Sex Differences in All-Cause and Cardiovascular Mortality, Hospitalization for Individuals With and Without Diabetes, and Patients With Diabetes Diagnosed Early and Late

Madonna M. Roche, msc[1]
Peizhong Peter Wang, md, phd[2]

OBJECTIVE—To compare risk of all-cause mortality, cardiovascular disease (CVD) mortality, acute myocardial infarction (AMI) mortality, stroke mortality, and hospitalizations for males and females with and without diabetes and those with diabetes diagnosed early and late.

RESEARCH DESIGN AND METHODS—We conducted a population-based retrospective cohort study including 73,783 individuals aged 25 years or older in Newfoundland and Labrador, Canada (15,152 with diabetes; 9,517 with late diagnoses).

RESULTS—Males and females with diabetes had an increased risk of all-cause mortality, CVD mortality, AMI mortality, and CVD hospitalizations compared with individuals without diabetes, and the risk was stronger in females than in males. For females, risks of all-cause mortality (hazard ratio [HR] 1.85 [95% CI 1.74–1.96]) and CVD hospitalizations (2.57 [2.24–2.94]) were significantly higher compared with their male counterparts (1.59 [1.51–1.69] and 1.92 [1.72–2.14]). Females with diabetes diagnosed late had an increased risk of CVD mortality (6.54 [4.80–8.91]) and CVD hospitalizations (5.22 [4.31–6.33]) compared with females without diabetes, and both were significantly higher compared with their male counterparts (3.44 [2.47–4.79]) and (3.33 [2.80–3.95]).

CONCLUSIONS—Females with diabetes have a greater risk of mortality than males with diabetes. CVD has a greater impact on females with diabetes than males, especially when diagnosed at a later stage. Different management strategies should be considered for males and females and those with early and late diagnoses of diabetes.

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Diabetes has become a health problem of increasing significance in the past two decades. The number of individuals with diabetes will reach 366 million in 2011 and will increase to 552 million by 2030 (1). In Canada, the age-standardized incidence and prevalence of diabetes have been increasing in recent years (2).

A challenge with type 2 diabetes is the late diagnosis of the disease because many individuals who meet the criteria are often asymptomatic. Approximately 183 million people, or half of those who have diabetes, are unaware they have the disease (1). Furthermore, type 2 diabetes can be present for 9 to 12 years before being diagnosed and, as a result, complications are often present at the time of diagnosis (3). Insulin resistance and β-cell dysfunction are largely responsible for the development of diabetes and its related complications, and both are present very early in the natural history of diabetes (4). However, the potential does exist to prevent or at least delay the onset of type 2 diabetes because several randomized control trials have shown that both lifestyle and pharmacologic interventions in adults are effective (5–8). In addition to preventing diabetes, it is also possible to reduce diabetes-related complications through intensive blood glucose control. Results from the UK Prospective Diabetes Study (UKPDS) have shown that intensive blood glucose control reduces diabetes-related complications (6–9). Early detection of type 2 diabetes is critical because effective and active management is essential for those with newly diagnosed diabetes who have not developed complications.

Cardiovascular disease (CVD) is the most common comorbidity associated with diabetes, and with 50% of those with diabetes dying of CVD it is the most common cause of death (1). Acute myocardial infarction (AMI) and stroke are other common comorbidities associated with diabetes. Individuals with diabetes have an increased risk of all-cause mortality and morbidity related to CVD, AMI, and stroke compared with individuals without diabetes (9–12). Although studies consistently have found that individuals with diabetes have a higher risk of mortality and hospitalizations compared with those without diabetes, results have been inconsistent when comparing males and females. Most studies have found that females with diabetes have a greater risk of mortality and hospitalizations than males with diabetes (9,10,12–17). Two previous meta-analyses found that diabetes is a stronger risk factor for CVD mortality in females than in males; however, studies that did not adjust for major CVD risk factors were included in these meta-analyses (18,19). A meta-analysis conducted by Kanaya et al. (20), which included studies that controlled for CVD risk factors, found that the risks associated with diabetes for coronary

From the [1]Research and Evaluation Department, Newfoundland and Labrador Centre for Health Information, St. John's, Newfoundland and Labrador, Canada; and the [2]Division of Community Health and Humanities, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada.
Corresponding author: Madonna M. Roche, donna.roche@nlchi.nl.ca.
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heart disease mortality, nonfatal myocardial infarction, and CVD were higher among females than males. However, the differences were not statistically significant.

Newfoundland and Labrador has the highest age-standardized prevalence of diabetes in Canada (2), and the age-standardized mortality and hospitalization rates for CVD, AMI, and stroke are some of the highest in the country (21,22). A better understanding of mortality and hospitalizations associated with diabetes for males and females is important to support diabetes prevention and management. Therefore, the objectives of this study were to compare the risk of all-cause, CVD, AMI, and stroke mortality and hospitalizations for males and females with and without diabetes and those with early and late diagnoses of diabetes.

RESEARCH DESIGN AND METHODS

—This study was a retrospective cohort study using administrative databases in Newfoundland and Labrador. Databases included were *1*) Canadian Chronic Diseases Surveillance System (CCDSS), which uses provincial health insurance registries, hospital discharge records, and fee-for-service physician claims to identify individuals with diabetes; *2*) the Clinical Database Management System, which contains hospital separation data; *3*) the Newfoundland and Labrador Medical Care Plan fee-for-service physician claims database; *4*) the NLCHI Mortality System; and *5*) Statistics Canada Annual Mortality Data Files. Ethical approval for this study was granted by the Health Research Ethics Authority of Newfoundland and Labrador.

Exposed and unexposed groups

The exposed group included all residents of Newfoundland and Labrador aged 25 years and older identified in the CCDSS as having diabetes diagnosed between 1 April 1998 and 31 March 2003. The CCDSS uses a nationally validated case definition to identify individuals with diabetes. One hospitalization or two or more fee-for-service physician claims with a diagnosis of diabetes within a 2-year period is required to be considered a diabetes case. Subjects remain in the CCDSS until a record of death is received or until they leave the province. The case definition used for the CCDSS has 86% sensitivity and 98% specificity for identifying individuals who had diabetes recorded in their primary care charts (23). The study entry date used for the exposed group was the diabetes case date.

Diabetes was classified as being diagnosed "early" and "late" depending on when diabetes-related comorbidities developed. Individuals early in the disease course would not have any diabetes-related comorbidities at the time of their case dates. On the contrary, a late-diagnosed diabetes patient would have comorbidities related to diabetes at the time of diagnosis. To classify those with diabetes diagnosed early and late, records for those with diabetes were linked to the Medical Care Plan and Clinical Database Management System data to identify when hospital and physician visits for diabetes-related comorbidities occurred, and these were compared with the diabetes case dates. Incident diabetes patients without any diabetes-related comorbidities within 6 months before or after the diabetes case date were classified as having early diagnoses, whereas those with a late diagnosis were defined as incident diabetes patients with diabetes-related comorbidities within 6 months before or after diagnosis. Some of the diabetes-related comorbidities that were used to define early and late status include retinopathy, neuropathy, nephropathy, coronary artery disease, peripheral arterial disease, cerebrovascular disease, and CVD.

Residents aged 25 years and older who had at least one hospitalization or physician visit between 1 April 1998 and 31 March 2003, and who were not identified in the CCDSS as having diabetes, were eligible to be included in the unexposed group. Using frequency matching by sex and 5-year age groups, each exposed individual was matched to four randomly selected individuals without diabetes.

Outcome and follow-up

The outcomes of interest were mortality and hospitalizations attributable to all causes, CVD (ICD-9 390–459; ICD-10-CA I00–I99), AMI (ICD-9 410; ICD-10-CA I21–I22), and stroke (ICD-9 430–436; ICD-10-CA I60–I64). The reference group used included individuals without diabetes for all analyses. Each outcome was assessed separately. Individuals who had a hospital separation or physician visit for CVD between 1 January 1995 and 31 March 1998 were excluded from the CVD analysis. Similar exclusions were made for the AMI and stroke analyses. For hospitalizations and all-cause mortality reported in this study, individuals were followed until 31 March 2008 (31 December 2007 for cause-specific mortality) or until one of two exit events (death or moved out of province). For the hospitalization analysis, hospitalization also was included as an exit event. Individuals who died before their study entry date (1 January 1995–31 March 2003) were identified by linking to the NLCHI mortality system and the Statistics Canada Annual Mortality Data Files and were excluded.

Covariates

Region of residence, comorbidities, and socioeconomic status were considered covariates in the analysis. An urban place of residence was defined as an area with $\geq$5,000 inhabitants, whereas a rural place of residence was defined as an area with $<$5,000 inhabitants. Approximately 5.5% (4,040) of the study subjects did not have information regarding place of residence. The most commonly occurring category was assigned to the missing cases. Comorbidities at baseline were estimated using the Charlson Comorbidity Index (24). Comorbidities were identified through diagnosis codes in the Clinical Database Management System data, and a comorbidity score, representing severity of illness, was assigned to each individual. Approximately 3.2% (2,338) of the study subjects did not have information regarding socioeconomic status, so values were imputed using the median value imputation method. Socioeconomic status scores were divided into five quintiles, with the first quintile representing the lowest income group and the fifth quintile representing the highest income group.

Statistical analysis

Characteristics of the study population are presented as means and proportions and stratified by sex, diabetes status, and early and late diabetes diagnosis status; χ^2 tests were used for categorical variables, and *t* tests were used for continuous variables. In the mortality analysis, person-time was calculated from study entry date to date of death, termination of health insurance coverage, or 31 December 2007. In the hospitalization analysis, all-cause, CVD, AMI, and stroke hospitalizations were assessed separately. For all-cause hospitalizations, the person-time was calculated from study entry date to date of first hospital admission for any cause, termination of health insurance coverage, date of death, or 31 March 2008. For

the CVD hospitalizations, date of first CVD hospital admission was used. Likewise, for AMI and stroke hospitalizations, date of first AMI hospital admission or stroke hospitalization was used, respectively. Cox proportional hazard models were used to calculate hazard ratios (HRs; with 95% CI). The main assumption of the Cox proportional hazard model is the proportional hazards assumption, which assumes the HR is constant over time. When the proportional hazards assumption was not met, an extended Cox model with an interaction term between survival time and the variable failing the proportional hazards assumption was applied (25). Interaction terms for diabetes and sex, early diagnosis and sex, and late diagnosis and sex were tested by the likelihood ratio test. When interactions were not significant, the analysis was not stratified by sex. All statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC) software.

RESULTS—The study sample consisted of 73,783 individuals, and mean age at baseline was 60.1 years (SD, 14.3 years). There were almost equal numbers of males and females: 37,790 (51.2%) and 35,993 (48.8%), respectively. Approximately half (53.9%) of the study sample lived in a rural area. Over the 10-year study period, 11,385 (15.4%) individuals died. The mean age at death was 77.9 years (SD, 11.0 years), and median survival time (time from diabetes diagnosis or study entry until death) was 43 months.

Characteristics of the study sample by diabetes status are presented in Table 1. For males, 20.5% (n = 7,751) had diabetes, whereas 20.6% (n = 7,401) of females had diabetes. The mean age at baseline was similar for males and females with and without diabetes. More males without diabetes lived in a rural area compared with males with diabetes ($P < 0.01$), whereas more females with diabetes lived in a rural area compared with females without diabetes ($P < 0.01$). Males and females with diabetes were more likely to die, to be younger at death, to have a shorter survival time, and to be admitted to the hospital than males and females without diabetes ($P < 0.01$). When admitted to the hospital, individuals with diabetes stayed longer than individuals without diabetes for both males (6.4 and 5.6; $P < 0.01$) and females (7.0 and 5.5; $P < 0.01$), respectively.

Characteristics of the diabetes sample by early diagnosis and late diagnosis status are presented in Table 2. Both males and females with late diagnoses were significantly older at the time of diagnosis than those with early diagnoses ($P < 0.01$). Males and females with late diagnoses of diabetes were more likely to be deceased at the end of the study period compared with those with early diagnoses ($P < 0.01$). Those with early diagnoses were younger at death compared with those with late diagnoses ($P < 0.01$); however, median survival time for both males and females with early diagnoses was significantly longer than that of those with late diagnoses ($P < 0.01$). During the study period, males and females with late diabetes diagnoses were more likely to be hospitalized ($P < 0.01$) and have a longer length of hospital stay compared with those with early diagnoses ($P < 0.01$).

Rates and HRs for mortality and hospitalizations by sex and diabetes status are shown in Table 3. Males with and without diabetes have higher rates of all-cause mortality and CVD hospitalizations than females. For CVD and AMI mortality, males without diabetes have higher rates than females; however, females have higher rates when diabetes is present. After adjustment for place of residence, socioeconomic status, and Charlson Comorbidity Index, both males and females with diabetes had an increased risk of dying of all causes and being hospitalized for CVD and AMI when compared with males and females without diabetes. The positive association between diabetes and all-cause mortality, CVD mortality, and AMI mortality was stronger in females than in males. Diabetes was positively associated with all-cause mortality (HR 1.85 [95% CI 1.74–1.96]) and CVD hospitalizations (2.57 [2.24–2.94]) for females, and the risk was significantly higher compared with their male counterparts (1.59 [1.51–1.69] and 1.92 [1.72–2.14]).

Rates and HR for mortality and hospitalizations by sex and early and late diabetes diagnoses status are shown in Table 4. An early diagnosis does not appear to have an impact on all-cause mortality, CVD mortality, AMI mortality, or stroke mortality. However, the hospitalization results show that an early diagnosis does increase the risk of all-cause, CVD, and AMI hospitalizations compared with individuals without diabetes. After adjusting for covariates, males with late diabetes diagnoses had an increased risk of all-cause and CVD mortality and hospitalizations compared with males without diabetes. Similar findings were found for females. A late diabetes diagnosis was positively associated with CVD mortality (HR 6.54 [95% CI 4.80–8.91]) and CVD hospitalizations (5.22 [4.31–6.33]) for females, and the risk was significantly higher compared with their male counterparts (3.44 [2.47–4.79] and 3.33 [2.80–3.95]).

CONCLUSIONS—In this population-based retrospective cohort study, mortality and hospitalizations for males and females with and without diabetes and for those with early and late diabetes diagnoses were examined. After adjustment for covariates, diabetes was positively associated with all-cause mortality and CVD hospitalizations for females, and the risk was significantly higher compared with their male counterparts. After adjusting covariates, an early diagnosis does not appear to have an impact on all-cause, CVD, AMI, or stroke mortality. However, the hospitalization results show that an early diagnosis does increase the risk of all-cause, CVD, and AMI hospitalizations. Males and females diagnosed late with diabetes had an increased risk of all-cause and CVD mortality and hospitalizations compared with those without diabetes. The risk of CVD mortality and hospitalizations for females with late diagnoses compared with females without diabetes was significantly higher when compared with their male counterparts. Although diabetes increases the risk of mortality and hospitalizations for both males and females, females are at a higher risk than males. CVD in particular has a greater impact on females with diabetes than males, especially when diabetes is diagnosed late.

Previous studies also have found that individuals with diabetes have an increased risk of mortality and morbidity related to all causes, CVD, AMI, and stroke compared with individuals without diabetes (9–12). This study also found that females with diabetes had an increased risk of all-cause mortality, CVD mortality, and CVD hospitalizations compared with females without diabetes, and this was significantly higher compared with their male counterparts. The majority of previous studies have supported the claim that females with diabetes are at greater risk for mortality and morbidity than males with diabetes (9,10,12–17). In addition, the results of this study show that CVD has a greater impact on females than males with diabetes.

It is not known why females with diabetes have an increased risk of mortality and hospitalizations compared with males

Table 1—*Characteristics of the study sample by diabetes status*

	Males (*n* = 37,790)			Females (*n* = 35,993)			Total (*n* = 73,783)		
	No diabetes (*n* = 30,039)	Diabetes (*n* = 7,751)	*P**	No diabetes (*n* = 28,592)	Diabetes (*n* = 7,401)	*P**	No diabetes (*n* = 58,631)	Diabetes (*n* = 15,152)	*P**
Mean age at baseline, years (SD)	59.4 (13.4)	59.2 (13.4)	0.289	60.9 (15.1)	60.6 (15.2)	0.109	60.1 (14.3)	59.9 (14.3)	0.059
Residing in rural area, % (*n*)	56.3 (16,913)	50.4 (3,906)	0.000	52.5 (15,007)	52.4 (3,879)	0.646	54.6 (31,984)	51.4 (7,785)	0.000
Deceased at study end, % (*n*)	14.5 (4,360)	23.8 (1,842)	0.000	12.1 (3,471)	23.1 (1,712)	0.000	13.4 (7,831)	23.5 (3,554)	0.000
Mean age at death, years (SD)	76.5 (10.2)	74.1 (11.0)	0.000	81.3 (10.7)	78.3 (11.2)	0.000	78.7 (10.7)	76.1 (11.3)	0.000
Median survival time, months†	46.2	40.4	0.000	46.2	41.6	0.000	46.2	41.0	0.000
Charlson Comorbidity Index, % (*n*)									
0	96.6 (29,017)	95.5 (7,406)	0.000	97.3 (27,825)	96.0 (7,107)	0.000	96.9 (56,842)	95.8 (14,513)	0.000
1–2	2.6 (781)	3.4 (265)		2.1 (612)	3.1 (226)		2.4 (1,393)	3.2 (491)	
≥3	0.8 (241)	1.0 (80)		0.5 (155)	0.9 (68)		0.7 (396)	1.0 (148)	
Socioeconomic status quintile, % (*n*)									
1	20.5 (6,154)	18.6 (1,442)	0.000	19.2 (5,486)	22.8 (1,687)	0.000	19.9 (11,640)	20.7 (3,129)	0.000
2	20.2 (6,079)	21.0 (1,625)		19.4 (5,539)	20.8 (1,536)		19.8 (11,618)	20.9 (3,161)	
3	20.0 (6,012)	19.3 (1,498)		20.2 (5,784)	20.1 (1,488)		20.1 (11,796)	19.7 (2,986)	
4	19.7 (5,930)	21.0 (1,631)		20.0 (5,712)	19.2 (1,424)		19.9 (11,642)	20.2 (3,055)	
5	19.5 (5,864)	20.1 (1,555)		21.2 (6,071)	17.1 (1,266)		20.4 (11,935)	18.6 (2,821)	
Hospitalizations, % (*n*)									
All-cause	58.5 (17,576)	72.3 (5,602)	0.000	59.5 (17,012)	74.6 (5,518)	0.000	59.0 (34,588)	73.4 (11,120)	0.000
CVD	17.5 (5,261)	28.9 (2,238)	0.000	12.3 (3,517)	22.9 (1,694)	0.000	15.0 (8,778)	26.0 (3,932)	0.000
AMI	6.0 (1,055)	8.6 (479)	0.000	3.4 (584)	6.1 (335)	0.000	4.7 (1,639)	7.3 (814)	0.000
Stroke	3.9 (694)	5.4 (302)	0.000	3.0 (507)	4.8 (267)	0.000	3.5 (1,201)	5.1 (569)	0.000
Mean length of stay, days (SD)									
All-cause	5.6 (14.5)	6.4 (15.2)	0.001	5.5 (14.6)	7.0 (17.4)	0.000	5.6 (14.5)	6.7 (16.4)	0.000
CVD	8.7 (16.4)	9.9 (32.3)	0.102	9.5 (20.6)	10.0 (18.4)	0.305	9.1 (18.3)	10.0 (27.1)	0.020
AMI	9.9 (12.2)	9.2 (8.3)	0.251	11.1 (17.2)	11.8 (17.4)	0.595	10.3 (14.2)	10.2 (12.9)	0.882
Stroke	25.8 (39.5)	20.8 (30.3)	0.054	17.8 (27.3)	24.3 (84.2)	0.191	21.2 (33.3)	22.7 (64.7)	0.519
Previous‡ CVD, % (*n*)	47.7 (14,318)	69.7 (5,403)	0.000	51.6 (14,751)	75.4 (5,578)	0.000	49.6 (29,069)	72.5 (10,981)	0.000
Previous‡ AMI, % (*n*)	2.7 (803)	5.1 (396)	0.000	1.5 (417)	3.0 (224)	0.000	3.1 (1,220)	4.1 (620)	0.000
Previous‡ stroke, % (*n*)	3.1 (935)	5.0 (389)	0.000	3.1 (884)	5.0 (371)	0.000	3.1 (1,819)	5.0 (760)	0.000

*Significance level = 0.05. †Time from diabetes diagnosis or study entry until death. ‡Previous hospital separation or physician visit.

Table 2—*Characteristics of the study sample by early and late diabetes diagnosis status*

	Males with diabetes (*n* = 7,751)			Females with diabetes (*n* = 7,401)			Total with diabetes (*n* = 15,152)		
	Early (*n* = 3,034)	Late (*n* = 4,717)	*P**	Early (*n* = 2,601)	Late (*n* = 4,800)	*P**	Early (*n* = 5,635)	Late (*n* = 9,517)	*P**
Mean age at baseline, years (SD)	53.9 (12.8)	62.6 (12.7)	0.000	53.6 (14.7)	64.4 (14.0)	0.000	53.7 (13.7)	63.5 (13.4)	0.000
Residing in rural area, % (*n*)	55.5 (1,684)	53.7 (2,535)	0.128	55.6 (1,447)	56.4 (2,708)	0.516	55.6 (3,131)	55.1 (5,243)	0.572
Deceased at study end, % (*n*)	13.2 (401)	30.5 (1,441)	0.000	11.7 (305)	29.3 (1,407)	0.000	12.5 (706)	29.9 (2,848)	0.000
Mean age at death, years (SD)	70.7 (12.5)	75.0 (10.4)	0.000	76.3 (12.6)	78.7 (10.8)	0.002	73.1 (12.8)	76.8 (10.8)	0.000
Median survival time, months† (SD)	46.2 (28.7)	38.8 (30.1)	0.000	45.8 (29.8)	40.7 (31.0)	0.008	46.1 (29.2)	39.7 (30.5)	0.000
Charlson Comorbidity Index, % (*n*)									
0	98.1 (2,977)	94.4 (8,987)	0.000	98.0 (2,549)	95.0 (4,558)	0.000	98.1 (5,526)	94.4 (8,987)	0.000
1–2	1.7 (51)	4.2 (396)		1.7 (44)	3.8 (182)		1.7 (95)	4.2 (396)	
≥3	0.2 (6)	1.6 (74)		0.3 (8)	1.3 (60)		0.2 (14)	1.4 (134)	
Socioeconomic status quintile, % (*n*)				23.3 (606)					
1	18.6 (565)	18.6 (877)	0.000	19.8 (516)	18.6 (877)	0.000	20.8 (1,171)	20.6 (1,958)	0.000
2	20.6 (624)	21.2 (1,001)		19.4 (504)	21.2 (1,001)	0.000	20.2 (1,140)	21.2 (2,021)	
3	20.6 (624)	18.5 (874)		20.3 (527)	18.5 (874)	0.000	20.0 (1,1128)	19.5 (1,858)	
4	21.2 (644)	20.9 (987)		17.2 (448)	20.9 (987)	0.000	20.8 (1,171)	19.8 (1,884)	
5	19.0 (577)	20.7 (978)			20.7 (978)	0.000	18.2 (1,025)	18.9 (1,796)	
Hospitalizations, % (*n*)									
All-cause	64.6 (1,960)	77.2 (3,642)	0.000	69.1 (1,798)	77.5 (3,720)	0.000	66.7 (3,758)	77.4 (7,362)	0.000
CVD	17.7 (538)	36.0 (1,700)	0.000	13.8 (360)	27.8 (1,334)	0.000	15.9 (898)	31.9 (3,034)	0.000
AMI	7.4 (144)	9.2 (335)	0.018	3.3 (60)	7.4 (275)	0.000	5.4 (204)	8.3 (610)	0.000
Stroke	2.9 (57)	6.7 (245)	0.000	2.6 (47)	5.9 (220)	0.000	2.8 (104)	6.3 (465)	0.000
Mean length of stay, days (SD)									
All-cause	4.9 (10.3)	7.2 (17.2)	0.000	5.1 (13.3)	8.0 (19.0)	0.000	5.0 (11.9)	7.6 (18.2)	0.000
CVD	8.2 (22.1)	10.4 (35.0)	0.148	7.5 (13.4)	10.9 (19.6)	0.000	7.9 (18.9)	10.6 (29.1)	0.001
AMI	9.2 (7.8)	9.2 (8.5)	0.992	8.1 (6.0)	12.6 (18.9)	0.001	8.9 (7.3)	14.3 (16.4)	0.017
Stroke	21.2 (62.9)	25.1 (88.5)	0.754	24.2 (35.0)	20.1 (29.2)	0.458	22.5 (52.0)	22.7 (67.2)	0.979
Previous‡ CVD, % (*n*)	40.2 (1,220)	88.7 (4,183)	0.000	48.4 (1,259)	90.0 (4,319)	0.000	44.0 (2,479)	89.3 (8,502)	0.000
Previous‡ AMI, % (*n*)	0.8 (23)	7.9 (373)	0.000	0.3 (9)	4.5 (215)	0.000	0.6 (32)	6.2 (588)	0.000
Previous‡ stroke, % (*n*)	1.5 (46)	7.3 (343)	0.000	1.7 (45)	6.8 (326)	0.000	1.6 (91)	7.0 (669)	0.000

*Significance level = 0.05. †Time from diabetes diagnosis or study entry until death. ‡Previous hospital separation or physician visit.

with diabetes. More males have diabetes diagnosed (2) and have diagnoses at lower BMI levels than females, which suggests that males are more susceptible to diabetes than females (26). One explanation is that CVD risk factors have a stronger impact on females than males. The Strong Heart Study compared differences in diabetes risk factors in males and females aged 45–74 years. Differences in waist-to-hip ratio, HDL cholesterol, apolipoprotein B, apolipoprotein A1, fibrinogen, and LDL size between females with diabetes and those without diabetes were greater than differences for males (13). Juutilainen et al. (16) investigated possible explanations for the stronger effect that diabetes has on the risk of coronary heart disease in females compared with males. Risk factors in the presence of diabetes were greater in females than in males at baseline. During follow-up, these risk factors were stronger contributors to diabetes-related coronary heart disease risk in females than in males. Moreover, Homko et al. (27) examined differences in CVD risk factors and risk perception among males and females with diabetes. Although A1C and fasting plasma glucose levels were similar, females with diabetes had higher cholesterol levels and were less likely to meet LDL and blood pressure targets. Although males and females had similar knowledge of CVD, females perceived their risk of CVD to be higher than males did. Also, females have an elevated risk of myocardial infarction and stroke before having diabetes clinically diagnosed, and risk of CVD in females begins to increase at least 15 years before diabetes is clinically diagnosed (28).

Another possible explanation is that CVD risk factors are less aggressively treated in females. Females with diabetes are less likely than males to have optimal blood glucose control (A1C <7%), to be prescribed aspirin and lipid-lowering medications, and to achieve recommended blood pressure and LDL cholesterol

Table 3—*Mortality and hospitalization rates and adjusted HRs* by sex and diabetes status*

	Males		Females		Total	
	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes
All-cause mortality						
Rate per 10,000 (*n*)	375.0 (1,842)	214.7 (4,360)	361.0 (1,712)	177.5 (3,471)	368.1 (3,554)	196.5 (7,831)
Unadjusted HR (95% CI)	1.74 (1.65–1.84)†	1.00 (reference)	2.03 (1.91–2.15)†	1.00 (reference)	—	—
Adjusted HR (95% CI)	1.59 (1.51–1.69)†	1.00 (reference)	1.85 (1.74–1.96)†	1.00 (reference)	—	—
CVD mortality						
Rate per 10,000 (*n*)	52.5 (82)	35.7 (386)	64.3 (77)	24.7 (238)	57.6 (159)	30.5 (624)
Unadjusted HR (95% CI)	1.46 (1.15–1.85)†	1.00 (reference)	2.60 (2.01–3.36)†	1.00 (reference)	—	—
Adjusted HR (95% CI)	1.50 (1.15–1.90)†	1.00 (reference)	2.45 (1.89–3.17)†	1.00 (reference)	—	—
AMI mortality						
Rate per 10,000 (*n*)	27.9 (127)	17.2 (330)	28.9 (130)	12.8 (239)	28.4 (257)	15.0 (569)
Unadjusted HR (95% CI)	1.62 (1.32–1.99)†	1.00 (reference)	2.25 (1.82–2.79)†	1.00 (reference)	—	—
Adjusted HR (95% CI)	1.48 (1.19–1.83)†	1.00 (reference)	1.96 (1.57–2.44)†	1.00 (reference)	—	—
Stroke mortality						
Rate per 10,000 (*n*)	17.0 (78)	9.7 (187)	21.0 (93)	11.7 (216)	18.9 (171)	10.7 (403)
Unadjusted HR (95% CI)	—	—	—	—	1.77 (1.48–2.12)†	1.00 (reference)
Adjusted HR (95% CI)	—	—	—	—	1.62 (1.35–1.94)†	1.00 (reference)
All-cause hospitalization						
Rate per 1,000 (*n*)	242.9 (5,602)	140.5 (17,576)	255.1 (5,518)	145.7 (17,012)	248.8 (11,120)	143.0 (34,588)
Unadjusted HR (95% CI)	—	—	—	—	1.64 (1.60–1.67)†	1.00 (reference)
Adjusted HR (95% CI)	—	—	—	—	1.61 (1.58–1.64)†	1.00 (reference)
CVD hospitalization						
Rate per 1,000 (*n*)	28.5 (418)	15.0 (1,603)	24.1 (277)	9.0 (871)	26.6 (695)	12.1 (2,474)
Unadjusted HR (95% CI)	2.91 (2.39–3.56)†	1.00 (reference)	4.61 (3.57–5.94)†	1.00 (reference)	—	—
Adjusted HR (95% CI)	1.92 (1.72–2.14)†	1.00 (reference)	2.57 (2.24–2.94)†	1.00 (reference)	—	—
AMI hospitalization						
Rate per 1,000 (*n*)	9.3 (425)	5.0 (985)	6.5 (297)	2.9 (553)	7.9 (722)	4.0 (1,538)
Unadjusted HR (95% CI)	—	—	—	—	1.57 (1.44–1.72)	1.00 (reference)
Adjusted HR (95% CI)	—	—	—	—	1.61 (1.48–1.75)†	1.00 (reference)
Stroke hospitalization						
Rate per 1,000 (*n*)	5.7 (265)	3.1 (608)	5.2 (236)	2.3 (445)	5.5 (501)	2.7 (1,053)
Unadjusted HR (95% CI)	—	—	—	—	1.58 (1.42–1.76)†	1.00 (reference)
Adjusted HR (95% CI)	—	—	—	—	1.31 (1.17–1.46)†	1.00 (reference)

Missing HRs indicate lack of significant group-by-sex interaction. *Adjusted for region of residence, socioeconomic status quintile, and Charlson Comorbidity Index. †$P < 0.01$.

Table 4—*Mortality and hospitalization rates and adjusted HR* by sex and early compared with late diabetes diagnosis status*

	Males		Females		Total	
	Early	Late	Early	Late	Early	Late
All-cause mortality						
Rate per 10,000 (*n*)	192.4 (401)	509.4 (1,441)	169.8 (305)	477.5 (1,407)	182.0 (706)	493.1 (2,848)
Unadjusted HR (95% CI)	—	2.37 (2.23–2.52)‡	—	2.68 (2.52–2.85)‡	0.92 (0.85–0.99)†	—
Adjusted HR (95% CI)	—	2.09 (1.97–2.23)‡	—	2.38 (2.23–2.53)‡	0.91 (0.84–0.98)†	—
CVD mortality						
Rate per 10,000 (*n*)	34.7 (43)	120.0 (39)	30.5 (28)	175.1 (49)	32.9 (71)	145.5 (88)
Unadjusted HR (95% CI)	—	3.39 (2.44–4.71)‡	—	7.14 (5.25–9.71)‡	1.07 (0.84–1.37)	—
Adjusted HR (95% CI)	—	3.44 (2.47–4.79)‡	—	6.54 (4.80–8.91)‡	0.99 (0.77–1.28)	—
AMI mortality						
Rate per 10,000 (*n*)	9.0 (18)	42.7 (109)	12.1 (21)	39.5 (109)	10.4 (39)	41.0 (218)
Unadjusted HR (95% CI)	—	—	—	—	0.70 (0.50–0.96)†	2.72 (2.33–3.18)†
Adjusted HR (95% CI)	—	—	—	—	0.70 (0.51–0.97)†	2.34 (1.98–2.76)†
Stroke mortality						
Rate per 10,000 (*n*)	4.5 (9)	26.6 (69)	12.2 (21)	26.5 (72)	8.1 (30)	26.5 (141)
Unadjusted HR (95% CI)	—	—	—	—	0.75 (0.52–1.09)	2.49 (2.06–3.02)‡
Adjusted HR (95% CI)	—	—	—	—	0.74 (0.51–1.08)	2.21 (1.81–2.70)‡
All-cause hospitalization						
Rate per 1,000 (*n*)	168.8 (1,960)	318.0 (3,642)	193.9 (1,798)	301.1 (3,720)	179.9 (3,758)	309.3 (7,362)
Unadjusted HR (95% CI)	1.18 (1.13–1.24)‡	2.05 (1.98–2.12)‡	1.30 (1.23–1.36)‡	1.91 (1.84–1.98)‡	—	—
Adjusted HR (95% CI)	1.17 (1.11–1.23)‡	1.89 (1.81–1.95)‡	1.26 (1.20–1.32)‡	1.75 (1.69–1.82)‡	—	—
CVD hospitalization						
Rate per 1,000 (*n*)	23.4 (277)	49.6 (141)	16.8 (151)	50.5 (126)	20.5 (428)	50.0 (267)
Unadjusted HR (95% CI)	—	3.34 (2.81–3.96)‡	—	5.73 (4.76–6.91)‡	1.70 (1.53–1.88)‡	—
Adjusted HR (95% CI)	—	3.33 (2.80–3.95)‡	—	5.22 (4.31–6.33)‡	1.64 (1.48–1.82)‡	—
AMI hospitalization						
Rate per 1,000 (*n*)	7.0 (142)	11.1 (283)	3.3 (59)	8.5 (238)	5.3 (201)	9.8 (521)
Unadjusted HR (95% CI)	—	1.63 (1.43–1.86)‡	—	2.24 (1.93–2.61)‡	1.14 (0.99–1.32)	—
Adjusted HR (95% CI)	—	1.64 (1.44–1.88)‡	—	2.15 (1.85–2.51)‡	1.27 (1.09–1.48)‡	—
Stroke hospitalization						
Rate per 1,000 (*n*)	2.6 (53)	8.1 (212)	2.6 (46)	6.9 (190)	2.6 (99)	7.5 (402)
Unadjusted HR (95% CI)	—	—	—	—	0.82 (0.67–1.01)	2.05 (1.82–2.29)‡
Adjusted HR (95% CI)	—	—	—	—	0.95 (0.78–1.17)	1.98 (1.76–2.23)‡

Missing HRs indicate lack of significant group-by-sex interaction. *Adjusted for region of residence, socioeconomic status quintile, and Charlson Comorbidity Index. †$P < 0.05$. ‡$P < 0.01$.

levels (29,30). In addition, results from the Newfoundland and Labrador Component of the Canadian Community Health Survey show that females with diabetes are less likely to be using insulin, to have their A1C levels tested, and to be prescribed aspirin and blood cholesterol medication compared with males with diabetes (31).

Barrett-Connor et al. (32) suggested that higher cardiovascular mortality risk observed in females with diabetes is a result of the larger survival advantage females have when diabetes is not present. This could explain the CVD and AMI mortality results found in this study. However, this does not explain the results for all-cause mortality and CVD hospitalizations because males had higher rates than females whether diabetes was present or not. In addition, risk of all-cause mortality and CVD hospitalizations were higher for females than for males.

Results from randomized controlled trials have found that the risk of microvascular complications can be reduced with intensive glucose control; however, the effect on macrovascular complications have been less clear (8,33). The UKPDS, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), Veterans Affairs Diabetes Trial (VADT), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) are randomized controlled trials that have been conducted to compare the effect of intensive glucose control with the effect of standard glucose control on CVD mortality and hospitalizations in patients with diabetes. These trials found that CVD events can be reduced with intensive glucose control; however, no significant effect on CVD mortality or all-cause mortality was found (8,33–36). In fact, the ACCORD trial was stopped early because of higher mortality in the intensive glucose control group compared with the standard control group (36). Moreover, the ADVANCE, VADT, and ACCORD trials showed higher rates of hypoglycemia and weight gain in the group that was treated more intensively (34–36).

A recent meta-analysis of randomized controlled trials found limited benefits of intensive glucose-lowering treatments on all-cause and CVD mortality and concluded that the harm associated with hypoglycemia may offset any potential benefits of intense glucose control (37). Alternatively, the UKPDS 10-year posttrial follow-up found that significant reduction in microvascular risk persisted, and significant reductions in myocardial infarction and all-cause mortality were seen in the intensive control group during follow-up. The authors used the term "legacy effect" to describe the continued benefit of intensive treatment (38).

Patients in the ADVANCE, VADT, and ACCORD trials had diabetes for a number of years before entering the trial, whereas patients in the UKPDS had newly diagnosed diabetes. This suggests that the same A1C target and treatment plan should not be applied to all patients with diabetes. Perhaps the focus should be not only on glucose control but, rather, on all CVD risk factors. The Canadian Diabetes Association Clinical Practice Guidelines provide recommended targets for glycemic control and suggest that treatment strategies should be individualized, with consideration given to presence of risk factors. Early and aggressive treatment has been suggested for patients with a shorter duration and without a history of CVD, whereas less aggressive treatment may be suitable for older patients with a longer duration and a history of CVD (39). However, this recommendation does not take into account the greater CVD risk that females with diabetes have. Perhaps a better approach would be to consider different treatment plans based on sex and timing of diabetes diagnosis.

Limitations

There are several strengths and limitations in this study. First, this was a large population-based cohort study with long follow-up time. In addition, multiple outcomes were studied and administrative data were used to identify hospital separations and deaths. However, there are also several limitations that need to be addressed. First, this was a retrospective cohort study and therefore not as strong as a prospective or intervention study. The CCDSS diabetes case definition does not differentiate between type 1 and type 2 diabetes. However, because most adults have type 2 diabetes diagnosed (1), it is unlikely to have a major impact on the results. Furthermore, the CCDSS diabetes case definition uses physician claims data. In Newfoundland and Labrador, one-third of the physicians in the province are paid on a salary basis. These physicians are not required to submit medical claims; therefore, information regarding these visits is not captured. As a result, the sample of diabetes cases may be less than the true number of incident cases. Also, some misclassification could have occurred because individuals with diabetes could have been classified as not having diabetes because a salaried physician provided most of their care. This also has the potential to impact findings by place of residence (urban or rural) because rural areas are largely serviced by salaried physicians.

Individuals who were hospitalized for CVD, AMI, or stoke before 1994 or 1995 cannot be identified. However, a washout period from 1 January 1995 to 31 March 1997 was applied to exclude those who had CVD, AMI, or a stroke event before the study start date and to help ensure that only newly diagnosed cases of diabetes were included.

Also, information regarding CVD risk factors was not available and thus could not be controlled for in the analysis. Finally, place of residence used in this study was the place of residence at the beginning of the study period. Movement from a rural to an urban region and vice versa throughout the 10-year study period could have occurred.

Conclusion

The results of this study show that females with diabetes have a greater risk of mortality than males with diabetes. CVD has a greater impact on females than males with diabetes, especially when diabetes is diagnosed at a later stage. Different management strategies should be considered for males and females and for those with early and late diagnoses of diabetes.

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M.M.R. conceptualized the study, acquired the data, performed data analysis, interpreted the results, and wrote the manuscript. P.P.W. contributed to the data analysis plan, contributed to discussion, and reviewed and edited the manuscript. M.M.R. is the guarantor of this work and, as such, had access to all study data and takes responsibility for the data analysis and contents of the article.

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