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3 **Stroke Incidence, Care, and Outcomes in First Nations People with Diabetes in Ontario,**
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6 **Canada: A Population-Based Cohort Study**
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42 **Funding:** Moira Kapral was supported by a Mid-Career Award from the Heart and Stroke
43 Foundation of Canada, Michael Green by the Brian Hennen Chair in Family Medicine, Morgan
44 Slater by a Health System Impact Fellowship from the Canadian Institutes of Health Research,
45 and Jennifer Walker by a Tier 2 Canada Research Chair in Indigenous Health. Funding is
46 provided by the Ontario SPOR SUPPORT Unit, which is supported by the Canadian Institutes of
47 Health Research and the Province of Ontario.. This study was supported by ICES, which is
48 funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC).
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53 **Competing interests:** All authors have no competing interests to declare
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56 Abstract word count: 242
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3 Text word count: 2206
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5
6 **Abstract**
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8 **Background:** First Nations people have high rates of diabetes, which is a risk factor for stroke.
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10 We studied the incidence, care, and outcomes of stroke and transient ischemic attack (TIA) in
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12 First Nations people in Ontario.
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15 **Methods:** Using linked, de-identified databases housed at ICES, we identified a cohort of people
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17 with prevalent diabetes between April 1, 1995 and March 31, 2015, and identified Status First
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19 Nations people from the Indian Register. We compared age-/sex-standardized stroke/TIA
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21 hospitalization rates, processes of care, and case-fatality in First Nations versus other Ontarians
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23 with diabetes.
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27 **Results:** Hospitalization rates for stroke/TIA declined over the study period, but were higher in
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29 First Nations people than other Ontarians in every year after 2006. Compared to other
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31 Ontarians, First Nations people hospitalized with stroke/TIA were equally likely to undergo
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33 neuroimaging within 24 hours (94.6% vs. 96.0%) and be discharged to inpatient rehabilitation
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35 (31.8% vs. 34.8%) but less likely to receive thrombolysis (6.3% vs. 11.0%) or carotid
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37 revascularization (1.4% vs. 2.7%). There was a trend toward increased age-/sex-standardized
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39 stroke case-fatality in First Nations people compared to other Ontarians at seven days (12% vs.
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41 8.4%), 30 days (19.2% vs. 15.9%) and one year (33.8% vs. 28.0%).
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47 **Interpretation:** Stroke incidence and case-fatality are higher in First Nations people compared
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49 to other people with diabetes. Future work should focus on determining Indigenous-specific
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51 determinants of health related to this disparity and implementing appropriate interventions to
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53 mitigate the risks and sequelae of stroke in First Nations people.
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3 **Background:** Stroke is a leading cause of death and disability in Canada and worldwide¹.

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6 Diabetes mellitus is a risk factor for stroke, and is also associated with an increased prevalence
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8 of other vascular risk factors including hypertension and hyperlipidemia²⁻⁵. Stroke incidence is
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10 higher in Indigenous compared to non-Indigenous populations in Australia, and, in Canada,
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12 diabetes mellitus occurs with a higher frequency and at an earlier age in First Nations people
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14 than in the general population⁶⁻⁹. These increased risks are the result of a complex set of
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16 determinants of health including contemporary and historic influences of colonization and
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18 marginalization experienced by First Nations people¹⁰.

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25 In the setting of acute stroke, interventions such as thrombolysis, mechanical thrombectomy,
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27 stroke unit care, and rehabilitation are associated with improved functional outcomes, while
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29 antithrombotic therapy, treatment of hyperlipidemia and hypertension, and carotid
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31 revascularization can decrease the risk of recurrent stroke and vascular death^{11,12}. However,
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33 many of these interventions require specialized stroke care resources that may not be available
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35 in all jurisdictions. First Nations people are more likely to live outside of urban settings where
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37 these services are most readily accessed.¹³

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44 Among First Nations people with diabetes, little is known about the risks and outcomes of
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46 stroke and this information gap is of critical importance to First Nations leadership and health
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48 providers who are faced with high rates of diabetes in their populations. In collaboration with
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50 the Chiefs of Ontario, we used linked population-based administrative databases from the
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3 province of Ontario, Canada, to study stroke incidence, process of acute stroke care, and stroke
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5 case-fatality in First Nations people compared to other Ontarians with diabetes.
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10 **Methods**

11 ***Data Sources and Study Cohort:***

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13 We used the study cohort of First Nations people and other Ontarians with diabetes described
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15 in the Methods paper by Slater et al¹³. Briefly, annual cohorts of Ontario residents with
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17 prevalent diabetes between April 1, 1995 and March 31, 2015 were identified from the
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19 Registered Persons Database linked with the Ontario Diabetes Database, and First Nations
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21 people were identified from the Indian Register. We then used the Discharge Abstract Database
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23 (DAD) maintained by the Canadian Institute for Health Information (CIHI) to identify
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25 hospitalizations for stroke or transient ischemic attack in each fiscal year ending March 31,
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27 2016, using validated International Classification of Diseases, 9th revision (ICD-9) and 10th
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29 revision, Canada (ICD-10-CA) diagnosis codes^{14,15}. These datasets were linked using unique
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31 encoded identifiers and analyzed at ICES. If an individual had more than one stroke or TIA
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33 hospitalization in a fiscal year (April 1 – March 31), only the first event was kept for analysis. We
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35 excluded records where the stroke or TIA diagnosis was flagged as questionable, as well as
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37 persons younger than 20 years or older than 105 years as of March 31 of the year of their
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39 stroke.
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49 ***Incident Stroke:***

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51 We calculated the crude rate of hospitalization for stroke or TIA in First Nations people (living in
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53 First Nations communities and outside of First Nation communities) and other people in
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3 Ontario and stratified by sex and age group (≤ 30 years, 30-49, 50-79 and 80 years and older).

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5 For First Nations people and other people in Ontario, we also calculated direct age- and sex-
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7 standardized rates and 95% confidence intervals (CI) of stroke or TIA hospitalization per
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9 100,000 people with diabetes using the 2001 Ontario population 20 years and older with
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11 diabetes as the standard population. Standardized rates were calculated for 5 one-year time
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13 periods: 1996, 2002, 2006, 2011 and 2015.
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18 ***Processes of Stroke Care and Outcomes:***

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20 We studied the following processes of stroke care and outcomes: (1) computed tomography
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22 (CT) or magnetic resonance imaging (MRI) scan within 24 hours of arrival at hospital in those
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24 with acute stroke or TIA; (2) thrombolytic therapy for ischemic stroke; (3) carotid
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26 revascularization (endarterectomy or stenting) within 90 days of admission for ischemic stroke;
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28 (4) discharge to home, inpatient rehabilitation, or long-term care following ischemic or
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30 hemorrhagic stroke hospitalization; and (5) mortality at 7-days, 30-days or 1 year following
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32 ischemic or hemorrhagic stroke hospitalization. Outcome rates were age- and sex-standardized
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34 to the 2001 Ontario population 20 years and older with diabetes. Only the first stroke or TIA
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36 event an individual had over the 5-year observation period was kept for analysis.
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45 We determined whether a patient had received a CT or MRI scan or thrombolysis from the DAD
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47 using a special project field that captures process measures specific to stroke and TIA. We
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49 determined rates of carotid revascularization using Canadian Classification of Intervention (CCI)
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51 codes in the DAD and allowing for 90-days of follow-up after stroke. We determined rates of
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3 discharge to home, rehabilitation or long-term care from the discharge disposition and the type
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5 of institution the individual was discharged to, if not discharged home.
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10 Seven-day, 30-day and 1-year mortality rates were determined for strokes occurring between
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12 April 1, 2011 and March 31, 2016. We used the Registered Persons Database (RPDB), a
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14 repository of demographic information about all persons in Ontario with a health card number,
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16 to determine a person's date of death, if applicable. Survival time was calculated as the
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18 difference between date of death and the date of admission to hospital.
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23 ***Ethics:***

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25 This work was undertaken as a collaboration between First Nations and academic researchers,
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27 and was guided by the First Nations principles of ownership, control, access and possession¹⁶. In
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29 addition to approval by the Chiefs of Ontario Data Governance Committee, the project was
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31 reviewed and approved by the Research Ethics Boards of Queen's University and Laurentian
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33 University.
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40 **Results:**

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42 Hospitalization rates for stroke and TIA among all people with diabetes in Ontario declined
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44 between 1996 and 2015, from 1,708 to 714/100,000 First Nations people and from 1,395 to
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46 517/100,000 other Ontarians (Figure 1). However, the rate of decline was less pronounced in
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48 First Nations people compared to other Ontarians such that stroke/TIA hospitalization rates
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50 were higher in First Nations people than in other Ontarians in every year after 2006 (Figure 1).
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54 The increased hospitalization rates in First Nations people were particularly marked in those
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3 aged under 64 years, with hospitalization rate for those aged 50-64 years 776.4/100,000 First
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5 Nations vs. 281.8/100,000 other Ontarians (Figure 2).
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10 Overall, 28,874 people with diabetes were hospitalized with a stroke or TIA between April 1,
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12 2011 and March 31, 2016, 536 of whom were First Nations people. Compared to other
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14 Ontarians with diabetes and stroke/TIA, First Nations people were younger (median age 63 vs.
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16 74 years), more likely to be female (53.5% vs. 46.8%) and more likely to live in rural areas
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18 (33.4% vs. 9.5%) (standardized difference of the mean > 0.10 for all comparisons; Table 1). First
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20 Nations people with stroke/TIA were as likely as other Ontarians to undergo neuroimaging
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22 within 24 hours of hospital arrival (94.6% vs. 96.0%), to be discharged to inpatient rehabilitation
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24 (31.8% vs. 34.8), and to undergo carotid revascularization for ischemic stroke or TIA (1.4% vs.
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26 2.7%), but were less likely to receive thrombolysis for ischemic stroke (6.3% vs. 11%) (Figure 3).
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28 Point estimates for age-/sex-standardized stroke case-fatality were higher in First Nations
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30 people than in other Ontarians at seven days (12% vs. 8.4%), 30 days (19.2% vs. 15.9%) and one
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32 year (33.8% vs. 28.0%), although the confidence intervals overlapped for all estimates (Figure
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34 4a). In analyses of one-year mortality stratified by age, the point estimates for mortality rates
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36 for First Nations people were higher than for other Ontarians among those aged 30 to 49 years
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38 (28.6% vs. 14.9%) and aged 50 to 64 years (27.4% vs. 21.1%), although the confidence intervals
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40 for these estimates again overlapped (Figure 4b). One-year post-stroke mortality rates were
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42 similar for First Nations and other people in Ontario among those aged over 65 years.
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54 **Discussion:**

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3 In this population-based study of people with diabetes in the province of Ontario, Canada, we
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5 found that overall hospitalization rates for stroke or TIA declined between 1996 and 2015,
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7 however, this decline was less marked in First Nations people than in other Ontarians. After
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9 2006, hospitalization rates for stroke/TIA were higher for First Nations people than other
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11 Ontarians, and this appeared to be mainly attributable to increased rates in those aged under
12
13 65 years. Compared to other Ontarians with diabetes and acute stroke, First Nations people
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15 were younger, more likely to live in rural areas, and more likely to be female, had similar use of
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17 brain imaging, inpatient rehabilitation, and carotid revascularization, and were less likely to be
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19 treated with thrombolysis. There was a trend toward higher stroke case-fatality in First Nations
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21 people compared to other Ontarians, and, for one-year mortality, this was mainly driven by
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23 higher mortality for First Nations people aged under 65 years.
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32 The finding of temporal declines in stroke incidence has been seen in other studies from other
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34 high-income countries¹⁷. However, these declines are not consistent across regions and groups
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36 of patients, and stroke incidence has been increasing in low- and middle-income countries and
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38 in younger people in high-income countries^{18,19}. Regional variations in stroke incidence are
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40 generally attributed to differences in the prevalence and management of stroke risk factors
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42 such as hypertension, diabetes, and atrial fibrillation², and our observed higher incidence of
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44 stroke/TIA in First Nations people compared to other Ontarians suggests that targeted stroke
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46 prevention strategies, including the identification and modification of vascular risk factors, may
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48 be needed for First Nations groups with diabetes. However, additional factors such as rurality
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50 and socioeconomic status can affect stroke risk, with diabetes mellitus being an important
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3 mediator of the association between socioeconomic deprivation and ischemic stroke risk^{20,21}. A
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5 focus on the social and Indigenous-specific determinants of health, including the ongoing
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7 impacts of colonization, is also needed to address the health of First Nations people^{10,22}. The
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9 finding that stroke incidence was particularly high for younger First Nations people suggests an
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11 urgent need to identify and address the causes of stroke in these younger adults, who may also
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13 have unique rehabilitation and reintegration needs after stroke, and who face reduced
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15 employability and productivity during peak working years^{23,24}.
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23 In individuals with suspected acute stroke, rapid neuroimaging with computed tomography or
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25 magnetic resonance imaging is recommended to confirm the diagnosis and to determine
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27 whether the stroke is ischemic or hemorrhagic^{11,25} and it is reassuring that almost all First
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29 Nations and other Ontarians underwent neuroimaging within 24 hours of presentation to
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31 hospital. However, First Nations people with ischemic stroke were less likely than other
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33 Ontarians to receive thrombolysis, which can improve outcomes after stroke. Our data sources
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35 do not allow us to determine the reasons for this difference, and further research is needed to
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37 understand whether the lower observed rates in First Nations people are due to appropriate
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39 patient selection based on presentation and clinical factors, lack of access to treatment, patient
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41 preferences, or other factors.
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50 Inpatient rehabilitation is recommended for people with stroke and residual functional deficits
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52 who are able to participate in a rehabilitation program²⁶. In Ontario, overall rates of discharge
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54 to inpatient rehabilitation after acute stroke were similar in First Nations people and others
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3 with diabetes. However, our data sources did not have information on functional status after
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5 stroke, and so further work is needed to determine whether rates of discharge to rehabilitation
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7 are appropriate based on the level of disability in each group.
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12 Point estimates for age/sex-adjusted mortality at 7, 30 and 365 days after stroke were higher
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14 for First Nations people than for other Ontarians. In analyses stratified by age, the increased
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16 one-year mortality in First Nations people appeared to be primarily attributable to deaths in
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18 those aged under 65 years. This elevated stroke case-fatality, combined with the higher
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20 observed stroke incidence in younger First Nations people, suggests that this represents a
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22 particularly vulnerable subgroup of young people with diabetes susceptible to both incident
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24 stroke and reduced survival after stroke. Targeted strategies are needed to understand and
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26 mitigate post-stroke mortality in this group.
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35 A number of study limitations merit comment. Our available data sources did not include
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37 information on many quality indicators of stroke care delivery, such as the use of vascular
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39 imaging, mechanical thrombectomy, stroke unit care, dysphagia screening, and medications for
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41 secondary stroke prevention²⁷. The lack of detailed clinical data did not permit an analysis of
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43 the underlying reasons behind the observed lower rates of thrombolysis and carotid
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45 revascularization in First Nations people, or an assessment of the use of rehabilitation services
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47 stratified by disability. We did not have information on stroke severity, which is the strongest
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49 predictor of mortality after stroke, and do not know why mortality rates were particularly high
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51 in younger First Nations people with diabetes. In addition, we did not have information on
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3 other important stroke outcomes such as functional status and quality of life²⁸. Finally, the
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5 relatively small sample size of First Nations people with stroke may have provided inadequate
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7 power to detect differences in care and outcomes in some subgroups of patients.
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13 This study suggests that First Nations people with diabetes are at increased risk of stroke and
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15 death from stroke compared to other Ontarians, and that these risks are particularly high for
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17 younger First Nations people. Multifaceted interventions that address traditional risk factors
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19 along with Indigenous-specific determinants of health are needed to mitigate the risks and
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21 consequences of stroke in First Nations people with diabetes.
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Table 1: Baseline characteristics of First Nations people and other Ontarians with diabetes hospitalized with stroke or transient ischemic attack (TIA) in Ontario, April 1, 2011 to March 31, 2016

	First Nations people with diabetes	Other people in Ontario with diabetes	Standardized difference of the mean
N	536	28,338	
Median age, years (IQR)	63 (55-71)	74 (65-81)	0.82
Female sex, n (%)	287 (53.5%)	13,274 (46.8%)	0.13
Age group, n (%)			
0-49	66 (12.3%)	1,065(3.8%)	0.32
50-64	231 (43.1%)	5,841 (20.6%)	0.5
65-79	190 (35.4%)	12,564 (44.3%)	0.18
80+	49 (9.1%)	8,868 (31.3%)	0.57
Rurality			
Urban	151 (41.7%)	19,265 (68.4%)	0.56
Semi-urban	90 (24.9%)	6,203 (22.0%)	0.07
Rural	121 (33.4%)	2,680 (9.5%)	0.61
Comorbidity			
Low (0-4 ADGs)	67 (12.5%)	3,158 (11.1%)	0.04
Medium (5-9 ADGs)	173 (32.3%)	9,979 (35.2%)	0.06
High (10+ ADGs)	296 (55.2%)	15,201 (53.6%)	0.03
Stroke type			
Hemorrhagic	55 (10.3%)	3,203 (11.3%)	0.03
Ischemic	372 (69.4%)	20,854 (73.6%)	0.09
TIA	109(20.3%)	4,281(15.1%)	0.14

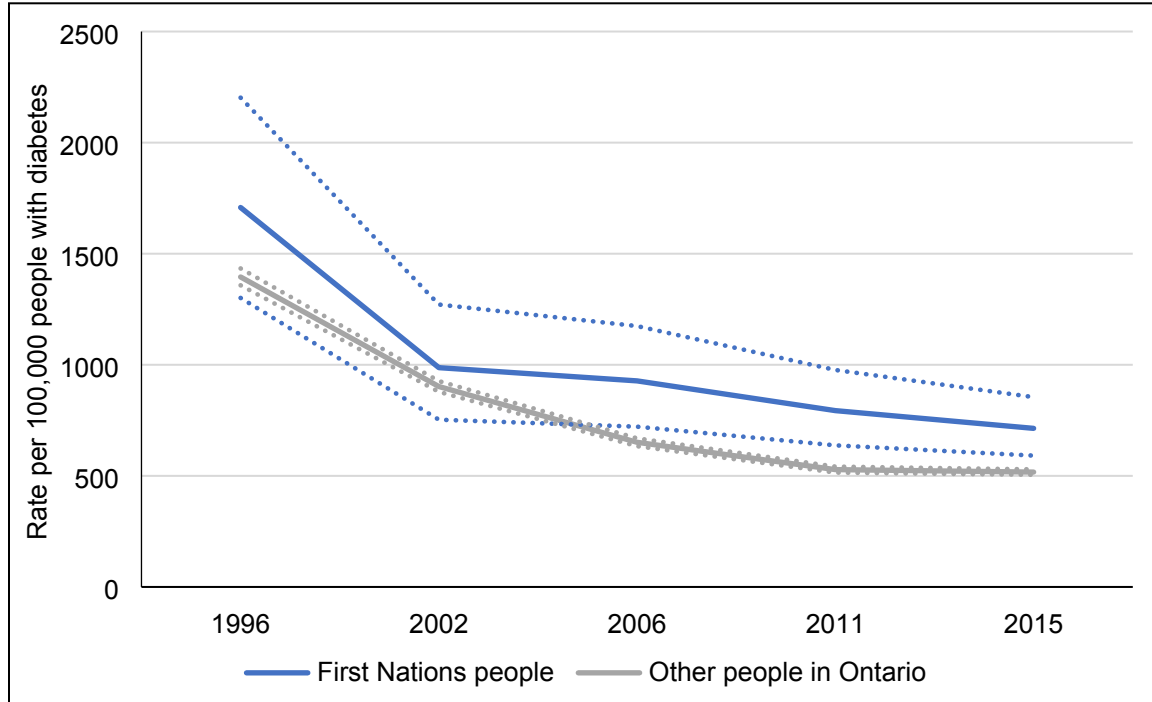
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NA – not available

IQR - interquartile range

ADG - aggregated diagnosis group

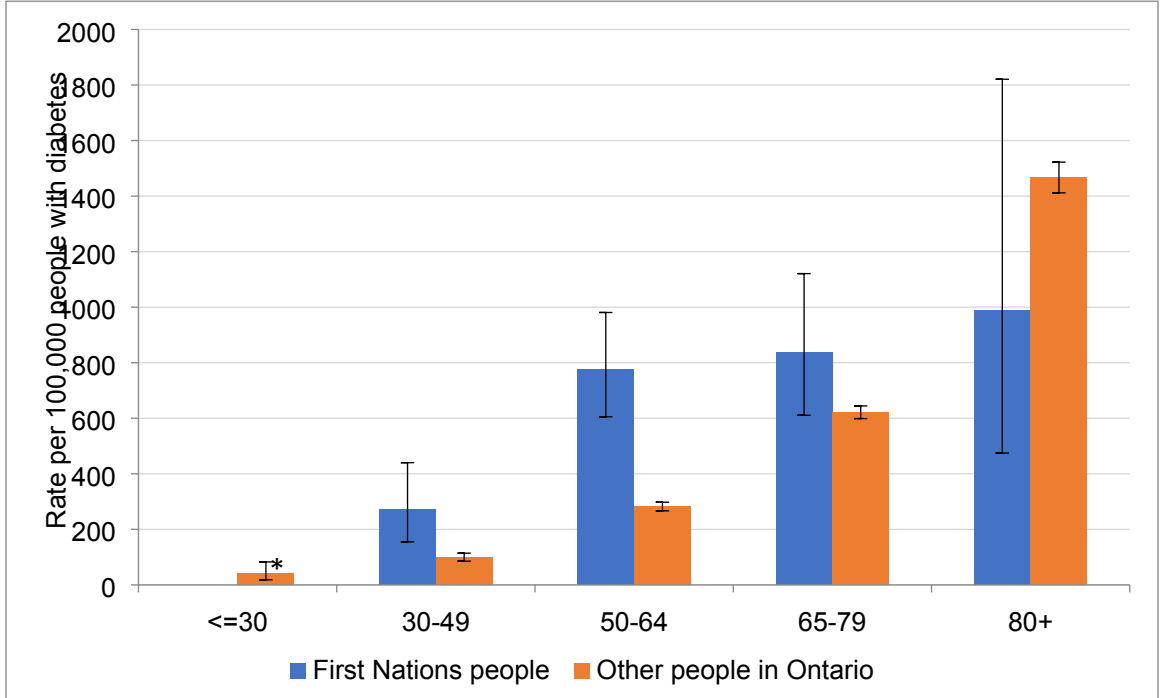
Figure 1: Age- and sex-standardized rate of acute stroke or transient ischemic attack (TIA) hospitalization and 95% confidence interval (CI) among First Nations people and other people in Ontario, per 100,000 people with diabetes, April 1, 1996 to March 31, 2015



Dotted lines represent 95% confidence intervals

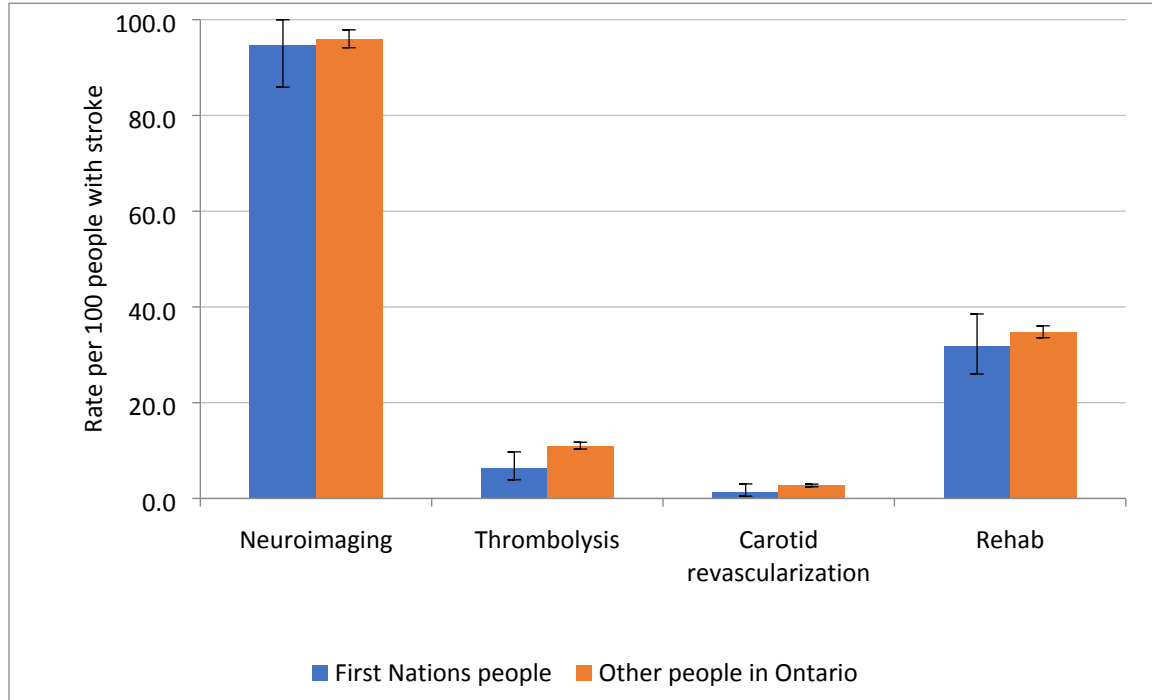
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Figure 2: Crude rate of acute stroke or transient ischemic attack (TIA) hospitalization and 95% confidence intervals among First Nations people and other people in Ontario with diabetes, by age group, April 1, 2015 to March 31, 2016



* data suppressed due to small cell sizes for First Nations people aged <= 30

Figure 3: Age- and sex-standardized rate and 95% confidence interval (CI) of neuro-imaging, thrombolysis, carotid revascularization procedures, and inpatient rehabilitation per 100 persons with event* among First Nations people and other people in Ontario with diabetes



Neuro-imaging included computed tomography or magnetic resonance imaging of the brain in those with acute stroke or TIA between April 1, 2012 and March 31, 2017.

Thrombolysis rates were calculated in those with ischemic strokes between April 1, 2012 and March 31, 2017.

Carotid revascularization rates were calculated in those with ischemic strokes between April 1, 2011 and March 31, 2016 and allowing for 90 days of follow-up.

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Figure 4a: Seven day, 30-day and 1-year age- and sex-standardized mortality rate and 95% confidence interval (CI) per 100 persons with acute stroke among First Nations people and other people in Ontario with diabetes, April 1, 2011 to March 31, 2016 (with follow-up to March 31, 2017)

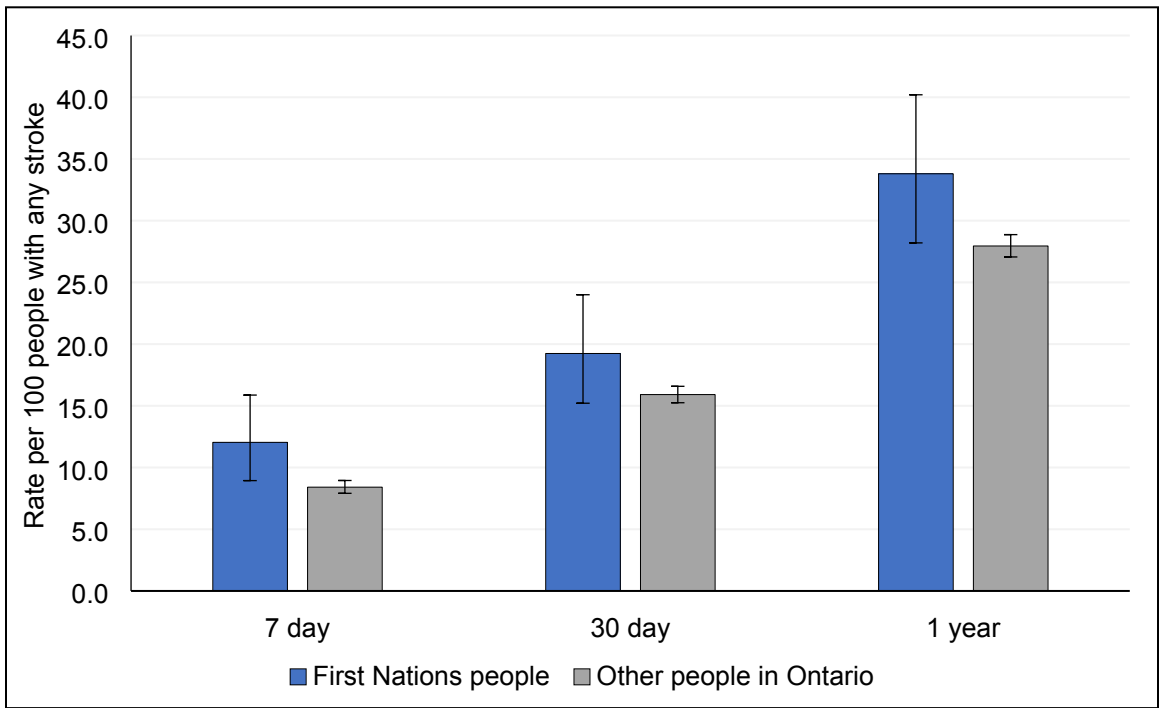
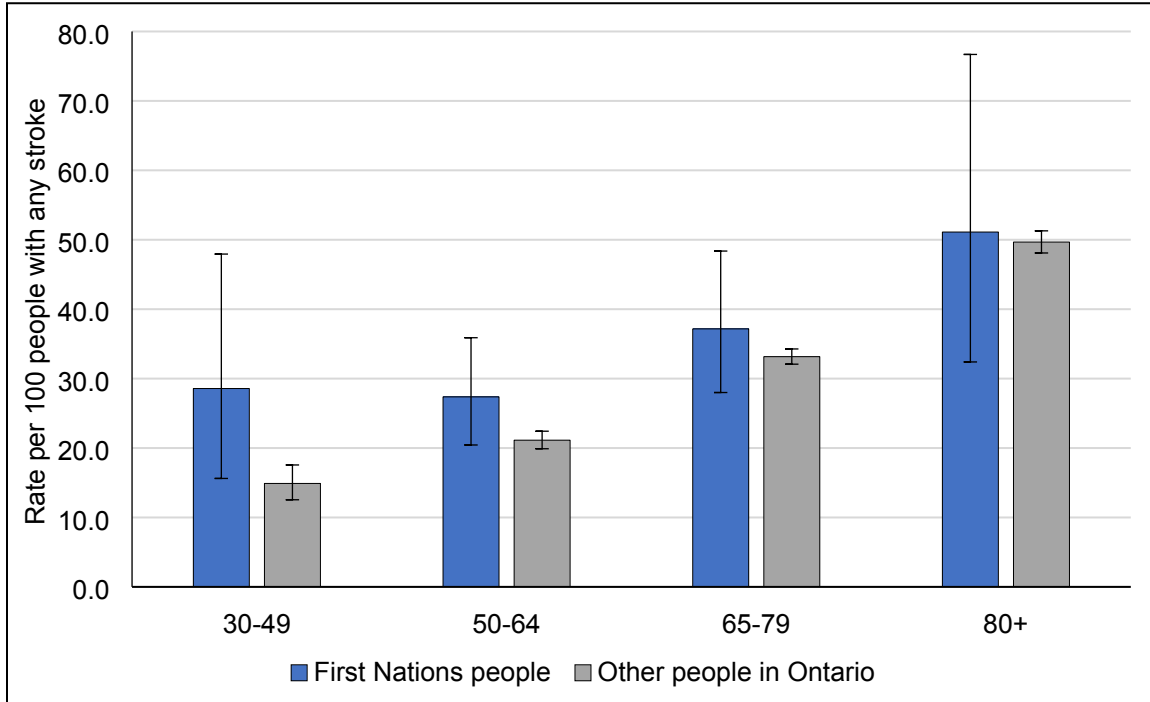


Figure 4b: 1-year crude mortality rate and 95% confidence intervals per 100 persons with acute stroke among First Nations people and other people in Ontario 30 years and older with diabetes, by age group, April 1, 2011 to March 31, 2016 (with follow-up to March 31, 2017)



Data for age group < 30 years suppressed due to small numbers

Acknowledgements:

Our partners through the early design, implementation and final dissemination of this project were the Chiefs of Ontario. Their many member contributions were key to the content and quality of the project. The authors also acknowledge the members of the Patient Advisory Committee for providing insightful and thoughtful input; their advice made a significant contribution in shaping the work. For a complete listing of the specific members of the Committee, see Green ME, Jones C, Walker JD, et.al; First Nations and Diabetes in Ontario. Toronto, ON: ICES. Forthcoming, 2019. We also wish to acknowledge the First Nations individuals from Big Grassy River, Alderville First Nation, Caldwell First Nation, Six Nations of the Grand River and Moose Cree First Nation living with diabetes who shared their personal experiences.

The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed in the material are those of the authors, and not necessarily those of CIHI.

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