3, 4
Coronary artery disease	Binary			
Current smoking	Binary			
Chronic kidney disease	Binary			
Cancer	Binary			
Teaching hospital	Binary			
Language fluency	Binary			

Abbreviations: IRCC – Immigration Refugee and Citizenship Canada; OSR – Ontario Stroke Registry; PCCF – Postal Code Conversion File; RPDB – Registered Person's Database; CIHI-DAD – Canadian Institute of Health Information-Discharge Abstract Database; NACRS – National Ambulatory Care Reporting System; ORGD – Office of Registrar General-Deaths; OLIS – Ontario Laboratories Information System.

Table 1.2. List of countries in each region selected.

World region	Countries included
Africa	Angola, Republic of Benin, Republic of Botswana, Burkina-Faso, Burundi, Federal Republic of Cameroon, Republic of Central African Republic, Chad, Comoros, the Democratic Republic Congo, People's Republic of the Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gambia, Ghana, Republic of Guinea, Guinea-Bissau, Republic of Ivory Coast, Kenya, Lesotho, Liberia, Madagascar, Malawi, Republic of Mali, Republic of Mauritania, Mauritius, Mayotte, Mozambique, Namibia, Republic of the Niger, Nigeria, Rwanda, Sao Tome and Principe, Sao Tome E Principe, Senegal, Seychelles, Sierra Leone, Democratic Republic of Somalia, Republic of South Africa, Republic of South Sudan, Swaziland, United Republic of Tanzania, Republic of Togo, Uganda, Zambia, Zimbabwe.
Caribbean	, Bermuda, Jamaica, Republic of Trinidad and Tobago, Barbados, Anguilla, Antigua and Barbuda, The Bahama Islands, Cayman Islands, Dominica, Grenada, Nevis, St. Kitts-Nevis, St. Lucia, St. Vincent and the Grenadines, Turks and Caicos Islands, British Virgin Islands, Cuba, Dominican Republic, Guadeloupe, Haiti, Martinique, US Virgin Islands, Aruba, Guyana, Surinam, French Guiana, Cape Verde Islands, St. Helena, Sint-Maarten
East Asia	Gabon Republic, Macau Sar, People's Republic of China, Taiwan, Hong Kong, Japan, Republic of Indonesia, Philippines, Myanmar (Burma), Malaysia, Singapore, Brunei, Cambodia, People's Democratic Republic of Korea, Republic of Korea, Laos, People's Republic of Mongolia, Thailand, Tibet, Socialist Republic of Vietnam, Nauru, Papua New Guinea, Fiji, New Caledonia, Vanuatu, The Solomons, Soloman Islands, Tuvalu, Kiribati, Guam, Republic of The Marshall Islands, Federated States of Micronesia, Republic of Palau, Cook Islands, Wallis And Futuna, Pitcairn Island, American Samoa, Western Samoa, French Polynesia, Tonga, Reunion, Macau, Commonwealth of the Northern Mariana Islands, Democratic Republic of East Timor
Latin America	Mexico, Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Republic of Panama, Panama Canal Zone, Puerto Rico,

	Argentina, Brazil, Chile, Colombia, Peru, Uruguay, Venezuela, Bolivia, Ecuador, Paraguay, Falkland Islands, Cape Verde Islands.
Middle East	Turkey, Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, Israel, Lebanon, Syria, Palestinian Authority (Gaza/West Bank), Cyprus, Iran, Iraq, Jordan, Kuwait, Saudi Arabia, Bahrain, Oman, Qatar, Republic of Yemen, People's Democratic Republic of Yemen, United Arab Emirates, Egypt, Algeria, Morocco, Tunisia, Libya, Western Sahara, Democratic Republic of Sudan.
South Asia	Sri Lanka, India, Pakistan, Bangladesh, Afghanistan, Bhutan, Nepal
Western countries	United Kingdom, Austria, Belgium, Luxembourg, Czechoslovakia, Czech Republic, Slovak Republic, Denmark, Estonia, Latvia, Lithuania, Finland, France, Germany, Greece, Hungary, Republic of Ireland, Italy, Malta, The Netherlands, Norway, Poland, Portugal, Azores, Madeira, Spain, Canary Islands, Sweden, Switzerland, Union of Soviet Socialist Republics, Croatia, Yugoslavia, Slovenia, Bosnia-Herzegovina Belarus, Moldova, Russia, Ukraine, Serbia and Montenegro, Republic of Serbia, Republic of Montenegro, Republic of Kosovo, Macedonia, Albania, Andorra, Bulgaria, Gibraltar, Iceland, Liechtenstein, Monaco, Romania, San Marino, Holy See, Australia, New Zealand, United States of America, Greenland, Montserrat, England, British Overseas Citizen, Northern Ireland, Scotland, Wales, Channel Islands, Cyprus, Belize

All data analyses will be performed using SAS 9.4 © 2002-2012 by SAS Institute Inc., Cary, NC, USA.

15 Research Questions

15.1 Stroke incidence

What is the association between immigration status and the incidence of stroke in adults (age ≥ 18 years) residing in Ontario, Canada?

Hypothesis

We hypothesize that immigrants will have a lower risk of stroke than long-term residents; however, this association will vary based on country of origin.

15.2 Acute care and outcomes on discharge

Are there differences in the quality of acute stroke care and disability on discharge following ischemic stroke in immigrants and long-term residents seen at acute care hospitals in Ontario, Canada?

Hypothesis

We hypothesize that there will be a delay in stroke onset to arrival time for immigrants compared to long-term residents, but there will be no differences in the quality of acute stroke care or disability on discharge following ischemic stroke between immigrants and long-term residents.

15.3 Long-term outcomes and secondary stroke preventive care

Following an ischemic stroke, do long-term outcomes of all-cause mortality and vascular event recurrence and secondary stroke preventive care vary between immigrants and long-term residents in Ontario, Canada?

Hypothesis

We hypothesize that the long-term outcomes of all-cause mortality and vascular event recurrence, and secondary stroke preventive following ischemic stroke will not vary between immigrants and long-term residents.

Chapter 2 Immigration Status and Stroke incidence

1 Overview

This chapter will compare the incidence of stroke and stroke types in immigrants and long-term residents using administrative databases.

2 Research Questions

1. Does the incidence of stroke and stroke subtypes vary between immigrants and long-term residents?
2. Does the association between immigration status and stroke incidence vary by age, country of origin of immigrants, and immigration class?

3 Study population

We identified all Ontario residents aged 18 to 105 years on January 1, 2003 (cohort start date) who were eligible for the provincial health insurance plan on this date and in the year prior using the provincial registered person's database. We excluded people residing in a long-term care home in the 5 years prior to the cohort start date and those with a history of stroke or transient ischemic attack in the 12 years prior to the cohort start date (using a stroke prevalence algorithm: hospital or emergency department visit with a diagnosis of stroke or TIA **OR** two (2) physician claims within 365 days with corresponding diagnostic code for stroke or TIA, details in Table 1.1).[124] Given that over 95% of immigrants reside in urban areas of the province, we excluded those living in non-urban areas (defined as those residing in a Canadian Census-defined geographic area with a population of less than 10,000 residents).

Using unique identifiers, we linked these individuals to administrative databases that are held securely at ICES. We obtained information on age, sex, neighbourhood-level income from population-based registry, census and postal-code files (see Table 1.1 for details). We also obtained information on comorbidities such as hypertension[126], diabetes[127], dyslipidemia, atrial fibrillation[131], chronic obstructive pulmonary disease (COPD)[128] and congestive heart failure (CHF)[129] using validated algorithms (Table 1.1).

4 Exposure of interest

We defined *immigrants* as those born outside of Canada who became permanent residents between January 1, 1985 and the cohort start date, whereas those born in Canada or those who arrived in Ontario prior to 1985 were considered *long-term residents.*

5 Outcomes of interest

Our primary outcome was occurrence of first-ever stroke, defined as an emergency department visit or an admission to an acute care hospital with the main diagnosis (most resource intensive diagnosis) of stroke, composite of ischemic stroke (ICD-10 code: ischemic stroke (H34.1, I63.x, I64.x), intracerebral hemorrhage (I61.x) or subarachnoid hemorrhage (I60.x, excluding I60.8) or TIA (G45.x excluding G45.4). This definition has a high sensitivity and specificity.[123] We elected to include "stroke, not otherwise specified" (I64.x) in the definition of ischemic stroke because after the directive from the Canadian Stroke Strategy in 2010, there was a reduction in the use of this code (almost halved) with a corresponding increase in the prevalence of ischemic stroke (I63.x), suggesting that with provision of brain imaging for all patients seen in emergency room or hospitalized, it was clear that that I64.x was possibly incorrectly used in patients with ischemic stroke.[124] Further, when the algorithm using ICD-10 codes (including I64.x in ischemic stroke) were compared to medical chart review, they were found to have a positive predictive value of over 85%.[123] We included TIA and emergency department visits as well as hospitalizations to minimize the impact of differential care-seeking behaviours and admission thresholds for minor events. The secondary outcomes were stroke subtypes of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, and TIA. If an individual had more than one event during follow-up, we included the first event in the primary analyses. We set the date of end of follow-up as March 31, 2018.

6 Statistical Analysis

6.1 Primary analyses

We reported standardized differences to compare baseline characteristics between immigrants and long-term residents. Standardized differences express the difference in means or prevalence between two populations as a proportion of the pooled standard deviation. We used the convention that standardized differences greater than 0.10 are considered to reflect a meaningful difference.[138]

We used age as the time-scale in the survival analyses to account for the differential age of cohort participants at the start of the cohort.[139] Thus, the unadjusted estimates from such models can be considered age-adjusted. We used cause-specific Cox proportional hazards models to calculate the unadjusted and adjusted hazard ratio (HR) of stroke or TIA in immigrants compared to long-term residents, adjusting for sex, neighbourhood-level income, hypertension, diabetes, dyslipidemia, atrial fibrillation, CHF and COPD. These models accounted for the competing risk of death and censored subjects at the end of the study period or at time of emigration (if alive and event free).[140] We obtained information regarding date of death through linkage to the death registry and that of loss to follow-up using multiple databases. We repeated the above analyses for each stroke subtype (ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage) and TIA separately.

Why use age as time-scale?

Conventionally, the time-scale used in survival analysis (or time to event analysis) is time on study, measured from the start date of the study to the end of the study. An alternate approach is to consider age of the participants as a time-scale, with change in the age of the participants from the start of the study to the end of the study considered as time elapsed. This approach was compared to the traditional approach by Korn et al. and they suggested that using length of follow-up (or time on study) as the time scale was “incorrect” when there is a wide age distribution of study participants at the start of the study.[139] They reported that using age as time-scale accounted for the age effects of an exposure on the disease incidence and adjusted for age in the analyses in contrast to adding age as a covariate when using time on study as the time-scale. As an advantage, using age as a time-scale could better account

for the left-censoring of the study participants compared to traditional methods.[139] Given that we included all urban Ontario residents, the cohort participants' age had a significantly large variation with some being 80 years and older and others being only 18 years old at cohort start date. In order to account for this wide age range at cohort start date, as well as the younger average age of immigrants compared to long-term residents, we used age as the time-scale when analyzing the risk of the outcome of interest during a set follow-up time.

6.2 Secondary analyses

Effect of age

Given the differences in the age distribution between immigrants and long-term residents in our cohort and to evaluate the age-dependent effect of immigration status on the incidence of stroke or TIA, we calculated piecewise unadjusted and adjusted HRs of stroke or TIA and stroke subtypes in immigrants compared to long-term residents in the following age groups: 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80 years or more. We adjusted for the following variables in the adjusted analyses: sex, neighbourhood-level income, hypertension, diabetes, dyslipidemia, atrial fibrillation, CHF and COPD.

Country of origin, immigration class, and acculturation

Based on their country of citizenship prior to arrival, we classified immigrants into seven major world regions: Western countries, Africa, Caribbean, Middle East, Latin America, East Asia, and South Asia (Table 1.2 for details on classification).[141] We calculated the adjusted cause-specific HR of stroke or TIA in immigrants from each of these seven world regions compared to long-term residents. We conducted similar analyses for ischemic stroke and intracranial hemorrhage separately.

We created three separate multivariable cause-specific hazards models to evaluate the effect of immigration class (refugee, economic or family class or other), time since arrival (> 5 year, 5 to 10 year, and ≥ 10 years), and age at arrival (< 25 years, 25-50 years, and ≥ 50 years) on the outcome of incident stroke or TIA. Time since arrival and age at arrival were considered proxies for the acculturation effect. In each of these three models, long-term residents were compared to immigrants using the immigration-related variable, separately.

7 Results

7.1 Baseline characteristics

We included 8 090 524 urban Ontario residents aged 18 years or over without a prior history of stroke or TIA. Of these, 1 216 557 (15.0%) were immigrants (Figure 2.1). Immigrants were younger (median age at cohort start 39 vs. 44 years, $P < 0.001$), more likely to reside in low-income neighbourhoods (34.5% vs. 18.9%, $P < 0.001$), and less likely to have comorbidities at baseline compared to long-term residents (Table 2.1).

7.2 Incidence of stroke and stroke subtypes

During 109 million-years of follow-up, we observed 235 336 TIA or stroke events. Compared to long-term residents, and using age as the time scale, the occurrence of the competing event of death was less common in immigrants (adjusted HR 0.46, 95% confidence interval 0.45-0.68), whereas loss to follow-up was more common in immigrants (adjusted HR 1.23, 95% CI 1.22-1.23). Immigrants were younger at the time of the stroke or TIA (median age 67 vs. 74 years, $P < 0.001$). Of the event types, ischemic stroke was the most common followed by TIA, intracranial hemorrhage and subarachnoid hemorrhage (Table 2.2).

Compared to long-term residents, immigrants had a lower crude incidence rate of stroke or TIA (10.9 vs. 24.5 per 10,000 person-years), and a lower crude hazard of stroke or TIA (HR 0.67, 95% CI 0.66-0.68), and this did not alter after accounting for sex, neighbourhood-level income and comorbidities (adjusted HR 0.67, 95% CI 0.66-0.68) (Table 2.2). In the adjusted analyses, compared to long-term residents, the reduction in the adjusted hazard in immigrants was greater for TIA (HR 0.53, 95% CI 0.51-0.54) than for ischemic stroke (HR 0.71, 95% CI 0.69-0.72), subarachnoid hemorrhage (HR 0.86, 95% CI 0.81-0.91) or intracranial hemorrhage (HR 0.89, 95% CI 0.85-0.93) (Table 2.2). Figures 2.2 to 2.6 highlight the non-linear age-dependent effect of immigration status on the incidence of stroke or TIA and subtypes, with lower adjusted HRs in immigrants compared to long-term residents with increasing age.

7.3 Country of origin and acculturation

Most immigrants to Ontario arrived from three regions: Western countries (i.e., Europe, USA, Australia or New Zealand) (28.2%), South Asia (20.0%), and East Asia (18.1%) (Table 2.1). Table 2.1 also shows the baseline characteristics of immigrants by region of origin.

The difference in the adjusted hazard of stroke or TIA between immigrants from Africa (HR 0.80, 0.74-0.85), the Caribbean (HR 0.95, 95% CI 0.91-1.00) or Latin America (HR 0.86, 95% CI 0.82-0.91) and long-term residents (comparison group) was less pronounced than that for other immigrants, and this was true for both ischemic stroke and intracranial hemorrhage (Figure 2.7). Immigrants from East Asia had a lower adjusted hazard of ischemic stroke (HR 0.63, 95% CI 0.60-0.66) compared to long-term residents but a higher adjusted hazard of intracranial hemorrhage (HR 1.09, 95% CI 1.00-1.19) (Figure 2.7). The adjusted HR of stroke or TIA in immigrants compared to long-term residents based on country of origin of the top 1% countries of origin (based on number of stroke/TIA events) is shown in Figure 2.8.

Most immigrants in Ontario were economic migrants (43.8%), and the median age at arrival was 30 years (Q1-Q3, 23-39 years), with a median duration of residence in Ontario of 9 years (Q1-Q3, 5-12 years). The difference in the adjusted rate of stroke or TIA in immigrants compared to long-term residents was less pronounced for refugees (HR 0.91, 0.88-0.94) than economic immigrants (HR 0.65, 95% CI 0.63-0.67) or family class immigrants (HR 0.64, 95% CI 0.63-0.66) (Table 2.3). Acculturation measured using age at arrival showed that, compared to long-term residents, immigrants who were older than 50 years at the time of immigration had a greater reduction in adjusted the hazard of stroke or TIA (HR 0.60, 95% CI 0.59-0.61) than immigrants who were younger than 25 years at the time of immigration (HR 0.86, 95% CI 0.81-0.92). There was a modest variation in the hazard of stroke or TIA in immigrants compared to long-term residents based on time since arrival (Table 2.3).

Table 2.1. Baseline characteristics of immigrant and long-term residents in Ontario, Canada at the start of cohort (January 1, 2003).

Characteristics	World region of immigrants							All immigrants	Long-term residents
	Africa	Caribbean	East Asia	Latin America	Middle East	South Asia	Western countries		
Total	57 960	86 916	220 715	93 226	104 901	243 843	344 256	1 216 557	6 873 967
Median age (Q1-Q3)	37 (28-45)	37 (29-46)	39 (32-48)	38 (29-47)	38 (30-47)	37 (29-48)	40 (31-48)	39 (31-48)	44 (32-57)
Female, n (%)	28,832 (49.7)	46,350 (53.3)	122,729 (55.6)	46,644 (50.0)	47,981 (45.7)	117,278 (48.1)	174,843 (50.8)	614 515 (50.5)	3 526 608 (51.3)
Neighbourhood-level income, n (%)									
Lowest quintile	28,825 (49.7)	36,951 (42.5)	73,471 (33.3)	36,936 (39.6)	35,341 (33.7)	98,944 (40.6)	87,144 (25.3)	420 112 (34.5)	1 300 077 (18.9)
Highest quintile	4,916 (8.5)	4,494 (5.2)	21,440 (9.7)	6,401 (6.9)	13,467 (12.8)	13,231 (5.4)	54,279 (15.8)	124 775 (10.3)	1 445 937 (21.0)
Comorbidities, n (%)									
Hypertension	6,726 (11.6)	14,128 (16.3)	27,109 (12.3)	11,458 (12.3)	10,617 (10.1)	32,746 (13.4)	33,827 (9.8)	148 859 (12.2)	1 356 624 (19.7)
Diabetes	3,117 (5.4)	6,346 (7.3)	9,538 (4.3)	5,951 (6.4)	4,903 (4.7)	21,552 (8.8)	10,011 (2.9)	66 474 (5.5)	433 368 (6.3)
Dyslipidemia	245 (0.4)	360 (0.4)	621 (0.3)	582 (0.6)	761 (0.7)	1,779 (0.7)	1,446 (0.4)	6 192 (0.5)	94 864 (1.4)
Atrial fibrillation	128 (0.2)	210 (0.2)	657 (0.3)	295 (0.3)	591 (0.6)	607 (0.2)	1,639 (0.5)	4 634 (0.4)	97 458 (1.4)
CHF	255 (0.4)	473 (0.5)	733 (0.3)	559 (0.6)	678 (0.6)	1,558 (0.6)	1,703 (0.5)	6 468 (0.5)	110 738 (1.6)
COPD	1,054 (1.8)	1,317 (1.5)	4,781 (2.2)	2,211 (2.4)	2,074 (2.0)	3,947 (1.6)	7,080 (2.1)	25 183 (2.1)	390 139 (5.7)

n = total number; % = proportion; Q1-Q3 = first and third quartile; age is in years; CHF – congestive heart failure; COPD – chronic obstructive pulmonary disease.

Table 2.2. Association between immigration status and incidence of stroke or TIA in Ontario, Canada between 2003 and 2018 (median follow-up of 15 years).

	Immigrants n = 1 216 557	Long-term residents n = 6 873 967	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Stroke or TIA	18 173 (10.9)	217 163 (23.4)	0.67 (0.66-0.68)	0.67 (0.66-0.68)
Stroke subtypes				
Ischemic stroke	11 604 (7.0)	135 377 (14.6)	0.71 (0.70-0.72)	0.71 (0.69-0.72)
Intracranial hemorrhage	4 959 (3.0)	78 289 (8.4)	0.89 (0.85-0.92)	0.89 (0.85-0.93)
TIA	2 436 (1.5)	22 198 (2.4)	0.52 (0.50-0.53)	0.53 (0.51-0.54)
Subarachnoid hemorrhage	1 312 (0.8)	9 858 (1.1)	0.87 (0.82-0.92)	0.86 (0.81-0.91)

Hazard ratio (HR) and confidence interval (CI) obtained using cause-specific hazards models using age as time-scale, and adjusted estimates obtained after adjusting for sex, neighbourhood-level income, and comorbidities (hypertension, diabetes, dyslipidemia, atrial fibrillation, congestive heart failure, and chronic obstructive pulmonary disease); values in parenthesis represent crude incidence rate per 10,000 person-years, with incidence defined as emergency room visit or hospitalization for outcome of interest using corresponding ICD-10 code.

Table 2.3. Risk of stroke or transient ischemic attack in immigrants compared to long-term resident based on immigration-related factors.

	N	n (rate per 10,000 person-years)	Adjusted HR (95% CI)
Long-term residents (comparison group)	6 873 967	217 163 (23.4)	1.00
Age at arrival			
< 25 years	360 932	2916 (2.0)	0.86 (0.81-0.92)
25 to 50 years	714 241	5365 (8.6)	0.75 (0.74-0.77)
> 50 years	141 384	9892 (49.3)	0.60 (0.59-0.61)
Time since arrival			
< 5 years	279 633	996 (7.9)	0.75 (0.73-0.78)
5 to 10 years	385 455	8575 (10.1)	0.64 (0.62-0.65)
≥ 10 years	551 469	8602 (12.9)	0.68 (0.66-0.69)
Immigration class			
Family or other	487 215	10 446 (6.8)	0.64 (0.63-0.66)
Refugee	196 480	2816 (15.7)	0.91 (0.88-0.94)
Economic	532 862	4911 (10.3)	0.65 (0.63-0.67)

Hazard ratio (HR) and confidence interval (CI) obtained using cause-specific piecewise hazards models using age as time-scale, and adjusted estimates obtained after adjusting for sex, neighbourhood-level income, and comorbidities (hypertension, diabetes, dyslipidemia, atrial fibrillation, congestive heart failure, and chronic obstructive pulmonary disease).

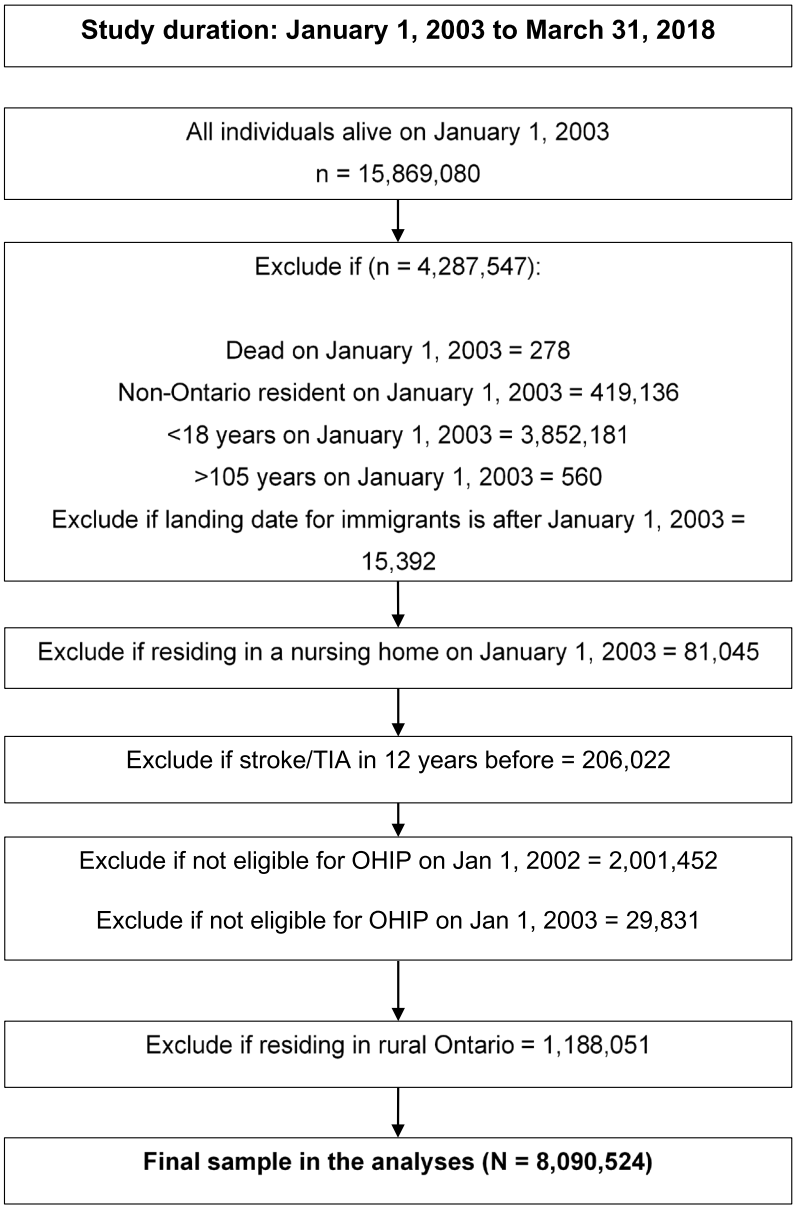


Figure 2.1. Cohort selection when evaluating the incidence of stroke or TIA in immigrants and long-term residents.

Footnote: transient ischemic attack (TIA), Ontario Health Insurance Plan (OHIP) – provincial health plan, landing date refers to the date when an immigrant became permanent resident of Ontario.

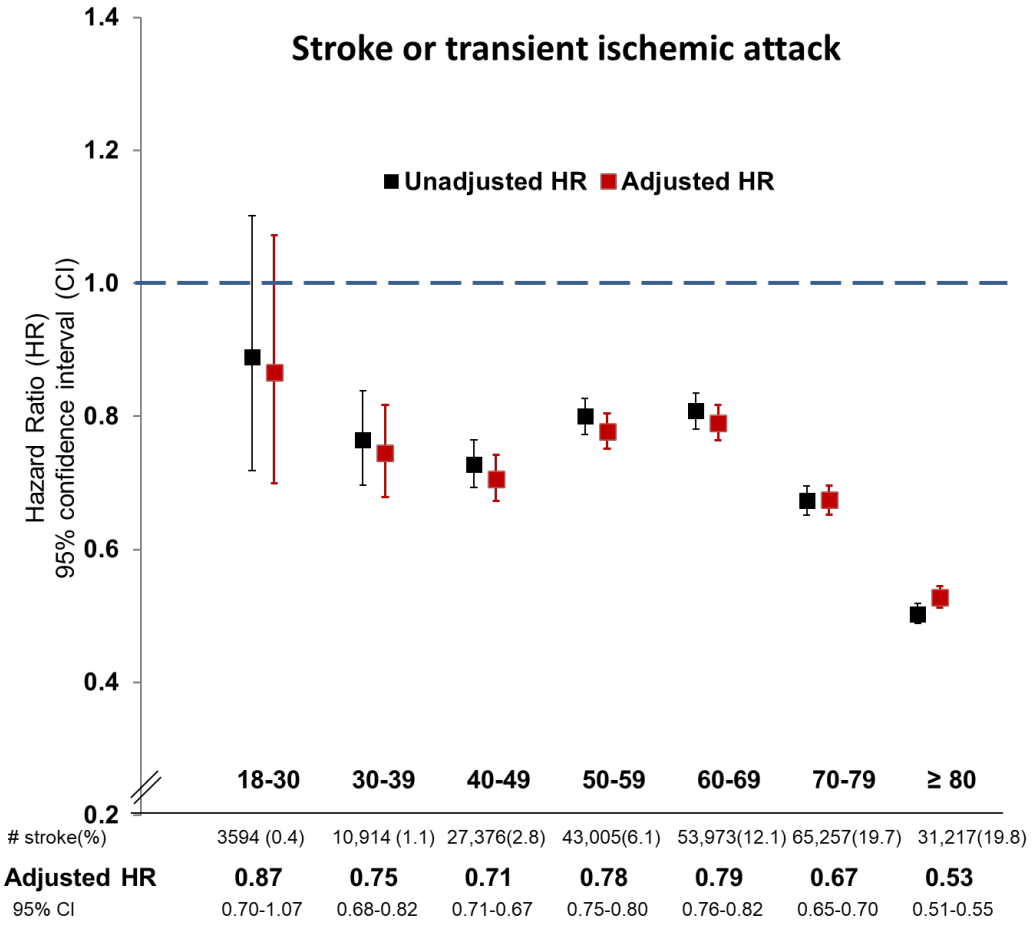


Figure 2.2. Effect of age on the association between immigration status and incidence of stroke or transient ischemic attack shown as unadjusted and adjusted HR of outcome in immigrants compared to long-term residents.

Footnote: Hazard ratio and confidence interval obtained using cause-specific piecewise hazards models using age as time-scale.

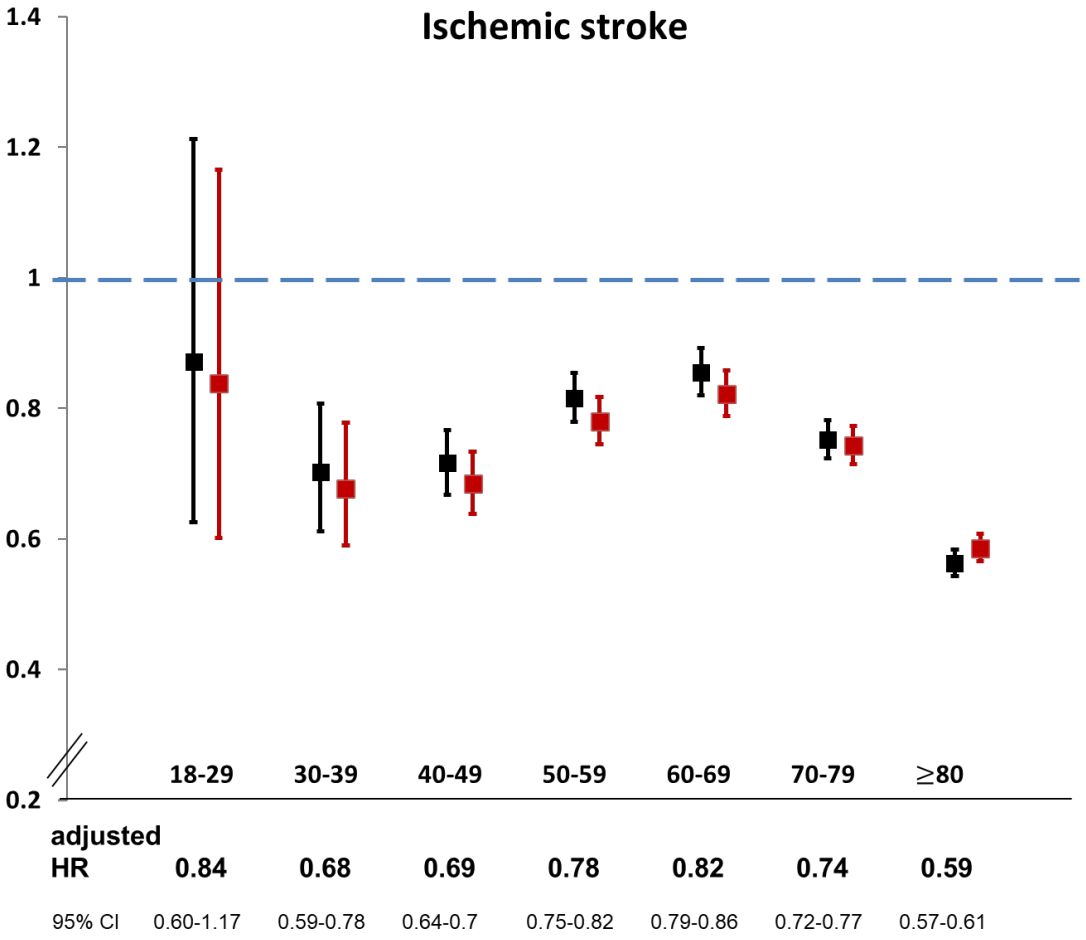


Figure 2.3. Effect of age on the association between immigration status and incidence of ischemic stroke in immigrants compared to long-term residents.

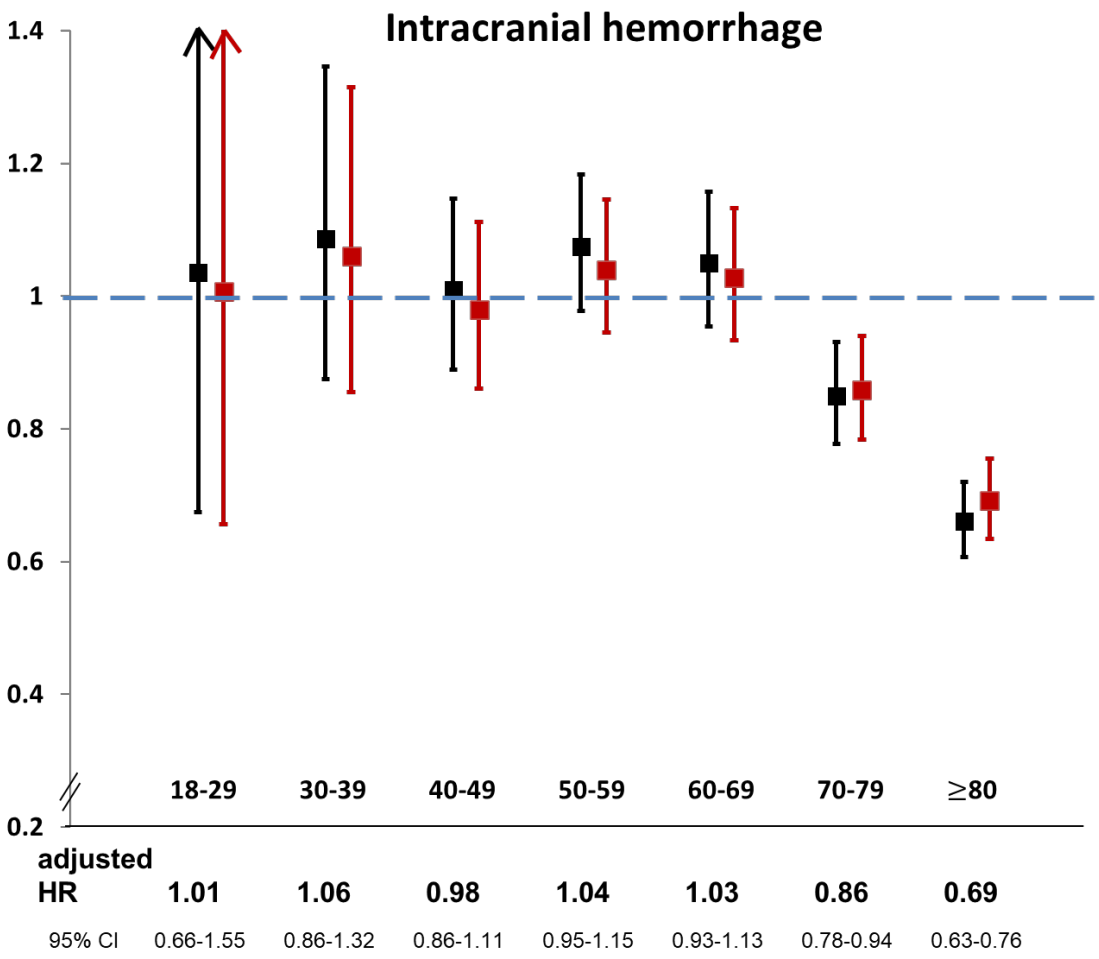


Figure 2.4. Effect of age on the association between immigration status and incidence of intracranial hemorrhage in immigrants compared to long-term residents.

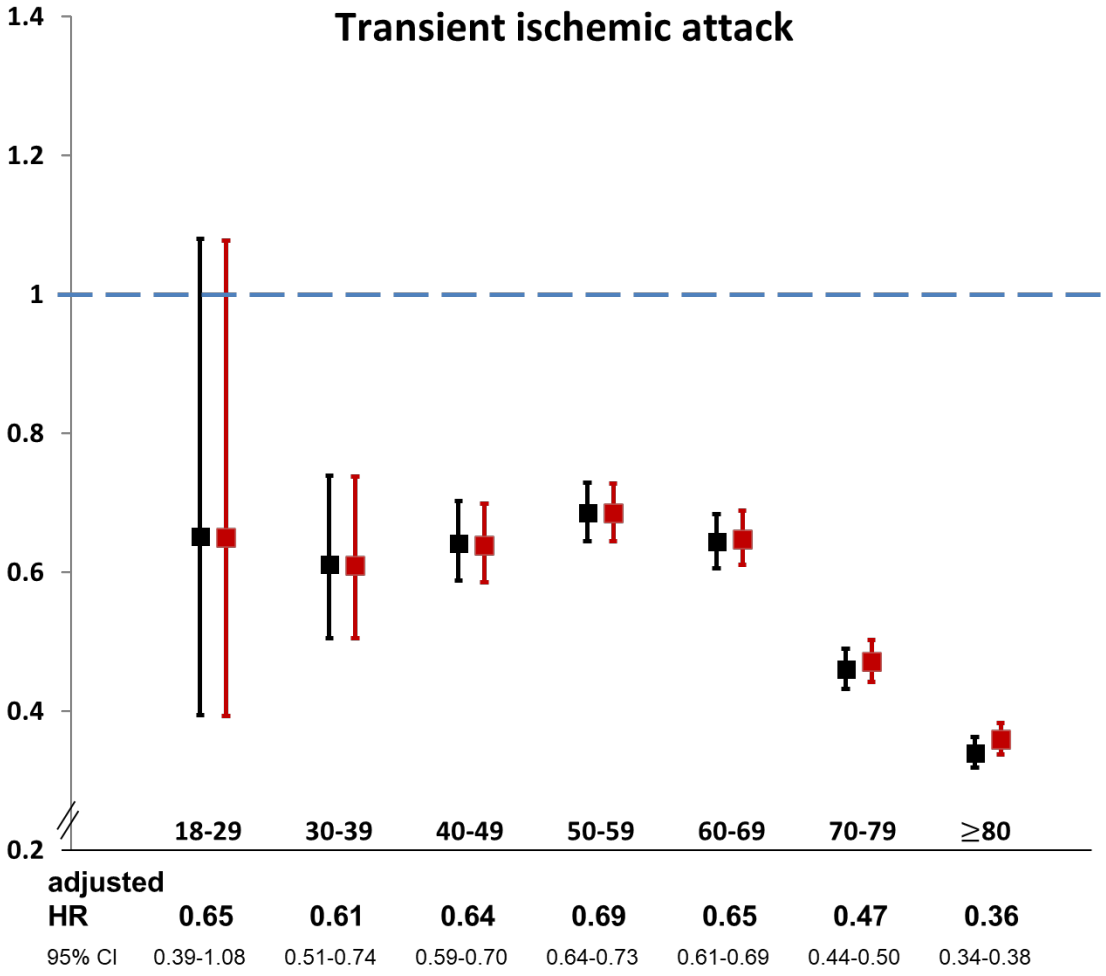


Figure 2.5. Effect of age on the association between immigration status and incidence of transient ischemic attack in immigrants compared to long-term residents.

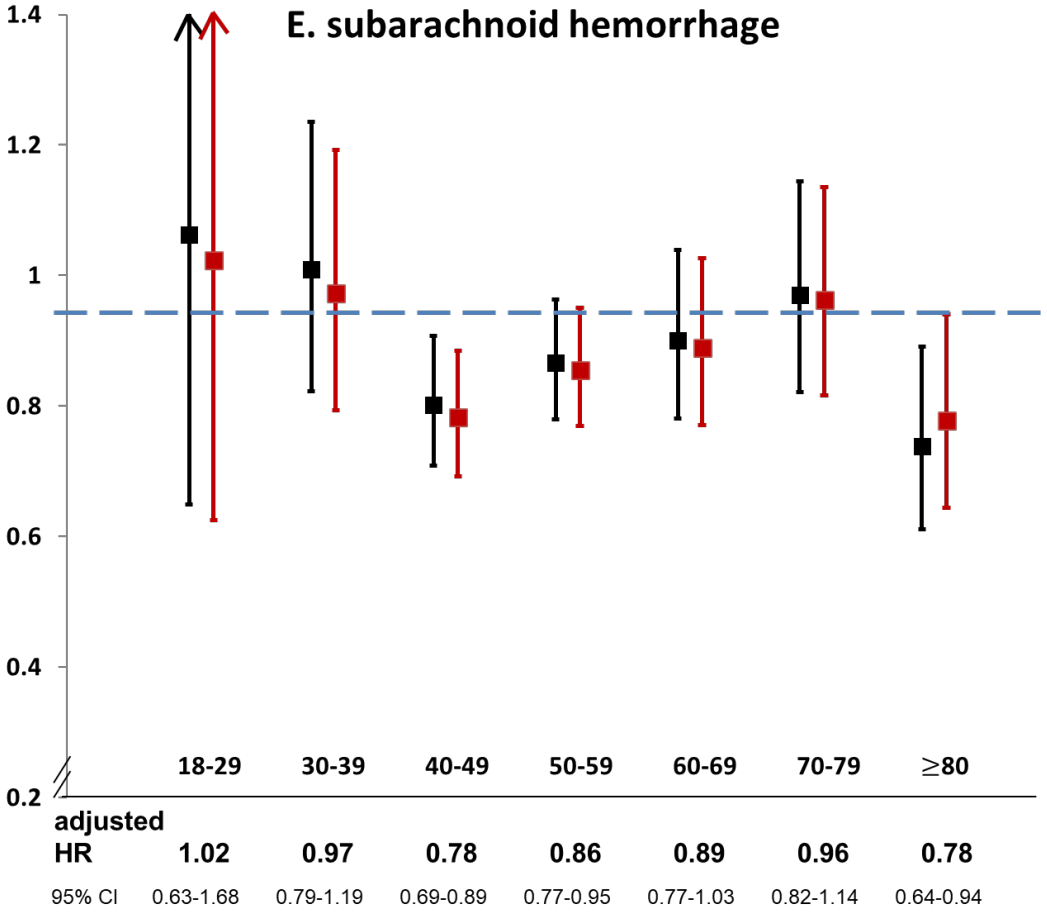


Figure 2.6. Effect of age on the association between immigration status and incidence of subarachnoid hemorrhage in immigrants compared to long-term residents.

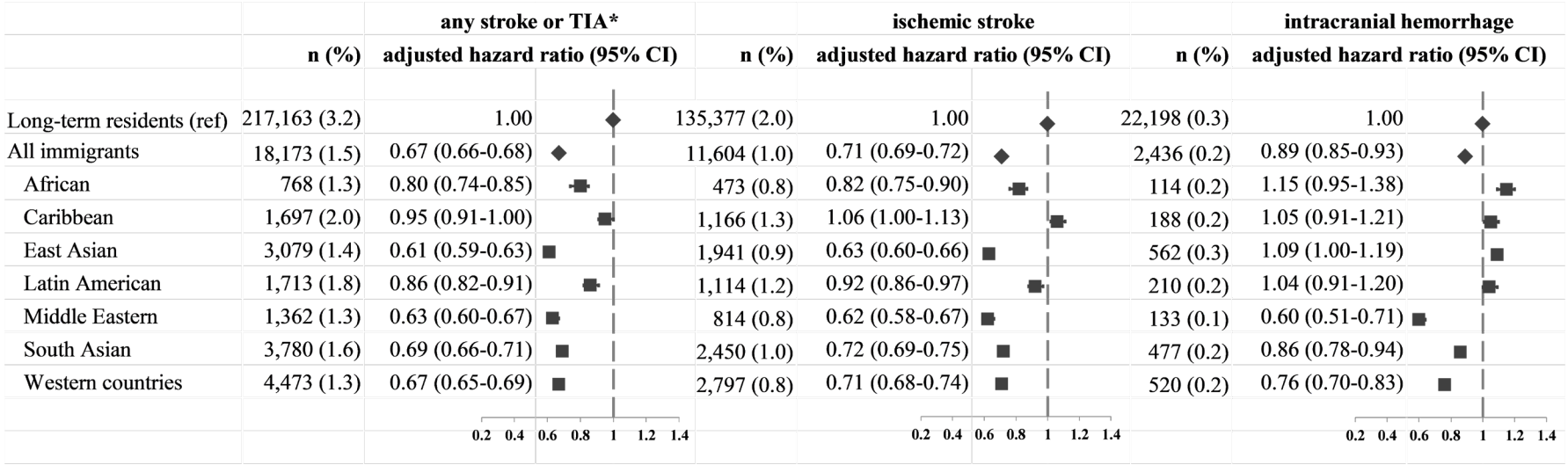


Figure 2.7. Adjusted hazard ratio (95% confidence interval) of stroke or TIA and subgroups of ischemic stroke and intracranial hemorrhage in immigrants compared to long-term residents based on country of origin.

Footnote: Hazard ratio and confidence interval obtained using cause-specific hazards models using age as time-scale adjusting for sex, neighbourhood-level income, and comorbidities (hypertension, diabetes, dyslipidemia, atrial fibrillation, congestive heart failure, and chronic obstructive pulmonary disease). *includes all stroke types and TIA.

Country of origin	n (%)	adjusted HR (95% CI)
Canada	217,163 (3.2)	1.00
Taiwan	78 (0.7)	0.30 (0.24-0.38)
United Kingdom	995 (0.9)	0.48 (0.45-0.51)
China	860 (1.0)	0.52 (0.49-0.56)
United States	298 (1.3)	0.58 (0.51-0.64)
Iran	377 (1.2)	0.58 (0.52-0.64)
Lebanon	208 (1.3)	0.58 (0.51-0.67)
South Korea	211 (1.2)	0.62 (0.54-0.71)
India	1901 (1.6)	0.65 (0.62-0.68)
Bangladesh	109 (1.0)	0.65 (0.54-0.78)
Israel	233 (1.7)	0.69 (0.61-0.79)
Phillipines	1417 (1.8)	0.70 (0.67-0.74)
Sri Lanka	1017 (1.9)	0.71 (0.66-0.75)
Portugal	443 (1.5)	0.71 (0.65-0.78)
Vietnam	350 (2.1)	0.72 (0.65-0.80)
Somalia	150 (1.0)	0.73 (0.62-0.85)
Pakistan	567 (1.2)	0.75 (0.67-0.79)
Ukraine	133 (1.3)	0.75 (0.63-0.89)
Trinidad and Tobago	443 (1.8)	0.80 (0.73-0.88)
Yugoslavia (former)	334 (1.6)	0.80 (0.72-0.89)
Russia	147 (1.3)	0.81 (0.69-0.95)
Iraq	167 (1.6)	0.82 (0.71-0.96)
Romania	264 (1.4)	0.84 (0.74-0.94)
El Salvador	198 (1.50	0.82 (0.74-0.98)
Polan	958 (1.6)	0.88 (0.82-0.93)
Afghanistan	183 (1.6)	1.00 (0.86-1.15)
Guyana	913 (2.7)	1.04 (0.97-1.11)
Jamaica	989 (2.1)	1.06 (0.99-1.13)

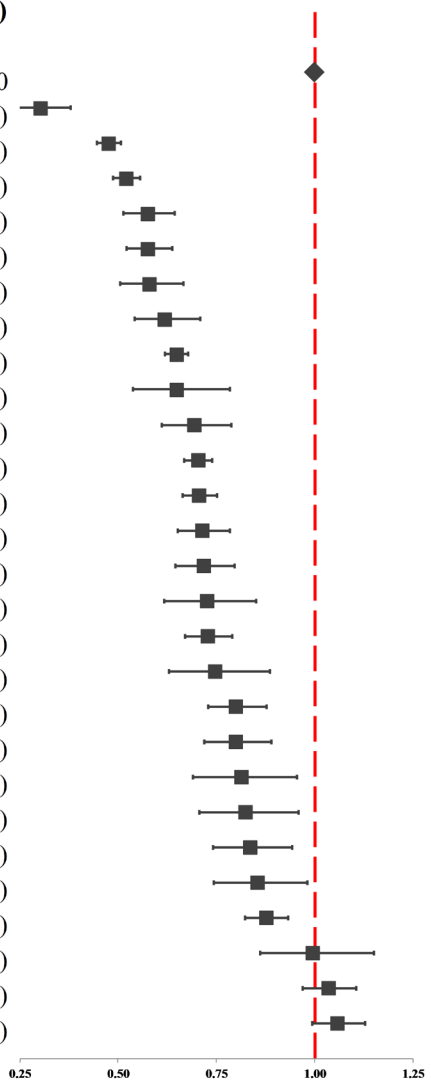


Figure 2.8. Adjusted hazard ratio (HR) of stroke or TIA in immigrants compared to long-term residents of Canada based on the country of origin of immigrants (depicting the top 1% countries from where immigrant originate).

8 Discussion

8.1 Summary

In this large-scale study from the most populous province of Canada (over 14 million people), immigrants had a 33% lower rate of stroke or TIA than long-term residents, with no change after accounting for baseline differences, and with variation in the association by age, stroke subtype, country of origin, and immigration class.

8.2 Key findings

The finding of a lower rate of stroke or TIA in immigrants compared to long-term residents is in keeping with previous reports that have found a lower incidence of stroke in foreign-born people compared to general populations in Denmark, Sweden, and the US[62,63,142], and is considered to be attributable to a healthy immigrant effect where through a self-selection process immigrants are generally healthier than host populations.[15,143] Age is the single most important risk factor for stroke[144], and immigrants were younger than the long-term residents in our cohort in keeping with selective migration of younger individuals.[145] However, the lower incidence of stroke in immigrants persisted even after using age as time-scale and accounting for other baseline differences, consistent with a previous Ontario study.[66] One proposed reason for this health advantage is that immigrants come from a health transition period where lifestyle or environmental risk factors such as diet and physical activity[104] confer a lower risk of cardiovascular diseases and cancer, a phenomenon sometimes referred to as *time travelling*.[24]

Of note, the association between immigration status and stroke incidence varied with age, with greater reductions in the hazard of stroke or TIA in immigrants compared to long-term residents with increasing age. Because only first stroke or TIA was included in the analyses, the younger age of immigrants at the time of the first event could mean that that the proportion of event-free older immigrants was lower than long-term residents and may partly

explain the impact of age. Another explanation may be a phenomenon termed *salmon bias,* whereby immigrants return to their home regions when they are older or closer to their death,[146] and these deaths would not be captured in our databases. We accounted for this in our analyses by censoring outcomes of these individuals at the time of loss to follow-up.

An international case-control study found that age at the time of stroke was lower in people living in South Asia, China, Southeast Asia and Africa compared to those living in Western Europe, North America or Australia,[147] with poor primary prevention and occurrence of vascular risk factors at an earlier age proposed as causes.[147,148] We also found that immigrants were younger at the time of stroke. Our study did not evaluate explanations for this finding, but previous work has found that immigrants have lower rates of primary care utilization than long-term residents, possibly due to challenges in navigating new healthcare systems and difficulty findings primary care physicians who speak their language.[149–151] Organizations involved in integrating immigrants in host nations and in reducing the burden of stroke can work to improve knowledge of and access to primary care in immigrants and promote the development of novel primary care-based models and interventions.[152–154]

The reduction in the hazard of TIA associated with immigration status was greater compared to other cerebrovascular event subtypes, consistent with other studies that have found a lower risk of TIA in immigrants.[155] This suggests the need to improve education about stroke or TIA symptoms in immigrants, to ensure that medical attention is sought for even minor symptoms.[156] In contrast, the reduction in the hazard of intracranial hemorrhage was not as large, suggesting persistence of a higher rate of intracerebral hemorrhage compared to other stroke types in people of low-middle income countries even after immigration to Canada.[45,157] These findings present an opportunity to improve primary prevention strategies that target early diagnosis and treatment of hypertension and other risk factors.

The association between immigration status and lower stroke incidence was less marked in African, Caribbean, and Latin American immigrants compared to those from other world

regions, and is in line with the higher risk of cerebrovascular events observed in Black Americans, in people of African or Caribbean descent in England, and in Latin/Hispanic communities in the US.[73,158,159] Further work is needed to determine whether these differential rates are due to variations in the prevalence or management of vascular risk factors such as hypertension, and to what extent such rates are mediated by neighbourhood-level factors, sociodemographic factors, and the immigrant experience.[118] Interestingly, East Asian immigrants had a lower adjusted hazard of ischemic stroke than long-term residents, but a higher adjusted hazard of intracranial hemorrhage. Previous research supports the observed diverging pattern for different stroke subtypes in East Asians.[160] A higher risk of intracranial small vessel atherosclerosis in East Asians has been implicated as a possible explanation for this phenomenon.[157]

Although all classes of immigrants had a lower incidence of stroke than long-term residents, the magnitude of this reduction was lower for refugees compared to other immigrants, suggesting that the healthy immigrant effect may not be observed when the migration is forced[161], or that assimilation may be less for refugees compared to skilled migrants who have higher education and can speak English or French.[162,163] Future work should evaluate health outcomes in immigrants using other measures of acculturation such as languages spoken or education prior to arrival, proportion of time spent in Canada, or other factors such as number of non-immigrant friends, or other self-reported acculturation scales.[105,164]

8.3 Strengths and limitations

Our study is strengthened by use of a large, population-based cohort from an entire province, and using age as a time-scale to account for differences in age between immigrants and long-term residents at cohort entry[139], and it is likely to provide valid estimates of the association between immigration status and incident stroke.

This study has some limitations. We classified immigrants as those who moved to Ontario after 1985, and considered immigrants who moved in Ontario before 1985 as long-term

residents. Thus, our findings are most generalizable to people who have immigrated within the past three decades. Second, we did not have information on potential risk factors such as education, family history, smoking, alcohol, diet, physical activity, or body mass index, and we also did not have information on screening or control of vascular risk factors such as hypertension.[45,147] Third, we only included incident strokes and TIAs resulting in an emergency department visit or hospitalization, and thus would have missed minor strokes or TIAs that did not result in hospital assessment. Fourth, we did not include cerebrovascular death in our estimation of stroke or TIA incidence.[45] Finally, we did not have information on stroke etiology.

8.4 Implications

The younger age at the time of stroke in immigrants suggests that premature stroke could be averted by regular and perhaps early screening of vascular risk factors in immigrant populations. The greater comparative likelihood of intracerebral hemorrhage compared to other stroke types in immigrants, especially in those from Africa, the Caribbean and East Asia, supports the need to improve screening and treatment of hypertension, the most important modifiable risk factor of stroke.[147] The overall lower rate of stroke or TIA in immigrants should prompt future studies to understand the mediators of this healthy immigrant effect, and use this knowledge to develop targeted primary preventative measures to reduce the risk of stroke in both immigrants and long-term residents.

Chapter 3 Immigration status, acute stroke care and short-term outcomes

1 Overview

This chapter will evaluate processes of acute stroke care and short-term outcomes following ischemic stroke between immigrants and long-term residents using data from the Ontario Stroke Registry.

2 Research Questions

1. Do processes of acute stroke care (use of ambulance, receipt of IV thrombolysis, and others) vary between immigrants and long-term residents?
2. Is disability on discharge (measured as modified Rankin Score) different in immigrants and long-term residents following ischemic stroke?

3 Study population

We used data from the OSR to identify a cohort of patients with ischemic stroke or transient ischemic attack (TIA) seen in the emergency department or hospitalized at any of the 11 regional (comprehensive) stroke centres between July 1, 2003 and March 31, 2013. We performed sensitivity analyses using people seen at non-stroke centres (see below). We excluded patients with hemorrhagic stroke, as the processes of care and outcomes for this group differ from those with ischemic stroke. We also excluded patients aged less than 18 years or greater than 105 years, and those with in-hospital stroke. If an individual had more than one emergency department (ED) visit and/or hospitalization for ischemic stroke or TIA during the study time frame, we included only the first event. Because over 95% of immigrants with ischemic stroke or TIA reside in urban areas (population greater than 10,000), we excluded patients who resided in rural regions at the time of their stroke to ensure geographic comparability between the exposure and the comparison groups.

The OSR was used to provide information on stroke type as well as clinical variables including time of stroke onset and hospital arrival, stroke severity based on the National Institutes of Health Stroke Scale (NIHSS; derived from the Canadian Neurological

Score[165,166]), in-hospital processes of care, and medications and disability at discharge (measured as modified Rankin scale, mRS). Validation by duplicate chart abstraction has shown excellent agreement for key variables in the OSR.[132] Using unique encoded identifiers, we linked the cohort to population-based administrative databases housed at ICES to provide information on comorbid conditions, and location of residence (including median neighbourhood income) (see Table 1.1 for data sources and algorithms for each variable).

4 Exposure of interest

Our exposure of interest was immigration status. We defined *immigrants* as those born outside of Canada who became permanent residents on or after January 1, 1985 whereas those born in Canada or those who arrived in Ontario prior to 1985 were considered *long-term residents.*

5 Outcome of interest

Our primary outcome was disability on discharge, a binary outcome, defined as a modified Rankin Scale (mRS) score of 3 to 5, among those with ischemic stroke. The modified Rankin scale is an internationally accepted scale with very good interobserver agreement (weighted kappa 0.91) to measure disability in patients who have suffered a stroke.[167] It is an ordinal scale with 7 levels: 0 to 6, where 0 is no residual symptoms and 6 is death, and value of 3 or more suggest moderate to severe disability such that one needs either some or considerable help with daily activities.[159]

Secondary outcomes in the cohort with ischemic stroke or TIA were the time of hospital arrival from the onset of stroke symptoms and arrival by ambulance. Secondary outcomes in the subgroup with ischemic stroke were: (1) stroke unit care; (2) thrombolysis in eligible patients (defined as those with ischemic stroke who arrived within the time window to receive thrombolysis and did not have any contraindications); (3) vascular imaging (any of CT or MR angiogram or carotid dopplers); (4) dysphagia screening; (5) Holter monitor and

echocardiography; (6) antiplatelet or anticoagulant drugs on discharge; (7) antihypertensive and lipid lowering drugs on discharge; and (8) length of hospital stay (see Table 1.1 for data source for each outcome). Most of these were obtained from the Ontario Stroke Registry. The provincial insurance plan provides coverage for these investigations and interventions.

6 Statistical Analysis

We compared baseline variables and stroke care delivery between immigrants and long-term residents using the Kruskal Wallis test for continuous variables, and the chi-square test for categorical variables. We reported standardized differences, which express the difference in means or prevalence between two populations as a proportion of the pooled standard deviation. We used the convention that standardized differences greater than 0.10 are considered to reflect a potentially meaningful difference.[138] Due to the large sample size, we elected to consider differences in process measures as being clinically meaningful using standardized differences, and did not put emphasis on statistical difference using P values.

6.1 Primary analyses

We used inverse probability of treatment weighting (IPTW) using the propensity score to account for differences in the distribution of baseline covariates between immigrants and long-term residents with ischemic stroke. Stabilized weights were derived from the estimated propensity scores. Weighted standardized differences were used to assess the similarity of immigrants and long-term residents after application of the IPT weights.[168] We then used log-binomial models to assess the effect of immigration status on disability on discharge (mRS between 3 and 5). The model was estimated using generalized estimating equation methods with an independent working correlation structure to account for the within-subject homogeneity induced by the weights. In a sensitivity analysis, we also assessed the association between immigration status and disability on discharge using an ordinal logistic regression model for ordinal levels of mRS scores.[169] Further, we calculated unadjusted, age- and sex-adjusted and IPT weights-adjusted hazard ratios (HR) of 30-day

mortality in immigrants compared to long-term residents using Cox proportional hazards models. We reported point estimates and 95% confidence intervals (CIs); and P values with 2-sided alpha level of 0.01 set as a cut-off for statistical significance, after Bonferroni correction for multiple testing.[170]

Why use IPTW analyses?

IPTW approach is one of several methods of using the propensity score.[171] Using the estimated propensity score, weights are derived that are equal to the inverse of the probability of receiving the treatment/exposure that the subject actually received. In the sample weighted using these 'inverse probability of treatment weights', the distribution of measured baseline covariates will be similar between treated and control subjects. Thus, measured confounding has been removed by incorporating these inverse probability of treatment weights. The propensity score was estimated by regressing immigrant status on measured baseline covariates.[172] This model adjusted for age, sex, neighbourhood-level income, hypertension, diabetes, dyslipidemia, previous stroke/TIA, and atrial fibrillation, congestive heart failure, coronary artery disease, kidney failure requiring dialysis, dementia, cancer, and Charlson comorbidity index score. The latter was developed to estimate 1-year mortality of patients admitted to the hospital or enrolled in research studies on the basis of the following comorbid conditions (weights in the parenthesis): myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes (weight = 1), hemiplegia, moderate or severe renal disease, diabetes with end organ damage, primary cancer (weight = 2), and moderate or severe liver disease, metastatic solid tumor, and AIDS (weight = 8).[173] This has been modified by subsequently with weights for the latter three categories as follows: and moderate or severe liver disease (weight =3), metastatic cancer, and AIDS (weight = 6).[174] We derived the modified Charlson score using multiple databases available at ICES. We did not adjust for baseline stroke severity because it was felt to be a factor in the

causal pathway between the association of immigration status and our primary outcome of interest.

We elected to use IPTW approach over conventional multivariable regression methods because a) propensity score methods have a slightly more empirical power than multivariable regression with low number of events per confounder[175], b) we were interested in reporting relative risk of our outcome in immigrants compared to long-term residents using log binomial models[176,177]; however, the latter often have "failed convergence" or numerical instability due to not respecting natural parameter constraints, especially in a multivariable adjusted model with multiple covariates[178,179], and c) IPTW approach would allow us to retain all cohort participants in analyses compared to propensity score matched analyses where only those who are matched are included[171].

6.2 Secondary analyses

Country of origin and acculturation measures

To evaluate the effect of country of origin, we calculated multivariable-adjusted risk ratios of being disabled on discharge in immigrant groups (based on WHO-world regions) compared to long-term residents using the original unweighted sample of people with ischemic stroke. We then used the same sample to examine the effect of acculturation on outcomes by conducting three separate analyses in which long-term residents were compared to subgroups of immigrants based on (1) time since immigration [3 levels: ≤ 5 years, 6 to 10 years, and > 10 years]; (2) age at arrival [2 levels: ≤ 50 years and > 50 years]; and (3) immigration class [3 levels: economic, refugee, and family or other]. These models adjusted for the same set of variables used for calculating IPT weights.

6.3 Sensitivity analyses

To examine whether our findings were generalizable to patients seen outside of regional stroke centres, we replicated our analyses in a separate cohort of adult patients, identified

from the OSR, with ischemic stroke or TIA residing in urban Ontario who were seen at non-stroke centres.

7 Results

7.1 Baseline differences

We included 34,987 patients with stroke and TIA who resided in urban Ontario and were seen at regional stroke centres (Figure 3.1). Of these 2,649 (7.6%) were immigrants from 122 different countries, with South Asian (17%), Filipino (9.1%) and Chinese (6%) being the most common ethnic groups based on country of origin (Table 3.1). Immigrants were younger than long-term residents at the time of their stroke (median age 67 vs. 76 years), were more likely to reside in lower income neighborhoods (proportion residing in the 20% of neighborhoods with the lowest median income 33.1% vs. 21.7%), and had a slightly greater stroke severity (mean NIHSS 7.7 vs. 7.0) (standardized difference $\geq$ 0.10 for all comparisons) (Tables 3.1 & 3.2, and Figure 3.2). Smoking and vascular risk factors were less common among immigrants, except for diabetes which was more common in immigrants compared to long-term residents (34.3% vs. 29.3 %) (Table 3.1 and Figure 3.2).

7.2 Differences in acute stroke care

There was no difference in the proportion arriving by ambulance or the time from onset of symptoms to hospital arrival between immigrants and long-term residents (Table 3.2). Immigrants were less likely than long-term residents to be diagnosed with TIA (29.0% vs. 34.2%), and, among those with TIA, less likely to be admitted to hospital (22.5% vs. 27.9%). In the subgroup of patients with ischemic stroke, processes of care were similar in immigrants and long-term residents, with no difference in stroke unit care, guideline-recommended investigations (vascular imaging, prolonged cardiac monitoring, and echocardiography), dysphagia screening, prescriptions of medications for secondary stroke prevention on discharge, or length of hospital stay. Immigrants were more likely than long-

term residents to receive thrombolysis (21.2% vs. 15.5%), were less likely to be treated with a palliative approach (7.3% vs. 13.0%), and had lower in-hospital mortality, albeit with standardized difference below 0.10 for the latter (8.2% vs 11.5%) (Table 3.2).

7.3 Primary analyses

After applying stabilized IPT weights to the cohort with ischemic stroke, the standardized differences of the baseline characteristics of interest between immigrants and long-term residents were all below 0.10 (Figure 3.2). In the unadjusted analysis, there was no difference in the probability of disability at discharge between immigrants and long-term residents. However, in both age- and sex-adjusted (aRR 1.15, 95% CI 1.11-1.20) and IPTW-adjusted analyses (aRR 1.18, 95% CI 1.13-1.22), immigrants had a higher probability of disability on discharge (Table 3). Of note, the age- and sex-adjustment was obtained by using IPT weights derived by only including age and sex. Observed association persisted when using ordinal regression to model the modified Rankin score on an ordinal scale (adjusted odds ratio of a higher modified Rankin score on ordinal scale 1.44; 95% CI, 1.31-1.57) (Table 3.3). We evaluated for model overspecification and influential observations in the log binomial models and for proportionality assumption in Cox models (mortality), and none of the assumptions were violated.

We found that immigrants had a lower rate of 30-day mortality than long-term residents (unadjusted HR 0.72; 95% CI 0.62-0.84); however, after accounting for age and sex the rate of 30-day mortality were similar in immigrants and long-term residents (age- and sex-adjusted HR 0.99; 95% CI 0.84-1.16). The rate of 30-day mortality was slightly higher in immigrants after full IPT weight adjustment, albeit with wide confidence intervals (HR 1.10; 95% CI 0.91-1.32).

7.4 Country of origin and acculturation

In patients with ischemic stroke, we found that immigrants from East Asia (aRR 1.20; 95% CI, 1.10-1.31) and South Asia (aRR 1.15; 95% CI, 1.05-1.28) were more likely to be disabled compared to long-term residents, whereas those from Latin America or Western/European regions of the world had similar outcomes to long-term residents (Table 3.4). Compared to long-term residents, the adjusted risk of disability in patients with ischemic stroke was higher in immigrants who arrived in Canada after the age of 50 years (aRR 1.13; 95% CI, 1.08-1.17) or in those who came as family class migrants (aRR 1.14; 95% CI 1.08-1.19) or refugees (aRR 1.13; 95% CI, 1.02-1.26) (Table 3.4).

7.5 Sensitivity analyses

There were 16,060 patients with ischemic stroke or TIA seen at non-stroke centres (Figure 3.1), of whom 1,396 (8.7%) were immigrants. At non-stroke centres, immigrants were less likely than long-term residents to arrive by ambulance (48.9% vs. 56.6%); had a longer time from stroke onset to hospital arrival (median 9 vs. 6 hours); were equally likely to receive thrombolysis (8.3% vs. 7.9%); and, in those who did not receive thrombolysis, this was more likely to be due to arriving too late (58.7% vs. 51.5%) (Tables 3.5 and 3.6, and Figure 3.3). Other process measures were similar between immigrants and long-term residents in the two cohorts. Similar to our primary cohort, in patients with ischemic stroke at non-stroke centres, immigrants were more likely to be disabled on discharge compared to long-term residents (IPTW-adjusted RR 1.09; 95% CI, 1.03-1.15) (Table 3.3).

Table 3.1. Characteristics of patients with ischemic stroke or TIA seen at regional stroke centres in Ontario, Canada between July 2003 and April 2013 (N = 34,987).

Characteristics	**Immigrants (n = 2,649, 7.6%)**	**Long-term residents (n = 32,338, 92.4%)**
Female, n (%)	1,256 (47.4)	16,033 (49.6)
Median age in years (Q1 - Q3)	67 (55-78)	76 (64-83)
Neighborhood-level quintile, n (%)		
Lowest quintile (1st)	876 (33.1)	7,032 (21.7)
Highest quintile (5th)	327 (12.3)	6,880 (21.3)
Treatment at a teaching hospital, n (%)	1,971 (74.4)	27,190 (84.1)
Fluent in English and/or French*	1,965 (74.1)	30,520 (94.4)
Comorbidities, n (%)		
Hypertension	1,854 (70.0)	23,681 (73.2)
Diabetes	909 (34.3)	9,486 (29.3)
Dyslipidemia	1,107 (41.8)	13,078 (40.4)
Current smoker	364 (13.7)	5,371 (16.6)
Coronary artery disease	471 (17.8)	7,340 (22.7)
Previous stroke/TIA	672 (25.4)	9,529 (29.5)
Atrial fibrillation	347 (13.1)	5,633 (17.4)
Dementia	126 (4.8)	2,995 (9.3)
Congestive heart failure	329 (12.4)	5,653 (17.5)
Cancer	134 (5.1)	2,786 (8.6)
Dialysis	84 (3.2)	882 (2.7)
Mean Charlson comorbidity index (SD)	1.99 ± 1.97	2.07 ± 2.0
Among immigrants only		
Top countries of origin		
Philippines	242 (9.1)	
India	204 (7.7)	
China, People's Republic of	153 (5.8)	
Sri Lanka	125 (4.7)	
Jamaica	115 (4.3)	

Poland	109 (4.1)
United Kingdom and Colonies	105 (4.0)
Pakistan	94 (3.5)
Guyana	93 (3.5)
Most common mother tongue	
English	442 (16.7)
Tagalog	214 (8.1)
Cantonese	186 (7.0)
Arabic	130 (4.9)
Russian	124 (4.7)
Level of education	
None	226 (8.5)
Secondary or Less	1429 (53.8)
Formal Trade Certificate or Apprenticeship or non-University certificate	352 (13.3)
Some University - No Degree	119 (4.5)
Bachelor's Degree	404 (15.2)
Some Post-Grad. Education (Master's, Doctorate or non-degree)	124 (4.7)

Q1-Q3 – 1st and 3rd quartile; SD – standard deviation; n – numbers, % - proportion of total n in column, *Where information on language was available.

Table 3.2. Processes of stroke care and outcomes in immigrants and long-term residents with ischemic stroke or TIA (N = 34,987).

	Immigrants n = 2,649	Long-term residents n = 32,338	Standardized difference	P value
Prehospital care				
Arrival by ambulance, n (%)	1,563 (59.0)	19,990 (61.8)	0.06	0.004
Median time from last seen normal to arrival in hospital, hours (Q1 – Q3)	4 (1-15)	4 (1-17)	0.04	0.08
Type of cerebrovascular event				<0.001
Ischemic stroke, n (%)	1,880 (71.0)	21,291 (65.8)	0.11	
TIA, n (%)	769 (29.0)	11,047 (34.2)	0.11	
Patients with TIA admitted to hospital, n (%)	173 (22.5)	3,086 (27.9)	0.13	0.001
Processes of stroke care in the subgroup of patients with ischemic stroke (n = 23,171)				
Received thrombolysis, n (%)	398 (21.2)	3,301 (15.5)	0.15	<0.001
Reason for no thrombolysis – too late, n (%)	795 (42.3)	9,196 (43.2)	0.02	0.45
Median door-to-needle time, minutes (Q1 – Q3)	73 (57-94)	72 (55-94)	0.03	0.54
Median time from last seen normal to thrombolysis, minutes (Q1 – Q3)	150 (120-185)	145 (117-180)	0.10	0.83
Stroke severity				
Mean NIHSS (SD)	7.7 (7.0)	7.0 (6.5)	0.10	<0.001
Median NIHSS (Q1 – Q3)	6 (2-11)	5 (2-11)	0.09	<0.001

Median length of stay, days (Q1-Q3)	7 (3-14)	7 (3-14)	0.04	0.11
Carotid imaging, n (%)	1,506 (80.1)	16,298 (76.6)	0.09	<0.001
Dysphagia screening, n (%)	1,185 (67.7)	13,211 (67.7)	0.00	0.96
Stroke unit care, n (%)	1,114 (59.3)	13,394 (62.9)	0.07	0.002
Echocardiography, n (%)	1,247 (66.5)	13,371 (62.9)	0.08	0.002
Holter, n (%)	657 (35.0)	6,843 (32.2)	0.06	0.012
Palliative status, n (%)	127 (7.3)	2,529 (13.0)	0.19	<0.001
Among those alive on discharge				
Anti-platelet or anti-coagulant agent on discharge, n (%)	2,284 (91.3)	27,180 (90.9)	0.01	<0.001
Anti-hypertensive agent on discharge, n (%)	1,645 (65.7)	20,137 (67.3)	0.03	0.73
Lipid-lowering agent on discharge, n (%)	1,594 (63.7)	18,232 (61.0)	0.06	<0.001
Outcomes on discharge[$]				
Dead on discharge	151 (8.2)	2,397 (11.5)	0.01	<0.001
Disabled on discharge (mRS 3 to 5)	920 (54.7)	9,762 (52.7)	0.04	0.11

Q1-Q3 – 1st and 3rd quartile; SD – standard deviation; n – number, % proportion; NIHSS – National Institutes of Health Stroke Scale; TIA – transient ischemic attack.

[$]only in patients with ischemic stroke.

Table 3.3. Disability following ischemic stroke among immigrants and long-term residents in Ontario, Canada.

	Immigrants # events (%)	Long-term residents (reference) # events (%)	Risk ratio (95% CI)	P value
Regional stroke centre				
Disabled on discharge*	920 (54.7)	9,762 (52.7)		
Unadjusted estimates			1.04 (0.99-1.09)	0.11
Age- & sex-adjusted†			1.16 (1.11-1.21)	<0.001
IPTW adjusted			1.18 (1.12-1.23)	<0.001
IPTW adjusted odds ratio (for each point increase on the mRS scale)			1.44 (1.31-1.57)	<0.001
Non- stroke centre				
Disabled on discharge*	468 (56.3)	4,174 (57.2)		
Unadjusted estimates			0.98 (0.92-1.05)	0.62
Age- & sex-adjusted†			1.16 (1.11-1.21)	<0.001
IPTW adjusted			1.09 (1.02-1.16)	<0.001
IPTW adjusted odds ratio (for each point increase on the mRS scale)			1.16 (1.02-1.32)	0.02

IPTW – inverse probability treatment weights obtained after accounting for: age (continuous), sex (male reference), income quintiles, diabetes, hypertension, dyslipidemia, CAD, congestive heart failure, dementia, dialysis dependence, current smoking, atrial fibrillation, prior stroke/TIA, cancer, Charlson comorbidity index.

*Disability defined as modified Rankin Scale (mRS) 3 to 5;

†IPT weights obtained after adjusting for age (continuous) and sex (male reference).

Reference – long-term residents formed the reference group when calculating the risk ratio (the risk of being disabled in immigrants compared to long-term residents).

Table 3.4. Disability after ischemic stroke in different groups of immigrants (based on region of origin, time since immigration, age at arrival, and immigration class) compared to long-term residents in Ontario, Canada.

	# events (%)	Disabled on discharge* aRR (95% CI)
Long-term residents	9,762 (52.7)	1.00 (reference)
Region of origin		
Africa	41 (59.4)	1.16 (0.96-1.40)
Caribbean	86 (55.8)	1.12 (0.98-1.28)
East Asia	209 (58.5)	1.20 (1.10-1.31)
Latin America	58 (44.6)	0.98 (0.82-1.17)
North Africa – Middle East	86 (54.8)	1.12 (0.99-1.28)
South Asia	134 (53.8)	1.15 (1.05-1.28)
Western/European	219 (50.2)	1.01 (0.93-1.10)
Time since immigration		
≤ 5 years	131 (49.1)	1.11 (1.00 – 1.23)
6 to 10 years	152 (55.5)	1.10 (1.01 – 1.21)
> 10 years	637 (55.8)	1.10 (1.06 – 1.15)
Age at arrival		
≤ 50 years	263 (40.9)	1.04 (0.96 – 1.14)
> 50 years	637 (64.6)	1.13 (1.08 – 1.17)
Immigration class		
Family or other	620 (60.1)	1.14 (1.08 – 1.19)
Refugee	140 (50.0)	1.13 (1.02 – 1.26)
Economic	159 (43.1)	1.09 (0.97 – 1.22)

aRR – adjusted risk ratio obtained using multivariable Poisson regression model adjusting for: age (continuous), sex (male reference), income quintiles, diabetes, hypertension, dyslipidemia, CAD, congestive heart failure, dementia, dialysis dependence, current smoking, atrial fibrillation, prior stroke/TIA, cancer, Charlson comorbidity index.

*Disability defined as modified Rankin Scale (mRS) 3 to 5.

Table 3.5. Non-stroke centres cohort. Characteristics of the cohort (N = 16,060).

Characteristics	Immigrants (n = 1,396), 8.5%	Long-term residents (n = 16,060), 91.5%
Female, n (%)	712 (51.0)	7,162 (48.8)
Median age in years (Q1 - Q3)	70 (58 – 79)	76 (65 – 84)
Neighbourhood-level quintile, n (%)		
Lowest quintile (1st)	406 (29.1)	2,890 (19.7)
Highest quintile (5th)	128 (9.2)	2,698 (18.4)
Treatment at a teaching hospital, n (%)	118 (8.5)	2,407 (16.4)
Fluent in English or French, n (%)	410 (29.4)	8,670 (59.1)
Comorbidities, n (%)		
Hypertension	999 (71.6)	11,192 (76.3)
Diabetes	559 (40.0)	4,822 (32.9)
Dyslipidemia	575 (41.2)	5,762 (39.3)
Atrial Fibrillation	161 (11.5)	2,393 (16.3)
Previous stroke/TIA	365 (26.1)	4,686 (32.0)
Dementia	79 (5.7)	1,379 (9.4)
Congestive heart failure	180 (12.9)	2,620 (17.9)
Coronary artery disease	265 (19.0)	3,748 (25.6)
Current smoker	127 (9.1)	2,070 (14.1)
Chronic kidney disease (on dialysis)	74 (5.3)	745 (5.1)
Mean Charlson comorbidity index (SD)	2.1 (2.0)	2.1 (2.0)

Q1-Q3 – 1st and 3rd quartile; SD – standard deviation; n – numbers, % - proportion of total N in column; TIA – transient ischemic attack.

Table 3.6. Non-stroke centres cohort. Processes of stroke care between immigrants and long-term residents with ischemic stroke or TIA in the cohort (N = 16,060).

	Immigrants n = 1,396	Long-term residents n = 16,060	Standardized difference	P value
Prehospital care				
Arrival by ambulance, n (%)	682 (48.9)	8,298 (56.6)	0.16	<0.001
Median times from last seen normal to arrival in hospital, hours (Q1 – Q3)	9 (2 – 24)	6 (2 – 19)	0.16	<0.001
Type of cerebrovascular event			0.17	<0.001
Ischemic stroke, n (%)	924 (66.2)	8,513 (58.1)		
TIA, n (%)	472 (33.8)	6,151 (41.9)		
Patients with TIA that are admitted to a hospital	116 (24.6)	1,689 (27.5)	0.07	0.18
Processes of stroke care in the subgroup of patients with ischemic stroke (n = 9,437)				
Received thrombolysis, n (%)	77 (8.3)	676 (7.9)	0.01	0.68
Reason for no thrombolysis – too late, n (%)	497 (58.7)	4,038 (51.5)	0.14	<0.001
Median door-to-needle time, minutes (Q1 – Q3)	58 (50-82)	66 (49-93)	0.15	0.24
Median time from LSN to thrombolysis, minutes (Q1 – Q3)	135 (115-191)	147 (113-189)	0.07	0.59
Mean NIHSS (SD)	6.4 (5.7)	6.2 (5.9)	0.04	0.29
Median NIHSS (Q1 – Q3)	5 (2-10)	4 (1-10)	0.07	0.06
Palliative status, n (%)	54 (6.0)	1,044 (12.7)	0.23	<0.001

Median length of stay, days (Q1-Q3)	7 (3-15)	7 (3-14)	0.07	0.043
Carotid imaging, n (%)	662 (71.6)	5,555 (65.3)	0.14	<0.001
Dysphagia screening, n (%)	504 (56.4)	4,872 (59.2)	0.06	0.10
Stroke unit care, n (%)	295 (31.9)	2,759 (32.4)	0.01	0.77
Echocardiography, n (%)	598 (64.7)	4,738 (55.7)	0.19	<0.001
Holter, n (%)	295 (31.9)	2,180 (25.6)	0.14	<0.001
Among those alive on discharge				
Anti-platelet or anti-coagulant agent on discharge, n (%)	782 (88.6)	6,730 (84.8)	0.11	0.83
Anti-hypertensive agent on discharge, n (%)	660 (74.7)	5,796 (73.0)	0.05	0.24
Lipid-lowering agent on discharge, n (%)	610 (69.1)	4,975 (62.7)	0.14	<0.001

Q1-Q3 – 1st and 3rd quartile; SD – standard deviation; n – numbers, % - proportion of total N in column; NIHSS – National Institutes of Health stroke scale.

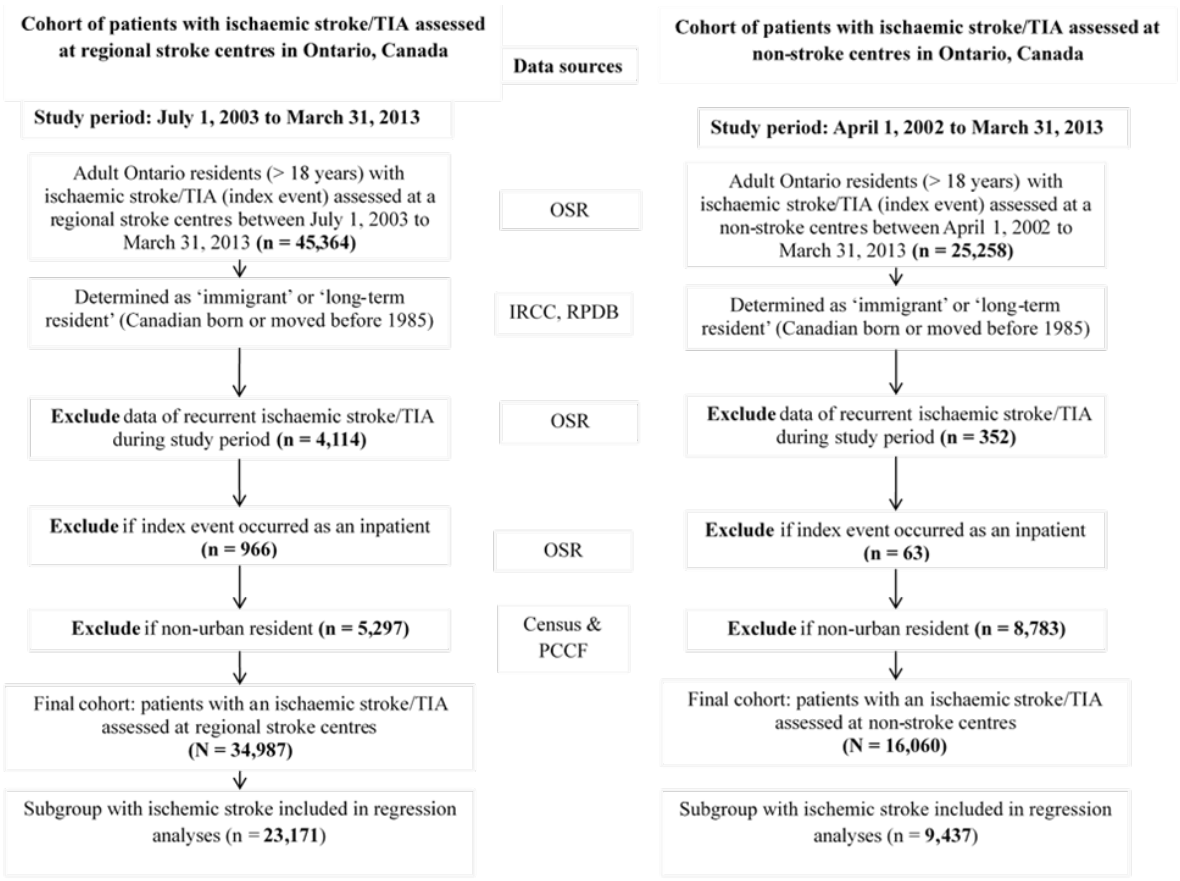


Figure 3.1. Flow diagram. Selection of the study cohorts.

Abbreviations: OSR – Ontario Stroke Registry IRCC – Immigration, Refugee and Citizenship Canada; PCCF – Postal Code^{OM} Conversion File; RPDB – Registered Person's Database.

Non-urban resident was defined as residing in a geographically defined area (based on postal code files) with population less than 10,000.

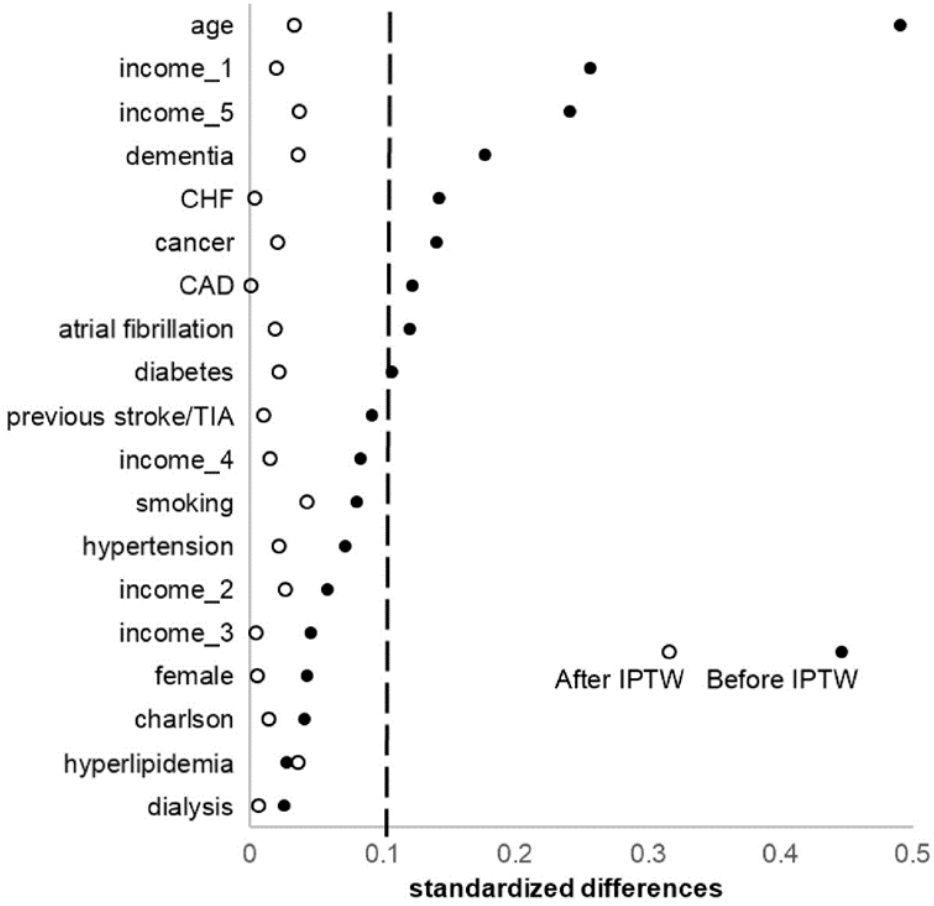


Figure 3.2. Regional stroke centres cohort. Balance between baseline characteristics assessed as absolute standardized differences between immigrants and long-term residents before (solid circles) and after (empty circles) applying inverse probability of treatment weights to the entire cohort.

Abbreviations: CAD – coronary artery disease; CHF – congestive heart failure; TIA – transient ischemic attack; income – refers to neighbourhood-level income quintile where 1 is the lowest and 5 is the highest income quintile; charlson refers to Charlson comorbidity index; and dialysis refers to chronic kidney disease requiring dialysis.

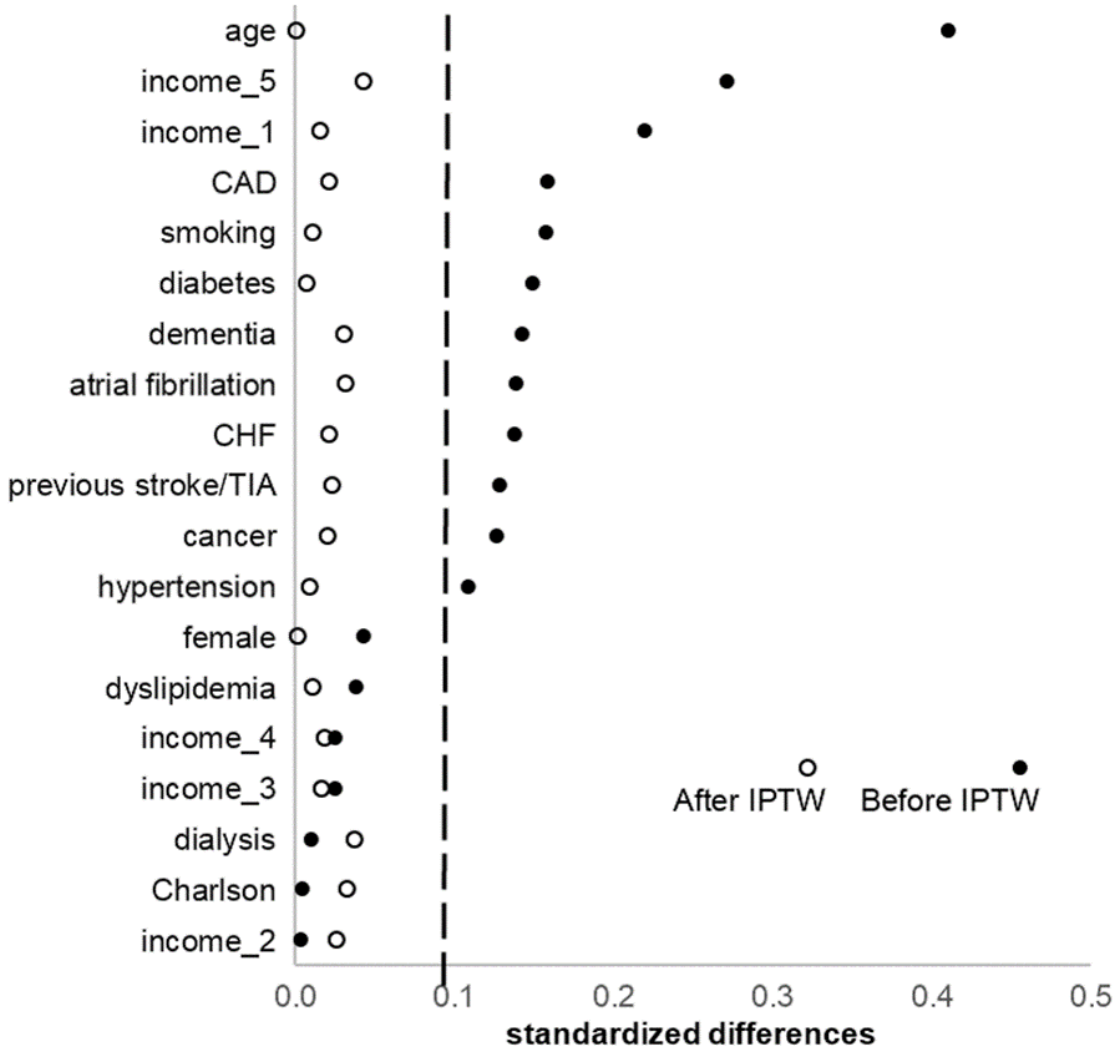


Figure 3.3. Non-stroke centres cohort. Balance between baseline characteristics assessed as absolute standardized differences between immigrants and long-term residents before (solid circles) and after (empty circles) applying inverse probability of treatment weights to the entire cohort.

8 Discussion

8.1 Summary

In this retrospective cohort study, we found that, compared to long-term residents, immigrants to Canada were younger at the time of stroke onset, had greater stroke severity and were less likely to present with TIA. In patients who had ischemic stroke, immigrants were more likely to be disabled at discharge than long-term residents. Processes of stroke care were similar in immigrants and long-term residents seen at stroke centres; however, among those patients seen at non-stroke centres, immigrants were less likely than long-term residents to arrive by ambulance and had a longer time between stroke onset and hospital arrival. Lastly, immigrants had similar 30-day mortality compared to long-term residents.

8.2 Key findings

The lower frequency of presentation with TIA among immigrants in our primary cohort aligns with previous research that reported a lower frequency of TIA diagnosis among ethnic groups in high-income countries compared to their White counterparts.[180] This may reflect differences in health-seeking behaviors or knowledge of stroke symptoms in immigrants compared to long-term residents or may be due to missed diagnoses of minor stroke and TIA in immigrants who present with acute transient or minor neurological symptoms.[11]

Our finding of a younger age at stroke onset in immigrants compared to long-term residents is consistent with previous studies suggesting that Asian Americans[79], Black British[181], and Chinese and South Asian Canadians[182] experience stroke at a younger age than their White counterparts. Potential explanations for this finding include an early onset of vascular risk factors, or suboptimal management of risk factors due to social stressors[183], lack of coverage for medications[184], or poor health literacy among immigrants.[185] In our cohort, vascular risk factors, except for diabetes, were less common in immigrants compared to long-term residents; however, we did not have information on the duration or management of

traditional vascular risk factors, or other risk factors such as lipoprotein levels, dietary habits or measures of obesity (such as waist-to-hip ratios).[186]

Compared to long-term residents, we found that immigrants with ischemic stroke at stroke centres were more likely to receive thrombolysis, and it is possible that this was due to greater stroke severity among immigrants as well as to a younger age at presentation. Despite the fact that more frequent receipt of thrombolysis would be expected to reduce post-stroke disability[144], immigrants with ischemic stroke were more likely than long-term residents to be disabled on discharge. This may be in part attributable to baseline difference in stroke severity, less frequent use of palliative care in immigrants compared to long-term residents[187] resulting in survival with greater disability, differences in processes of care related to language fluency[188] or (less likely) differences in post-thrombolysis complications.[79] This finding is consistent with a prior study that reported an adjusted odds ratio of 1.4 (95% CI 1.0-1.9) for institutionalization at the time of discharge, a proxy measure for disability, among immigrants compared to long-term residents with stroke.[66]

Previous studies have mainly focused on the incidence of stroke deaths in immigrants, rather than stroke case-fatality. A population-based study in Ontario found a lower age-standardized rate of cardiovascular death among immigrants compared to long-term residents [0.8 vs. 1.5 cardiovascular deaths/1000 person-years among men, and 0·4 vs. 0·7 among women].[21] In contrast, a study from England and Wales found that immigrants had higher age-standardized cerebrovascular disease mortality rates than long-term residents, with variation based on country of origin and with the highest mortality among South Asians immigrants.[189] Our findings are consistent with a previous Canadian study which used new receipt of a provincial health card as a proxy for immigration status and reported no difference in 30-day or 1-year mortality stroke or TIA between immigrants and long-term residents[66].

Immigrants are a heterogeneous group, and we were interested in assessing the impact of acculturation on the association between immigration status and outcomes. With the

exception of those immigrants who arrive from Western or European countries and Latin America, most immigrants had a higher risk of being disabled on discharge following ischemic stroke. We found higher disability after ischemic stroke among immigrants who were older at the time of arrival to Canada (age > 50 years), and among refugee and family class migrants compared to long-term residents. A higher incidence of age- and sex-standardized diabetes has been reported in refugees and family class migrants to Canada compared to the economic class migrants.[113] Mexican immigrants residing in the US for more than 10 years were found to have higher risk of self-reported stroke compared to those who resided less than 10 years.[190] Compared to long-term residents, the incidence of stroke among immigrants to Denmark who resided in Denmark for less than 5 years (HR 0.77; 95% CI 0.66–0.91) was different than those residing more than 5 years (HR 0.96; 95% CI 0.88–1.05).[191] Unlike previous studies[21,192], we categorized the time since immigration variable into 3 categories (≤ 5, 6 to 10, and >10 years) which could explain why this variable did not modify the association in our analyses. Our findings support the need for further work to evaluate how different measures of acculturation influence stroke outcomes.

8.3 Strengths and limitations

Our study is strengthened by its use of a population-based registry to provide clinical characteristics, linked with government data to provide detailed information on immigration-related variables and administrative data to provide complete outcome ascertainment, and with the use of advanced statistical methods for confounder adjustment.

However, certain limitations merit discussion. We did not have information on use of endovascular thrombectomy as this treatment was adopted after the study timeframe. The study was conducted in Canada where all registered residents have health coverage for hospital and physician services, and so our finding of similar stroke care in immigrants and long-term residents may not hold true in jurisdictions with different health care systems. We restricted our cohort to urban dwellers to account for the fact that over 95% of immigrants

reside in these areas, and our findings may not be generalizable to immigrants who settle in non-urban areas. We did not have information on undocumented immigrants who are not eligible for provincial health care insurance. We could only assess social integration of immigrants using proxy measures such as time in Canada and age at arrival, and other important measures such as sense of belonging, dietary habits, and health literacy were not available.[183] Finally, we focused on stroke rather than other neurological or cardiovascular conditions because of the importance of stroke as a cause of death and disability, and because of the existence of well-defined evidence-based guidelines for acute stroke care. However, we anticipate that some of our findings may be applicable to immigrants with other conditions.

8.4 Implications

The younger age at stroke onset in immigrants suggests that improved cardiovascular risk screening and primary prevention in these groups could be a focus of future study. The lower frequency of presentation with TIA and the delay from symptom onset to presentation suggests that immigrants may benefit from education to recognize the symptoms of stroke or TIA and understand the importance of early evaluation.[193] The less frequent use of palliative care among immigrants with stroke suggests that differences exist in end-of-life approaches between immigrants and long-term residents.[187,192] Finally, there is an opportunity for further research to confirm the finding of greater disability following ischemic stroke among immigrants compared to long-term residents, to understand the reasons for this finding, such as the potential mediating effects of language fluency or stroke severity, and to identify strategies to address this, such as early identification and treatment of post-stroke complications or by early rehabilitation.[194]

Chapter 4 Immigration status and long-term outcomes

1 Overview

This chapter will evaluate the outcomes of all-cause mortality and vascular event recurrence (composite of stroke, TIA and myocardial infarction) and the quality of secondary stroke preventive care following ischemic stroke in immigrants compared to long-term residents using linked data from the Ontario Stroke Registry and administrative databases.

2 Research Questions

1. Do long-term outcomes (mortality and vascular event recurrence) following ischemic stroke vary between immigrants and long-term residents?
2. Does the association between immigration status and long-term outcomes following ischemic stroke vary based on age, ethnicity, country of origin of immigrants, and immigration class?

3 Study population

We used the Ontario Stroke Registry (OSR) to identify patients presenting to a hospital in Ontario with ischemic stroke between April 1, 2002 and March 31, 2013.[195] The OSR is a province-wide registry that included a population-based sample of patients with stroke seen at any of the province's 150 acute care institutions, with stroke determined by clinical presentation and confirmed by brain imaging, and with data collection performed by chart review by trained abstractors with clinical expertise. We linked these patients to population-based provincial administrative databases including the death registry, the cause of death register, and hospitalization and acute care or emergency room visit databases. Unlike Chapter 3, we combined the cohorts of patients seen at stroke centres and non-stroke centres for the purposes of this study. We did so to because a) it allowed us to increase the overall sample size of our cohort, and b) short-term outcomes across immigration status were similar in patients seen at stroke centres and non-stroke centres. The end of follow-up was on March 31, 2018.

We determined place of residence and neighbourhood-level income using linked 2006 Census and postal-code data. We obtained clinical information (history of atrial fibrillation, dyslipidemia, cancer, dementia, kidney disease, palliative status, and smoking) from the OSR. The OSR also provided information on care during hospitalization, stroke severity based on the Canadian Neurological Scale (CNS)[165], and disability on discharge measured using the modified Rankin scale (mRS). We used validated databases and algorithms to identify other variables such as hypertension[126], diabetes[127], and congestive heart failure[129] (Table 1.1).

Inclusion and exclusion criteria

We excluded patients without a valid provincial health insurance number that permitted linkage to administrative databases, those aged over 105 or younger than 18 years, and those who had an acute ischemic stroke while an inpatient for another medical condition. If an individual had more than one stroke during the study time frame, we included only the first event. Because over 95% of immigrants resided in urban centres (population over 10,000), we excluded individuals who resided in non-urban areas to allow for appropriate comparisons.

4 Exposure of interest

We classified individuals as *long-term residents* if they were born in Canada or they were born outside of Canada but moved to Canada before 1985 (inception year for recording immigration data by the Ministry). Those born outside of Canada and arriving after 1985 were considered *immigrants*.

Using the validated surname algorithm described in Chapter 1, Section 13.3, we categorized the entire population into three different ethnic groups: Chinese (positive predictive value 91.9%), South Asian (positive predictive value 89.3%) or other.[137] The “other” category is

mostly comprised of those of Caucasian ethnicity in long-term residents, though not exclusively.[137]

5 Outcomes of interest

Our primary outcome was all-cause mortality, determined, along with date of death, from the provincial death registry. Cardiovascular mortality was a secondary outcome, obtained from the provincial register that assigns cause of death based on death certificates. Those with ICD-10 codes I20-25 or I60-69 as the most responsible cause of death were considered to have cardiovascular mortality.

We were also interested in vascular event recurrence [a composite outcome of stroke/transient ischemic attack (TIA) or myocardial infarction] following the index stroke, identified based on hospitalizations and/or emergency room visits with ICD 10 codes I63.x, H34.1 (ischemic stroke), G45.x excluding G45.4 (TIA), 161.x (intracerebral hemorrhage), I64.x (unspecified stroke), or I21 or I22 (myocardial infarction). We elected to include MI and stroke together because previous reports have reported a higher risk of vascular events following an ischemic stroke[196], and because we were interested in understanding the burden of total vascular disease. If a patient had both stroke and myocardial infarction, only the information on the first event was included for the composite end-point. We also separately studied the risk of having another stroke or TIA using similar methodology.

We considered the date of the index stroke as time zero for mortality analyses, and the date of discharge from either an acute care hospital or an inpatient rehabilitation centre as time zero for the analyses of recurrent vascular events. As a result, a recurrence of vascular event during index episode of hospitalization or rehabilitation will not be captured. This was done due to limitation of administrative databases to disentangle between index and recurrent event of the same type during an episode of hospitalization or rehabilitation.

6 Statistical Analysis

6.1 Primary analyses

We computed stabilized inverse probability treatment (IPT) weights to account for baseline differences between immigrants and long-term residents on a set of pre-specified baseline measures that included age, sex, neighbourhood-level income, vascular risk factors (hypertension, diabetes, high cholesterol, atrial fibrillation, smoking history, congestive heart failure), medical co-morbidities (dementia, chronic kidney disease requiring dialysis, cancer, Charlson comorbidity index), and treatment at a regional stroke centre or a teaching hospital.[172] The IPT weights were obtained by fitting a logistic regression model with immigration status as the outcome and the variables of interest as independent variables. We applied IPT weights and assessed balance between immigrants and long-term residents by calculating weighted standardized differences, which expresses the difference of means or prevalence between two groups as a proportion of the pooled standard deviation, with standardized differences of above 0.10 considered potentially meaningful (Figure 4.1).[168] We created two sets of weights. The first set of IPT weights only include age and sex whereas the second set included all variables, allowing us to report age- and sex- and fully-adjusted models using IPTW methodology.

We used the Kaplan-Meier method to compare adjusted long-term mortality between immigrants and long-term residents using the weighted sample.[196] The event of interest was death from any cause during the follow-up period, and patients were censored if they were alive at the end of follow up (March 31, 2018) or at the time of emigration (if this occurred prior to March 31, 2018).[197] We then developed Cox proportional hazards regression models to obtain unadjusted and IPT weight-adjusted hazard ratios (HR) of death for immigrants compared to long-term residents.

We reported point estimates and 95% confidence intervals for each outcome measure, and set $P < 0.005$ as the threshold for statistical significance after using Bonferroni's method to account for multiple comparisons.[170]

Determining loss to follow-up

One potential explanation for an observed mortality advantage in immigrants compared to non-immigrants is a phenomenon termed the *salmon effect,* whereby immigrants return to their home countries when they are gravely ill (described in detail in Chapter 1, section 5.3).[42] Thus, they are lost to follow-up in studies that calculate mortality rates in immigrants. Previous work in both observational studies and randomized controlled trials has shown that unbalanced loss to follow-up in two comparison groups can lead to biased estimates of association.[40,41] Thus, it is important to have appropriate and complete follow-up when studying the association between immigration status and long-term outcomes.

We determined each person's date of last contact with the health system by using administrative databases to identify any contact with the health care system such as a visit to a doctor's office, refill of prescriptions (in those over 65 years), hospitalization or emergency visits, receipt of home care, or admission to a rehabilitation facility (see details of this estimation in Table 4.1) until January 31, 2020. This date was only chosen to determine residence of cohort participants as required by the databases shown in Figure 4.2. Those alive on March 31, 2018 (end date of follow-up) with last health system contact prior to this date were flagged as *lost to follow-up* at the date of last health system contact (Figure 4.2). We used this method to estimate loss to follow-up in this cohort because the cohort consisted of patients with ischemic stroke and they would be expected to have some contact with health care system for follow-up for secondary stroke prevention.

6.2 Secondary analyses

We performed similar analyses using cause-specific HRs for the outcome of cardiovascular mortality, accounting for the competing risk of death from other causes, and for vascular event recurrence and stroke recurrence, accounting for the competing risks of death.

Effect of age

We evaluated whether age at the time of stroke modified the association between immigration status and outcomes by stratifying the analyses into two groups (≤ 75 years and > 75 years at the time of stroke) and calculating IPT weight-adjusted hazard ratios in immigrants compared to long-term residents in each stratum.

Ethnicity

In the full unweighted sample, we evaluated the interaction of ethnicity and immigration status on mortality and vascular event recurrence by including an interaction between ethnicity and immigration status in multivariable cause-specific Cox regression models, adjusting for the same set of variables used for calculating the IPT weights.

Country of origin and acculturation factors

We divided the immigrants into seven major world regions (Africa, Caribbean, Middle East, Latin America, East Asia, South Asia, and Europe and Western nations) based on their country of citizenship prior to arrival as per the classification used in previous studies (Table 1.2)

In the unweighted sample, we developed multivariable cause-specific hazard regression models using a competing event framework and calculated adjusted hazards of death and vascular event recurrence in each of these immigrant groups with long-term residents as the reference group. We adjusted for the same set of variables used for calculating IPT weights. Similarly, we used the following three immigration-related variables to evaluate the effect of

acculturation: time since immigration (≤ 5 years, 6 to 10 years, and > 10 years), age at arrival (≤ 50 years, and > 50 years), and immigration class (economic, refugee, family, or other). For each of these three immigration-related variables, we conducted a separate analysis in which long-term residents were compared to immigrants using the given immigration-related variable, separately.

6.3 Sensitivity analyses

Stroke severity and palliative care status

In an *ad-hoc* exploratory analyses, we added stroke severity (measured as a continuous variable using the Canadian Neurological Stroke Score) and palliative care status to re-calculate IPT weights, and then obtained the IPT weight-adjusted hazard ratio of death in immigrants compared to long-term residents, overall, and stratified by age.

6.4 Exploratory analyses

Among those who survived 30-days following ischemic stroke, we evaluated the quality of diabetes and dyslipidemia management in the first year following ischemic stroke. We compared the following between immigrants and long-term residents: 1) glucose and lipid monitoring – proportion of people receiving serum tests for Hemoglobin A1c (HbA1c) (in people with diabetes) and low-density lipoprotein (LDL) within 1 year, and 2) in those who had these tests, proportion of people meeting target LDL level of less than 2 mg/dL and target HbA1c level < 7% (in people with diabetes). We could not determine other important measure of secondary prevention (hypertension control) because of lack of available data on ambulatory blood pressure monitoring. We wanted to select stroke survivors who did not die in the first 30-days following ischemic stroke because we wanted to study quality of diabetes and dyslipidemia management in ambulatory care.

In a subgroup of older stroke survivors (65 years or older) who survived one year following ischemic stroke, and were not discharged to an acute care facility or complex continuing

care, we evaluated the following between immigrants and long-term residents: 1) proportion of people who filled a statin prescription; 2) among those who filled statin prescriptions, proportion of those who were adherent to medication, defined as proportion of days covered (PDC) over 80%[198]; 3) among those who were diagnosed with atrial fibrillation, proportion of people who filled a prescription of warfarin; and 4) among those who filled warfarin prescription, proportion of those who were adherent to warfarin, defined as PDC over 80%. Proportion of days covered was derived by dividing the total number of days covered with the drug of interest by the number of days in the follow-up period (set to 365 days).[199] The total number of days covered by a drug was derived by adding up all the days of supply of drug prescriptions for each patient. A PDC over 80% has been widely considered good adherence for any drug use when using administrative databases.[200] We limited these analyses to this specific subgroup as the drug data from Ontario Drug Benefit plan is only available for those over 65 years, and we needed data for an entire year following ischemic stroke to evaluate drug adherence as noted above.

We used Chi-square tests for above comparisons and obtained P values to report statistical significance between immigrants and long-term residents. We also reported weighted standardized differences between immigrants and long-term residents for the above comparisons. Standardized differences express the difference of means or prevalence between two groups as a proportion of the pooled standard deviation, with standardized differences of above 0.10 considered meaningful difference.[138]

7 Results

7.1 Baseline characteristics

Our study sample included 31,918 adults with ischemic stroke, of whom 2740 (8.6%) were immigrants (Figure 4.3). Immigrants were younger than long-term residents at the time of the index stroke (median age 70 vs. 76 years). Other baseline characteristics are reported in Table 4.2. Diabetes was more common in South Asian immigrants (46.9%) and South Asian

long-term residents (49.7%) compared to other groups (Table 4.3). Immigrants were more likely to be discharged to an inpatient facility providing complex care (12.2% vs. 8.0%) and less likely to be discharged to a long-term care facility (4.6% vs. 9.6%) after hospitalization compared to long-term residents (Table 4.2).

7.2 Primary outcomes

We observed 20,048 (62.9%) deaths during 168,885 person-years follow up, of which 9,005 (44.9%) were secondary to cardiovascular disease (Table 4.4). The adjusted cumulative mortality rates at 1, 5, 10 and 15 years were lower in immigrants compared to long-term residents, with greater divergence after 10 years (Figure 4.4 and Table 4.5). The unadjusted hazard of death was lower in immigrants compared to long-term residents (HR 0.65; 95% confidence interval 0.61-0.68) but the mortality advantage in immigrants was attenuated after accounting for age and sex (0.87; 0.82-0.92), using separate IPT weights that include only age and sex, and other comorbid conditions applying the IPT weights (HR 0.94; 0.88-1.00) (Table 4.6). There was no change in these estimates in sensitivity analyses where palliative care and stroke severity were added to IPT weight calculation (HR 0.92; 0.86-0.99). The unadjusted hazard of cardiovascular mortality was again lower in immigrants compared to long-term residents (HR 0.70; 0.64 to 0.77), but was similar after adjustment using IPT weights (HR 1.04; 0.93-1.17).

In the sample of patients who survived to discharge from acute care or rehabilitation (n = 28,148), 7830 (27.8%) had a recurrent vascular event (stroke or myocardial infarction) and 6,620 (23.5%) had a recurrent stroke (Table 4.6). The adjusted cumulative incidence of vascular event recurrence at 1, 5, 10, and 15 years was similar in immigrants and long-term residents (Table 4.5 and Figure 4.4), as was the HR of vascular event recurrence (HR 0.96; 0.89-1.04) in unadjusted models, after accounting for age and sex (HR 1.04; 0.96-1.13) and in fully adjusted models (HR1.01; 0.92-1.11) (Table 4.6). The hazard of stroke recurrence

was also similar in immigrants and long-term residents in the fully adjusted models (HR 1.04; 0.94 to 1.15).

7.3 Effect of age

In the analyses stratified by age at the time of stroke, being an immigrant was associated with a lower adjusted hazard of death in those aged 75 years and younger (HR 0.82, 0.74-0.91) in the fully adjusted models, but not in those aged over 75 years (HR 0.99; 0.91-1.08) (Table 4.6). Age at the time of stroke did not affect the association between immigration status and vascular event recurrence (Table 4.6).

7.4 Ethnicity and Immigration status

The adjusted hazard of death was higher among South Asian immigrants compared to South Asian long-term residents (HR 1.30; 1.05-1.61), similar in Chinese immigrants compared to Chinese long-term residents (HR 0.96; 0.79-1.15) and lower in immigrants of other ethnic origin compared to the long-term residents of other ethnicity (HR 0.89; 0.83-0.95) (P interaction for ethnicity and immigration on mortality = 0.003) (Table 4.7). There was no difference in the risk of vascular event recurrence between immigrants and long-term residents within ethnic groups (P interaction = 0.12) (Table 4.7).

7.5 Country of origin and acculturation

With the exception of immigrants from South Asia, point estimates for the adjusted hazard ratio of death were below 1.00 in immigrants from all regions compared to long-term residents, with the greatest survival advantage seen in immigrants from East Asia (HR 0.75; 0.65-0.86) (Figure 4.5). There was some variation in the adjusted hazard of all-cause mortality based on acculturation measures, with economic migrants (HR 0.90; 0.85-0.96) and those who arrived after the age of 50 years (HR 0.90; 0.84-0.95), having lower risk than long-term residents. The adjusted hazard of vascular event recurrence was higher in immigrants from Africa, the Caribbean, South Asia, and Latin America compared to long-

term residents (Figure 4.5). There was no variation in the association between immigration status and vascular event recurrence based on immigration class, time since immigration or age at arrival (Figure 4.5).

7.6 Exploratory analyses

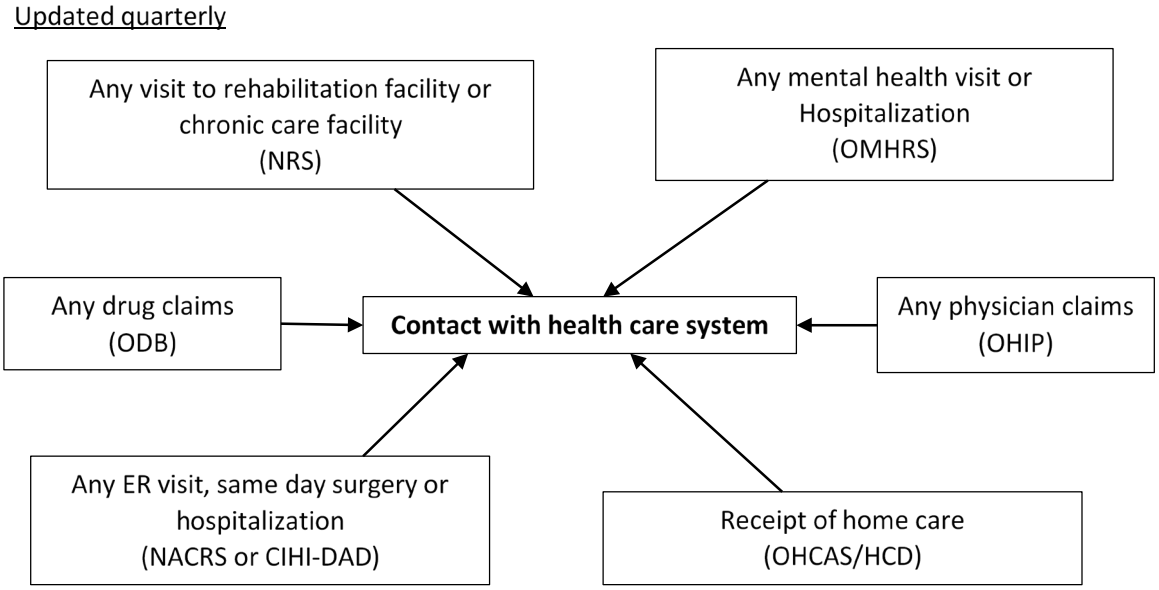
For the monitoring of serum HbA1c and LDL, our cohort consisted of 27,896 people who had survived 30 days following ischemic stroke, of whom 2510 (9.0%) were immigrants. Compared to long-term residents, immigrants were more likely to have serum LDL (35.4% vs. 27.4%, P < 0.001, standardized difference = 0.18) and serum HbA1c (28.7% vs. 22.3%, P < 0.001, standardized difference = 0.15) tested within one year of ischemic stroke. Of those who received these tests, compared to long-term residents with diabetes, immigrants with diabetes were less likely to reach the target HbA1c levels (< 7%) (52.7 vs. 59.7, P = 0.01, standardized difference = 0.14).; whereas, among everyone, immigrants and long-term residents were equally likely to meet target LDL levels (< 2 mg/dL) (66.9 vs. 63.7, P = 0.08, standardized difference = 0.07).

We identified 15,372 eligible older stroke survivors (65 years or over and survived for a year following stroke) to evaluate statin use, of whom 1065 (6.9%) were immigrants. The proportion of immigrants and long-term residents who filled a statin prescription during the one year following ischemic stroke was similar (83.8% and 80.8%, P = 0.45, standardized difference = 0.08) and among those who filled these prescriptions, both immigrants and long-term residents had equal adherence to statin, defined as more than 80% days covered in a year (66.3% vs. 67.5%, P = 0.28, standardized difference = 0.04).

We included 3,269 eligible older stroke survivors with atrial fibrillation in the analyses to evaluate warfarin use, of whom 198 (6.1%) were immigrants. A greater proportion of immigrants filled warfarin prescription during the one year following ischemic stroke compared to long-term residents (81.8% vs. 76.6%, P<0.001, standardized difference = 0.13); however, among those who filled these prescriptions, both immigrants and long-term

residents had similar adherence to warfarin (67.3% vs. 63.1%, P = 0.24, standardized difference = 0.08).

Table 4.1. Administrative databases used to determine date of last health system contact and statistics on contact with health care system in Ontario.



Abbreviations:

NRS – National Rehabilitation Reporting System; ODB – Ontario Drug Benefit; NACRS – National Ambulatory Care Reporting System; CIHI-DAD – Canadian Institute for Health Information-Discharge Abstract Database; OHCAS – Ontario Home Care Administration System; HCD – Home Care Database; OHIP – Ontario Health Insurance Plan Claims Database; OMHRS – Ontario Mental Health Reporting System

% of eligible people with some health care contact in 2015

	Age in years (grouped)				
Sex	0-19	20-35	36-65	66-84	≥ 85
Male	85%	69%	80%	95%	94%
Female	86%	85%	88%	96%	96%

Table 4.2. Characteristics of included patients with ischemic stroke in Ontario, Canada between April 2002 and March 2013 (N = 31,923).

Characteristics	Immigrants (n = 2,740, 8.6%)	Long-term residents (n = 29,178, 91.4%)	Standardized difference
Female, n (%)	1,317 (48.0)	14,348 (49.2)	0.02
Median age in years (Q1 - Q3)	70 (57-79)	76 (65-84)	0.41
Neighbourhood-level quintile, n (%)			
Lowest quintile (1st)	884 (32.2)	6,521 (22.3)	0.22
Highest quintile (5th)	281 (10.2)	5,636 (19.3)	0.26
Fluent in English and/or French, n (%)	1,843 (67.2)	26,869 (92.1)	0.20
Comorbidities, n (%)			
Hypertension	1,982 (72.3)	22,011 (75.4)	0.07
Diabetes	1,033 (37.7)	9,234 (31.6)	0.13
Dyslipidemia	1,147 (41.8)	11,569 (39.6)	0.04
Current smoker	355 (12.9)	5,182 (17.8)	0.13
Coronary artery disease	511 (18.6)	7,073 (24.2)	0.14
Previous stroke/TIA	692 (25.2)	8,184 (28.0)	0.06
Atrial fibrillation	391 (14.3)	5,692 (19.5)	0.14
Cancer	135 (4.9)	2,544 (8.7)	0.15
Dialysis	119 (4.3)	1,109 (3.8)	0.03
Dementia	149 (5.4)	3,024 (10.4)	0.18
Congestive heart failure	385 (14.0)	5,652 (19.4)	0.14
Median Charlson comorbidity index, (Q1-Q3)	2 (1-3)	2 (1-3)	0.03
Treatment at a teaching hospital, n (%)	1,402 (51.1)	18,733 (64.2)	0.27
Treatment at a regional stroke centre, n (%)	1,845 (67.3)	20,984 (71.9)	0.10
Median NIHSS, (Q1-Q3)	5 (2-11)	5 (2-10)	0.01
Received thrombolysis, n (%)	460 (16.8)	3,879 (13.3)	0.08

Admitted to the hospital, n (%)	2,318 (84.5)	24,986 (85.6)	0.03
Palliative status, n (%)	175 (7.5)	3,453 (13.8)	0.20
Median days in an intensive care unit, (Q1-Q3)	1 (1-3)	2 (1-4)	0.28
Dead on discharge, n (%)	211 (7.7)	3,269 (11.2)	0.12
Disabled on discharge (mRS 3 to 5), n(%)	1,347 (54.8)	13,597 (53.8)	0.02
Median mRS on discharge (Q1-Q3)	3 (2-4)	3 (2-4)	0.05
Discharge destination among those alive, n (%)	1,347 (54.8)	13,597 (53.8)	0.02
Home or retirement home	1,294 (51.1)	12,648 (48.8)	0.07
Inpatient rehabilitation centre	771 (30.5)	8,091 (31.2)	0.02
Long-term care	116 (4.6)	2,495 (9.6)	0.20
Inpatient facility providing complex care[$]	309 (12.2)	2,070 (8.0)	0.16
Median duration of follow-up in years, (Q1-Q3)	6.0 (2.9-8.8)	5.3 (1.1-7.9)	0.23

Q1-Q3 – 1st and 3rd quartile; SD – standard deviation; n – numbers, % - proportion of total N in column TIA – transient ischemic attack, NIHSS - National Institutes of Health Stroke Scale derived in part from the Canadian Neurological Scale, mRS – modified Rankin Scale; Std Diff – standardized difference, which expresses the difference between the means of two populations as a proportion of the pooled standard deviation. [$]includes acute care hospital or complex continuing facilities.

Table 4.3. Baseline characteristics of the cohort by ethnicity.

	Immigrants (n = 2,740, 8.6%)			**Long-term residents (n = 29,178, 91.4%)**		
	Chinese n=358 (13.1)	South Asian n=288 (10.5)	Other n=2,094 (76.4)	Chinese n=524 (1.8)	South Asian n=310 (1.1)	Other n=28,348 (97.1)
Female	166 (46.4)	138 (47.9)	1,012 (48.3)	277 (52.9)	138 (44.5)	13,935 (49.2)
Median age in year	75 (63-82)	70 (58-77)	69 (56-79)	76 (66-84)	72 (62-81)	76 (65-84)
Neighbourhood-level quintile						
Lowest quintile (1st)	99 (27.7)	75 (26.0)	709 (33.9)	124 (23.7)	63 (20.3)	6,333 (22.3)
Highest quantile (5th)	41 (11.5)	20 (6.9)	220 (10.5)	102 (19.5)	60 (19.4)	5,475 (19.3)
Fluent in English or French	183 (51.1)	211 (73.3)	1,582 (75.5)	322 (61.5)	273 (88.1)	26,691 (94.2)
Comorbidities						
Hypertension	263 (73.5)	216 (75.0)	1,503 (71.8)	406 (77.5)	242 (78.1)	21,367 (75.4)
Diabetes	103 (28.8)	135 (46.9)	795 (38.0)	192 (36.6)	154 (49.7)	8,886 (31.3)
Dyslipidemia	127 (35.5)	136 (47.2)	881 (42.1)	222 (42.4)	151 (48.7)	11,190 (39.5)
Current smoker	38 (10.6)	20 (6.9)	295 (14.1)	52 (9.9)	31 (10.0)	5,103 (18.0)
CAD	48 (13.4)	64 (22.2)	399 (19.1)	75 (14.3)	80 (25.8)	6,921 (24.4)
Previous stroke or TIA	85 (23.7)	90 (31.3)	518 (24.7)	109 (20.8)	92 (29.7)	7,984 (28.2)
Atrial Fibrillation	57 (15.9)	34 (11.8)	300 (14.3)	95 (18.1)	45 (14.5)	5,553 (19.6)

Dementia	18 (5.0)	13 (4.5)	117 (5.6)	49 (9.4)	26 (8.4)	2,948 (10.4)
CHF	31 (8.7)	54 (18.8)	298 (14.2)	82 (15.6)	57 (18.4)	5,513 (19.4)
Cancer	23 (6.4)	6 (2.1)	107 (5.1)	30 (5.7)	16 (5.2)	2,499 (8.8)
CKD	10 (2.8)	21 (7.3)	88 (4.2)	23 (4.4)	12 (3.9)	1,080 (3.8)
Median Charlson Index	2 (1-3)	3 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Treatment at regional stroke centre	227 (63.4)	163 (56.6)	1,460 (69.7)	362 (69.1)	223 (71.9)	20,382 (71.9)
Treatment at teaching hospital	196 (54.7)	100 (34.7)	1,106 (52.8)	349 (66.6)	138 (44.5)	18,248 (64.4)
Median NIHSS	5 (3-11)	6 (2-12)	5 (2-11)	6 (2-12)	5 (2-12)	5 (2-10)
Received thrombolysis	50 (14.0)	54 (18.8)	356 (17.0)	83 (15.8)	50 (16.1)	3,747 (13.2)
Admitted to a hospital	303 (84.6)	240 (83.3)	1,773 (84.7)	455 (86.8)	254 (81.9)	24,278 (85.6)
Palliative care status	27 (8.9)	22 (9.2)	126 (7.1)	55 (12.1)	22 (8.7)	3,372 (13.9)
Median days in intensive	1 (1-7)	1 (1-2)	1 (1-4)	4 (2-9)	1 (1-3)	2 (1-4)
Dead on discharge	23 (7.6)	29 (12.1)	154 (8.7)	60 (13.2)	21 (8.3)	3,151 (13.0)
Disabled on discharge (mRS 3 to 5)	187 (68.0)	135 (65.2)	941 (59.1)	252 (64.9)	136 (59.1)	12,356 (59.5)
Discharge destination among those alive						

Home or retirement home	102 (36.4)	99 (46.9)	799 (49.4)	153 (38.7)	103 (44.2)	9,284 (44.0)
Inpatient rehabilitation centre	112 (40.0)	68 (32.2)	589 (36.4)	148 (37.5)	84 (36.1)	7,823 (37.0)
Long-term care	26 (9.3)	11 (5.2)	71 (4.4)	60 (15.2)	15 (6.4)	2,130 (10.1)
Inpatient facility providing complex care	29 (10.4)	29 (13.7)	135 (8.3)	27 (7.3)	28 (12.0)	8,090 (50.4)
Median duration of follow-up in years	6.0(2.7-8.1)	5.6 (1.7-8.3)	6.0 (3.0-9.0)	5.7 (1.1-8.1)	6.0 (1.8-8.6)	5.3 (1.1-7.9)

Footnote: n (%) for categorical variables, and median (Q1-Q3) for continuous variables. Abbreviations: transient ischemic attack (TIA), coronary artery disease (CAD), congestive heart failure (CHF), chronic kidney disease (CKD), National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS).

Table 4.4. Cause of death in immigrants and long-term residents who died during follow-up.

Death due to any cause	Immigrants N = 1,261	Long-term residents N = 18,787	Standardized difference
Cause of death as per death registry	n (%)	n (%)	
Major cardiovascular disease	582 (46.2)	8415 (44.8)	0.03
Cancer	120 (9.5)	2,048 (10.9)	0.08
Respiratory	63 (5.0)	1,080 (5.7)	0.01
Central nervous system	20 (1.6)	344 (1.8)	0.02
Endocrine or diabetes	58 (4.6)	784 (4.2)	0.01
Mental Health	33 (2.6)	755 (4.0)	0.02
Genitourinary	32 (2.5)	443 (2.4)	0.08
Digestive	24 (1.9)	407 (2.2)	0.01
Trauma or other injuries	-	145 (0.8)	0.05
Blood	-	119 (0.6)	0.06
Other cardiovascular disease	-	24 (0.1)	0.06
Other causes	59 (4.7)	921 (4.9)	0.03
Cause of death unknown	261 (20.7)	3302 (17.6)	0.08

n (%) for some categories not shown as the n < 5.

Table 4.5 Mortality and vascular event recurrence following ischemic stroke in immigrants and long-term residents of Ontario

Adjusted cumulative incidence % (95% confidence interval)				
	All-cause mortality		**Vascular event recurrence**	
Time	Immigrants	Long-term residents	Immigrants	Long-term residents
1 year	23.1 (21.5-24.7)	23.7 (23.2-24.2)	12.8 (11.5-14.1)	12.1 (11.7-12.5)
5 years	43.7 (41.8-45.6)	45.1 (44.6-45.7)	22.1 (20.5-23.8)	23.0 (22.5-23.5)
10 years	61.2 (59.1-63.3)	65.7 (65.1-66.3)	28.3 (26.4-30.2)	28.7 (28.1-29.3)
15 years	76.8 (72.2-80.8)	81.8 (80.6-82.9)	31.3 (28.9-33.6)	31.3 (30.6-32.1)

Adjusted for age (continuous), sex (male reference), neighbourhood-income quintiles, diabetes, hypertension, dyslipidemia, coronary artery disease, congestive heart failure, dementia, dialysis dependence, current smoking, atrial fibrillation, prior stroke/TIA, cancer, Charlson comorbidity index, treatment at a teaching hospital, and treatment at a regional stroke center using inverse probability inverse weights.

Table 4.6. The association between immigration status and long-term outcomes in patients with ischemic stroke in Ontario, Canada.

Outcomes of interest	Immigrants		Long-term residents		Hazard ratio (95% CI) in immigrants compared to long-term residents		
	Events n (%)	Total	Events n (%)	Total	Unadjusted	Age- and sex-adjusted^£	IPTW-adjusted^
All-cause mortality[&]	1,261 (46.1)	2,743	18,787 (64.5)	29,185	0.65 (0.61-0.68)	0.87 (0.82-0.92)	0.94 (0.88-1.00)
≤ 75 years	532 (29.7)	1,758	6,014 (43.1)	13,965	0.67 (0.62-0.74)	0.78 (0.71-0.85)	0.83 (0.75-0.92)
> 75 years	741 (75.8)	978	12,797 (84.3)	15,179	0.87 (0.81-0.94)	0.95 (0.88-1.02)	1.00 (0.92-1.09)
Vascular event recurrence[&]	710 (28.4)	2,502	7,120 (27.8)	25,646	0.96 (0.89-1.04)	1.04 (0.96-1.13)	1.01 (0.92-1.11)
≤ 75 years	483 (29.2)	1,657	3,342 (28.1)	11,890	1.04 (0.94-1.14)	1.10 (1.00-1.22)	1.01 (0.91-1.10)
> 75 years	227 (26.9)	845	3,468 (27.7)	12,515	0.97 (0.85-1.11)	0.98 (0.85-1.13)	0.96 (0.83-1.10)

^Using cause specific Cox regression model; [£]these are obtained using IPT weights derived from models accounting for age and sex alone; [&]subgroups based on age at the time of stroke: ≤ 75 years and > 75 years.

CI – confidence interval; IPTW – inverse probability treatment weights obtained after adjusting for: age (continuous), sex (male reference), income quintiles, diabetes, hypertension, dyslipidemia, coronary artery disease, congestive heart failure, dementia, dialysis dependence, current smoking, atrial fibrillation, prior stroke/TIA, cancer, Charlson comorbidity index, treatment at a teaching hospital, and treatment at a regional stroke centre.

Table 4.7. The interaction between immigration status and ethnicity on long-term outcomes following ischemic stroke in Ontario, Canada.

	Immigrants		Long-term residents		Adjusted Hazard Ratio (95% CI)[&]	$P_{interaction}$^
	Events, n (%)	Total	Events, n (%)	Total		
All-cause mortality						0.003
Chinese	175 (49.0)	357	290 (55.6)	522	0.96 (0.79-1.15)	0.47
South Asian	148 (51.4)	288	159 (51.5)	309	1.30 (1.05-1.61)	<0.001
Other	938 (44.9)	2089	18,338 (64.8)	28,288	0.89 (0.83-0.95)	-
Vascular event recurrence						0.11
Chinese	67 (20.5)	327	125 (27.5)	454	0.77 (0.57-1.04)	0.05
South Asian	86 (33.7)	255	88 (31.3)	281	1.13 (0.84-1.53)	0.68
Other	557 (29.0)	1920	6907 (27.7)	24,911	1.06 (0.97-1.16)	-

[&]Using cause specific Cox regression model; ^test of interaction between immigration status and ethnicity where immigration status is binary (yes vs. no) and ethnicity is categorical with 'Other' as the reference group, we report P values of an overall join test, and of ethnicity-specific tests of interaction; CI – confidence interval; IPTW – inverse probability treatment weights obtained after adjusting for: age (continuous), sex (male reference), income quintiles, diabetes, hypertension, dyslipidemia, coronary artery disease, congestive heart failure, dementia, dialysis dependence, current smoking, atrial fibrillation, prior stroke/TIA, cancer, Charlson comorbidity index, treatment at a teaching hospital, and treatment at a regional stroke centre.

'Other' category consisted mostly of those of Caucasian ethnicity.

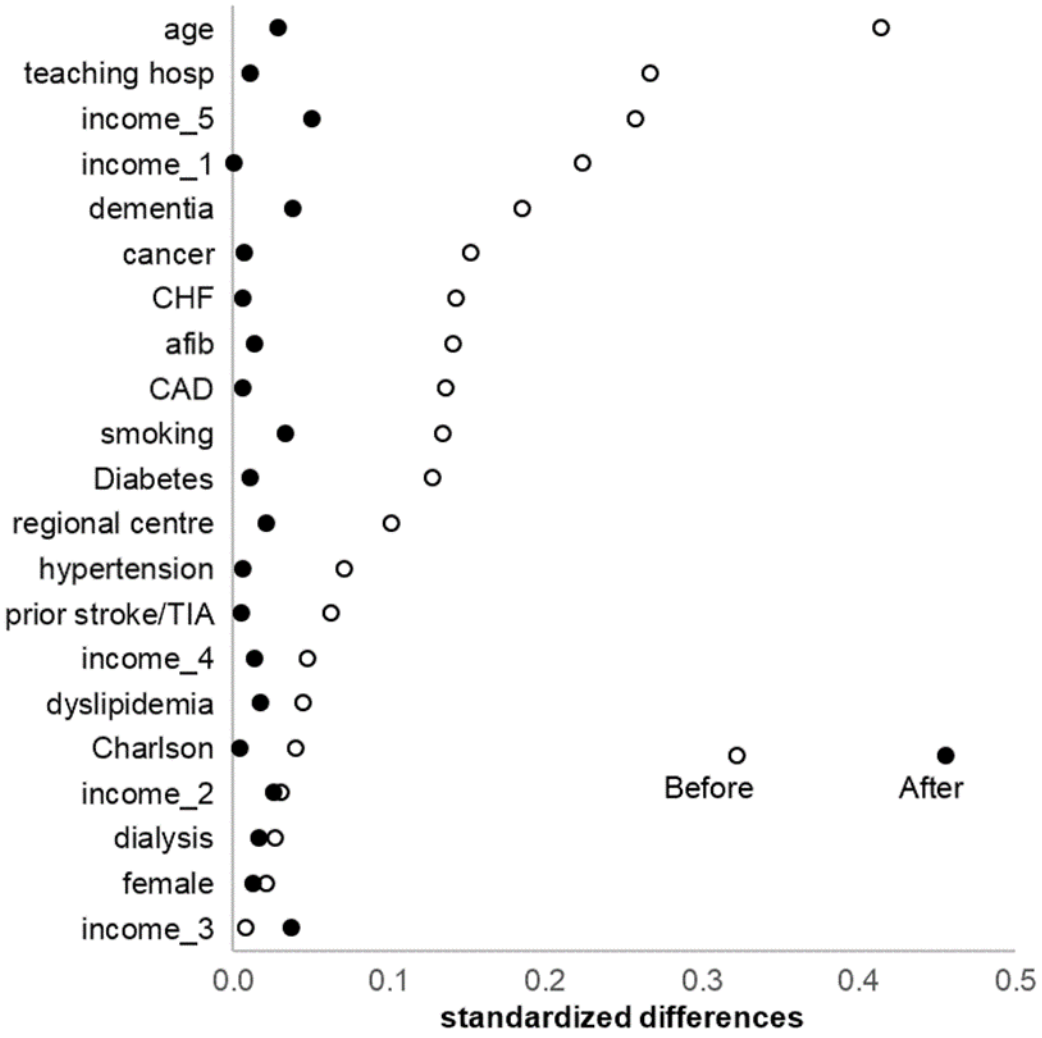


Figure 4.1. Balance before and after application of inverse probability treatment (IPT) weights to the cohort of patients with ischemic stroke.

Abbreviations: Teaching hosp – teaching hospital, CHF – congestive heart failure, afib – atrial fibrillation, CAD – coronary artery disease, TIA – transient ischemic attack, Charlson – Charlson comorbidity index, income_x – income quintiles where x represent a particular quintile.

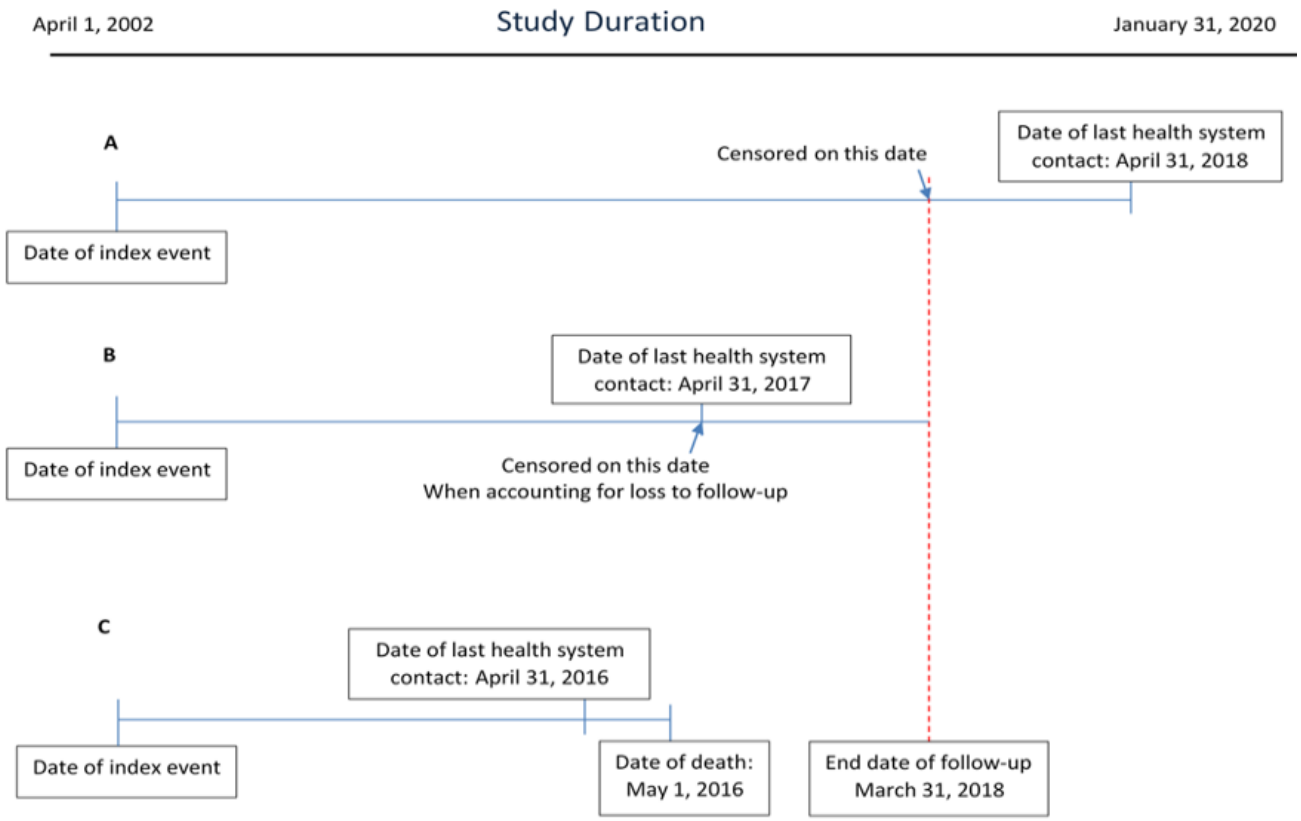


Figure 4.2. Hypothetical cases to illustrate loss to follow-up using administrative database. Subject A was not to lost to follow-up, Subject B would be considered lost to follow-up, and Subject C had the event of interest (death) and so is not considered lost to follow-up.

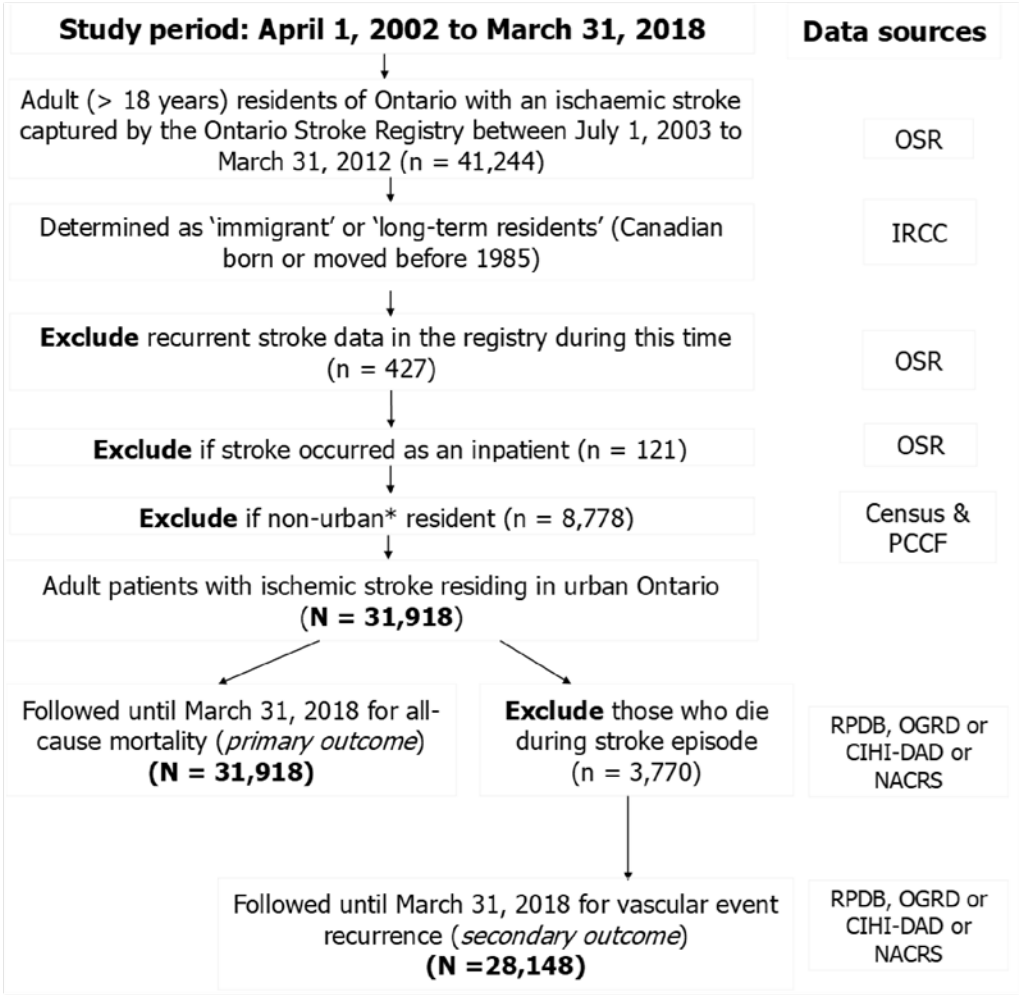


Figure 4.3. Participant selection for the study.

Footnote**:** OSR – Ontario Stroke Registry IRCC – Immigration, Refugee and Citizenship Canada; PCCF – Postal Code^{OM} Conversion File; CIHI-DAD – Canadian Institute of Health Information Discharge Abstract Database; NACRS – National Ambulatory Care Reporting Systems Metadata; RPDB – Registered Person's Database.

Non-urban resident was defined as residing in an area with population less than 10,000.

Stroke episode defined as time from index stroke to discharge from inpatient facility such that an incident stroke can be captured using administrative database.

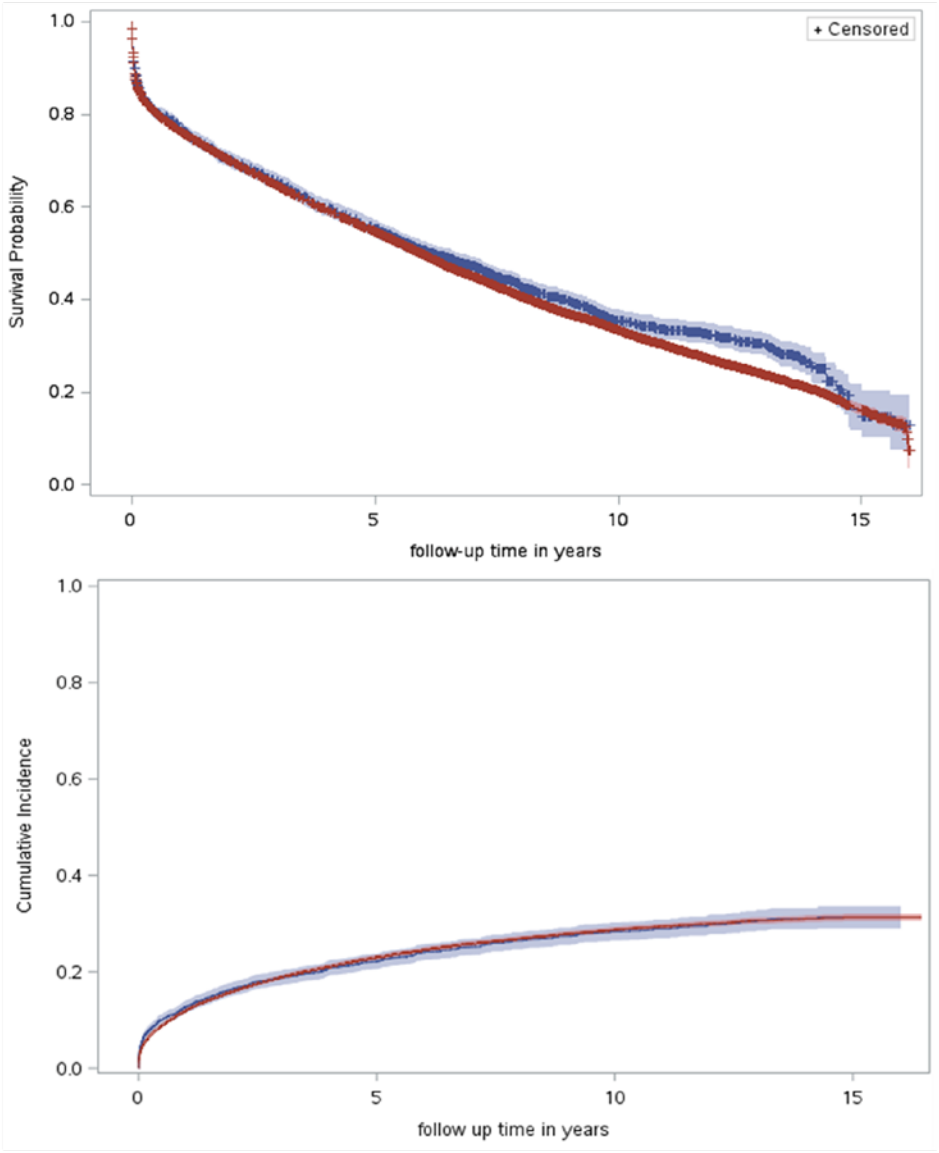


Figure 4.4. All-cause mortality and vascular event recurrence following ischemic stroke in immigrants and long-term residents.

Footnote: Inverse probability treatment weight-adjusted survival curves for all-cause mortality (top) and cumulative incidence curves for vascular event recurrence (bottom) following ischemic stroke among immigrants (blue) and long-term residents (red) in Ontario from April 2002 to March 2018.

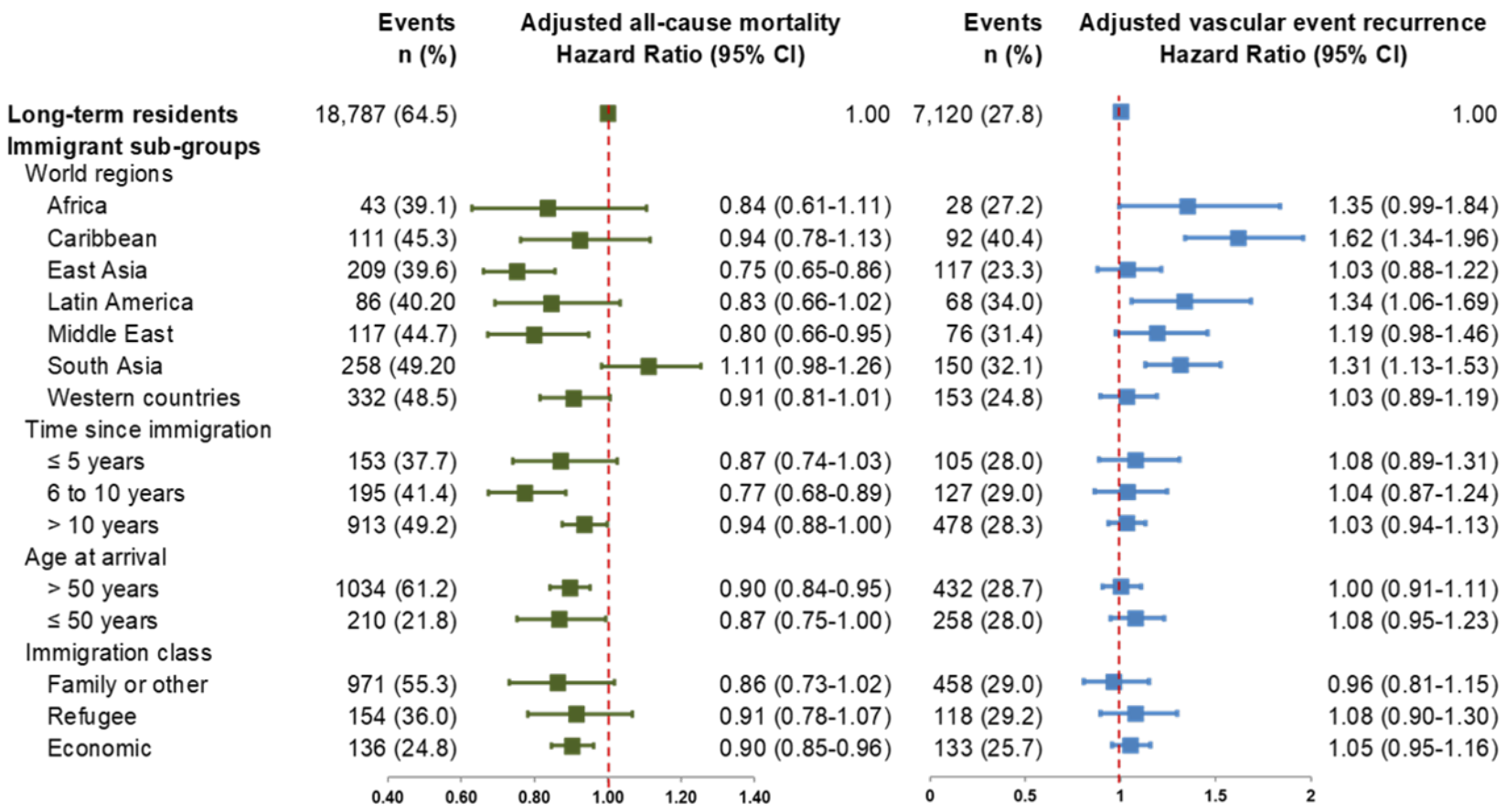


Figure 4.5. Results of multivariable proportional hazards models to evaluate effect of acculturation on mortality and vascular event recurrence following ischemic stroke.

8 Discussion

8.1 Summary

Using data from over 30,000 patients with ischemic stroke, we found that immigrants had a lower age- and sex-adjusted hazard of death, but not vascular event recurrence, compared to long-term residents in Ontario, Canada. However, the association between immigration status and mortality was attenuated after adjustment for comorbid conditions, and varied with age at stroke onset, ethnicity, and region of origin.

8.2 Key findings

Our finding of a cumulative risk of death at 15 years after ischemic stroke of 81.8% in long-term residents is consistent with previous studies.[201,202] Age is an important predictor of all-cause mortality following stroke.[203] We found that immigrants were younger than long-term residents at the time of their stroke and this suggests that primary preventative measures in immigrants could be improved to reduce this burden of ischemic stroke at a younger age. Despite this, immigrants had lower mortality than long-term residents in both unadjusted and age- and sex-adjusted models suggesting the presence of a healthy immigrant effect.[13] The lower hazard of death associated with immigration status was attenuated after adjustment for comorbid conditions and other factors, consistent with a previous Canadian study.[66] It is likely that the multivariable adjusted models adjusted for some factors (such as vascular risk factors) in the causal pathway for the association between immigration status and mortality following ischemic stroke. Of note, in patients who had their stroke before the age of 75 years, we found that immigrants maintained a survival advantage, even after accounting for comorbid conditions, stroke severity, and palliative status. It is possible that the distribution of unmeasured confounders such as life-style factors (alcohol use, body mass index, or dietary habits) or secondary preventative care may vary between immigrants and long-term residents depending on the age at the time of stroke. This would require further rigorous evaluation in other populations.

Having a recurrent stroke is associated with a two-fold increase in 30-day mortality compared to a first stroke, emphasizing the importance of studying stroke recurrence risk.[204,205] Our finding of a 23.0% cumulative risk of vascular event recurrence in long-term residents at 5 years, and 28.7% at 10 years is lower than that described in previous studies, likely because the cumulative risks in our study were adjusted for various demographic and vascular risk factors rather than age alone.[206] We found that this risk was similar in immigrants and long-term residents both before and after adjustment for vascular risk factors, and that this association was not modified by age at the time of stroke. Provision of health insurance through the provincial plan may have mitigated the risk of stroke recurrence in immigrants to Ontario, as lack of health coverage has been associated with higher cardiovascular disease incidence in ethnic and immigrant minority groups in other jurisdictions.[207]

We found that the association between immigration status and mortality was modified by ethnicity, derived using last name algorithm, with lower mortality in immigrants compared to long-term residents of non-South Asian, non-Chinese ethnicity, and with higher mortality in immigrants compared to long-term residents of South Asian ethnicity. South Asian ethnicity is associated with a high burden of vascular risk factors, especially diabetes, and a higher burden of cardiovascular disease as a result.[208] One study of people with diabetes found a higher hazard of stroke recurrence, but a lower post-stroke mortality in South Asians compared to non-South Asians[114] similar to previous studies that have also found either a lower or similar risk of cardiovascular mortality in South Asians compared to Caucasians, a phenomenon sometimes known as the incidence-outcome paradox in South Asians.[209] In comparison, Chinese immigrants appear to have a lower incidence of coronary heart disease but higher short-term mortality following acute myocardial infarction compared to Caucasians, an incidence-outcome paradox which is the opposite of that observed in South Asians.[210] While these paradoxes could be due to index event bias, a form of collider bias,[211] most previous studies have not studied immigration status and ethnicity together, and our

findings suggest that the interaction of immigration status and ethnicity, and not either alone, should be considered when studying outcomes in ethnic groups following ischemic stroke.

We found that the risk of vascular event recurrence varied by region of origin, which can be considered a proxy for ethnocultural characteristics. The hazard of vascular event recurrence was higher in immigrants from Africa, Caribbean and Latin America compared to long-term residents, even after accounting for differences in vascular risk factors. This is similar to previous studies that reported higher cardiovascular recurrence in Black British[181] and Latino Hispanic groups in the US.[212,213] In the US, the National Healthcare Quality Report (2018) found that Black and Hispanic Americans received worse care than Whites for more than 35% of quality measures, including metrics like statin prescription following ischemic stroke.[214] Thus, more work is required to understand and mitigate the individual, sociopolitical, and environmental factors that may contribute to the observed disparities among immigrant ethnic groups in care and outcomes following ischemic stroke.[207,215]

The health of immigrants will be affected not only by ethnicity and ancestry but also by immigration class and by the immigrant experience including immigration-related stress, discrimination, and underemployment.[216] One study reported better survival following stroke in immigrants in Denmark than in Danish-born people, with a relatively better survival in family-reunified migrants than refugees.[62] In contrast to previous studies on the effect of acculturation on immigrant health, we did not find a significant variation in the hazard of death or vascular event recurrence based on immigration class, time since immigration or age at arrival.[156,217] However, a full understanding of the effect of the immigrant experience on immigrant health would require future studies that employ a life-course context to better understand the social determinants of health in immigrants.[207]

In a Canadian study of patients with acute ischemic stroke, ethnic differences in filling prescriptions of statins, and warfarin were noted, with Chinese and South Asian patients more likely to fill statin prescriptions than other Canadians (Chinese 43.5%, South Asian

50.8% and Other 41.9%).[218] In those diagnosed with atrial fibrillation, the adjusted OR of warfarin use was lower in Chinese compared to other Canadians (adjusted OR 0.75; 95% CI 0.59-0.95) but was similar in South Asian and other Canadians.[218] Immigration status was not studied as part of this study. A systematic review of cardiac medication adherence in South Asians found that non-adherence to cardiac medications among South Asians was multifaceted, and medication side effects, costs, and forgetfulness were commonly reported reasons for non-adherence.[219] Educational intervention during six months post-discharge following an acute coronary syndrome was associated with better adherence and lower discontinuation rates in all participants, irrespective of immigration status in a Danish study, suggesting that secondary prevention can be improved by better knowledge and understanding the rationale for drug adherence.[220] We were not able to identify other studies on the quality of diabetes and dyslipidemia management in immigrants following stroke. Our findings of higher or equal monitoring of serum LDL and HbA1c levels in immigrants compared with long-term residents, but a lower proportion of immigrants attaining target diabetes control (HbA1c < 7%) compared to long-term residents need further evaluation to determine whether these results are replicable and, if so, to understand what is driving these differences.

8.3 Strengths and limitations

Key strengths of our study include the use of linked population-based administrative databases that allowed follow-up to 16 years, and the ability to account for right-censoring due to emigration. This is an important factor when studying long-term outcomes in immigrants, as the healthy immigrant effect may in part be driven by late life emigration back to home countries, resulting in a falsely low mortality rate in immigrants (a phenomenon known as “salmon bias”).[197]

Certain limitations merit discussion. First, for some of the analyses, ethnicity was determined using surname algorithms to identify those of Chinese and South Asian descent, and despite

the excellent positive predictive property of the algorithm, misclassification is possible and the algorithm tends to exclude those of South Asian descent with Muslim and Christian surnames. In addition, even within these categories, people identified as being of South Asian or Chinese descent cannot be considered homogeneous as these groups will include individuals from different countries of origin with differing biological and behavioural risks. Furthermore, the 'other' (non-South Asian, non-Chinese) category may be more diverse for immigrants than for long-term residents, who are more likely to be of Caucasian descent, thus requiring a cautious interpretation of interaction between immigration status and ethnicity for mortality outcomes.[137] We were also not able to identify immigrants who arrived to Canada prior to 1985, and so the comparison group of long-term residents will include immigrants who have resided in Ontario for more than 18 years. While this could partly explain the younger age of immigrants at the time of stroke, the mortality advantage in immigrants was noted even after accounting for age, and was also noted in the subgroup of people less than 75 years at the time of their stroke, suggesting that misclassification did not have significant impact on the observed association. Second, data on risk factors such as diet, physical activity, and obesity were not available, nor was information on the severity or duration of other known risk factors such as diabetes, hypertension and hyperlipidemia.[221] We also did not have information on secondary preventative measures, or the extent to which individuals were adherent to such measures, information on the ethnic composition of neighborhoods, or information on the lived experiences of immigrants which could include factors like discrimination or racism.[218,222,223] Further, our findings of the quality of diabetes and dyslipidemia control and medication adherence require cautious interpretation because these were obtained from those who survived for at least one year post-stroke and may undercount poor adherence in those who die early. Lastly, our findings may not be generalizable to patients residing in non-urban centres, jurisdictions with health care systems not similar to that of Canada, or non-documented immigrants who may not be eligible for coverage under the provincial health care plan.

8.4 Implications

Our finding of lower mortality after ischemic stroke supports the concept of a healthy immigrant effect, due to a selective migration pattern whereby the healthy are more likely to migrate[224]; however, the magnitude and the direction of this effect is not homogeneous across all immigrants. Future studies should focus on understanding and addressing the factors associated with stroke at a young age in immigrants, on studying the various sociodemographic factors that affect immigrants' health and on developing appropriate screening and preventive measures to reduce the burden of ischemic stroke and its consequences in both immigrants and long-term residents.

Chapter 5 Discussion

1 Summary

Immigration is a fundamental human behaviour, and, similar to other behaviours, it also has implications on human health. This work aims to fill the gap in current knowledge on the effects of immigration on health, pertaining to stroke, a leading cause of disability and death worldwide.

In chapter 2, we studied the incidence of stroke in immigrant groups in Ontario, and two important findings emerged: stroke incidence is lower in immigrants than long-term residents, yet, stroke occurs at a younger age in immigrants. While the overall lower incidence could be due to a *healthy immigrant effect,* evidenced by lower rates of vascular risk factors in immigrants compared to long-term residents, the younger age at the time of stroke could either be due to the variation in age distribution of immigrants and long-term residents, the latter being older, or due to onset of vascular risk factors at an early age or poorly managed vascular risk factors. Immigration status also has age-dependent effects on stroke incidence, with similar risk of stroke at younger ages (below 30 years) and a greater reduction in risk in immigrants at older ages (after 50 years) that requires further studies to delineate the reasons. Further, there is variation in these associations based on immigration class and country of origin, with African, Caribbean and Latin American immigrants having a relative higher risk of stroke than other immigrant groups. Knowledge of this complex relationship of immigration status and associated immigration-specific characteristics can help develop targeted primary preventative efforts for both immigrants and long-term residents.

In chapter 3, we evaluated the quality of acute stroke care in immigrants and long-term residents with ischemic stroke or TIA. We found that immigrants receive similar or better acute stroke care compared to long-term residents. However, among people with ischemic stroke, immigrants are more likely to be disabled on discharge despite a similar mortality rate at 30 days. A greater stroke severity and a less frequent use of palliative care services use in

immigrants compared to long-term residents may be some explanations for this finding. Despite being young at the time of stroke, the greater stroke severity and higher disability in immigrants compared to long-term residents requires further investigation.

In chapter 4, we evaluated the long-term outcomes following ischemic stroke in immigrants and long-term residents. Immigrants have a lower all-cause mortality compared to long-term residents, especially in those who have stroke at a younger age (below 75 years). This is partly due to the younger age of immigrants at the time of stroke; however, the association persists even after adjusting for age. Compared to other immigrant groups, mortality is higher in South Asian immigrants, whereas vascular event recurrence is higher in Latin American, African and Caribbean immigrants, suggesting the need to develop targeted secondary stroke prevention strategies for different immigrant groups. Further, there is an interaction between immigration status and ethnicity for our outcomes of interest, suggesting the need for further detailed evaluation of the reasons for poor outcomes in immigrant ethnic minority groups.

2 Limitations

A major limitation of the included work is lack of a comparative non-immigrant group, for some analyses, consisting of people of similar ethnic and cultural background as the immigrants, other than those of South Asian or East Asian origin. This limits our ability to definitely disentangle the immigration- and ethnicity-effects in our observed associations. One way to get around this limitation would be to study the incidence rate of stroke and outcomes following stroke in immigrants in Ontario based on different countries of origin, and compare these rates to those observed in home countries. Another approach could include a comparison group of second-generation immigrants so that when comparing them to first-generation immigrants, one can eliminate the ethnicity effect. Unfortunately, the latter would require accounting for secular trends in the stroke incidence and outcomes over two generations, and also require extended follow-up. We did not have information on second generation immigrants in Ontario.

Second, we could only evaluate acculturation based on time in Ontario and age at arrival. However, acculturation is a highly nuanced concept and it varies depending on individual circumstances. This may be one reason why we were unable to show the acculturation effect with the two measures available to us: time since immigration and age at arrival. Measures such as dietary change, having friends of different ethnic/cultural background, sense of belonging, and languages spoken at home are some methods by which acculturation has been measured in the past. We did not have access to such self-reported measures and future work could be undertaken to evaluate this using data by linking self-reported survey data to administrative data or by mix-methods or qualitative research to evaluate acculturation.

Third, we found that the age distribution of immigrants was significantly different than that of long-term residents, with immigrants being generally younger than long-term residents in cohorts of people both with and without stroke. Therefore, we specifically evaluated the effect of this age difference on our outcomes using different methods. However, age remained an important modifier of the association between immigration status and stroke incidence and outcomes. Immigrants who move when they are older (60 years and above) have a considerably different health status than that of immigrants who move at an early age, and than that of host populations 60 years and above. Even though we allowed for long duration of follow-up (up to 15 years), we believe that it may be inadequate to account for the impact age on our findings. Ideally, one should be able to compare the rate of stroke incidence and outcomes over a lifespan in young immigrants and long-term residents.

While this work highlights differences in stroke incidence and outcomes in immigrants and long-term residents, we were unable identify the drivers of the observed effects. Qualitative studies of immigrant groups experiencing stroke symptoms as well as health care providers could reveal important information that can be used in the future to develop targeted interventions.

We recognize that being an immigrant is closely related to various other social determinants of health such as education, income, neighbourhood-level effects, work conditions, social isolation and racism or discrimination, of all which have been associated with health outcomes. Providing unadjusted and age- and sex-adjusted estimates may provide some insights on the influence of these and other factors, and could capture the influence of lived experiences of immigrants; however, we were unable to fully evaluate the mediating roles of these factors in our observations, nor were we able to measure self-perceived discrimination or racism.

3 Future projects

We have highlighted the incidence and outcomes of stroke in immigrants and long-term residents; however, our understanding of the quality of primary and secondary prevention in these groups is poor and deserves future study. Further, experiences prior to and upon immigration vary between men and women, and these experiences can influence their health, so future work should evaluate the potential for sex and gender differences in stroke care and outcomes in immigrant groups.[225,226] An interaction between immigration status and vascular risk factors, especially that of diabetes in South Asians, and hypertension in African and Caribbean immigrants would be another clinically meaningful interaction to evaluate in future studies, with the goal of identifying targets for secondary prevention to reduce the risk of mortality and vascular event recurrence in these immigrant groups.

Future qualitative studies may be helpful in understanding factors that influence stroke care and outcomes in immigrants. Specific areas for study could include knowledge of stroke symptoms and the necessary steps required when having these symptoms, as well as attitudes and preferences for stroke care interventions and palliative care use in immigrant and non-immigrant groups. Studying post-stroke care, such as out-of-pocket expenses for rehabilitation services not covered under provincial health insurance plan, access to home care services, and informal care giving can help understand the extent to which stroke affects

lives of patients and their families, and whether it is varies by immigration status. Qualitative studies on the lived experience of immigrants with stroke may be helpful in identifying unmet needs and designing interventions to address these.

4 Implications

The findings of this dissertation highlight the challenges in studying health outcomes of immigrant populations because these populations are not homogeneous. However, they all have a common element – the act of immigration and the lived experience of an immigrant. Therefore, the principles of the association between immigration status and health outcomes found in these projects may be applicable to other medical conditions. While the magnitude of the association will vary based on the disease studied, we doubt that the direction of effects will vary. This research work supports the healthy immigration effect, the return migration (salmon effect) or higher rate of loss to follow-up in immigrants, and, to some degree, the acculturation effect. The existence of these epidemiological phenomena has been contentious, and this body of work offers important insights.

The dissertation also highlights the need to evaluate and improve primary stroke prevention in immigrants by improving access to, and knowledge of preventative primary care, and by development of culturally sensitive public health campaigns to improve knowledge of stroke symptoms. Furthermore, the quality of secondary stroke prevention and its impact on vascular event recurrence and mortality deserves detailed evaluation. Lastly, the variation in observed associations based on country of origin of immigrants should stimulate further research to evaluate biological and social factors for the observed variation based on country of origin.

Curriculum Vitae

Name: Manav V. Vyas

Research training

07/2015-present	PhD, Institute of Health Policy, Management and Evaluation, University of Toronto, Canada
07/2017-present	Clinician Investigator Program (CIP), University of Toronto, Toronto, Canada
09/2010-06/2012	MSc, Epidemiology & Biostatistics, Western University, London, Ontario, Canada
09/2010-06/2012	Canadian Institutes of Health Research Strategic Training Program in Vascular Research, Canada

Clinical training

07/2017	EEG certification, Canadian Society of Clinical Neurophysiologists
07/2012-06/2017	Neurology, Fellow of the Royal College of Physicians of Canada
07/2003-06/2009	MBBS, Smt. NHL Municipal Medical School, Gujarat University, India

Awards & scholarships

2019-2021	CIHR Fellowship Award, Canadian Institutes of Health Research, Canada

2019-2020	Prince Mahidol Marmot Research Fellow, University College London, United Kingdom
2018-2019	Heart & Stroke Richard Lewar Centre of Excellence/CANHEART SPOR Studentship Award, Canada
2018	American Academy of Neurology (AAN) Future Clinical Researcher in Neurology and Neuroscience, USA
2018	AAN Young Investigator Award (declined), USA
2015	OSOTF Unilever/Lipton Graduate Fellowships in Neurosciences, Canada

Publications

1. **Vyas MV**, Laupacis A, Austin PC, Fang J, Silver FL, Kapral MK. Association between immigration status and acute stroke care: a retrospective study. *Stroke.* 2020 May; 51(5):1555-1562. [PhD paper #1]

2. **Vyas MV**, Austin PC, Fang J, Laupacis A, Silver FL, Kapral MK. Immigration Status, Ethnicity, and Outcomes following Ischaemic Stroke. *Neurology. Accepted*. October 2020 [PhD paper #2]

3. **Vyas MV**, Fang J, Austin PC, Cheung M, Laupacis A, Silver FL, Kapral MK. Immigration status and mortality: the importance of accounting for lost to follow-up. *BMJ Open. Under review.* June, 2020. [Comprehensive paper]

4. **Vyas MV,** Austin PC, Pequeno P, Fang J, Silver FL, Laupacis A, Kapral MK. Incidence of stroke by immigration status: a retrospective study of 8 million adults. *To be Submitted. January, 2021.* [PhD paper #3]

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