Cardiovascular Complications and Mortality After Diabetes Diagnosis for South Asian and Chinese Patients

A population-based cohort study

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OBJECTIVE—Many non-European ethnic groups have an increased risk for diabetes; however, the published literature demonstrates considerable uncertainty about the rates of diabetes complications among minority populations. The objective of this study was to determine the risks of cardiovascular complications and of mortality after diabetes diagnosis for South Asian and Chinese patients, compared with European patients.

RESEARCH DESIGN AND METHODS—A population-based cohort study identified all 491,243 adults with newly diagnosed diabetes in Ontario, Canada, between April 2002 and March 2009. Subjects were followed until March 2011 for the first occurrence of any cardiovascular complication of diabetes (coronary artery disease, stroke, or lower-extremity amputation) and for all-cause mortality. Median follow-up was 4.7 years.

RESULTS—The crude incidence of cardiovascular complications after diabetes diagnosis was 17.9 per 1,000 patient-years among European patients, 12.0 among South Asian patients, and 7.7 among Chinese patients. After adjusting for baseline characteristics, the cause-specific hazard ratios (HRs) for cardiovascular complications relative to European patients were 0.95 (95% CI 0.90–1.00; $P = 0.056$) and 0.50 (0.46–0.53; $P < 0.001$) for South Asian and Chinese patients, respectively. Mortality was lower for both minority groups (adjusted HR for South Asian patients 0.56 [95% CI 0.52–0.60]; $P < 0.001$; for Chinese patients 0.58 [0.55–0.62]; $P < 0.001$).

CONCLUSIONS—Chinese patients were at substantially lower risk than European patients for cardiovascular complications after diabetes diagnosis, whereas South Asian patients were at comparable risk. Mortality after diabetes diagnosis was markedly lower for both minority populations.

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Many non-European ethnic groups have an increased prevalence (1,2) and incidence (3,4) of diabetes mellitus; however, the published literature demonstrates considerable uncertainty about the rates of diabetes complications among minority populations. Studies in the U.S. have shown African American and Hispanic populations to have rates of cardiovascular complications similar to or lower than those of Europeans (5,6). Mortality rates are decreased for Hispanic populations with diabetes and increased for African Americans (7,8). Data are limited in other ethnic groups, however, and also from other countries where universal health care systems may mitigate some barriers to care for minority patients.

The two largest minority ethnic groups in Canada are South Asians (ancestry from the Indian subcontinent) and Chinese (ancestry from China, Hong Kong, or Taiwan) (9). Our previous research has shown that people with diabetes from these two groups have equitable utilization and quality of care (10,11). The objective of this study was to examine whether outcomes of care were also equitable. We sought to determine the risk of cardiovascular complications and of mortality after diagnosis with diabetes, comparing South Asian and Chinese patients with those of European ancestry.

RESEARCH DESIGN AND METHODS

Study design and data sources

We conducted a population-based cohort study drawing from health care databases from the government-funded health insurance program of the Ontario Ministry of Health and Long-Term Care, a program available to all permanent residents of the province. The data sources used in the study included demographic details for all residents of Ontario, abstracts of all hospitalizations and emergency department visits, and all claims from physicians and clinical laboratories for fee-for-service reimbursement. We also used the Ontario Diabetes Database, a registry that identifies all people with physician-diagnosed nongestational diabetes in Ontario. When validated against chart review, the Ontario Diabetes Database was found to have a sensitivity of 86% and a specificity of 97% (12). Although the database does not distinguish between types of diabetes, the vast majority of patients have type 2 diabetes. Individuals are linked between these databases and across time by unique health card number.

Study population

The study population included all adults aged ≥18 years in Ontario diagnosed

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with diabetes between 1 April 2002 and 31 March 2009. The date of cohort entry was the date of diagnosis with diabetes. Individuals must have been a resident of Ontario for at least 2 years before diagnosis to ensure that new arrivals to the province who had prevalent diabetes were not inadvertently labeled as having incident cases as a result of the absence of previous data. Because the vast majority of ethnic minority populations in Ontario live in urban areas (9), individuals living in rural areas were excluded to ensure comparability of the exposure groups.

Exposure and outcomes

The exposure of interest was the patient's ethnicity. There are no ethnic identifiers in Canadian health care data, so assignment was based on surnames, with two lists of surnames validated in this population used to identify people with South Asian and with Chinese origins (13). Both lists demonstrate excellent positive predictive values when compared with self-reported ethnicity (89.3% for South Asian and 91.9% for Chinese) (13). People whose surnames were not on either list were labeled as "European," as only 11% of the Ontario population is from minority ethnic groups other than South Asian or Chinese (9).

The primary outcome of interest was the first occurrence after diabetes diagnosis of cardiovascular complications, defined as hospitalization for coronary artery disease (acute myocardial infarction, acute coronary syndromes, percutaneous coronary intervention, or coronary artery bypass surgery), stroke, or lower-extremity amputation. Diagnoses on these records were coded according to the ICD-10; procedures were coded according to the Canadian Classification of Health Interventions. Patients whose diabetes was diagnosed concurrently with their admission for a cardiovascular complication remained in the cohort. Each component of the composite primary outcome was considered as a separate secondary outcome, as was all-cause mortality (defined from dates of death recorded in the demographic data). All subjects in the cohort were followed until 31 March 2011; thus each subject was followed for at least 2 and up to 9 years.

Baseline characteristics determined for each patient included age, sex, socioeconomic status (determined by linking patient postal codes with census data to determine the mean neighborhood household income level, divided into quintiles), hypertension (data obtained from a validated disease registry) (14), other comorbidity before diabetes diagnosis (according to the components of the Charlson comorbidity index, including previous myocardial infarction, heart failure, peripheral and cerebrovascular disease, dementia, chronic obstructive pulmonary disease, renal disease, and cancer) (15), and the number of primary care visits in the year before diabetes diagnosis (as a measure of health care access and utilization).

Statistical analyses

We accounted for the competing risk of mortality by using two different analytical approaches (16). First, we used Cox proportional hazards to jointly model the effect of ethnicity on the cause-specific hazard of the primary outcome and on the competing risk of death. In doing so, we modeled the effect of ethnicity on the hazard of the primary outcome, treating death as a censoring event, while simultaneously modeling the effect of ethnicity on the hazard of death, treating the primary outcome as a censoring event. Second, a Fine-Gray competing risk regression model was used to model the effect of ethnicity on the subdistribution hazard function of the primary outcome, treating death as a competing event. Because the Fine-Gray model was computationally intensive and gave results similar to those of the Cox proportional hazards model, we used both analytical approaches only for the primary outcome; all other analyses used only the first approach. Thus the Cox proportional hazards was used to model the effect of ethnicity on the cause-specific hazard of each component of the primary outcome. A separate model was used to estimate the effect of ethnicity on all-cause mortality. All models were adjusted for patient baseline characteristics. The assumption of proportionality was verified by plotting log[–log(survival)] versus log(time) to assess parallelism.

A three-way interaction among age, sex, and ethnicity was introduced into the Cox model for the primary outcome to test for effect modification. In addition, because the median income of South Asian and Chinese people in Canada is 25–35% lower than that of European people (9), we sought to evaluate the influence of socioeconomic status by determining the event rate in each socioeconomic stratum for each ethnic group. The statistical significance of the trend across strata was tested in each ethnic group with a Cox proportional hazards model with the ordinal categorical measure of socioeconomic status modeled as a continuous independent variable.

As a sensitivity analysis to evaluate the potential impact of unmeasured confounding, we used the framework of Lin et al. (17) to determine the difference in the prevalence of a dichotomous unmeasured confounder between South Asian and Chinese populations and the European population that would be required to nullify the observed associations for the primary outcome and for mortality.

To explore the possibility that differences in diabetes screening intensity might explain differences in the rate of progression to cardiovascular complications after diagnosis, we compared between ethnic groups the number of glucose and HbA_{1c} tests performed for each patient in the 2-year period before diabetes diagnosis.

All statistical analyses were performed with the SAS statistical software package, version 9.2.

Ethics approval

The study was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

RESULTS—There were 593,466 adults in Ontario who were diagnosed with diabetes between April 2002 and March 2009. We excluded 33,492 people who had lived in Ontario for <2 years before diagnosis and a further 68,731 who lived in rural areas, leaving 491,243 subjects in the study. Of them, 22,342 (4.5%) were South Asian and 20,646 (4.2%) were Chinese. Their baseline characteristics are shown in Table 1. Compared with European patients, the mean age at diagnosis of diabetes was more than 6.5 years younger for South Asian patients and nearly 2 years younger for Chinese patients. In addition, individuals from both minority groups had strikingly fewer baseline cardiovascular and other comorbidities at diagnosis. The median follow-up time was 4.7 years (interquartile range 3.0–6.5).

Cardiovascular complications occurred in 37,782 European patients (8.4%), compared with 1,332 South Asian patients (6.0%) and 782 Chinese patients (3.8%). In the multivariate models adjusting for the differences in baseline characteristics and accounting for the competing risk of death, the cause-specific hazard ratios (HRs) for the primary outcome relative to European patients

Table 1—*Baseline characteristics of patients newly diagnosed with diabetes in Ontario, Canada*

	European	South Asian	Chinese	*P*
N	448,255	22,342	20,646	
Age (years), mean ± SD	58.3 ± 14.9	51.6 ± 13.6	56.5 ± 14.4	<0.001
Age-group (years)				<0.001
18–34	6.0	9.9	5.7	
35–44	13.0	22.6	15.5	
45–54	22.5	26.8	26.1	
55–64	24.6	22.4	21.7	
65–74	19.0	13.0	19.1	
≥75	14.9	5.3	11.9	
Sex				<0.001
Female	48.3	44.4	46.4	
Male	51.7	55.6	53.6	
Socioeconomic status				
Lowest	22.6	28.0	20.8	<0.001
2	21.7	25.7	24.9	
3	19.8	22.1	19.9	
4	18.8	14.3	18.9	
Highest	17.0	9.6	15.3	
Missing	0.1	0.1	0.1	
Comorbidities				
Hypertension	54.6	41.8	47.5	<0.001
Myocardial infarction	1.2	0.8	0.3	<0.001
Congestive heart failure	1.2	0.4	0.4	<0.001
Peripheral vascular disease	0.4	0.1	0.2	<0.001
Cerebrovascular disease	0.7	0.3	0.5	<0.001
Dementia	0.4	0.1	0.1	<0.001
Chronic obstructive pulmonary disease	1.2	0.3	0.3	<0.001
Renal disease	0.6	0.3	0.4	<0.001
Cancer	1.6	0.6	1.2	<0.001
Primary care visits in the year before diabetes diagnosis				<0.001
0	7.2	4.7	4.6	
1	10.1	9.1	10.3	
2–6	47.9	46.6	48.1	
7–12	24.0	26.8	26.1	
≥13	10.8	13.0	10.8	

Data are percentages of patients except as marked.

were 0.95 (95% CI 0.90–1.00; $P = 0.056$) and 0.50 (0.46–0.53; $P < 0.001$) for South Asian and Chinese patients, respectively (Table 2). The use of subdistribution HRs instead to account for the competing risk of death gave virtually identical results: 0.96 (0.91–1.02; $P = 0.18$) for South Asian patients and 0.51 (0.47–0.55; $P < 0.001$) for Chinese patients.

Table 2 shows the incidence rates and cause-specific HRs for each of the components of the primary outcome. South Asian patients had a coronary artery disease risk similar to that of European patients, but Chinese patients had a substantially lower risk. The reverse was true for stroke. Both minority populations had markedly lower risks for lower-extremity amputation.

The all-cause mortality was 22.2 deaths per 1,000 patient-years for European patients (Table 2). In contrast, all-cause mortalities for South Asian and Chinese patients were markedly lower. Even after adjusting for baseline differences, the hazards for mortality for both minority groups remained more than 40% lower than that of European patients.

Supplementary Fig. 1 shows the results of the model examining the primary outcome, including a three-way interaction among age, sex, and ethnicity. Men were at higher risk for cardiovascular complications than women, older patients were at higher risk than younger patients, and Chinese patients were at lower risk than European or South Asian patients.

Income was inversely associated with the risk for cardiovascular complications among European patients; that is, lower income patients were more likely to develop cardiovascular complications than higher income patients (Fig. 1, $P < 0.001$). In contrast, income was positively associated with cardiovascular complications for South Asian patients ($P = 0.04$) and was not associated with complications for Chinese patients ($P = 0.7$).

In the sensitivity analysis, if the prevalence of an unmeasured confounder that quadrupled the hazard for cardiovascular complications were 5% in the Chinese population, then its prevalence would have to be 40% in the European population to explain the reduced risk for cardiovascular complications observed in the study. An unmeasured confounder that quadrupled the hazard for mortality with a prevalence of 5% in the South Asian and Chinese populations would have to have had a prevalence of 29–31% in the European population to explain the observed reduced hazard for mortality.

European patients underwent a mean of 2.47 ± 2.31 laboratory tests for diabetes screening in the 2 years before diabetes diagnosis. This exceeded the number of tests for South Asian or Chinese patients (2.38 ± 1.89 and 2.37 ± 1.83, respectively, $P < 0.001$). Even after age and sex standardizing, neither minority population exceeded the number of screening tests for European patients.

CONCLUSIONS—In this population-based sample of nearly 480,000 people with newly diagnosed diabetes followed for a median of 4.7 years, Chinese patients developed fewer cardiovascular complications than did European patients, independent of differences between the populations in the age of diabetes onset, socioeconomic status, hypertension, and other comorbidities. Risk for South Asian patients was similar to that for European patients. In addition, mortality was more than 40% lower for both minority groups compared with European patients. Both minority groups were younger and, partially as a consequence, had fewer baseline cardiovascular and other comorbidities than did European patients. Nonetheless,

Table 2—*Incidence rates and HRs for cardiovascular complications and all-cause mortality after diabetes diagnosis*

	European incidence	South Asian				Chinese			
		Incidence				Incidence			
		Crude	Standardized*	HR† (95% CI)	*P*	Crude	Standardized*	HR† (95% CI)	*P*
Any cardiovascular complication‡	17.9	12.0	16.8	0.95 (0.90–1.00)	0.056	7.7	8.1	0.50 (0.46–0.53)	<0.0001
Coronary artery disease	13.7	10.2	13.8	1.01 (0.95–1.07)	0.8	4.7	4.9	0.39 (0.36–0.43)	<0.0001
Stroke	3.9	2.0	3.2	0.82 (0.72–0.94)	0.004	3.0	3.3	0.91 (0.81–1.02)	0.1
Lower-extremity amputation	0.7	0.1	0.2	0.31 (0.19–0.49)	<0.0001	0.2	0.2	0.30 (0.19–0.48)	<0.0001
All-cause mortality	22.2	7.0	12.6	0.56 (0.52–0.60)	<0.0001	10.9	12.2	0.58 (0.55–0.62)	<0.0001

Crude and age- and sex-standardized (events per 1,000 person-years) and adjusted HRs relative to the European population for cardiovascular complications and all-cause mortality after diabetes diagnosis. *Standardized to the European population on age and sex. †Cause-specific HRs for cardiovascular complications and HRs for all-cause mortality, adjusted for age, sex, socioeconomic status, hypertension, previous comorbidity, and primary care visits before diabetes diagnosis. ‡Includes coronary artery disease, stroke, and lower-extremity amputation.

there remained striking differences in cardiovascular complications and mortality even after adjusting for these differences. For example, South Asian patients had a dramatically lower risk for mortality despite an equivalent risk for cardiovascular complications, suggesting that cardiovascular disease may be less fatal for South Asians with diabetes than for Europeans. This surprising finding warrants further exploration.

Chinese patients were at lower risk for coronary artery disease than European patients. Notably, South Asian patients were at comparable risk for coronary artery disease to European patients, suggesting that the well-recognized increased risk of coronary artery disease among South Asians may be driven by the prevalence of diabetes, rather than an independently increased risk for coronary artery disease (18,19). The converse was seen for stroke: South Asian patients were at a lower risk than European patients, and Chinese patients were at a similar risk. The risk for lower-extremity amputation for both minority groups was

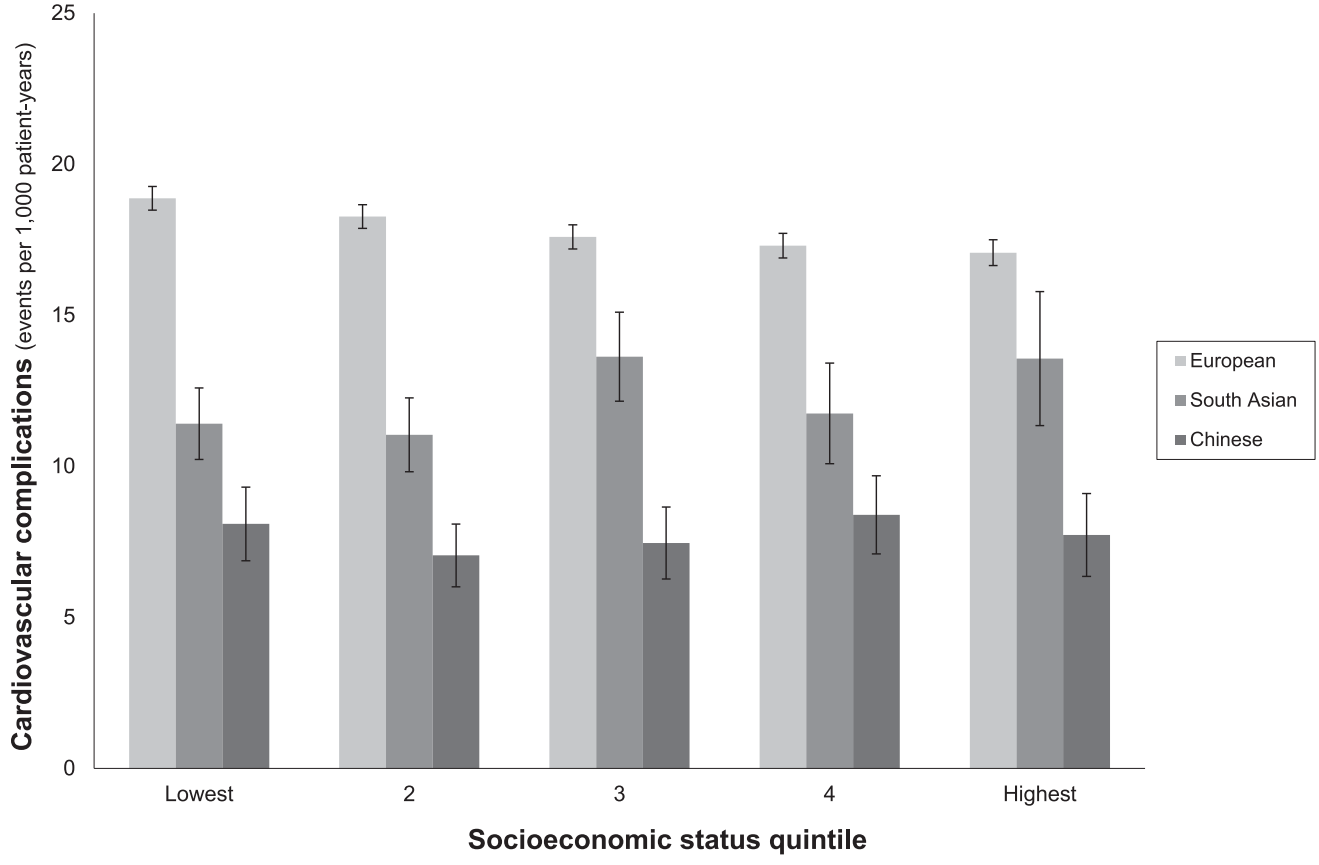

Figure 1—*Incidences of cardiovascular complications after diabetes diagnosis for European, South Asian, and Chinese patients, stratified by socioeconomic status.*

nearly 70% lower than for European patients. In general, Chinese men had a similar risk for cardiovascular complications as European men 2 decades younger, whereas Chinese women were at similar risk to European women 1 decade younger (Supplementary Fig. 1).

Differences in socioeconomic status can influence diabetes care through many mechanisms (20)—including adherence to recommended diets and medications, access to care, and providers' perceptions and quality of care delivered—and can influence patient outcomes, even in publicly funded health care systems (21). The median income of South Asian and Chinese people in Canada is substantially lower than that of European people (9), and Canadian minorities are 50% more likely to be classified as "low income" than are people of European origin (22). We found that the relationship between income and cardiovascular complications was entirely different in the three populations studied: whereas European patients showed an inverse relationship between income and complications, South Asian patients showed a positive relationship, and income and the risk for complications were not related in Chinese patients. An inverse relationship between income and diabetes complications might be explained by differences in access to care, even in the Canadian health care system (23,24). For example, although physician and hospital services are universally available without charge, drug reimbursement is not. Furthermore, maintenance of healthful diets, regular physical activity, and other self-care behaviors may be more difficult for poorer patients (25,26). In contrast, the direct relationship between income and complications in South Asian populations may reflect the effects of acculturation, because wealthier individuals often adopt more westernized lifestyles and diets (27,28). Thus our data show that European populations demonstrate the typical socioeconomic gradient seen in high-income countries, where cardiovascular disease, its risk factors, and other diseases are more common among the poor (29). In contrast, South Asian populations in Canada continue to demonstrate the gradient seen in low-income countries, where cardiovascular disease is more common among the wealthy (29).

The slower progression to cardiovascular complications and mortality after diabetes diagnosis in minority populations could occur for several possible reasons. Minorities may receive more intensive diabetes screening, leading to diagnosis earlier in the course of disease and thus apparent lengthening of time to complications. This is unlikely to be an explanation, however, because the European patients in our cohort had received more diabetes screening tests in the 2 years before diagnosis than had the South Asian or Chinese patients. Furthermore, previous studies have shown that the prevalence of undiagnosed diabetes is no different between minority groups and the European-origin population in Canada (30). Alternatively, better quality of care and cardiovascular risk factor control for minority populations could lead to better prevention of cardiovascular complications. This is also unlikely to explain the study's findings, as our previous work has shown that quality of diabetes care for South Asian and Chinese populations in Ontario, including control of cardiovascular risk factors, is similar to that of European patients (11). There may be other unmeasured factors differing between the minority and European patients that could explain these findings; however, the sensitivity analyses showed they would have to be more strongly predictive of cardiovascular complications or mortality and also be more imbalanced among the groups than any of the known traditional risk factors (31) to nullify the observed associations. Thus the most likely explanation for our findings is that new-onset diabetes in South Asian and Chinese patients is less severe or is a less potent risk factor for cardiovascular disease and mortality than it is in European patients, leading to slower progression to complications after diagnosis.

There are few previous studies with which to compare our results. American studies of ethnic disparities in diabetes outcomes have focused mostly on black and Hispanic populations; those that have studied Asian populations have generally aggregated them together (5,8,32,33). A recent study from an American managed care organization examined diabetes complications in 7,000 disaggregated Asian subjects (34). It found, similar to our study, that South Asian subjects were at equivalent risk for myocardial infarction as Europeans, whereas Chinese, Japanese, and Filipino subjects were at lower risks. All Asian subgroups were at markedly lower risk for lower-extremity amputation, with variability among them in the magnitude of the reduced risk. Cross-sectional British studies examining cardiovascular complications among South Asians with diabetes have had heterogeneous results (35–39). All-cause mortality was lower for South Asians than for Europeans among patients with diabetes >75 years of age, but not younger populations (35). A smaller previous Canadian study that used a similar methodology also found a reduction in cardiovascular complications and mortality among South Asian and Chinese diabetes patients than among Europeans (4).

This study has a number of strengths to highlight. It used longitudinal data after an inception cohort of newly diagnosed patients. Thus unlike previous cross-sectional studies, we could examine incidence of cardiovascular complications. Moreover, because these data were population based and from a single-payer health care system, there were no events missed as result of care being delivered in a setting not captured in the data. This study is also by far the largest ever conducted on ethnic variation in diabetes complications, with data on nearly 500,000 patients for up to 9 years.

There are some limitations to highlight. First, the data did not include important clinical variables that might influence cardiovascular complications, such as diabetes treatments or glycemic and other risk factor control. For example, cigarette smoking and obesity are less prevalent among South Asian and Chinese populations than among the European population (31). Our previous research, however, has shown few differences in cardiovascular risk factor control or in the quality of diabetes care among ethnic groups (11). In addition, the sensitivity analyses we conducted showed that any unmeasured confounding would have to be both very strongly predictive of risk and very heavily imbalanced among the groups to explain the findings of the study. Second, differences in screening rates among ethnic groups could partially explain the observed results if, for example, South Asian and Chinese patients received more intensive diabetes screening and therefore were diagnosed at an earlier stage of disease. We found, however, that European patients in this study had actually received more screening tests before diagnosis than had the minority patients, and a previous Canadian diabetes screening study found that undiagnosed diabetes was no less common in ethnic minority groups than in the European population (30). It would, of course, be

impracticable to characterize metabolically an entire population longitudinally to identify the onset of diabetes more precisely; rather, the time of clinical diagnosis is a clinically meaningful and relevant starting point. Third, we assigned ethnicity according to surnames lists that have been validated within this population (13), with high positive predictive value but poor sensitivity. So although virtually all members of the cohorts identified by each list are truly from the respective minority groups, some minority individuals will not have been captured in the cohorts. This limitation would, if anything, tend to narrow any observed differences between ethnic groups. Nonetheless, ascertainment of ethnicity would be strengthened if population-level Canadian health care data included ethnic identifiers. Fourth, the minority groups in this study consisted only of people with South Asian and Chinese ancestry. Individuals from other ethnic groups that may be at increased risk for diabetes, including Afro-Caribbean and Aboriginal people, share many of their surnames with the European population in Canada, making surnames unsuitable for identification of these ethnic groups. These populations are instead included in the European population in this study, and their potentially varying risks for cardiovascular disease could influence the observed risk for the European population. Given that these other minority populations make up only 11% of the population, however, the magnitude of this influence is minimal. Finally, neighborhood-level rather than individual-level income was used to assign socioeconomic status. The neighborhoods used, however, are small (median population 500) and relatively homogeneous, and neighborhood income correlates well with individual-level measures (40).

In summary, this study found that the development of cardiovascular complications after the diagnosis of diabetes is similar between South Asian and European patients but is substantially lower for Chinese patients. In particular, the risk for lower-extremity amputation is markedly lower for both minority groups. Mortality after diabetes diagnosis is lower for both South Asian and Chinese patients than for European patients, even after adjusting for the older age of onset and greater comorbidity among the European patients. We have previously shown that the utilization and quality of care are similar between these populations, so the differences in cardiovascular disease burden and mortality may occur because new-onset diabetes in South Asian and Chinese patients is less severe in European patients. Understanding the underlying genetic, physiologic, metabolic, or behavioral mechanisms that lead to this protection for Asian populations may help in the development of new strategies to reduce the risk of diabetes complications in the overall population.

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B.R.S. designed the study, researched the data, wrote the manuscript, contributed to the discussion, and reviewed and edited the manuscript. J.C.V. designed the study, researched the data, contributed to the discussion, and reviewed and edited the manuscript. M.C., J.V.T., S.S.A., P.C.A., D.G.M., and J.E.H. contributed to the discussion and reviewed and edited the manuscript. B.R.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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