A Contemporary Estimate of Total Mortality and Cardiovascular Disease Risk in Young Adults With Type 1 Diabetes: The Pittsburgh Epidemiology of Diabetes Complications Study

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OBJECTIVE

The degree to which mortality and cardiovascular disease (CVD) incidence remains elevated in young U.S. adults with type 1 diabetes (T1DM) is unclear. We determined contemporary rates for adults <45 years old with long-standing, childhood-onset T1DM from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study.

RESEARCH DESIGN AND METHODS

Members of the EDC Study cohort <45 years old during the 1996–2012 follow-up period (*n* = 502) were studied. Mortality and CVD rates were calculated for those aged 30–39 and 40–44 years. Data from the background Allegheny County, Pennsylvania, population were used to calculate age- and sex-matched standardized mortality (SMR) and incidence rate ratios (IRR).

RESULTS

In both age groups, the SMR for total mortality was ∼5 (95% CIs: 30–39-year-olds, 2.8, 7.2; 40–44-year-olds, 3.4, 7.8). CVD mortality SMRs ranged from 19 (95% CI 11, 32) to 33 (95% CI 17, 59). Hospitalized CVD IRR was ∼8 (95% CIs: 30–39-year-olds, 2.5, 18.9; 40–44-year-olds, 4.5, 12.8); revascularization procedures account for much of the increased risk. For all outcomes, the relative risk was larger in women. Participants aged 30–39 years had 6.3% (95% CI 3.8, 9.8) absolute 10-year CVD risk, approaching the American College of Cardiology/American Heart Association–recommended cut point of 7.5% for initiation of statin therapy in older adults.

CONCLUSIONS

Total and CVD mortality and hospitalized CVD are all significantly increased in this contemporary U.S. cohort of young adults with long-standing T1DM. These findings support more aggressive risk factor management in T1DM, especially among women.

Type 1 diabetes (T1DM) is consistently associated with increased mortality, though the excess risk may have recently decreased (1). Large differences in T1DM mortality are seen internationally, with in general a smaller excess mortality in Europe than in the U.S. (1). Excess mortality also differs by sex, with women having greater excess mortality than men (2). Recent reports from the Scottish Registry Linkage Study and the Swedish

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National Diabetes Register both show that T1DM continues to be associated with an increased mortality across all age groups, with younger women being at particularly high risk (3,4). Furthermore, another report from Australia suggests that younger patients (<40 years) with T1DM are not experiencing a decline in diabetes mortality, in contrast to other causes and age groups (5). Contemporary data from the U.S. focused on young adults with long-duration T1DM are however lacking, though the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study shows lower all-cause mortality with intensive diabetes therapy compared with conventional therapy (6).

Atherosclerotic cardiovascular disease (CVD), including coronary artery disease (CAD), is a major complication of T1DM (7). During the 1980s, in the U.S., CVD risk was much greater in T1DM compared with the general population (8,9), a finding that has persisted for CVD mortality (10,11), despite data from the DCCT/EDIC study showing a reduction in CVD incidence with intensive insulin therapy (12). The Scottish Registry Linkage Study now concludes that although the relative risk for CVD mortality associated with T1DM has declined, there remains a significantly elevated risk compared with the general population (3). The new American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines have proposed a 10-year CVD risk threshold of ≥7.5% for statin therapy for those aged 40–75 years with an LDL cholesterol >70 mg/dL (13), but there are no clear guidelines for patients with long-duration childhood-onset T1DM aged <40 years.

As there are no reports from the U.S. quantifying contemporary mortality and CVD risk in young adults with long-duration T1DM, our objective was to determine such rates for individuals <45 years old with long-standing, childhood-onset T1DM from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. We thus examined rates in the EDC cohort for the years 1996–2012 and compared these to the age-matched background population in Allegheny County, Pennsylvania.

RESEARCH DESIGN AND METHODS

Study Design and Population

The Pittsburgh EDC Study is a prospective cohort study of childhood-onset (<17 years old) T1DM. All participants were diagnosed, or seen within 1 year of diagnosis, at Children's Hospital of Pittsburgh between 1950 and 1980. The cohort has been described in detail elsewhere (14,15). In brief, participants have been followed since 1986–1988, initially with biennial examinations for 10 years and thereafter with biennial questionnaires and further examinations at 18 and 25 years postbaseline. The current analyses were restricted to EDC participants who were <45 years old during the 1 January 1996 to 31 December 2012 follow-up period (n = 502). Research protocols were approved by the University of Pittsburgh institutional review board, and all participants provided written informed consent.

Ascertainment of Mortality and Cardiovascular Outcomes

In the EDC Study, mortality was ascertained using medical records, death certificates, autopsy reports, and/or interview with next of kin. Causes of death were classified using all available information according to the Diabetes Epidemiology Research International system (16) by a committee of physicians. CVD mortality was defined as fatal CAD, myocardial infarction, or stroke as either the primary or a contributing cause of death. Incidence of nonfatal CVD events (i.e., myocardial infarction, hospitalized coronary artery bypass graft, hospitalized angioplasty, and stroke) was self-reported by the study participant and confirmed by medical records.

Mortality data for the 1996–2012 age-matched background Allegheny County, Pennsylvania, population were obtained through the Allegheny County Health Department, provided by the Division of Health Informatics, Pennsylvania Department of Health (the Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions). The data were abstracted using the Pennsylvania Department of Health Epidemiologic Query and Mapping System by selecting total deaths and, separately, coronary heart disease deaths (ICD-10/ICD-9: I11, I20–I25, I516/402, 410–414, and 4292) and stroke deaths (ICD-10/ICD-9: I60–I69/430–438). CVD hospitalization data for the age-matched background Allegheny County, Pennsylvania, population were only available for the years 2004–2010, abstracted from Pennsylvania Health Care Cost Containment Council data, and obtained through the Allegheny County Health Department.

Risk Factor Assessment

All risk factor data were collected at the 1996–1998 baseline for these analyses. HbA_1, lipids, and lipoproteins were measured on fasting blood samples. HbA_1 values were converted to DCCT-aligned HbA_{1c} using a regression equation derived from duplicate assays (DCCT HbA_{1c} = 0.14 + 0.83[EDC HbA_1]) (17). Serum total cholesterol and triglycerides were determined enzymatically (18,19), and HDL cholesterol was determined using a modified precipitation technique (20,21). LDL cholesterol levels were calculated from the measurements of total cholesterol, triglycerides, and HDL cholesterol using the Friedwald equation (22). Use of lipid-lowering therapy was self-reported. Blood pressure readings were taken according to the Hypertension Detection and Follow-Up protocol (23), and hypertension was defined as having blood pressure >140/90 or self-reported use of blood pressure–lowering therapy. Urinary albumin was measured by immunonephelometry (24). Albumin excretion rate (AER) was calculated for each of three timed urine samples (24-h, overnight, and 4-h collections obtained over a 2-week period); the median of the three AERs was used in analyses. Current smoking status was self-reported.

Statistical Analyses

Analyses to quantify total mortality, CVD mortality, and CVD event rates included EDC data from the complete follow-up period between 1996 and 2012. Crude rates were calculated for the age groups 30–39 and 40–44 years as the total number of events per 100,000 person-years with 95% CIs. Outcomes were defined as total mortality, CVD mortality (i.e., fatal CAD or stroke), total CVD (i.e., fatal CAD or stroke, myocardial infarction, nonfatal stroke, or hospitalized coronary artery bypass graft or angioplasty), ACC/AHA CVD (i.e., fatal CAD or stroke, nonfatal myocardial infarction, or nonfatal stroke), and total CAD (i.e., total CVD excluding fatal/nonfatal stroke).

To quantify the excess risk of total mortality, CVD mortality, and CVD incidence in the EDC cohort, the expected number of events for each age group

was calculated by multiplying the person-years at risk in the EDC cohort by the mortality and CVD incidence rates in the background Allegheny County population. Standardized mortality (SMR) and incidence rate ratios (IRR) were calculated, as appropriate, as the ratio of the observed number of events in EDC to the calculated expected number of events. The 95% CIs were calculated based on a Poisson distribution. Due to the hospitalization data for the background Allegheny County population being restricted to 2004 to 2010, comparisons to the general population were carried out by restricting the EDC data to participants who were <45 years old between 2004 and 2010 and performing a comparison of their CVD rates to the Allegheny County data. To address the possibility of survivor bias in EDC, a sensitivity analysis was performed in which all mortality and CVD events occurring between ages 30 and 44 ascertained during the complete 1986–2012 EDC Study follow-up were included. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and the Open Source Epidemiologic Statistics for Public Health calculators (25).

RESULTS

Of the 391 participants who contributed follow-up between ages 30 and 39, 6.6% (*n* = 26) had at least one CVD event, and 4.3% (*n* = 17) died during the 1996–2012 follow-up period. Of the 474 participants contributing follow-up between ages 40 and 44, 9.3% (*n* = 44) had at least one CVD event, and 4.9% (*n* = 23) died. In both age groups, those who had CVD events or died were at baseline (Table 1) more likely to have hypertension, be using blood pressure–lowering therapy, and have higher AER. Current smoking was associated with CVD in those aged 30–39 years and mortality in those aged 40–44 years. LDL cholesterol was associated with CVD in those aged 30–39 years, but not in those 40–44 years old. HbA_{1c} did not differ in either age group by mortality or CVD status.

Total and CVD Mortality

Age-matched comparisons of total and CVD mortality between the EDC cohort and the background Allegheny County population are presented in Table 2. Total mortality was 4.6 times higher than background in the 30–39-year age group (SMR 4.6 [95% CI 2.8, 7.2]) and 5.3 times higher in the 40–44-year age group (SMR 5.3 [95% CI 3.4, 7.8]). In both age groups, the relative increase in mortality was greater in women (Table 2). CVD mortality showed greater relative increases than total mortality (aged 30–39: SMR 33.3 [95% CI 16.9, 59.4]; aged 40–44: SMR 19.4 [95% CI 11.1, 31.9]), and women again had greater relative increases.

CVD Incidence Rates

CVD incidence rates for EDC participants are shown in Table 3. Using the total CVD definition, which includes hospitalized revascularization procedures, young adults aged 30–39 years had a CVD rate of 961 events/100,000 person-years (95% CI 643, 1,385), and those aged 40–44 years had a rate of 2,322 events/100,000 person-years (95% CI 1,713, 3,076). Using the ACC/AHA definition of CVD, which does not include revascularization procedures, the rates decrease to 628 events/100,000 person-years (95% CI 379, 984) in those aged 30–39 years and 1,478 events/100,000 person-years (95% CI 1,003, 2,100) in those aged 40–44 years. For CAD, including hospitalized

Table 1—Baseline (1996–1998) characteristics by 1996–2012 total mortality and CVD event status

Age group*	Characteristic	Overall	Died during follow-up	Alive through follow-up	CVD event	No CVD
30–39 years	Total *n* (*n* with clinical data)	391 (260)	17 (10)	374 (252)	26 (14)	365 (246)
	Diabetes duration (years)	25.1 (5.0)	24.8 (5.2)	25.1 (5.0)	25.3 (5.5)	25.1 (5.0)
	Female sex†	49.4 (193)	66.7 (12)	48.5 (181)	50.0 (11)	49.3 (182)
	HbA_{1c} (%)	8.4 (1.4)	8.5 (0.8)	8.4 (1.5)	9.0 (1.5)	8.4 (1.4)
	HbA_{1c} (mmol/mol)	68.5 (15.6)	69.0 (9.2)	68.0 (16.2)	74.8 (16.4)	68.2 (15.6)
	LDL cholesterol (mg/dL)	116.4 (31.2)	122.0 (35.4)	116.2 (31.1)	132.9 (37.1)	115.3 (30.6)
	HDL cholesterol (mg/dL)	53.3 (13.6)	61.0 (22.6)	53.0 (13.1)	50.9 (14.5)	53.4 (13.6)
	Triglycerides (mg/dL)‡	94 (66–144)	94 (73–180)	94 (66–143)	139 (82–180)	93 (66–132)
	Lipid-lowering therapy†	5.1 (19)	13.3 (2)	4.8 (17)	14.3(3)	4.6 (16)
	Hypertension†	25.8 (76)	50.0 (9)	24.6 (69)	52.6 (11)	23.9 (66)
	Blood pressure–lowering therapy†	18.6 (68)	39.0 (7)	17.7 (62)	47.6 (10)	16.9 (58)
	AER (μg/min)‡	11.5 (5.8–77.4)	310.6 (209–1,717)	10.7 (5.6–56.8)	296.7 (18.9–1,369)	10.5 (5.6–50.2)
	Current smoker†	19.8 (73)	25.0 (4)	19.6 (69)	38.1 (8)	18.7 (65)
40–44 years	Total *n* (*n* with clinical data)	474 (318)	23 (9)	451 (310)	44 (25)	430 (293)
	Diabetes duration (years)	27.5 (6.2)	29.0 (5.7)	27.4 (6.2)	28.3 (5.9)	27.4 (6.3)
	Female sex†	49.4 (234)	41.7 (10)	49.8 (224)	40.5 (17)	50.2 (217)
	HbA_{1c} (%)	8.4 (1.5)	8.7 (1.6)	8.4 (1.5)	8.6 (2.1)	8.3 (1.4)
	HbA_{1c} (mmol/mol)	67.7 (16.1)	71.8 (17.1)	67.6 (16.0)	70.4 (23.1)	67.4 (15.3)
	LDL cholesterol (mg/dL)	118.2 (31.2)	109.5 (28.6)	118.4 (31.3)	122.9 (31.0)	117.8 (31.2)
	HDL cholesterol (mg/dL)	53.8 (14.0)	61.1 (25.5)	53.6 (13.5)	55.5 (17.3)	53.7 (13.7)
	Triglycerides (mg/dL)‡	90 (66–129)	114 (73–125)	89 (66–129.5)	99.5 (76–154)	89 (66–126)
	Lipid-lowering therapy†	5.8 (26)	15.8 (3)	5.3 (23)	10.5 (4)	5.3 (22)
	Hypertension†	31.7 (115)	62.5 (10)	30.3 (105)	50.0 (17)	29.8 (98)
	Blood pressure–lowering therapy†	23.0 (102)	47.4 (9)	21.9 (93)	42.1 (16)	21.2 (86)
	AER (μg/min)‡	12.5 (5.7–57.2)	81.8 (34.8–527.8)	11.0 (5.6–51.6)	42.0 (14.4–201.3)	10.7 (5.6–50.9)
	Current smoker†	17.3 (77)	42.1 (8)	16.2 (69)	25.6 (10)	16.5 (67)

Data are mean (SD) unless noted. *Participant included in an age group if contributed any follow-up within the age range; †data are % (*n*); ‡data are median (interquartile range).

Table 2—Total and CVD mortality rates by age and sex in the EDC Study and background Allegheny County population (1996–2012)

		EDC Study cohort (1996–2012)			Allegheny County (1996–2012)			
Event	Age and sex	Events	Person-years	Rate per 100,000 person-years (95% CI)	Events	Person-years	Rate per 100,000 person-years (95% CI)	SMR (95% CI)
Total mortality	30–39	17	2,705	628 (379, 984)	3,817	2,765,085	138 (134, 142)	4.6 (2.8, 7.2)
	Men	6	1,352	444 (180, 920)	2,537	1,354,618	187 (180, 195)	2.4 (0.97, 5.0)
	Women	11	1,353	813 (428, 1,409)	1,280	1,410,467	91 (86, 96)	9.2 (4.8, 15.9)
	40–44	23	1,895	1,214 (790, 1,787)	3,590	1,551,328	231 (224, 239)	5.3 (3.4, 7.8)
	Men	13	983	1,322 (738, 2,195)	2,266	750,841	302 (289, 314)	3.3 (1.8, 5.4)
	Women	10	912	1,096 (558, 1,946)	1,324	800,487	165 (157, 174)	6.7 (3.4, 11.9)
CVD mortality*	30–39	10	2,705	370 (188, 658)	312	2,765,085	11 (10, 13)	33.3 (16.9, 59.4)
	Men	4	1,352	296 (94, 712)	213	1,354,618	16 (14, 18)	18.5 (5.9, 44.7)
	Women	6	1,353	443 (180, 920)	99	1,410,467	7 (6, 8)	63.4 (25.7, 131.8)
	40–44	14	1,895	739 (421, 1,207)	583	1,551,328	38 (35, 41)	19.4 (11.1, 31.9)
	Men	8	983	814 (379, 1,539)	412	750,841	55 (50, 60)	14.8 (6.9, 28.1)
	Women	6	912	658 (267, 1,363)	171	800,487	21 (18, 25)	31.6 (12.8, 65.7)

*Fatal CAD or stroke.

revascularizations, those aged 30–39 years had a rate of 850/100,000 person-years (95% CI 553, 1,253), whereas the rate for those aged 40–44 years was 2,005/100,000 person-years (95% CI 1,443, 2,714).

Age-matched IRRs of CVD rates between the EDC cohort and the background Allegheny County population during 2004–2010 are presented in Fig. 1 (the absolute CVD rates are presented in Supplementary Table 1). EDC participants aged 30–39 and 40–44 years had a total CVD rate 7.8 times higher than background (95% CIs 2.5, 18.9 and 4.5, 12.8, respectively). If revascularization procedures are excluded, using the ACC/AHA CVD definition, the rate for EDC participants aged 30–39 years decreases and is no longer significantly increased over background (relative risk [RR] 4.9 [95% CI 0.8, 16.3]). For those aged 40–44 years, using the ACC/AHA CVD definition reduced the rate to 653/100,000 person-years (95% CI 239, 1,441), 4.6 times higher than background (95% CI 1.7, 10.3). For CAD alone, EDC participants aged 30–39 years had 12-fold higher risk than background (RR 12.1 [3.8, 29.2]), whereas those aged 40–44 years had eightfold higher risk (RR 8.4 [4.4, 14.6]). For all definitions and both age groups, women in the EDC cohort had higher excess risk over background compared with men, despite men having higher absolute risk.

Table 3—CVD incidence rates by age and sex in the EDC Study (1996–2012)

Event	Age (years) and sex	Events	Person-years	Rate per 100,000 person-years (95% CI)
Total CVD*	30–39	26	2,705	961 (643, 1,385)
	Men	14	1,352	1,036 (591, 1,690)
	Women	12	1,353	887 (481, 1,503)
	40–44	44	1,895	2,322 (1,713, 3,076)
	Men	26	983	2,645 (1,772, 3,797)
	Women	18	912	1,974 (1,211, 3,041)
ACC/AHA CVD†	30–39	17	2,705	628 (379, 984)
	Men	8	1,352	592 (275, 1,121)
	Women	9	1,353	665 (325, 1,217)
	40–44	28	1,895	1,478 (1,003, 2,100)
	Men	18	983	1,831 (1,123, 2,823)
	Women	10	912	1,096 (558, 1,946)
CAD‡	30–39	23	2,705	850 (553, 1,253)
	Men	14	1,352	1,036 (591, 1,690)
	Women	9	1,353	665 (325, 1,217)
	40–44	38	1,895	2,005 (1,443, 2,714)
	Men	23	983	2,340 (1,525, 3,435)
	Women	15	912	1,645 (959, 2,638)

*Fatal CAD or stroke, nonfatal myocardial infarction, nonfatal stroke, or hospitalized coronary artery bypass graft or angioplasty; †ACC/AHA atherosclerotic CVD definition (fatal CAD or stroke, nonfatal myocardial infarction, or nonfatal stroke); ‡CAD (fatal CAD, nonfatal myocardial infarction, or hospitalized coronary artery bypass graft or angioplasty).

Sensitivity Analysis

When the estimates for total mortality and total CVD events were repeated including the entire 1986–2012 follow-up, EDC participants aged 30–39 years had 10-fold greater total mortality (95% CI 7.2, 13.5) and 22-fold greater CVD incidence (17.1, 28.2) than background. In those aged 40–44, EDC participants had ninefold higher mortality (6.3, 11.7) and 13-fold greater CVD incidence (10.0, 16.1) than background.

CONCLUSIONS

These results demonstrate that for a contemporary cohort of young adults <45 years old with long-duration T1DM from the Pittsburgh EDC Study, total mortality, CVD mortality, and hospitalized CVD events remain significantly increased compared with the age-matched background population. Total mortality was increased approximately fivefold, whereas CVD mortality was increased 20–30-fold. Hospitalized CVD events were increased eightfold, with revascularization procedures accounting for much of the increased risk. If revascularization procedures are excluded, CVD risk was increased four- to fivefold. For CAD alone, the increase in risk was even larger than for CVD, at 8–11 times that of background. For all outcomes, the relative risk in women was larger than for men.

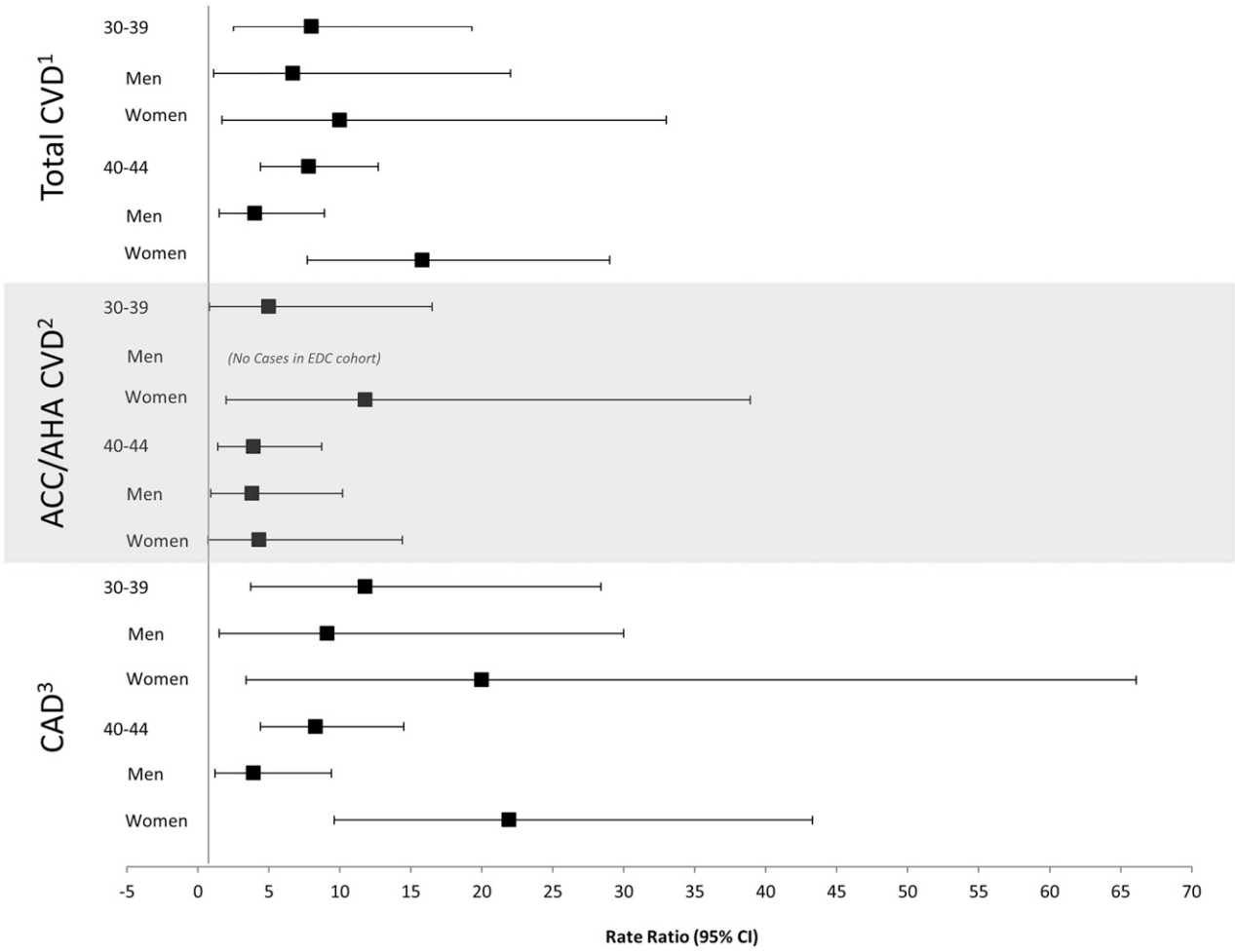

Figure 1—IRR for the EDC Study cohort compared with the background Allegheny County population, 2004–2010. [1]Fatal CAD or stroke, nonfatal myocardial infarction, nonfatal stroke, or hospitalized coronary artery bypass graft or angioplasty; [2]ACC/AHA atherosclerotic CVD definition (fatal CAD or stroke, nonfatal myocardial infarction, or nonfatal stroke); [3]CAD (fatal CAD, nonfatal myocardial infarction, or hospitalized coronary artery bypass graft or angioplasty).

Relative Risk of Mortality

The excess risk of mortality associated with T1DM in the current analyses is consistent with prior reports. A systematic review of 23 reports on population-based T1DM cohorts concluded that T1DM is associated with excess mortality worldwide (1). The magnitude of excess risk varied widely, from none in a small cohort from Iceland (26) to an estimated 8.5-fold excess in a cohort from Cuba (27). In a 2010 report from Allegheny County, Pennsylvania, sixfold excess mortality was observed by 20 years of diabetes duration (28).

More recently, the Scottish Registry Linkage Study reported age-specific mortality and CVD rates (3). Total mortality for men aged 30–39 years with T1DM was 3.4 times that of the general population, whereas it was 5.2 times that of the general population for women in the same age group. The SMR for total mortality in women 30–39 years old was markedly higher in this study in the EDC cohort, at 9.2. In the Scottish report, the T1DM population aged 40–49 years had 4 and 4.7 times higher mortality than the general population for men and women, respectively. These increases were again lower than seen in the EDC cohort, but as our data examined 40–44-year-olds, these results are not directly comparable. Importantly, at any given age, the EDC cohort represents a longer duration of diabetes than the Scottish Registry Linkage Study, which includes adult-onset cases of T1DM, thus yielding a median T1DM duration of 17.5 years that at baseline is significantly shorter than that of the exclusively childhood-onset T1DM EDC cohort (26.6 years). This difference in the length of exposure to T1DM may explain the lower excess mortality seen in the Scottish study.

Another recent report, from the Swedish National Diabetes Register, showed that even for patients with T1DM who had on-target glycemic control (for the past 8 years), both total and cardiovascular mortality were increased compared with the general population (4). When examined by age and sex, regardless of glycemic control, the study reported that men 18–49 years old had three- to fourfold greater total mortality than the general population, whereas women in the same age range had more than fourfold greater total mortality. Relative increases were larger for cardiovascular deaths, especially for women, in whom CVD mortality was more than seven times that of the general population. These relative increases are again lower than in the EDC cohort, particularly for CVD mortality. The Swedish National Diabetes Register also includes adult-onset cases of

T1DM and has an average diabetes duration of 20.4 years, again shorter than that of the EDC cohort, which may partially explain the lower excess mortality. In a separate report on data from the Swedish National Diabetes Register, life expectancy between the time periods of 2002–2006 and 2007–2011 was found to have increased by ~2 years in men but was unchanged in women (29).

In a population-based study from Australia during two time periods, 1997–2003 and 2004–2010, T1DM was also consistently associated with increased total mortality across both sexes and all age groups, except in children <10 years old (30). For men 30–39 years old, the SMR was 4.1 in both time periods and 4.7 and 4.4, respectively, for those aged 40–49 years in each time period. For women, SMRs were 4.6 and 5 in those aged 30–39 years and 4.7 and 4.2 in those aged 40–49 years. The current SMRs for total mortality in the EDC cohort are comparable to the Australian report for men, but are markedly higher in women. A 2010 report from the Allegheny County T1DM Registry also showed a greater excess mortality in women with T1DM (28). The higher relative mortality observed in women in the EDC and the Allegheny County T1DM Registry compared with the other populations discussed may reflect differences in access to health care across countries, but this hypothesis is difficult to assess. A higher relative risk for women was also noted in a recent meta-analysis of 26 T1DM studies, in which the pooled excess risk of all-cause mortality associated with T1DM was 37% higher in women (2). Interestingly, in a DCCT-eligible subgroup of EDC participants, the mortality rate of 363 out of 100,000 (95% CI 202, 604) is very similar to the rate of 346 out of 100,000 (95% CI 272, 440) observed in the DCCT conventional treatment arm (6), lending support to the generalizability of the DCCT data in the U.S.

Relative Risk of CVD

Our finding that young adults with T1DM remain at increased risk of CVD is also consistent with other recent reports. In the Scottish Registry Linkage Study, men and women with T1DM aged 20–39 years had CVD risk 4.8 and 5.5 times that of the general population, respectively (3). The sex difference was larger for those aged 40–49 years, in whom men with T1DM had 3.1 times the risk of the general population, whereas women with T1DM had more than fivefold excess risk. The sex difference in the EDC cohort supports the finding that women with T1DM have greater excess CVD risk than men, but the excess was larger than seen in the Scottish study (3). The aforementioned meta-analysis reported that the sex difference was greater for CAD incidence than for mortality (2), which is also consistent with our findings. In the pooled results from the meta-analysis, women with T1DM were >13 times more likely to have a CAD event than women without diabetes, whereas men with T1DM were ~6 times more likely (2). It has been suggested that the effect of hyperglycemia and diabetes on vascular risk is greater in women than in men, possibly due to poorer glycemic control in women (2,31). However, Colhoun et al. (32) also reported that the greater excess risk in women with T1DM was not explained by a worse CVD risk factor profile for women compared with men. The relative excess being greater in women than men also likely reflects CVD being rarer in women in this age group in the general population. In the EDC Study, depressive symptomatology was found to be associated with CAD incidence in women, but not in men, suggesting that nontraditional risk factors may also help explain sex differences (33).

Absolute Risk of CVD

Despite this consistent evidence that young adults with T1DM are at increased risk of CVD mortality and morbidity, treatment guidelines are based on extrapolations from data on type 2 diabetes and the general population due to a lack of trial data in T1DM. The validity of using these extrapolations has been questioned (34). The 2013 ACC/AHA guidelines recommend high-intensity statin therapy in individuals between ages 40 and 75 years with diabetes and ≥7.5% estimated 10-year risk of CVD (13). In these analyses of the EDC cohort, young adults 40–44 years old had a 10-year ACC/AHA definition CVD risk of 14.8%, greatly exceeding this limit. The guidelines state that, in individuals with diabetes who are <40 years, the decision to begin statin therapy should be individualized (13). In this study, in the EDC cohort, young adults 30–39 years old had a 6.3% 10-year CVD risk (ACC/AHA definition), which approaches the recommended cut point of 7.5%. However, three additional CVD events occurred in the 30–39-year-old age group prior to the 1996 baseline used in these analyses and ~5% of 30–39-year-olds in the EDC were already on lipid-lowering medication at baseline (Table 1), with the proportion rising to 20% by 2012 (data not shown). Thus, it is likely that the 10-year CVD risk would exceed 7.5% if it were possible to include the prevalent cases and account for existing lipid-lowering therapy. Additionally, if hospitalized revascularization procedures are included in the CVD definition, the 10-year risk in 30–39-year-olds increases to 9.6%. These results suggest that CVD risk in young adults with T1DM duration >20 years who are 30–39 years old is most likely high enough to merit the use of statin therapy, given current ACC/AHA thresholds. Furthermore, a recent report has suggested that an individualized approach to statin therapy may be more appropriate, which would further justify statin use in this group of patients with T1DM (35).

Risk Factors

In both of the age groups studied, baseline hypertension, AER, and smoking rates were higher at baseline in those who died and those who developed CVD versus those who did not. Interestingly, LDL cholesterol was higher in the 30–39-year-olds who developed CVD compared with the noncases, but in the 40–44-year-olds, LDL cholesterol did not differ from noncases. Unfortunately, a full analysis of risk factors is not possible in this report owing to space and the lack of comparable data in the Allegheny County population, but risk factors have been reviewed previously (7) and more recently reported from the DCCT/EDIC study, in which updated weighted-mean HbA_{1c} was found to be a strong predictor of CVD incidence, second only to age, whereas LDL cholesterol was a significant but weaker predictor (36). These results stress the need for both intensive glycemic control and lipid-lowering therapy, to prevent CVD events.

Strengths and Limitations

A limitation of these analyses is therefore the failure to consider risk factors and their trajectories over time. However, our objective in this study was to quantify

mortality and CVD risks in young adults from the EDC Study overall, primarily to address the issue of appropriateness of statin therapy. Subsequent risk factor levels would not be available to clinicians when determining treatment regimens. Furthermore, the current guidelines are based on absolute 10-year CVD risk rather than cholesterol goals.

Another limitation is the small number of events observed in the EDC Study and the resulting wide CIs around the risk estimates, particularly for CVD mortality and hospitalized events. However, using the lower limit of the CIs as the most conservative scenario, the risk in this T1DM cohort is still dramatically increased compared with background. These data also represent participants with a range of prior risk factor profiles and diabetes treatment experiences. This issue of changing treatment availability (i.e., increasing availability of HbA_{1c} and self-monitoring of blood glucose) is, however, largely addressed by examining young adults <45 years old in a contemporary period of 1996–2012, such that all follow-up occurred after the results of the DCCT were adopted in clinical practice, and the vast majority of prior treatment was in the modern era. Thus, this is an accurate representation of the clinical population physicians are currently treating and should increase the generalizability of these results. Another limitation is the potential for "survivor bias" due to deaths occurring prior to follow-up. This issue may lead to an underestimation of the CVD risk of the EDC cohort, as the highest-risk participants may have died prior to the beginning of follow-up. We have attempted to assess this possibility by performing a sensitivity analysis. The resulting estimates provide an upper limit to the excess mortality and CVD risk in these young adults. A further limitation of the background population data is the restricted availability of CVD hospitalization data to 2004–2010 and the lack of other data surrounding the death like hospital records and next of kin interviews. Also, using the available data set from Allegheny County, it is not possible to identify which individuals have T1DM, which, in addition to the EDC participants who are already using lipid-lowering therapy, leads to a potential underestimation of the relative increased risk of the EDC cohort. The EDC is a hospital-based cohort from southwestern Pennsylvania, which may restrict the generalizability of these results. However, it has previously been shown that the epidemiologic characteristics (14) and the mortality experience (37) in the hospital-based EDC cohort closely reflect that of the population-based Allegheny County T1DM cohort for participants who were diagnosed during the same period.

Finally, the strengths include the Pittsburgh EDC being a well-characterized cohort with ~30 years of prospective follow-up to date. EDC deaths and CVD events were verified using death certificates, interviews with next of kin, autopsy reports, and medical records and classified by a committee of physicians using all available information.

Conclusion

Total mortality, CVD mortality, and hospitalized CVD events remain significantly increased in this U.S. contemporary cohort of young adults <45 years old with long-duration T1DM compared with the background population. As has been consistently demonstrated across international studies, the relative increase in risk is greater for women than for men. These findings support the need for more aggressive CVD risk-factor management, including statin therapy for young adults with long-standing T1DM.

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