Peripheral arterial disease in Ontario First Nations people with diabetes: a longitudinal population-based cohort study

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Competing Interests: none to declare

Abstract

Background: Peripheral arterial disease is an important vascular complication of diabetes. It may lead to amputation, which significantly impacts patients' quality of life. First Nations people in Ontario have a significant and growing burden of diabetes.

Methods: Using healthcare administrative databases, we identified annual cohorts from 1995 to 2014 of all people in Ontario with diabetes, and identified those who were First Nations using the Indian Register. We identified angiography, revascularization procedures and amputations and each population, and then determined the mortality rate in those who had an amputation.

Results: First Nations people received angiography procedures at a slightly higher rate to other people in Ontario, while their rate of revascularization was comparable. However, they had amputations at 3- to 5-times the frequency of other Ontario residents. First Nations people had increased mortality after amputation (adjusted hazard ratio 1.15, 95% confidence interval 1.05 to 1.26), with median survival of only 3.5 years.

Interpretation: First Nations people in Ontario had a markedly increased risk for amputation compared to other Ontario residents, and their mortality rate after amputation was 15% higher.

Introduction

Peripheral arterial disease (PAD) is an important vascular complication of diabetes. More than one in five people with symptomatic PAD have diabetes. (1) The most common symptom of PAD is intermittent claudication, but over one half of patients have other atypical symptoms, with reduced activity and impaired quality of life. (2) PAD can progress to critical limb ischemia which is characterized by rest pain, tissue loss or gangrene. As a result, PAD can lead to lower-extremity amputation, which is one of the most feared complications of diabetes and significantly impacts quality of life. (3),(4) In fact, more than 80% of lower-extremity amputations in Canada occur in patients with diabetes. (5) As a marker for generalized atherosclerosis, PAD also portends other cardiovascular disease such as myocardial infarction or stroke.

First Nations people in Ontario have a significant and growing prevalence of diabetes that exceeds that of other people in the province. (6) Previous research has also suggested that First Nations people have a disproportionate burden of PAD. (7) For example, a physical examination screening study in a northern Manitoba First Nations community found a 41% prevalence of impaired pulses and a 15% prevalence of foot ulcer history. (8) The objective of this study was to compare the diagnosis, treatment and complications of PAD between First Nations people and other people in Ontario living with diabetes.

Methods

ICES maintains comprehensive linked administrative datasets related to Ontario's single payer publicly funded healthcare system. The general approach to cohort creation, description of the major data sets used and a description of the characteristics of the study cohorts are described in detail elsewhere. (9) In brief, we examined annual cohorts of all individuals with diagnosed diabetes in Ontario, and identified those who were First Nations using the Indian Register.

Using the Discharge Abstracts Database of all hospital admissions in Ontario, we examined age- and sex-adjusted rates for lower-extremity angiography to diagnose PAD, and for revascularization procedures (angioplasty or bypass) to treat PAD, in each fiscal year between 2002 and 2014. We then examined age- and sex-adjusted rates of lower-extremity amputations in each fiscal year between 1995 and 2014. They were separated into minor (toe or foot) or major (at the ankle, below the knee or above the knee), and excluded any procedures where the diagnosis recorded on the same hospitalization was for malignant or benign lower-extremity tumours, trauma, frostbite or burns. We also examined age-adjusted rates for men and women separately, and sex-adjusted rates by age, in fiscal year 2014 only.

We then analyzed all individuals who had major amputations between 2002 and 2014, and followed them forward until March 2018 for the outcome of all-cause mortality. We counted the first amputation during the time period in individuals who had more than one. We compared First Nations people with other people in Ontario using a Cox proportional hazards model, adjusting for age and sex, with censoring on loss of Ontario healthcare coverage. The adjusted survival curve was plotted.

Analyses were conducted using SAS Enterprise Guide version 7.1 (Cary, NC). The project was approved by the Chiefs of Ontario Data Governance Committee. The study also received research ethics review from Queen's University and Laurentian University.

Results

The demographic characteristics of the population under study are described separately. (6) Table 1 shows the characteristics of the annual cohort from two years, 2002 and 2014. First Nations people with diabetes have a greater proportion of females and are younger than other people in Ontario with diabetes, and are more likely to live in rural areas.

Figure 1A shows the age- and sex-adjusted rate of lower-extremity angiography procedures. These procedures have decreased in frequency over time among both First Nations and other people in Ontario. Figure 1B shows the rates of revascularization procedures, including both angioplasty and bypass surgery. Figure 1C shows the age- and sex-adjusted rates of lower-extremity amputation. In both populations and across time, about half of all amputations were minor (toe or foot) and half were major (ankle or higher). (10) Figure 2 shows the amputation rates by age and sex for 2014 only.

We then followed the 12,847 individuals who had a major amputation between 2002 and 2014. Figure 3 demonstrates their survival. Mortality risk after amputation was very high, with a median survival of 3.5 years among First Nations people, and 4.1 years among other people. The age- and sex-adjusted hazard ratio for mortality among First Nations people was 1.15 (95% confidence interval 1.05 to 1.26, p=0.002) compared to other Ontario people.

Interpretation

First Nations people with diabetes received lower-extremity angiography procedures to diagnose PAD at a rate only slightly higher than that of other people in Ontario. The decline in angiography use over time in both populations likely reflects increasing use of newer technologies such as CT or MR angiography, which were not captured in this study. Similarly, First Nations people undergo revascularization procedures to treat PAD at comparable rates. However, their rate of lower-extremity amputation, a devastating outcome for patients with PAD, is 3- to 5-fold higher than that of other people in Ontario. These discordant findings suggest that PAD may be underdiagnosed or undertreated among First Nations people with diabetes, so many patients may not come to medical attention until irreversible complications have already occurred, necessitating amputation. Amputation rates were increased in males compared to females among both First Nations people and other people in Ontario. Amputation rates

increased with age, and it was in the youngest age group (≤44 years) where First Nations people had the greatest disparity, with amputation occurring more than 6 times as frequently than in other people in Ontario. This increased risk attenuated by age ≥65 years but was still nearly 4-fold. Amputation was strongly predictive of mortality, with median survival of only 3.5 years after amputation among First Nations people, 0.6 years shorter than among other people in Ontario.

The etiology for this high burden of amputation may be driven in part by the high prevalence of many of the risk factors for PAD, including smoking and hypertension. (11) Yet, the magnitude of incremental risk for other macrovascular complications of diabetes faced by First Nations people, including coronary artery disease and stroke, (12),(13) is not nearly as dramatic as it is for amputation. Therefore, they are likely other factors contributing to this risk. For example, First Nations people may face barriers to screening for milder degrees of PAD, resulting in missed opportunities for early intervention and presentation with more advanced disease. A previous study found that First nations amputation rates in Manitoba varied by specialist consultation rate and by tribal council, suggesting that healthcare access may be an important factor. (14) In addition, First Nations people may have an increased risk for distal polyneuropathy as a complication of diabetes, which would increase the risk of foot ulcers that could eventually necessitate amputation. Unfortunately, this was not an outcome that could be ascertained using our data.

Our results corroborate previous research from Alberta, that found an approximately 3-fold increased risk of amputation for First Nations people compared to non-First Nations people. (15) Previous research has found that lower socioeconomic status is an important independent predictor of amputation in people with diabetes in Ontario, (16) and First Nations people have marked disparities in socioeconomic measures. (17),(18) However, a Manitoba study of First Nations people found that average income at the tribal council level was not associated with

amputation rates. (14) A Manitoba study found that First Nations people were more likely to require amputation for an emergent indication (such as gangrene or nonhealing foot ulcer), but there was no difference in perioperative morbidity or long-term mortality. (19) Another Manitoba study compared outcomes for patients undergoing amputation between First Nations and Métis people with non-Indigenous people. (20) Rehabilitation utilization and duration were similar, but First Nations/Métis people were less likely to experience phantom pain post-amputation. We were not able to examine rehabilitation utilization in our study.

This study has many important strengths. The study was a participatory research collaboration between academics and representatives of First Nations communities, who were involved throughout the study. In addition, we conducted a population-based study of all people across Ontario, and used provincial healthcare administrative databases that capture all outcome events with no missing data. Thus, the study had sufficient sample size to be adequately powered to examine rare events such as amputation. However, there are some important limitations to highlight. Using administrative data, we were only able to identify angiography as a diagnostic test for PAD. Other diagnostic tests, such as ultrasound, CT or MRI could not be identified as diagnostic tests specifically for PAD using the available data. In addition, we could only identify major surgical procedures for PAD: revascularization and amputation. Less severe manifestations of PAD, such as symptoms of impaired circulation, foot ulcers, or arterial blockages not suitable for intervention could not be ascertained. In addition, the data on diagnostic testing or surgical procedures will undercount procedures for Ontarians living in the northwest of the province, where specialist services may be referred to Winnipeg, Manitoba. As a result, we may have underestimated the procedural or surgical rates among those living in this area, which includes a large population of First Nations people.

In summary, although First Nations people with diabetes have comparable rates of procedures to diagnose and treat PAD as other people with diabetes in Ontario, they have a markedly

increased risk for amputation. This increased risk is particularly striking amongst younger people. These discordant results suggest that PAD is underdiagnosed or undertreated among First Nations people in Ontario. Amputation markedly impacts quality of life, and is associated with a very high mortality rate that is 15% higher for First Nations people compared to other people in Ontario. These results demonstrate the health inequities faced by First Nations people, and the impact of social, economic and cultural determinants of health. (17) Future research is needed to understand what barriers First Nations people face to receive adequate PAD care, and what interventions are necessary to achieve equitable PAD outcomes for First Nations people in Ontario.

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Table

Table 1. Demographic characteristics of First Nations and other people in Ontario with diabetes, 2002 and 2014.

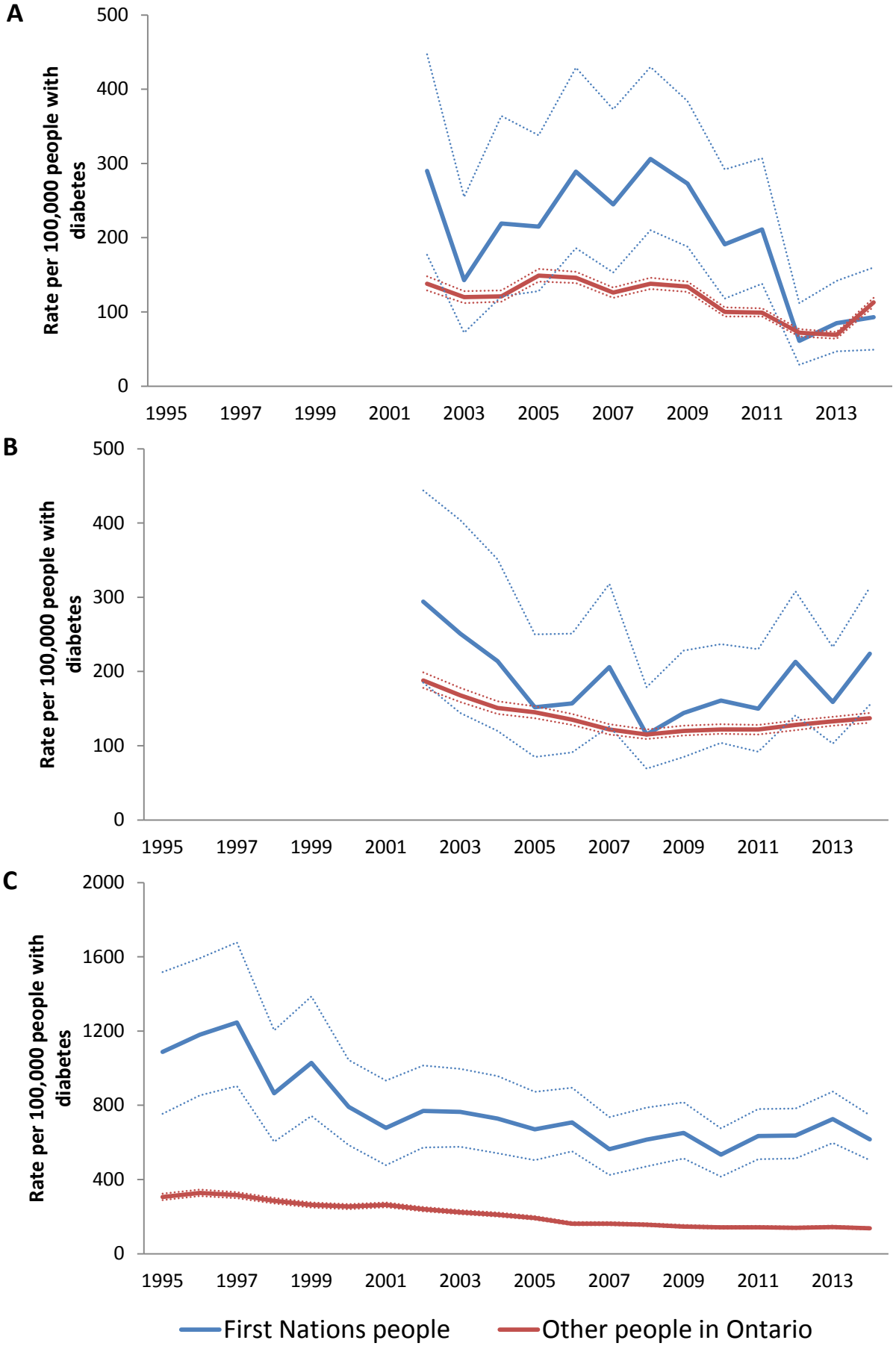
Demographic characteristic		2002		2014	
		First Nations people	Other people in Ontario	First Nations people	Other people in Ontario
N		13,573	680,880	23,011	1,364,136
Sex	Male	6,074 (44.8%)	354,541 (52.1%)	10,687 (46.4%)	709,016 (52.0%)
	Female	7,499 (55.2%)	326,339 (47.9%)	12,324 (53.6%)	655,120 (48.0%)
Age (years)	0-19	175 (1.3%)	7,517 (1.1%)	289 (1.3%)	11,558 (0.8%)
	20-34	1,396 (10.3%)	29,581 (4.3%)	1,615 (7.0%)	42,553 (3.1%)
	35-49	4,222 (31.1%)	118,063 (17.3%)	5,654 (24.6%)	190,112 (13.9%)
	50-64	5,056 (37.3%)	225,880 (33.2%)	9,238 (40.1%)	472,026 (34.6%)
	65-74	1,908 (14.1%)	164,265 (24.1%)	4,108 (17.9%)	337,358 (24.7%)
	75+	816 (6.0%)	135,574 (19.9%)	2,107 (9.2%)	310,529 (22.8%)
Rurality	Urban	3,228 (37.8%)	480,927 (71.3%)	6,277 (42.6%)	989,684 (73.0%)
	Semi-urban	2,780 (32.6%)	134,164 (19.9%)	4,587 (31.1%)	262,062 (19.3%)
	Rural	2,526 (29.6%)	59,893 (8.9%)	3,865 (26.2%)	103,246 (7.6%)
Comorbidity	Low	3,074 (22.7%)	114,536 (17.0%)	4,959 (21.7%)	246,154 (18.2%)
	Medium	5,526 (40.9%)	295,761 (43.8%)	8,850 (38.7%)	576,794 (42.6%)
	High	4,925 (36.4%)	265,363 (39.3%)	9,086 (39.7%)	531,150 (39.2%)

Figure headings

Figure 1: Age- and sex-adjusted rates and 95% confidence intervals among First Nations people and other people in Ontario of A) lower-extremity angiography, B) revascularization procedures, and C) lower-extremity amputation

Figure 2: Age-adjusted rates by sex and sex-adjusted rates by age of lower-extremity amputation among First Nations people and other people in Ontario, 2014.

Figure 3: Adjusted survival curve after major lower-extremity amputation for First Nations people and other people in Ontario.


A
B
C
Rate per 100,000 people with diabetes
0
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200
300
400
500
1600
1200
800
2000
1995
1997
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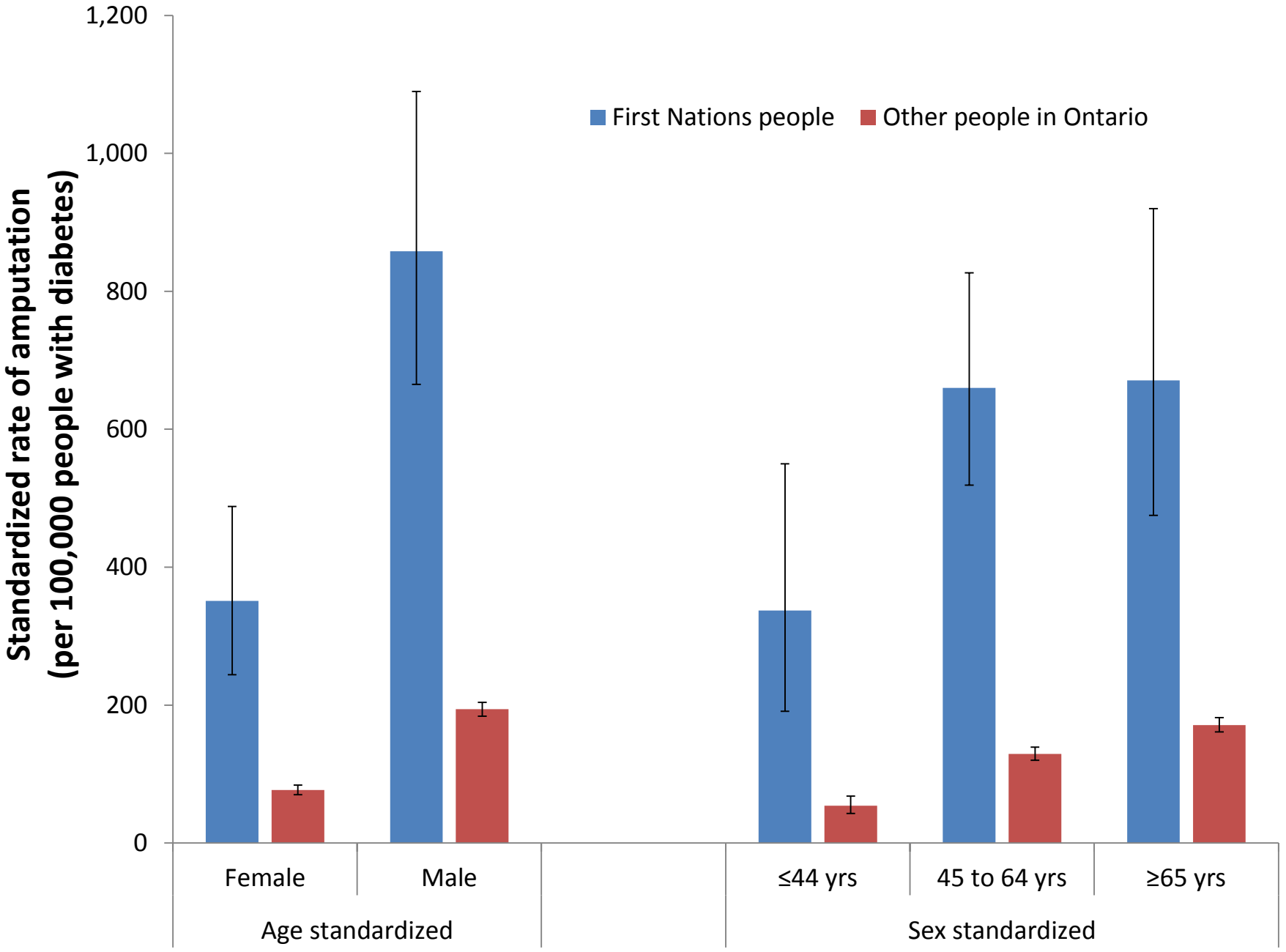
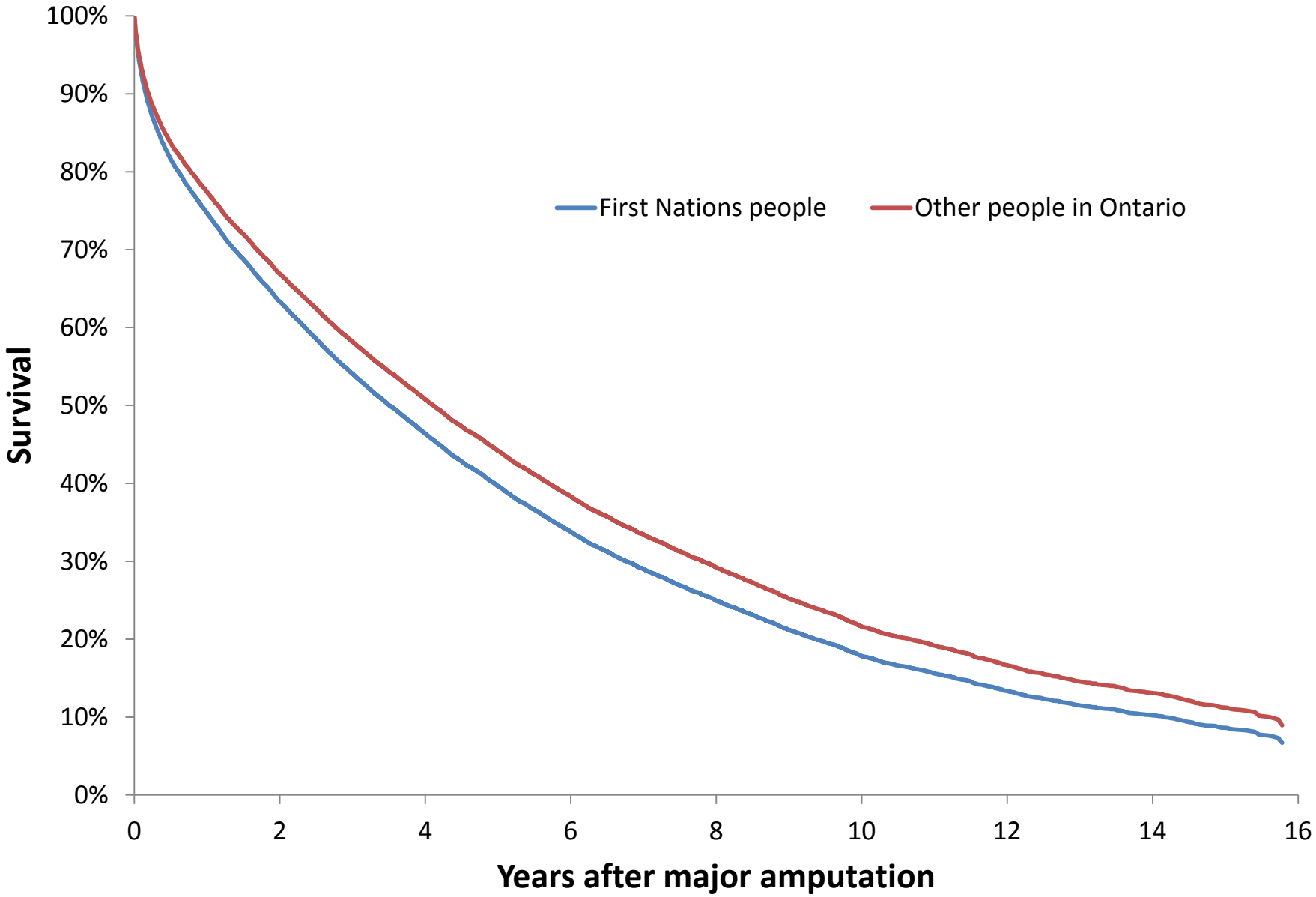
2013
First Nations people
Other people in Ontario





STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	6, Figures

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	6-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.