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Title	**Stroke hospitalizations in First Nations People with Diabetes in Ontario, Canada: a population-based cohort study**
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Reviewer 1	Withheld
Institution	Withheld
Author response	We thank this reviewer for identifying a number of clinically relevant considerations related to interpretation of our study findings. Unfortunately, most of these questions cannot be answered with the databases used for this study [details withheld], but we have now addressed these in the discussion and hope that these can be studied in future research projects.
Reviewer 2	Olena Seminog
Institution	University of Oxford, Nuffield Department of Population Health, Oxford, UK
Reviewer comments and author response	1. **In the abstract, you claim that First Nations people are less likely to receive thrombolysis or carotid revascularisation, and that there was a trend towards increased age-standardised case-fatality. In the interpretation paragraph, you reported higher case-fatality in First Nations people. However, the analysis did not produce any evidence to support this. The confidence intervals for rates reported in the paper overlapped, indicating that there was no difference between the two groups. Please, make changes to the abstract, and refrain from making conclusions which are not supported by study findings.** As noted above, we had initially written the paper with the aim of describing the point estimates and confidence intervals, rather than focusing on specific p-values and cut-offs for statistical significance. However, we have now substantially modified the text to remove detailed discussion of findings that did not reach statistical significance. 2. **In the title of the paper and through the text, please use stroke hospitalisation rates instead of incidence, because the study population did not include community stroke patients and those who died with stroke out-of-hospital.** We have made this change. 3. **Introduction. Please, add a few sentences to describe the health-care system in Ontario, and whether First Nations people have the same access to hospitals, and are captured in the DAD dataset, as others in Ontario.** We have added a paragraph to the methods section, p. 5, describing the study setting: "This study was conducted in Ontario, Canada's most populous province, with an estimated population of 13 million[14]. Provincial residents, including First Nations people, have universal access to hospital and physician services and diagnostic tests." 4. **It is a standard research practice to report rates for men and women separately. Please, in table 1, and on figures 1-4, report rates for men and women separately.** We have edited the exhibits and now show stroke hospitalizations and one-year case-fatality for men and women separately. 5. **Methods. All stroke and TIA cases were lumped together. This creates several issues. First, a significant proportion of TIA are not reported on hospital discharge statistics, because these patients don't get admitted. Discuss this in limitations. Second, TIA are less severe than ischaemic or haemorrhagic stroke, if the proportion of TIA is higher in one of the two subpopulations in the study, this could result in lower case-fatality and better outcomes. Please, consider doing all analyses excluding TIA, or at least report a sensitivity analysis excluding TIA.** TIA and stroke are only grouped for analyses of hospitalization rates, with the rationale that admission thresholds might vary in different populations or regions, and that patients with TIA and minor stroke represent important opportunities for secondary prevention of larger disabling strokes. TIAs are not included in the analyses of case-fatality or other outcomes, with the exception of neuroimaging. We have now attempted to make this clearer in the methods, p. 7. We have also added a secondary analysis of hospitalizations with TIA excluded, with findings similar to those seen in the main cohort. 6. **In the section on "Data sources and study cohort", provide a more detailed description of the data sources and study cohort, giving a reference to a published**

paper is not sufficient. You have used the Registered Persons Database linked with the Ontario Diabetes Database, please, describe the limitations of the datasets, what is a likely proportion of people with diabetes missing from the dataset. Provide more information about the Indian Register. Is the registration mandatory for First Nations people? If it is voluntarily, what is the proportion of First Nations People in Ontario who are missing from the register? Discuss in the limitations section what might prevent some of First Nations People from being on the Indian Register; are the disabled and sicker individuals less likely to be registered, is there a stigma for being on the register. Discuss the potential impact of using a linkage to the dataset of self-selected cohort of First Nations people on study findings and interpretation.

Of note, this paper is part of a large series of papers using the same cohort and accompanied by a detailed methods paper which includes this information. However, we have added more information on these datasets to the limitations section, p. 13: "The Ontario Diabetes Database does not distinguish between Type 1 and Type 2 diabetes and only identifies individuals who sought health care and were diagnosed with diabetes. First Nations people who are not registered with the Indian Register, including those who are members of First Nations communities not recognized by the federal government, were excluded from this study. We do not have information on the completeness of the Indian Register, or on the characteristics of people who might have been excluded."

7. **Please, list the ICD 9 and 10 codes that were used to identify stroke and TIA. Was subarachnoid haemorrhage included? Have you used inpatient data only or combined them with the emergency department records?**

We have now included these codes in an Appendix. As noted in the methods, p. 5, we only used inpatient hospitalization data. We have now explicitly stated that using hospitalization data means that we did not include patients discharged from the ED without admission, as well as those who did not seek hospital care at all or who died before hospital presentation (p. 6): "We did not include people who died from stroke prior to hospital presentation, those who never sought hospital care, or those who were discharged from the emergency department without admission."

8. **In the methods section, please, provide a detailed information on how the hospitalisation and mortality rates were calculate, explicitly saying what was in the numerator and denominator. In particular, describe how you calculated mortality rates reported on Figure 4a, 4b. You might have confused percentage and rate. My impression is that you have reported case-fatality on Figure 4 a and 4 b, not mortality. There is a mismatch between the titles of figures 4 a and 4 b, and the content. The title says it is the rate, but the contents of figures suggest that it might be percentage. In the abstract and main text, the results from these figures are presented as %, see page 3 and 8. Figure 3 is probably reporting a percentage as well, but you've used a term rate instead.**

The reviewer is correct that we present case-fatality as described in the abstract and text. We have reviewed the manuscript and corrected instances where this was described as a rate. We have now explicitly stated the numerator and denominator in the methods section, p. 8.

9. **Please, explain why you calculated hospitalisation rates for 1996, 2002, 2006, 2011 and 2015? Is the data not available for individual years? If data permits, please, calculate and report annual rates for every year between 1996 and 2015?**

We have now reported rates for every year (see revised Figure).

10. **Although, the data come from the same linked datasets, there is no consistency between time-periods covered by the data used for different parts of analyses. While analysis of hospitalisation trends covered 5 individual years, the analysis of age-specific and age-standardised mortality is done using data for a period 2011 to 2016 . It is unclear why different years were used for analysis presented on figure 1 (1996, 2002, 2006, 2011, 2015) and figure 2 (2015-2016), while figure 3 has a mixture of data from 2012 to 2017, and 2011 to 2017, and the time period for the rehabilitation data is not provided. How did you make a decision about which years should be included for the analysis? Please, stay consistent, or provide an explanation why it is not possible to use data for the same time period for all analyses in the study.**

We agree with the reviewer that the different dates of analysis are confusing. This is the

result of the availability of certain variables in specific years and by the need to be consistent with the cohorts used for other projects in a series of related papers. We have now attempted to clarify this in the methods and in the footnotes for the exhibits.

11. **Standardisation method. You have made an unusual choice of using the 2001 Ontario population with diabetes as the standard population. What were the reasons for that? When doing the age and sex-standardisation for population rates (hospitalisation, incidence and mortality), it is generally accepted to use the direct method of standardisation, and apply rates to one of the published standard populations, for example European Standard Population or World Standard Population. I appreciate that there is a case for using an internal study population for standardised case-fatality, but not for hospitalisation rates.**
This standardization method was selected for consistency with the other chapters in this linked series of publications.

12. **Was there a difference in the length of hospital stay between First Nations people and others, and has it improved over the study years? This might indirectly indicate a severity of stroke.**
We considered analyzing this, but were concerned that the findings would be difficult to interpret. Many First Nations people in Canada live in rural areas where length of stay may be related to distance to acute care facilities or to the availability of inpatient rehabilitation or outpatient services, rather than stroke severity.

13. **A few times in the paper, the authors have made statements not supported by study findings, I have listed these below.**
Thank you. We have responded to these below.

14. **Results and figures. Remove "the rate of decline was less pronounced in Fist Nations people", because you did not do a test to assess the slope of the reduction in rates. Change the wording of the sentence "… were particularly marked in those under 64 years", and report the actual findings, for example, analysis of age-specific rates showed that hospitalisation rates were higher in the First Nations people aged 50-64, but not in other age groups (and maybe 30-49, it is not clear from figure 2, whether the CIs overlap in this age group or not).**
We have amended the results section, pp. 8-9: "Hospitalization rates for stroke and TIA among all people with diabetes in Ontario declined between 1996 and 2015, from 1,708 to 714/100,000 First Nations people and from 1,395 to 517/100,000 other Ontarians. However, stroke/TIA hospitalization rates were higher in First Nations people than in other Ontarians in most years after 2006 (Figure). In 2015, hospitalization rates in First Nations people were higher than in other Ontarians in those aged 30 to 49 years [First Nations 271.0/100,000, 95% confidence interval (CI) 154.9 to 440.1 vs. other Ontarians 98.96/100,000, 95% CI 85.3 to 114.2] and 50-64 years (First Nations 776.4/100,000, 95% CI 605.2 to 980.9 vs. other Ontarians 281.8/100,000, 95% CI 266.5 to 297.8) but were similar in those aged 65 years and older (Table 1)". .

15. **On page 8, remove "but were less likely to receive thrombolysis for ischeamic stroke (6.3% vs. 11%)" , again, there was no statistically significant difference in rates, as CIs overlapped.**
The confidence intervals did not overlap, but it was difficult to appreciate this in the figure. We have now added the confidence intervals to the text, p. 9 and shown the findings in a table rather than a figure so that the confidence intervals are more easily read.

16. **The age-specific hospitalisation rates reported on figure 2, were calculate for a period 2015-2016, which doesn't overlap with the time for which hospitalisation trends analysis was done. Therefore it is incorrect to use these findings to explain higher hospitalisation rates in earlier years.**
Agree. We have amended the discussion, p. 10: "However, in most years after 2006, hospitalization rates for stroke/TIA were higher for First Nations people than other Ontarians."

17. **In discussion, can you, please, draw in some comparisons with other studies of stroke in people with diabetes reported in other parts of Canada and international studies, in particular, from Australia on rates of stroke in Aboriginal populations? This might help to put reported here hospitalisation rates in the context, because the rates seem a little high.**

We have expanded the discussion to comment on stroke hospitalization rates in Australian Aboriginal populations. Our rates are higher than those reported in general populations, but are similar to those previous reported in people with diabetes in Ontario. We have now added this information to the discussion, p. 12: "Our finding of higher stroke hospitalization rates in Indigenous compared to non-Indigenous people, particularly in younger age groups, is consistent with previous research from Australia[8,9,28]. Although our observed stroke incidence rates are higher than those seen in the general population in Canada and elsewhere, similar rates were found in a previous study of people with diabetes in Ontario, and presumably reflect the excess stroke risk associated with diabetes[29]"

18. **Page 10, line 33-45, please, remove a sentence "First Nations people with ischemic stroke were less likely than other ", because your analysis did not produce statistically significant findings to support this claim.**
As noted above, the differences in thrombolysis use were statistically significant.

19. **Page 11, line 13, remove a sentence "Point estimates for age/sex-adjusted mortality at 7, 30 and 365 days after stroke were higher for First Nations people than for other Ontarians". First, it is a repetition of results (p8, line 33-40), second, while it might be okay to report point estimates in results, in the discussion it could be misleading for readers. Your analysis shows that the rates and their confidence intervals for mortality at 7, 30 days and 1 year are overlapping, suggesting that there was no difference between First Nations people and other Ontarians.**
We have retained the comment about point estimates as we think that this is important information but have edited the text substantially to emphasize that these were not statistically significant.

20. **Page 11, lines 20-21, Check my previous comment on reporting case-fatality versus mortality, so far in the methods or results sections there is nothing describing how case-fatality was calculated.**
This information is now included in the methods, p. 8: "We used the Registered Persons Database (RPDB), a repository of demographic information about all persons in Ontario with a health card number, to determine all-cause mortality after stroke, regardless of location, and date of death, if applicable. The numerator was the number of deaths within each time frame (7, 30 and 365 days) and the denominator was the number of hospitalizations for stroke within each fiscal year. Survival time was calculated as the difference between date of death and the date of admission to hospital."

21. **Page 11. Line 23, replace incidence with hospitalisation**
We have made this change.

22. **Page 11, line 43-47. Remove the sentence, "The lack of detailed clinical data did not permit an analysis of the underlying reasons behind the observed lower rates of thrombolysis and carotid revascularization in First Nations people", as explained above, you did not produce statistically significant evidence suggesting that the rates of thrombolysis and carotid revasc were lower in First Nations people.**
We have removed the comment about carotid revascularization.

23. **P12, line 16-19, remove "increased … risk of death from stroke compared to other Ontarians", because it is not true based on your study results. Rephrase the second part of the sentence, so that it is clear that First Nations people with diabetes aged 50-64 are at increased risk of hospitalisation for stroke compared to other Ontarians, but you did not find evidence suggesting and increased risk of death.**
We have made this change.

24. **In the limitation section, discuss if Fist Nations people are more likely to be treated in the community and less likely to go to a hospital with stroke, in particular with TIA or minor stroke, than others in Ontario, and how this could impact the study findings.**
We have addressed this in the limitations section, p. 13. The anticipated effect on the study findings is uncertain.

25. **First Nations People have higher hospitalisation rates for stroke than others in Ontario since 2006, how much of this increase might be due to a trend over time towards increased referral and investigations of First Nations people, or increased awareness of stroke signs and about early hospitalisation in First Nations people.**
This study does not provide information on the reasons behind our findings. We have now

expanded on this in the limitations section, and hope that our study will provide baseline information that can inform more detailed studies in the future.

26. **Can difference in socio-economic status explain hospitalisation trends or higher rates of age-specific hospital admission rates in younger people? Is it possible to adjust analysis for socio-economic status and rurality?**
We agree that factors such as socioeconomic status and risk factor prevalence may explain some of the stroke risk in younger people. Unfortunately, these additional analyses are beyond the scope of this study. In particular, the administrative data available to us only provide area-level rather than individual-level socioeconomic status estimates, and prior work suggests that these are not sufficiently accurate for use in large rural regions and in First Nations people.
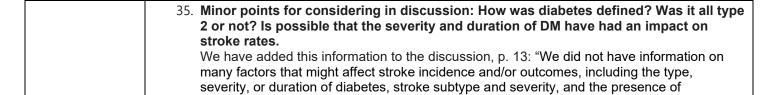
27. **Limitations. Does your study cohort include those cases of stroke where a patient died before being admitted to a hospital? The most severe cases of stroke are often fatal, and these people die before reaching a hospital. Do you know what was the proportion of fatal out-of-hospital strokes in First Nations people compared to others? discuss this in the limitations section.**
We did not include cases of stroke where a patient died before hospital arrival. We have clarified this in the methods and discussed in the limitations section.

28. **Table and Figures. General point, present all rates and proportions for men and women separately. A minor point, instead of crude rates, it is better to say age-specific rates.**
We have now presented hospitalization and case-fatality stratified by sex.

29. **Table 1, delete standardised difference of the mean. Remove **, as there are no suppressed values in the table.**
Thank you, we have removed the comment after **. We have removed the column showing the standardized difference of the mean.

30. **Figure 1. Present annual rates for every year between 1996 and 2015, if data is available, or explain why not in methods.**
We have made this change (see new Figure).

31. **Figure 2. Age-specific rates presented on figure 2 might better fit in a table. Consider reporting age-specific rates for every calendar year in the study to show the pattern of changes, or at least report rates in the first and the last years of the study. No need to suppress small cell sizes, because it is a rate. Hence the rate are small and any comparisons in this age group are not informative, you could combine the two youngest age groups under 30 and 30-49 in one age group <=49.**
We agree with the reviewer that a table is preferable for reporting the findings, and have made this change. We are unable to report age-specific rates for all study years as there is limited funding available for new analyses.

32. **Figures 3, 4a, 4b, the axis are wrong. You confused the rate with percentage. These results would better fit in a table than a bar chart. Consider, presenting rates for individual years, or at least the first and last year of the study, not all years lumped together. Figure 3. Why there is an inconsistency in time-periods for different procedures? There is no information on study years for rehabilitation. Please, use data covering the same time period for all procedures, if possible.**
We agree with the reviewer that the data are better presented in a table, and have replaced Figures 3 and 4 with a table. As noted above, we agree that using data covering the same time period would have been ideal, but we were limited by the availability of information on variables in only certain years, and by the need to use cohorts that were consistent with companion papers. We have attempted to make this clearer in the methods and in the exhibit footnotes.

33. **Figure 3. Which codes were used to identify ischaemic stroke? Describe how the rates/percentages were calculated in methods. Provide a description for an asterisk symbol that appears next to event, or delete it.**
We have made these changes.

34. **Suggestion: add a figure with trends in standardised stroke mortality rates (similar to figure 1 with trends in hospitalisation rates)**
We agree that this would be a nice addition, but is beyond the scope of this project.

| | 35. **Minor points for considering in discussion: How was diabetes defined? Was it all type 2 or not? Is possible that the severity and duration of DM have had an impact on stroke rates.**

We have added this information to the discussion, p. 13: "We did not have information on many factors that might affect stroke incidence and/or outcomes, including the type, severity, or duration of diabetes, stroke subtype and severity, and the presence of hyperglycemia at the time of presentation." |