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Title	Kidney disease and care among First Nations People with diabetes in Ontario, Canada: a population-based cohort study
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Reviewer 1	Bethany Foster
Institution	Nephrology, Montreal Children's Hospital, Montréal, Que.
General comments (author response in bold)	It would be of interest to know the contributions of glycemic control, socioeconomic status and distance of residence from the care facility to the differences between First Nations and non-First Nations people. **We agree that this would be an interesting analysis, and that there are many other factors too that are likely contributing to the differences we observed, but this was not the focus of the current manuscript.** **We calculated standardized proportions for age and sex only to ensure that these values were not skewed by different distributions of age and sex among First Nations people. We did not standardize values (or adjust in our Cox proportional hazards analysis) based on any other factors such as these, since the purpose was not to look at the independent associations between First Nations people and kidney disease prevalence or incidence, but rather recognizing that differences in comorbidity may be on the causal pathway for kidney disease.** **In a follow-up study we can look at determinants of health and potential predictors for the discrepancy in kidney disease prevalence (mostly end-stage kidney disease) between First Nations people and other people in Ontario. We have mentioned this in the Interpretation section. (Last sentence before the Limitations section in the Interpretation.)** There are several factors that may influence development of CKD and progression to CKD, including glycemic control--which may be influenced by socioeconomic factors. It would be of interest to compare glycemic control (are HbA1C values available?) between First Nations and non-First Nations and to include this in the models. I would expect that HbA1C values would be available and could be compared. If there are major differences in glycemic control between First Nations and non-First Nations, this could explain the difference in prevalence of CKD. Knowing this would provide a reasonable target for intervention. If there are NOT differences in glycemic control, this would also be of interest because it would indicate that disparities exist despite similar glycemic control-- which may suggest biologic/ genetic differences in predisposition to CKD/ ESRD. There is some evidence that a proportion of diabetics with CKD have CKD related to a kidney disease other than diabetes (i.e. a co-morbid glomerulonephritis). There is also evidence that glomerulonephritis is more common in First Nations people than non-First Nations people. Some effort to determine whether this is playing a role in the disparities would be valuable. **We did not look at the impact of glycemic control in this manuscript. This study was done within a larger series of projects that focused across the spectrum of diabetes care, including complications and determinants of health (hopefully all to be published within CMAJ and CMAJ Open). Based on these other study findings, we do mention in the interpretation section that the higher risk of kidney disease may have been due to poor quality of diabetes care.**

	We also recognize that kidney disease can be caused by other factors and conditions other than diabetes, so we are planning a follow-up study to look at similar metrics among all people with kidney disease and not just those with diabetes. (N/A) Are any SES measures available to be able to compare First nations with other Ontarians in the same SES stratum? This would be of interest to help understand reasons for the observed differences. It is also possible that genetic differences could contribute. It would improve the manuscript if some of the contributing factors could be identified. This may help determine how best to address the disparity. **SES is available as a geographic variable (i.e. income quintile based on postal code) in our data sources, however, based on the reasons stated above, we decided not to account for differences in SES in our analyses. Furthermore, our measure of SES may not be accurate for First Nations individuals residing on a reserve. (N/A)** If similar proportions of First nations and other people received kidney transplants, I don't follow why this might suggest poorer access for First nations. Please clarify. **There are similar proportions of patients who received kidney transplants between the two groups, but a higher proportion of First Nations people who received chronic dialysis and with eGFR <15 mL/min. Therefore, it would also follow that kidney transplant rates should be higher among First Nations people if they had similar access, but it seems like more people are on dialysis or potentially having conservative care rather than a kidney transplant.** **I changed the wording of 'end-stage kidney disease' to 'chronic dialysis' to try and clarify this in the Interpretation. (Second paragraph in the Interpretation section.)** Additional attention to identifying the factors responsible for the disparities would increase the impact of the study. **Thank you for this comment. As mentioned above, we believe this would be out of the scope of this current manuscript, but agree that this would be an impactful follow-up study. (N/A)**
Reviewer 2	Kevin He
Institution	Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, MI
General comments (author response in bold)	1. Could the authors provide more details for the implementation of direct standardization. **We had added two references for the direct standardization method we used to obtain our estimates and our confidence intervals:** **1. Age standardization of death rates: Implementation of the year 2000 standard. Robert N Anderson and Harry M Rosenberg. National Vital Statistics Report, Vol 47 No 3, October 7, 1998. Centers for Disease Control and Prevention.** **2. Confidence intervals for directly standardized rates: A method based on the gamma distribution. Michael P Fay and Eric J Feuer. Statistics in Medicine, Vol 16, 791-801, 1997. (Highlighted references in Methods > Analysis section.)** 2. Could the authors provide confidence intervals for the standardized proportions?

	This will be helpful to determine whether these proportions for first nations are significantly higher than the general population. **Yes, we have now added confidence intervals to the table. (Table 2)**
Reviewer 3	Aminu Bello
Institution	Division of Nephrology, University of Alberta, Edmonton, Alta.
General comments (author response in bold)	1. The study objectives were to describe the epidemiology of CKD and ESRD as well as quality of CKD care. So I thought it's tangential to go on the differential uptake of dialysis treatments (receipt of chronic dialysis, dialysis modality options [in-center vs home]) as well as comparing travel distance to dialysis among the study groups. This distracts from the key study objective, and should be removed and targeted to another paper. **We appreciate your perspective on this. We had considered the prevalence of end-stage kidney disease to also include the type of treatment of in-centre versus home dialysis. We recognize that the distance to travel to receive chronic dialysis seems outside of the scope of our objectives, but this was an important component of end-stage kidney disease care that was raised by our First Nation patient and community partners. We added the assessment of travel distance to receive in-centre dialysis to the objective statement. (Last paragraph in the Introduction section.)** 2. Definition for CKD: This was based on the standard guideline recommendation (KDIGO). It is unclear in the methods how this criterion was followed. Did you use 2 eGFR values at least 3 months apart? **No, we used only the most recent serum creatinine and urine ACR values to classify patients into the KDIGO risk groups, rather than using two values. We now clarify this in the measures section. (Second last sentence in first paragraph of Methods > Measures section.)** The albuminuria testing was extremely erratic in the study (<20% of the population had this test), and thus problematic to include this in the definition for CKD. **Based on the denominators in Table 2 10,746 people in the First Nations group had an ACR and serum creatinine value compared to 15,344 who had a serum creatinine value (10,746/15,344 or 70%), and there was a similar proportion for the other Ontario group.** **I believe the <20% you refer to was for the quality indicators looking at repeat testing among those who had an initial eGFR <60 mL/min or ACR >3 mg/mmol. This was not the proportion of people who we used to capture those with chronic kidney disease. (N/A)** Please explain the rationale for including chronic dialysis in the CKD definition. Why was kidney transplantation not included if dialysis was considered in the definition? For clarity, I suggest eliminating dialysis and/or transplant completely in the CKD definition and cohort. **We did not want to underestimate the prevalence of chronic kidney disease by not capturing those who are on dialysis, but we agree that this is misleading since those with kidney transplantation are not captured. We now define prevalence of chronic kidney disease based on the laboratory values only and have eliminated both dialysis and kidney transplant from this definition. (Last sentence in first paragraph of Methods > Measures section. First sentence in Results > Prevalence of kidney disease section. Table 2)**

	3. Please enumerate the 'consensus-based quality indicators for early-stage care". Is the consensus referring to expert guideline recommendations or this was a separate process conducted for this study? **The mention of consensus-based indicators is referring to a previous publication which used a modified Delphi panel to identify indicators for chronic kidney disease care in the primary care setting (for most indicators that we assessed here), and the Ontario Renal Network's KidneyWise toolkit for the two nephrology referral indicators. We have referenced both of these. (References highlighted in last paragraph of Methods > Measures section.)** 4. I think the key message for this study was the finding that the age/sex-standardized prevalence of CKD was almost similar between the two population groups (Indigenous vs non-Indigenous) (22.5% vs. 18.9%), but there was a higher prevalent burden of ESRD (2.9% vs. 1.0%), and higher incident risk of ESKD (9.3 vs. 4.7 events per 10,000 person-years). Is the inference here a higher progression rate to ESRD in the Indigenous group? **We have discussed this more explicitly in the Interpretation and Conclusion sections now, mentioning that there was a 'slightly' higher risk of chronic kidney disease but a '3-times higher risk' of end-stage kidney disease, suggesting a higher progression rate. (Second paragraph in Interpretation section. First sentence in Conclusion section.)** How did the two population groups compare in terms of other consequences for CKD (incident cardiovascular events, mortality, hospitalizations)? This would be an interesting analysis for the reader. **We did not look at other downstream outcomes of kidney disease between the two groups in this manuscript, as our focus was only on the kidney-specific measures. However, this study was done within a larger series of projects that focused across the spectrum of diabetes measures including cardiovascular complications (hopefully all to be published within CMAJ and CMAJ Open). (N/A)** 5. It is quite fascinating that the quality of CKD care was similar in both groups but the Indigenous group was less likely to receive laboratory testing and appropriate monitoring. Could you speculate on the possible reasons for this discrepant observation? **We did not want to place too much emphasis on this apparent care gap, since there are some limitations with the laboratory data that may be responsible for some or even all of this observed difference. This has already been described in the limitations section:** **"…outpatient laboratory tests done in some hospitals may be covered under the hospital's global budget and not reimbursed through fee-for-service billing codes. If First Nations people were more likely to receive outpatient laboratory tests at these hospitals compared to other people in Ontario, this could partly explain the lower proportion who received tests to confirm or monitor their kidney function." (Last two sentences in first paragraph of Limitations section.)** Minor Please describe even if briefly on the approach to diabetes cohort creation and linkage of administrative databases. It is not enough to leave this for the reader to

	look up in Slater et al. (2019). **We provided some more details on how we created these cohorts including the database we used to identify diabetes diagnosis and the range of dates for a diagnosis. (First sentence in Methods > Data Sources section. First sentence in Methods > Cohort Assembly section.)** Provide additional information (useful for non-Canadian readers) on the study setting to include a description of the Canadian provincial system, Province of Ontario and health system structure. **We have added more description on Ontario and the health system structure:** **"Ontario – Canada's most populous province with over 14 million residents – has universal, publically funded healthcare that is managed both provincially (for the majority of Ontarians) and federally (for specific populations, including some First Nations people)." (First sentence in Methods > Study Design and Research Setting section.)** Please also describe the Indigenous population structure, and be consistent with the use of terminologies "First Nations" or "Indigenous". These are used interchangeably in the manuscript. **The population we studied included only Status First Nations people, and no other Indigenous groups in Canada such as Métis or Inuit. We have clarified that they are 'Status' First Nations people only.** **The term Indigenous is only used once in the Interpretation section and this was to describe a population from a previous study in Australia that included 'Indigenous' people and did not differentiate between Indigenous groups. (First sentence in Methods > Data Sources section.)** Please use preferably terms such as "non-Indigenous or non-First Nation" to refer to "other people of Ontario" **This manuscript was part of a series of 12 related studies on First Nations people with diabetes. To ensure consistency in language across our studies and our manuscripts, we have all described the comparison group as 'other people in Ontario'. This was the preferred terminology based on discussion with our community partners. (N/A)** Provide additional information on First Nations status (Indian Register). What is it? This is particularly relevant for non-Canadian audience of this journal. **We added the following information to clarify:** **"We used the Indian Register data, which is owned and controlled by First Nations people and held at ICES as a data custodian. This database includes information on demographics, band transfers, and deaths of all Status (Registered) First Nations people recognized under the Indian Act." (Second sentence in second paragraph of the Methods > Study Design and Research Setting section.)** Describe what you mean by the international scale for risk of adverse kidney disease-related outcomes. This isn't a commonly used term but I think you are referring to the KDIGO Heat map. **Yes, we are referring to the KDIGO heat map. We have clarified this in the methods section and removed this wording from the results section.** **(Second last sentence in first paragraph of the Methods > Measures section.**

	First paragraph in the Results > Prevalence of kidney disease section.) Results: Under Quality of early-stage kidney care. It is not enough to state: “See Table 3 for the proportion of people with diabetes meeting quality of early-stage kidney care indicators”. Please provide a summary of the results and then cite the table. **We had provided a summary of these results below this sentence, but we have now removed the sentence about referring to table 3 and instead reference this at the end of each paragraph in this section. (Results > Quality of early-stage kidney care section.)** Discussion: describe the impact of intergenerational colonization among First Nations people on health, and how that links to the study findings. **We have added to this sentence in the Interpretation:** **“Furthermore, the intergenerational impact of colonization among First Nations people is an important determinant of health and could have also influenced the risk of end-stage kidney disease”. (Second last sentence in Interpretation section before Limitations.)** Relevance of findings: Describe the policy initiatives to minimize the risk and burden of kidney disease among Indigenous **Further research is needed to better understand the causal factors for the higher observed risk of kidney disease among First Nations people in order to inform future policy initiatives. We have added a sentence about this in the Interpretation section. (Last sentence prior to the Limitations section in the Interpretation.)**