All-Cause Mortality Trends in a Large Population-Based Cohort With Long-Standing Childhood-Onset Type 1 Diabetes

The Allegheny County Type 1 Diabetes Registry

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OBJECTIVE — Although management of type 1 diabetes improved dramatically in the 1980s, the effect on mortality is not clear.

RESEARCH DESIGN AND METHODS — We report trends in 30-year mortality using the Allegheny County (Pennsylvania) childhood-onset (age <18 years) type 1 diabetes registry (n = 1,075) with diagnosis from 1965–1979, by dividing the cohort into three diagnosis year cohorts (1965–1969, 1970–1974, and 1975–1979). Local (Allegheny County) mortality data were used to calculate standardized mortality ratios (SMRs).

RESULTS — As of 1 January 2008, vital status was ascertained for 97.0% of participants (n = 1,043) when mean age ± SD and duration of diabetes were 42.8 ± 8.0 and 32.0 ± 7.6 years, respectively. The 279 deaths (26.0%) observed were 7 times higher than expected (SMR 6.9 [95% CI 6.1–7.7]). An improving trend in SMR was seen by diagnosis cohort at 30 years of diabetes duration (9.3 [7.2–11.3], 7.5 [5.8–9.2], and 5.6 [4.0–7.2] for 1965–1969, 1970–1974, and 1975–1979, respectively). Although no sex difference in survival was observed (P = 0.27), female diabetic patients were 13 times more likely to die than age-matched women in the general population (SMR 13.2 [10.7–15.7]), much higher than the SMR for men (5.0 [4.0–6.0]). Conversely, whereas 30-year survival was significantly lower in African Americans than in Caucasians (57.2 vs. 82.7%, respectively; P < 0.001), no differences in SMR were seen by race.

CONCLUSIONS — Although survival has clearly improved, those with diabetes diagnosed most recently (1975–1979) still had a mortality rate 5.6 times higher than that seen in the general population, revealing a continuing need for improvements in treatment and care, particularly for women and African Americans with type 1 diabetes.

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Type 1 diabetes is known to be associated with an increased risk of mortality compared with that for the general population. Type 1 diabetes leads to hyperglycemia, which is linked to a number of acute (e.g., diabetic ketoacidosis) and chronic (e.g., diabetic nephropathy and cardiovascular disease) complications (1). With the advent of blood glucose self-monitoring, A1C testing, and use of ACE inhibitors, treatment for type 1 diabetes improved tremendously during the 1980s and 1990s (2–4). Despite these improvements, however, type 1 diabetes complications still frequently lead to premature mortality. Recent reports from Western Europe have shown long-term mortality (≥15 years follow-up) in type 1 diabetes to be 3–4 times that of the general population (5,6); however, long-term population-based data on type 1 diabetes mortality in the U.S. have been limited, and mortality ranges from 5 to 7 times that of the general population (7).

Using a large population-based type 1 diabetes cohort in Allegheny County (Pittsburgh), Pennsylvania diagnosed between 1965 and 1979, we now extend the long-term mortality trends to between 28 and 43 years of follow-up after diagnosis and explore differences in mortality rates by sex, race (Caucasian vs. African American), and calendar year of type 1 diabetes diagnosis.

RESEARCH DESIGN AND METHODS

— The Allegheny County Type 1 Diabetes Registry cohort included all individuals with a diagnosis of childhood-onset (aged <18 years) type 1 diabetes in Allegheny County between 1 January 1965 and 31 December 1979 who were given insulin treatment at diagnosis. Individuals were identified through a periodic review of hospital records and validated by contacting pediatricians throughout the county, with ascertainment exceeding 95% (8). Individuals were excluded if diabetes developed due to a secondary cause (i.e., cystic fibrosis, Down syndrome, or use of steroids). A total of 1,075 eligible participants were included in the Allegheny County Type 1 Diabetes Registry cohort, which has been part of an international study (Diabetes Epidemiology Research International [DERI]) comparing mortality in population-based type 1 diabetes cohorts across countries (9–11). The study protocol was

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Table 1—*Demographic characteristics of the Allegheny County Type 1 Diabetes Registry cohort by sex and race as of 1 January 2008*

	Male	Female	Caucasian	African American	Total
n	558	517	996	79	1,075
Vital status confirmed	97.8 (546)	96.1 (497)	97.7 (973)	88.6 (70)§	97.0 (1,043)
Male	—	—	52.7 (525)	43.0 (34)	52.0 (559)
Caucasian	94.1 (525)	91.1 (471)	—	—	92.7 (996)
Diagnosis					
1965–1969*	32.0 (179)	34.1 (176)	32.9 (328)	34.2 (27)	33.0 (355)
1970–1974*	38.1 (213)	34.4 (178)	36.7 (366)	31.6 (25)	36.4 (391)
1975–1979*	29.7 (166)	31.5 (163)	30.3 (302)	34.2 (27)	30.6 (329)
Age at diabetes diagnosis (years)	11.0 ± 4.3	10.8 ± 4.0	10.8 ± 4.2	11.4 ± 4.3	10.9 ± 4.2
Mean diabetes duration (years)†	32.4 ± 6.9	31.5 ± 8.2	32.3 ± 7.4	27.3 ± 8.0§	31.9 ± 7.6
Mean age (years)†	43.4 ± 7.6	42.3 ± 8.4‡	43.2 ± 7.9	38.7 ± 8.6§	42.8 ± 8.0
Person-years of follow-up	18,082.3	16,280.8	32,202.6	2,160.6	34,363.1

Data are % (*n*) or means ± SD. *Ascertainment rates by diagnosis cohort: 1965–1969, 96.6%; 1970–1974, 97.4%; and 1975–1979, 97.0%. †Diabetes duration and age at death or last follow-up. ‡$P < 0.05$; §$P < 0.01$.

approved by the University of Pittsburgh Institutional Review Board.

Vital status was determined as of 1 January 2008, by contacting all participants initially by letter with a health update questionnaire and consent form. Individuals who failed to respond to mailings were contacted by telephone. Deaths not initially identified through this process were discovered by searching both the Social Security Death Index (SSDI) and the National Death Index (NDI). Death certificates (or NDI data) were obtained to confirm each death. With one exception, reports of all deaths were thus confirmed by either a death certificate or the SSDI/NDI.

Statistical analysis

Distributional characteristics for each variable were assessed for normality. Student *t* test and one-way ANOVA were used to compare variables between groups, with adjustment for multiple comparisons using the Bonferroni correction. Diagnosis year was categorized into three groups (1965–1969, 1970–1974, and 1975–1979) to evaluate temporal trends in overall as well as sex- and race-specific mortality. Age at diabetes onset was categorized as prepubertal (<10 years), peripubertal (10–14 years), and postpubertal (>14 years). The χ^2 (or Fisher exact) test was used to compare categorical variables between groups, as appropriate. Variables were then made available in multivariable Cox proportional hazards regression models using backward selection. The proportional hazards assumption was assessed visually and confirmed by testing time-dependent interaction variables.

Expected mortality was estimated using the person-years method based on general population life tables for Allegheny County, Pennsylvania (12). Age-, sex-, and race-adjusted standardized mortality ratios (SMRs) were calculated as the observed divided by the expected number of deaths in each age, sex, and race category, and 95% CIs were determined with the Poisson distribution. Mortality rates and SMRs were compared using rate ratio (RR) analyses and calculating 95% CIs (13). Statistical significance was considered at $P < 0.05$. All analyses were completed using SPSS 17.0 (SPSS, Chicago, IL).

RESULTS — Demographic characteristics of the Allegheny County type 1 diabetes registry cohort are presented by sex and race in Table 1. Vital status as of 1 January 2008 was verified for 1,043 participants (ascertainment rate 97.0%) providing 34,363 total person-years of follow-up. Vital status verification did not differ by sex ($P = 0.11$) or by age at diabetes onset (mean ± SD, confirmed 10.8 ± 4.2 vs. unconfirmed 12.2 ± 4.2 years; $P = 0.07$). However, Caucasians were more likely to be traced than African Americans (97.7 vs. 88.6%, respectively; $P < 0.001$). No differences in ascertainment rates existed by diabetes diagnosis year (data not shown).

Over a median 33.0 years of follow-up, 279 total deaths (26.0%) occurred in this population 138 male and 141 female), which was seven times higher than that seen in the local general population (SMR 6.9 [95% CI 6.1–7.7]). The mean ± SD age and duration of diabetes at follow-up were 42.8 ± 8.0 and 32.0 ± 7.6 years, respectively. A much higher proportion of African Americans died during follow-up compared with Caucasians (50.6 vs. 24.0%, respectively; $P < 0.001$). As a result, the mean duration of follow-up (diabetes duration) and the mean age for African Americans in this cohort were both ~5 years less than that for Caucasians (Table 1). Mean follow-up duration did not differ by sex, but mean age at follow-up was significantly lower for women ($P = 0.02$).

Overall and 30-year mortality rates by sex, race, and diabetes diagnosis cohort are presented in Table 2. The overall mortality rate was 812 per 100,000 person-years (95% CI 717–907). African American mortality rates were significantly higher than Caucasian rates overall and at the 30-year follow-up time point ($P < 0.001$), and rates were also higher in women than in men, but this difference was not significant. Individuals with diabetes diagnosed at age <10 years (prepubertal) in this type 1 diabetes cohort had significantly lower mortality rates than those with peripubertal (age 10–14 years) and postpubertal (age >14 years) onset both overall and at the 30-year follow-up ($P < 0.01$). Mortality rates decreased in a stepwise manner by diabetes diagnosis cohort, with mortality in the 1965–1969 group significantly higher than that in the 1975–1979 group overall (RR 1.86; $P < 0.001$) and at 30 years of follow-up (1.51; $P = 0.02$). Given the differential ascertainment by race, sensitivity analyses were performed based on participants lost to follow-up being either all dead or all alive, and all significant comparisons by race, age at onset, and diagnosis cohort remained robust to misclassification.

Results from a multivariable Cox regression model for overall mortality can be found in supplementary Table 1 (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-1170/DC1). Sex was not significant in the multivariable model and was not included in the final model. Race, age at onset, and year of diagnosis all significantly predicted mortality in type 1 diabetes (both categorically and continuously). Adjusted mortality risk for African Ameri-

Table 2—*Overall and 30-year mortality rates by sex, race, and diabetes diagnosis cohort*

	Overall			30-year		
	Deaths	Follow-up time (person-years)	Mortality rate (95% CI) per 100,000 person-years	Deaths	Follow-up time (person-years)	Mortality rate (95% CI) per 100,000 person-years
Overall	26.0 (279)	34,363.1	811.9 (716.6–907.2)	18.8 (202)	30,046.2	672.3 (579.6–765.0)
Sex						
Male	24.7 (138)	18,082.3	763.2 (635.8–890.5)	17.0 (95)	15,805.4	601.1 (480.2–721.9)
Female	27.3 (141)	16,280.8	866.1 (723.1–1,009.0)	20.7 (107)	14,240.8	751.4 (609.0–893.7)
Race†						
Caucasian	24.0 (239)	32,202.6	742.2 (648.1–836.3)	17.1 (170)	28,016.9	606.8 (515.6–698.0)
African American	50.6 (40)	2,160.6	1,851.3 (1,277.6–2,425.1)*	40.5 (32)	2,029.3	1,576.9 (1,030.5–2,123.3)*
Age at onset†						
<10 years	20.7 (84)	13,530.3	620.8 (488.1–753.6)	11.9 (48)	11,623.9	412.9 (296.1–529.8)
10–14 years	28.6 (112)	12,368.0	905.6 (737.8–1,073.3)*	22.7 (89)	10,853.8	820.0 (649.6–990.4)*
>14 years	29.9 (83)	8,464.9	980.5 (769.6–1,191.5)*	23.4 (65)	7,568.6	858.8 (650.0–1,067.6)*
Diagnosis cohort‡						
1965–1969	37.2 (132)	12,277.6	1,075.1 (891.7–1,258.5)	22.3 (79)	9,877.2	799.8 (623.4–976.2)
1970–1974	23.5 (92)	12,584.8	731.0 (581.7–880.4)*	18.9 (74)	10,937.9	676.5 (522.4–830.7)
1975–1979	16.7 (55)	9,500.7	578.9 (425.9–731.9)*	14.9 (49)	9,231.1	530.8 (382.2–679.4)*

Data are % (*n*) unless otherwise indicated. *$P < 0.05$ for rate ratio compared with first group within each category. †$P < 0.01$ for χ^2 comparisons of deaths overall and at 30-year follow-up. ‡$P < 0.01$ for χ^2 comparisons of deaths overall only.

cans was 3.2 times higher than that for Caucasians. Each additional year in age at diabetes diagnosis conferred a 7% increased mortality risk (hazard ratio 1.07, 95% CI 1.04–1.10), and risk of death decreased by 6% for each additional calendar year of diabetes diagnosis over the 15-year period of diabetes diagnosis (1965–1979) in this cohort.

Survival curves based on Kaplan-Meier life table analyses are presented in Fig. 1. Cumulative survival after diagnosis of type 1 diabetes in this cohort was 98.2% at 10 years, 93.1% at 20 years, 80.9% at 30 years, and 68.4% at 40 years. Survival curves did not differ by sex (30-year survival for men vs. women 82.6 vs. 79.0%) (Fig. 1*A*) but were significantly worse for African Americans than for Caucasians (30-year survival 57.2 vs. 82.7%, respectively) (Fig. 1*B*). Significant improvement in survival was seen across the diabetes diagnosis cohorts (Fig. 1*C*), and, when separated by sex or race (supplementary Fig. 1*A–D*, available in an online appendix), a declining trend in mortality was seen across all race and sex groups. However, only survival in men ($P = 0.02$) and in Caucasians ($P = 0.05$) showed a significant improvement across diagnosis cohorts. Improvement in survival was also seen by age at diabetes onset, with the prepubertal group (age <10 years) having significantly better survival than that in either the peri- or postpubertal groups.

Finally, we calculated SMRs for this cohort compared with the local age-, sex- and race-matched general population (supplementary Table 2, available in an online appendix). Thirty years after diagnosis of diabetes, mortality was more than 7 times higher than that seen in the local general population (SMR 7.4 [95% CI 6.4–8.4]). The SMR for women is nearly three times higher than that for men (13.2 vs. 5.0; $P < 0.05$), whereas the SMRs by race were identical (African American 7.5 vs. Caucasian 7.4). An improving trend in SMR was seen by diagnosis cohort at 30 years of diabetes duration (9.3 [7.2–11.3], 7.5 [5.8–9.2], and 5.6 [4.0–7.2] for 1965–1969, 1970–1974, and 1975–1979, respectively).

The SMRs over time (5-year follow-up intervals) are shown in Fig. 2 by sex, race, and diabetes diagnosis cohort. SMRs at 5-year follow-up are very high in the Allegheny County cohort, especially in women and in the earlier diagnosis cohorts (1965–1969 and 1970–1974). Mortality within the 1st year of diagnosis (onset mortality) was relatively common in this cohort (10 deaths) and occurred almost exclusively in women ($n = 9$), driving the extremely high female SMR at 5 years of follow-up. Women have consistently had SMRs of ≥10, whereas SMRs in men range between 1.8 and 5.0 over 30 years of follow-up (Fig. 2*B*). SMRs did not differ significantly by race but were consistently lower in African Americans over time (Fig. 2*C*). Steady improvements in SMRs have been seen over time between the 1965–1969 and 1975–1979 diagnosis cohorts, even after 30 years of type 1 diabetes duration (Fig. 2*D*).

CONCLUSIONS — These results expand on previously published reports from the Allegheny County Type 1 Diabetes Registry cohort with an additional 9 years of follow-up (7,9). Of note, now with a range of 28–43 years of type 1 diabetes duration, the risk of dying is 7 times higher than that of the local general population, with significant improvements in SMR for those with diabetes diagnosed most recently in this cohort. This SMR (7.4 [95% CI 6.4–8.4]) is higher than that reported by Nishimura et al. (7) for this cohort for the 1999 follow-up (SMR 5.2 [4.4–6.0]), perhaps reflecting an increasing effect of long-term complications, which are keeping mortality rates much higher in individuals with type 1 diabetes compared with the general population.

This is the largest population-based type 1 diabetes cohort with at least 25 years of follow-up in the U.S. A recent population-based 20-year follow-up study in New Zealand showed the highest SMRs in individuals with type 1 diabetes diagnosed at age <30 (3.3 for men and 4.3 for women) (14). A nationwide Norwegian cohort with childhood-onset (age <15 years) type 1 diabetes recently reported SMRs of 3.9 (male) and 4.0 (female) after 20 years of follow-up (6). Similar results were seen by sex in the

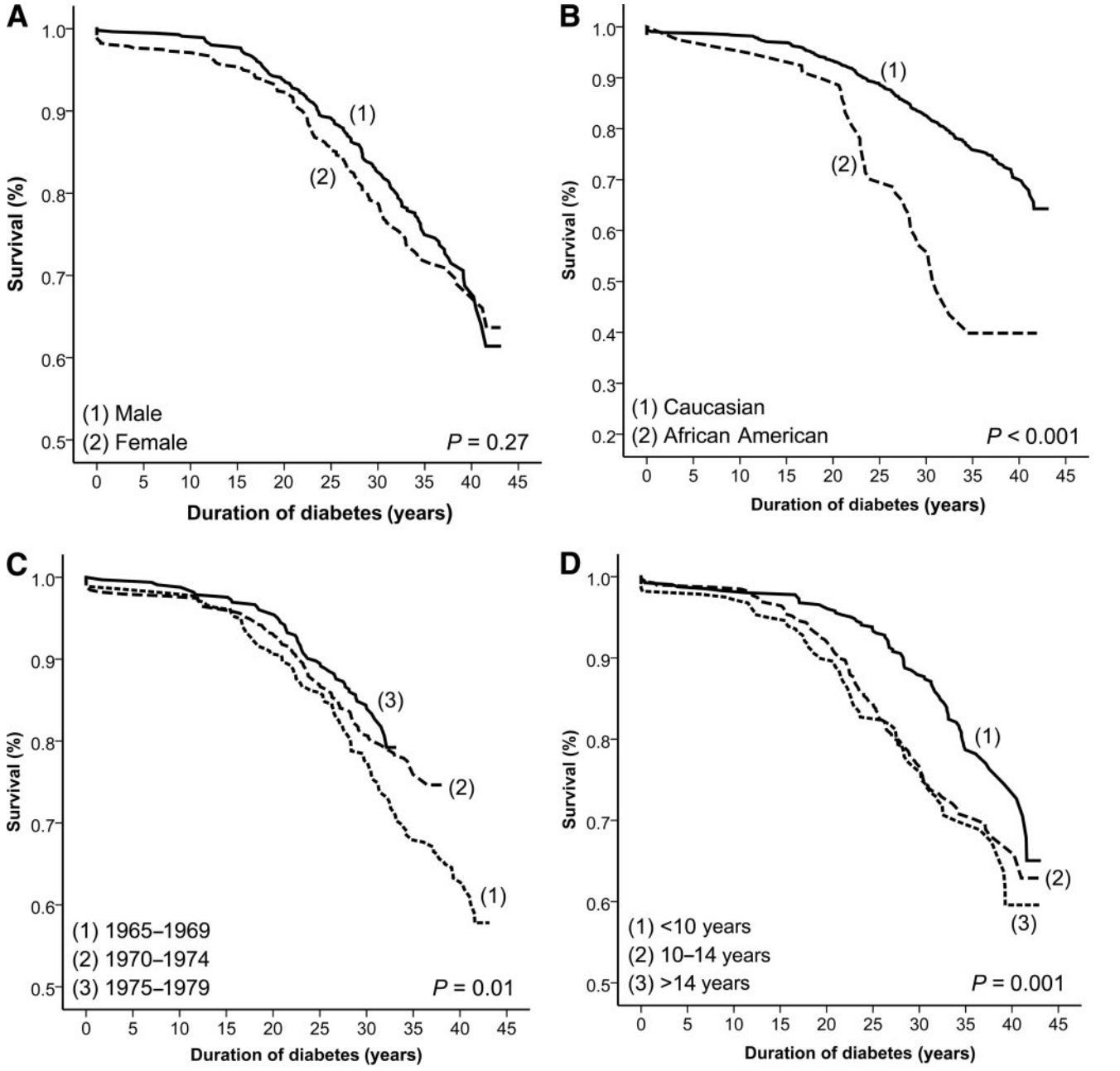

Figure 1—*Life-table analyses by sex* (A)*, race* (B)*, diagnosis cohort* (C)*, and age at onset* (D) *for individuals with type 1 diabetes between 1965 and 1979 in the Allegheny County type 1 diabetes registry cohort.* P *values calculated using the log-rank test.* C*: 1965–1969 vs. 1970–1974,* P = *0.02, and 1965–1969 vs. 1975–1979,* P = *0.02.* D*: <10 vs. 10–14 years,* P = *0.002, and <10 vs. >14 years,* P < *0.001.*

Diabetes U.K. Cohort Study with a mean 13.4 years of follow-up (male SMR 2.7; female SMR 4.0) (15). Other recent reports of all-cause mortality in population-based cohorts of type 1 diabetes exist, with SMRs ranging from 1.8 to 4.2, but their follow-up is limited (<10 years), which is the most likely reason for their lower SMRs (16–18).

The markedly higher mortality seen in our U.S. type 1 diabetes cohort is clearly limited to women, for the men have SMRs that are very comparable to those reported in other long-term follow-up studies (New Zealand, Norway, and the U.K.) (6,14,15). However, directly comparing SMRs across countries is not appropriate because SMR differences may result from either methodological or cohort differences among these studies. To what extent these differences reflect our different health care system and a potential lack of access in the U.S. is difficult to determine. National measures of health care performance and other national economic measures have been shown to contribute to complications in individuals with type 1 diabetes (19).

Compared with their respective general populations, women with type 1 diabetes had an SMR nearly 3 times higher than that of men with type 1 diabetes. This finding is partially reflective of the much lower mortality rates for young women in the general population. Long-term mortality rates do not differ by sex in type 1 diabetes, consistent with our previous findings (7), but are markedly different from the findings in New Zealand,

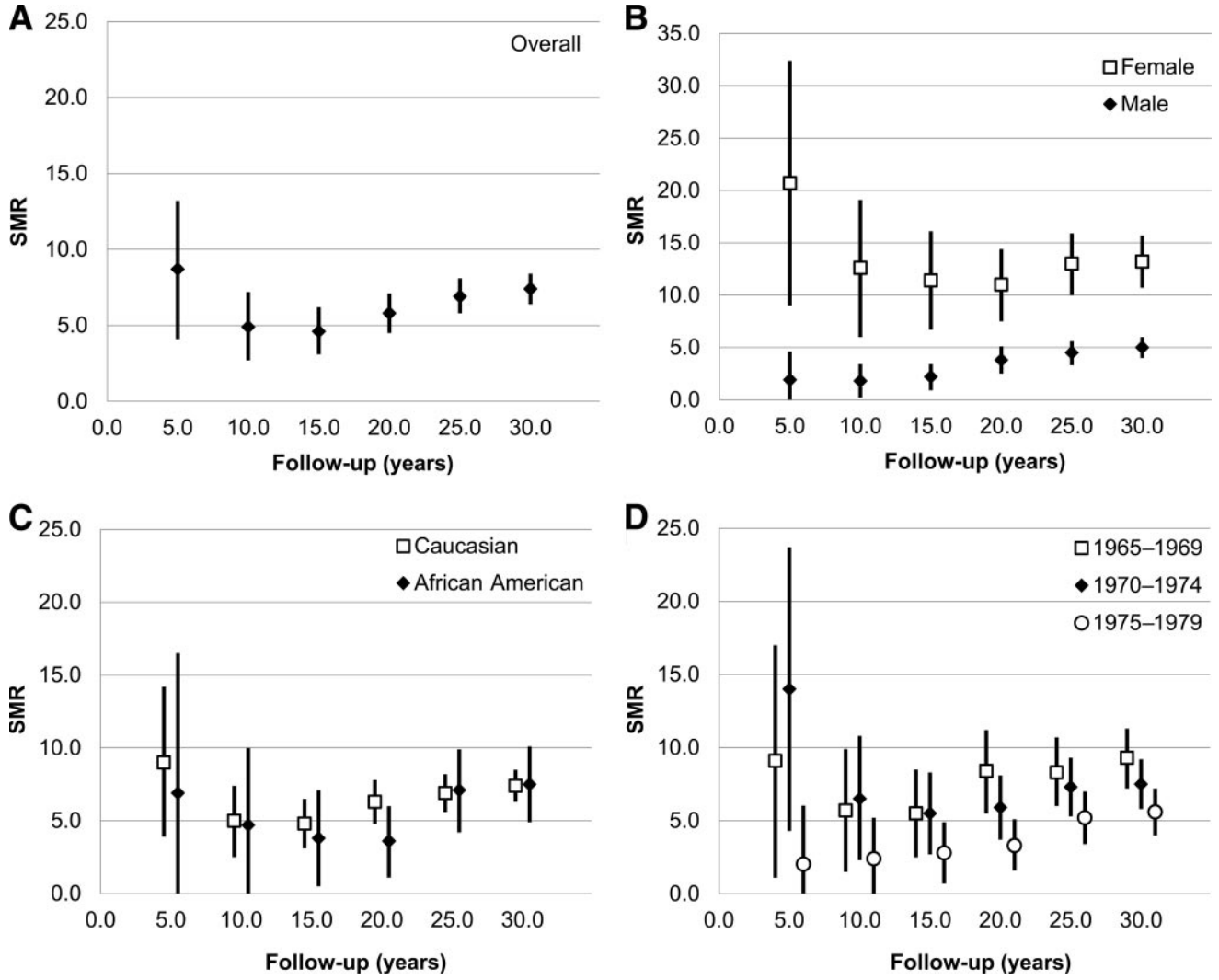

Figure 2—*SMRs and 95% CIs for the overall (*A*) Allegheny County Type 1 Diabetes Registry cohort and by sex (*B*), race (*C*), and diagnosis cohort (*D*) at 5-year intervals of follow-up. C and D are spaced around the 5-year intervals for visual clarity; however, all SMRs are calculated at the same 5-year follow-up points.*

Norway, and the U.K. The respective male-to-female mortality RRs for these studies are 1.23 in New Zealand, 2.26 in Norway, and 1.29 in the U.K compared with 0.80 for our study. The reason for this discrepancy is unclear, but it appears that female sex completely lost its general survival advantage in our diabetes population.

Despite race being a significant predictor of mortality within the Allegheny County cohort (hazard ratio 3.2), no differences in SMR were seen by race, the African American SMR tending to be lower than the Caucasian SMR during follow-up (Fig. 2*C*). This seemingly contradictory result can be explained by the extremely high mortality rates seen in young African-Americans in the general population, particularly resulting from violent deaths (20). Thus, although mortality rates in type 1 diabetes are 2–3 times higher in African Americans, this excess can be attributed to the background African American mortality rates and not to their diabetes. In a 3-year follow-up of 725 African Americans with a mean 9-year duration of type 1 diabetes, SMRs for men and women were 7.0 and 10.5, respectively, compared with those for the local general African American population (21).

Temporal improvements in mortality have been reported in other type 1 diabetes studies. A report from the U.K. on individuals in whom type 1 diabetes was diagnosed (age <17 years) between 1940 and 1989 (n = 845) showed a fourfold decrease in SMRs between the 1940s cohort and the 1980s cohort (9.4 vs. 2.4, respectively) (22). A large Danish study of mortality reported an increase of 15 years to the life expectancy of type 1 diabetic patients diagnosed over a 40-year period between 1933 and 1972 (23). The reasons for temporal improvements in our cohort remain unclear, but an examination of cause-specific mortality is currently underway to determine whether chronic diabetes complications are being delayed or prevented in the youngest cohort (1975–1979) because of advances in care and to help explain the dramatic differences in SMRs by sex.

Onset mortality (death within the 1st year of diagnosis) improved in this cohort. The 1975–1979 diagnosis cohort had only one onset death compared with four and five in the 1965–1969 and

1970–1974 cohorts, respectively. These results are consistent with other studies and correspond to improvement in diagnosis and care at onset (24).

Finally, this cohort is part of the DERI Study group with Finland (n = 5,148) and Japan (n = 1,410), exploring mortality differences in childhood-onset (age <18 years) type 1 diabetes in three countries (all diagnosed between 1965 and 1979). The most recent report compared mortalities in Japan and Finland after at least 15 years of follow-up (5). The SMR for Japan was significantly higher (12.9) than that of Finland (3.7). The comparable SMR for our population was 5.8, which remains consistent with previous reports from DERI showing U.S. mortality rates sandwiched between Japanese and Finnish mortality rates (9,11).

A few key limitations with this follow-up study must be addressed. First, these population-based data reflect the type 1 diabetes experience of individuals in Southwestern Pennsylvania with diabetes diagnosed between 1965 and 1979 and may not be representative of the entire U.S., of individuals not of African American or Caucasian ethnicity, or of those with diabetes diagnosed earlier or later than this cohort. In addition, 3% of the Allegheny County type 1 diabetes registry cohort was lost to follow-up, and vital status could not be determined for these individuals. Thus, the mortality rates might be slightly inflated. Thorough searches of both the SSDI and the NDI give us confidence that most (if not all) of these 32 individuals are still living. In addition, the analysis is limited to only a few key demographic variables (age at onset, race, and sex), as other key socioeconomic and clinical were not ascertained for all participants at study inception (8). Finally, because diabetes in all individuals in this cohort was diagnosed before major modern-day advances in type 1 diabetes treatment (self-monitoring of blood glucose, A1C testing, and ACE inhibitors), the specific effect of these advances cannot be properly examined here.

Key strengths of this study include the size of this population-based cohort (n = 1,075) and the 97% ascertainment rate after ≥25 years of follow-up. In addition, we now have sufficient follow-up data for temporal trend and other analyses in African Americans, providing important information for this understudied type 1 diabetes population (21).

In summary, these results are encouraging and provide contemporary, population-based mortality figures for individuals with long-standing type 1 diabetes. Women in our cohort die at a rate similar to that of men, a result warranting further exploration, as younger women die much less frequently than younger men in the general U.S. population. These data illustrate that mortality rates are clearly decreasing in those in whom type 1 diabetes was diagnosed more recently; however, those with diabetes diagnosed most recently (1975–79) still die at rates 5 times higher than that of the general population. Thus, continuing improvements in treatment and care are essential, particularly in women and African Americans with type 1 diabetes.

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A.M.S. provided study concept and design, obtained funding, acquired data, analyzed and interpreted data, provided statistical analysis, wrote the manuscript, and reviewed/edited the manuscript. D.J.B. and R.E.L. provided study concept and design, analyzed and interpreted data, and reviewed/edited the manuscript. S.F.K. provided study concept and design, analyzed and interpreted data, provided statistical analysis, and reviewed/edited the manuscript. T.J.O. provided study concept and design, obtained funding, analyzed and interpreted data, wrote the manuscript, reviewed/edited the manuscript, provided administrative, technical, or material support, and supervised the study.

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