The 30-Year Natural History of Type 1 Diabetes Complications

The Pittsburgh Epidemiology of Diabetes Complications Study Experience

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Declining incidences in Europe of overt nephropathy, proliferative retinopathy, and mortality in type 1 diabetes have recently been reported. However, comparable data for the U.S. and trend data for neuropathy and macrovascular complications are lacking. These issues are addressed using the prospective observational Pittsburgh Epidemiology of Childhood-Onset Diabetes Complications Study. Participants were stratified into five cohorts by diagnosis year: 1950–1959, 1960–1964, 1965–1969, 1970–1974, and 1975–1980. Mortality, renal failure, and coronary artery disease (CAD) status were determined on the complete cohort (n = 906) at 20, 25, and 30 years. Overt nephropathy, proliferative retinopathy, and neuropathy were assessed at 20 and 25 years on the subset of participants with a clinical examination. There was a decreasing trend by diagnosis year for mortality, renal failure, and neuropathy across all time intervals ($P < 0.05$), with the 1950–1959 cohort having a fivefold higher mortality at 25 years than the 1970s' cohorts. Proliferative retinopathy and overt nephropathy showed nonsignificant declines at 20 years ($P < 0.16$ and $P < 0.13$, respectively) and no change at 25 years. CAD event rates, which were lower than the other complications, also showed no trend. Although some type 1 diabetes complications (mortality, renal failure, and neuropathy) are declining, others (CAD, overt nephropathy, and proliferative retinopathy) show less favorable changes by 30 years. *Diabetes* 55:1463–1469, 2006

A decreasing incidence of diabetes complications, particularly overt nephropathy and proliferative retinopathy, has been reported in the type 1 diabetes population around the world over the past 15–20 years (1–3). Mortality rates have also been decreasing (4–6), most likely reflecting better management and the declining morbidity. Improved metabolic control, facilitated by the advent of self-monitoring of blood glucose and HbA_{1c} (A1C) testing and stimulated by the results of the Diabetes Control and Complications Trial (7), along with better blood pressure management (1–3,5,6) are likely to be major contributors. However, Rossing et al. were unable to show decreasing rates for diabetic nephropathy (8) and retinopathy (9) after 15 years in a hospital-based cohort, whereas Brown et al. (10), using a historical comparison of type 2 diabetic patients, demonstrated an unchanged prevalence of proliferative diabetic retinopathy, despite improved levels of glycemia and blood pressure. Furthermore, few data exist for neuropathy or macrovascular complications. We therefore report the cumulative incidence (and incidence density), up to 30 years, by diagnosis cohort (1950–1980) of all major type 1 diabetes complications in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study.

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RESEARCH DESIGN AND METHODS

The EDC study is a representative (11) prospective type 1 diabetes cohort, now entering its 18th year of follow-up. The EDC baseline examinations were conducted between 1986 and 1988, and participants were examined biennially thereafter. Figure 1 shows the recruitment tree for the study. A total of 1,124 patients were eligible for the study, having been diagnosed or seen within 1 year of diagnosis at Children's Hospital of Pittsburgh between 1 January 1950 to 31 May 1980 and living within 100 miles or 2.5 h from Pittsburgh. Of the 1,124 eligible patients, 145 (13%) had died before baseline (1986–1988) and 191 (17%) chose not to participate. A total of 788 (70%) participated, with 130 (16%) providing survey information only.

Demographic details for the follow-up cohort analyzed in this report are listed in Table 1 (n = 906, excluding 3 predeceased with no death certificate and 24 without follow-up for the relevant durations [total = 27]). Of the predeceased, 88% were diagnosed at or before 1964, whereas 67% of the survey-only and exam participants were diagnosed after 1964. Predeceased were included where possible (mortality, renal failure, and coronary artery disease [CAD]), whereas for other complications, the analyses were limited to those diagnosed after 1964.

At the baseline examination, mean age was 28 years and diabetes duration 19 years. The current analyses are based on 906 subjects (81% of those initially eligible [n = 1,124]) who comprise three groups: those who died before baseline exam (predeceased, n = 145), those who provided survey information at baseline and at the 12-year follow-up (survey only, n = 130), and those who had a full baseline examination (exam, n = 658). Some follow-up information has been obtained on 97.1% (n = 906/933) of the total cohort (99% of those examined, 85% of survey-only participants, while death certificates were obtained on 99% of the predeceased).

These 906 participants with follow-up were classified into five separate cohorts according to their year of diabetes diagnosis: 1950–1959, 1960–1964, 1965–1969, 1970–1974, and 1975–1980. Cumulative incidence was examined at three separate time intervals: 20, 25, and 30 years of diabetes. Follow-up was censored on 31 December 2000. Some complications, i.e., mortality, renal failure, and coronary artery disease, which can be determined by death

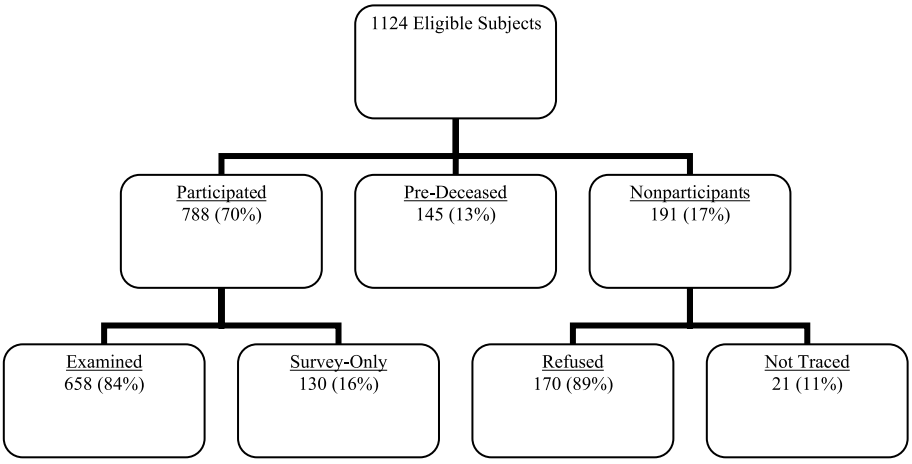

FIG. 1. The Pittsburgh EDC study recruitment tree, from the Children's Hospital of Pittsburgh Registry, 1 January 1950 to 31 May 1980.

certificates and surveys, were analyzed in the total cohort (n = 906), while other complications, which require examination, i.e., overt nephropathy and neuropathy, are analyzed only in the examined subjects. Because of high mortality before the baseline exam (1986–1988) in those diagnosed between 1950 and 1964 (33%), these complications are only analyzed in the examined post-1964 diagnosis cohorts (n = 319) where the survival bias is minimal (mortality <3%).

Mortality. For the death of an exam or survey-only participant, the next-of-kin was contacted and a copy of the death certificate, and where appropriate the hospital record, was requested. Death certificates for the predeceased had been previously obtained (4). Data were reviewed by a physician mortality classification committee (chaired by T.J.O.), which classified deaths according to standard procedures (12).

Renal failure. Self-reported renal transplantation or renal dialysis defined renal failure in the exam and survey-only participant groups. For the predeceased cases, a mention of renal failure on the death certificate was accepted, in which case the duration of diabetes at death was considered the duration at the onset of renal disease.

CAD. For exam and survey-only participants, CAD status was defined as CAD death, a history of myocardial infarction confirmed by Q-waves on electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, or angiographic stenosis ≥50% confirmed by hospital records, including revascularization. For the predeceased, mention of myocardial infarction and/or CAD on the death certificate was accepted.

Proliferative retinopathy. Proliferative retinopathy was based on stereoscopic fundus photographs of fields 1, 2, and 4 with a Zeiss camera, read by the Fundus Photography Reading Center, University of Wisconsin–Madison and classified according to the modified Arlie House system (13). For individuals refusing fundus photographs or not attending any particular exam, proliferative retinopathy was defined as receiving laser therapy for proliferative diabetic retinopathy (n = 43). Duration was determined from onset of diabetes to the date of the laser procedure and/or date of fundus photography. To date, 202 EDC examination participants have been identified as having proliferative retinopathy and self-reported laser therapy. Of those 202 participants, 126 (62%) also had study fundus photographs, confirming their proliferative retinopathy status.

Overt nephropathy. Overt nephropathy was defined as an albumin excretion rate >200 μg/min in at least two of three timed urine collections (24-h, overnight, and post-clinic) (14,15). In the absence of urine, a serum creatinine >2 mg/dl or renal failure was accepted.

Confirmed distal symmetric polyneuropathy. Confirmed distal symmetric polyneuropathy (CDSP) was defined by the Diabetes Control and Complications Trial (16) clinical exam protocol showing the presence of two or more of the following: symptoms, sensory and/or motor signs, and/or reduced/absent tendon reflexes consistent with distal symmetric polyneuropathy, in the presence of an abnormal age-specific vibratory threshold (Vibratron II testor).

Symptomatic autonomic neuropathy. Symptomatic autonomic neuropathy was determined by abnormal heart rate response to deep breathing (expiration/inspiration ratio [<1.1]) and at least two autonomic symptoms (17).

Risk factors. All participants completed a questionnaire concerning demographic and medical history information before each exam. An ever-smoker was a person who smoked ≥100 cigarettes over their lifetime. Blood pressure was measured with a random zero sphygmomanometer (18). Hypertension was defined as ≥140/90 mmHg or use of antihypertensive medication.

Stable A1C was measured by ion exchange chromatography (Isolab, Akron, OH) and subsequently by automated high-performance liquid chromatography (Diamat; BioRad, Hercules, CA). Readings with the two methods are almost identical (r = 0.95). Our upper limit of normal for A1C is 7.3%; thus, values are higher than current A1C values. Total, HDL, and LDL cholesterol and triglycerides were determined as previously described (19–23).

Statistical analysis. The SPSS/PC statistical software (SPSS, Chicago, IL) was used for all analyses. For each duration (20, 25, and 30 years), a participant was classified as a case if he or she had experienced the event by that duration using his or her closest examination or survey (± 2 years). If data on an individual were not available at the duration of interest, but that individual was later a noncase, that person was included as a noncase at the specific duration. However, if that individual was later identified as a case, he or she was not counted as a case until the duration of interest included the duration at complication diagnosis.

Life-table analyses were only appropriate for mortality, since subjects were not followed from diagnosis (mean baseline duration was 19 years), and thus duration at complication diagnosis is unknown for baseline prevalent cases. For mortality, Kaplan-Meier life tables (log-rank tests) and Cox proportional hazards modeling were used.

Cohort differences for continuous data were assessed using a one-way ANOVA (with Bonferroni corrections for multiple comparisons) and Student's t tests. Categorical variables were compared using a χ^2 statistic. Logistic regression was also used to control for age at onset of diabetes. Generalized linear regression models were used to test for trends in the data. Incidence

TABLE 1
Composition (n) and demographic characteristics of diagnosis onset cohort: the Pittsburgh EDC study

	1950–1959 cohort	1960–1964 cohort	1965–1969 cohort	1970–1974 cohort	1975–1980 cohort	Total
n	235	153	172	167	179	906
Predeceased (n)	93	35	14	1	—	143
Exam (n)	122	102	136	143	149	652
Survey only (n)	20	16	22	23	30	111
Age at onset (mean ± SD)*	7.8 ± 3.9	8.1 ± 3.8	8.1 ± 4.3	8.6 ± 3.9	9.1 ± 3.8	8.3 ± 3.9
Sex (% male)	54	54	49	51	44	50.4

*P < 0.01, significant trend.

TABLE 2
Incidence density per 100 person-years for type 1 diabetes complications by diabetes duration: the Pittsburgh EDC study (12-year follow-up data)

	Number of events	Duration		
		<20 years	20–30 years	Overall
Mortality	183	0.56 (0.46–0.69)	1.59 (1.27–1.97)	0.79 (0.67–0.91)
Renal failure	128	0.43 (0.33–0.54)	1.34 (1.02–1.72)	0.63 (0.52–0.74)
CAD including revascularization	76	0.17 (0.11–0.25)	0.98 (0.72–1.30)	0.36 (0.28–0.45)
CAD (fatal) and myocardial infarction	55	0.12 (0.07–0.18)	0.76 (0.53–1.04)	0.26 (0.19–0.34)
		<20 years	20–25 years	Overall
Overt nephropathy	114	1.4 (1.1–1.6)	1.23 (0.59–2.26)	1.33 (1.10–1.60)
Distal symmetric polyneuropathy	124	1.2 (0.98–1.5)	3.83 (2.64–5.37)	1.48 (1.23–1.76)
Symptomatic autonomic neuropathy	57	0.83 (0.62–1.1)	0.36 (0.07–1.1)	0.78 (0.59–1.0)
Proliferative retinopathy	182	1.59 (1.34–1.88)	5.40 (4.00–7.12)	1.95 (1.66–2.23)

Data in parentheses are 95% CIs.

density was also calculated for the three durations, <20 years, and 20–30 years and overall by dividing the number of individuals developing a first event by the person-years of observation for those at risk during the specified duration interval.

RESULTS

The current analyses focus on the 906 subjects, with some follow-up as shown in Table 1 where a significant trend ($P < 0.01$) toward increasing age at diagnosis with later cohorts was noted. There was no difference in the sex distribution by cohort.

Incidence densities are shown in Table 2. As can be seen, complication risk is highest for proliferative retinopathy in both duration strata and >5% per year for those with 20–25 years' duration. Also evident is the greater risk after 20 years' duration for each complication (increase two- to threefold, in general) except for overt nephropathy, which shares a similar rate irrespective of duration, and symptomatic autonomic neuropathy, which occurred rarely ($n = 3$) in the 20- to 25-year duration interval.

Cumulative mortality at 20 years was reduced by 84%, i.e., from 22% (1950–1959) to 3.5% (1975–1980). At 25 years, mortality declined by 80% from 35% (1950–1959) to 7% (1970–1974), while mortality was 41% lower at 30 years, i.e., having fallen from 39% (1950–1959) to 23% (1965–1969).

Life-table analyses (Fig. 2) showed for each cohort a better survival than seen for those diagnosed in all earlier cohorts, with two exceptions: 1969–64 vs. 1950s ($P = 0.9$) and 1975–1980 vs. 1970–1974 ($P = 0.8$). Controlling for age at onset of diabetes did not alter these findings. There were no inter-cohort differences in mortality rates by sex, but males had higher rates at each time point, which was significant in the 1970–1974 cohort at both 20 and 25 years ($P < 0.05$).

A significant improvement in renal failure rates was also noted (Fig. 3*A*) for individuals diagnosed after 1964. At 20 years, 4% of those diagnosed after 1964 had developed renal failure versus 16% for those diagnosed in the 1950s. At 30 years' duration, renal failure rates had fallen from 31% (1950s) to 18% (1965–1969). Overall, males were more likely to have renal failure by 30 years (33 vs. 24%, $P < 0.05$), with this difference being significant within the 1950–1959 cohort (38 vs. 23%, $P < 0.05$).

CAD rates of events and procedures (Fig. 3*B*) were similar across diagnosis cohorts at 30 years. Because revascularization interventions may have increased with time, analyses were repeated, with CAD limited to myocardial infarction or CAD death (Fig. 3*C*). No cohort differences were seen at either 20 or 30 years (pooled rates of 3.5 and 15%, respectively), whereas at 25 years (overall rate was 8%), the rates were marginally lower in the latter cohorts ($P < 0.30$). CAD rates were similar by sex within each cohort.

Figure 4 shows the cumulative incidence in the exam population of proliferative retinopathy, overt nephropathy, symptomatic autonomic neuropathy, and CDSP at 20 and 25 years' duration. At 20 years, a nonsignificant declining trend ($P < 0.16$) was evident, with rates for proliferative retinopathy (Fig. 4*A*) decreasing from 38% (1965–1969) to 26.5% (1975–1980), whereas no difference was seen at 25

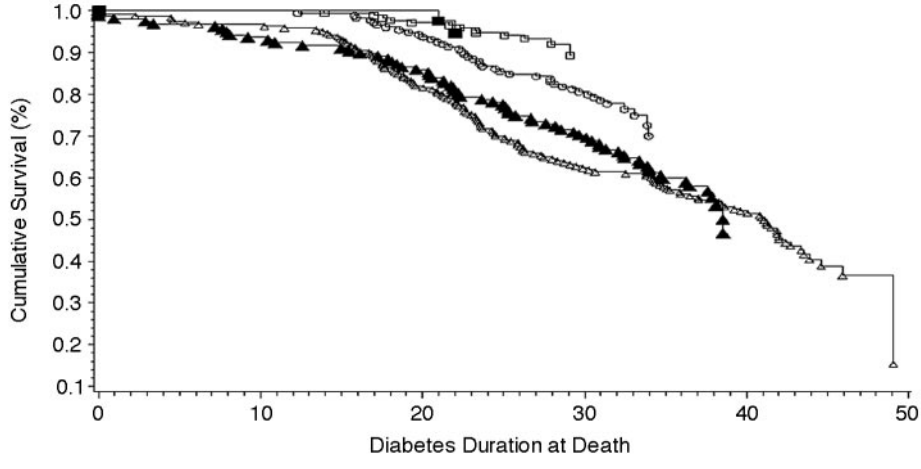

FIG. 2. All-cause mortality by diagnosis cohort: the Pittsburgh EDC study. △, 1950–1959; ▲, 1960–1964; ○, 1965–1969; □, 1970–1974; ■, 1975–1980.

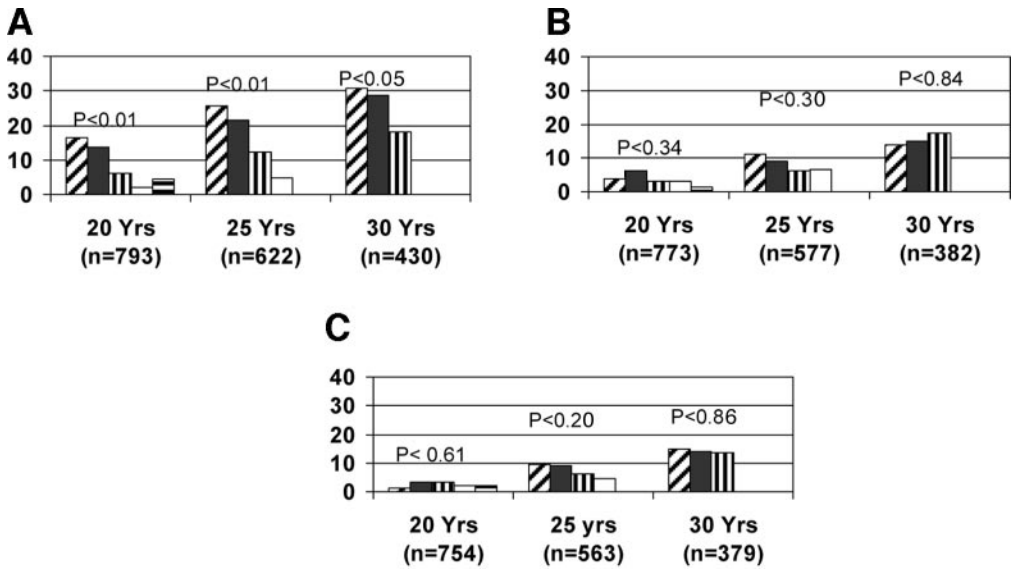

FIG. 3. Cumulative incidence (%) by duration of diabetes: the Pittsburgh EDC study: diagnosed between 1950 and 1980. ▨, 1950–1959; ■, 1960–1964; ▥, 1965–1969; □, 1970–1974; ▤, 1975–1980. *A*: Renal failure. *B*: Total CAD (events and procedures). *C*: CAD events (myocardial infarction and CAD deaths only). *P* values adjusted for age at onset of diabetes.

years when ~53% of the participants had proliferative retinopathy.

A nonsignificant decline was also seen for overt nephropathy (Fig. 4*B*) at 20 years (1975–1980 cohort rates [19%] were 37% lower than the 1965–1974 cohorts). However, the cumulative incidence rates at 25 years were similar, with a pooled incidence of 32%. To compare with previous Steno data (24), Fig. 5 was constructed and displays incidence by 2-year diabetes duration intervals for the two studies. The early peak incidence at 16 years in the Steno data are clearly absent in the later EDC data. Symptomatic autonomic neuropathy showed a steady decline across all cohorts (Fig. 4*C*) at 20 years ($P < 0.05$) and at 25 years ($P < 0.06$). CDSP (Fig. 4*D*), however, showed a more significant lower trend at both 20 years ($P < 0.01$) and 25 years ($P < 0.05$).

There were no differences in overt nephropathy, proliferative retinopathy, symptomatic autonomic neuropathy, or CDSP rates at 20 and 25 years by sex. Because of the increasing age of onset with year of diagnosis, all cumulative incidence results were repeated after stratification by median age of onset (8.5 years for the total cohort; 8.9 years for the exam subjects diagnosed after 1964). Similar patterns were seen for both strata, as reported above for the whole population (data not shown).

Table 3 shows risk factor characteristics at 25 years' duration for exam participants diagnosed after 1964 by cohort. Only A1C levels showed a significant difference, being lower in the 1970–1974 cohort than the 1965–1969 cohort.

DISCUSSION

These data suggest the natural history of type 1 diabetes complications is improving, with major declines in total mortality and renal failure rates in individuals diagnosed after the mid-1960s and for neuropathy in those diagnosed in the 1970s. However, declines are not so impressive for overt nephropathy and proliferative retinopathy, and any favorable patterns seen at 20 years have largely disappeared by 25 years' duration. Although CAD event rates are low, no difference in cumulative incidence at 30 years was seen ($P < 0.84$). Event rates are high for individuals having a diabetes duration of 20–30 years (and thus aged in their early 30s at the time of the event), having a 1.5% annual risk of mortality and a 1% annual risk of a major

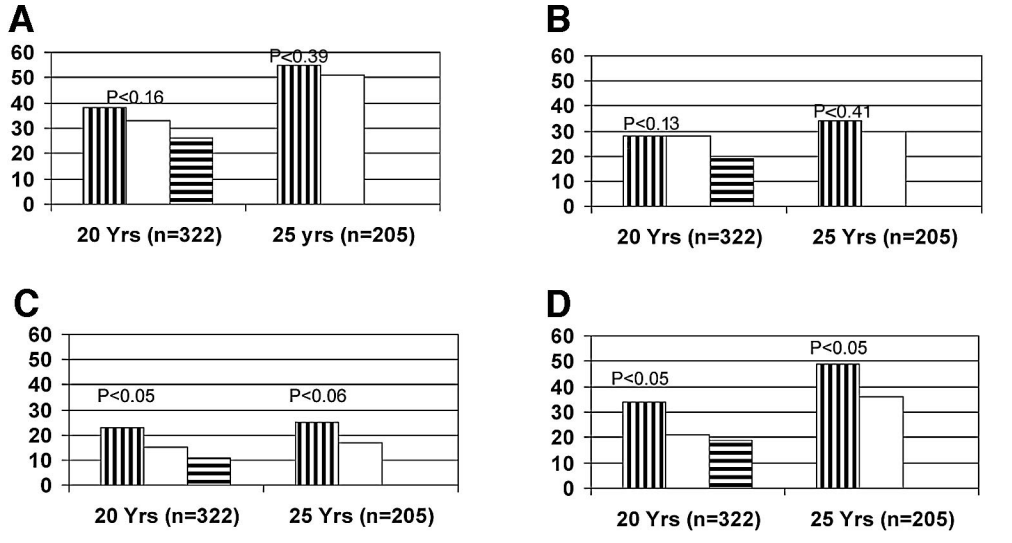

FIG. 4. Cumulative incidence (%) by duration of diabetes: the Pittsburgh EDC study: restricted population, examined cohort diagnosed between 1965 and 1980. ▥, 1965–1969; □, 1970–1974; ▤, 1975–1980. *A*: Proliferative retinopathy (adjusted for age of onset). *B*: Overt nephropathy (adjusted for age of onset). *C*: Symptomatic autonomic neuropathy (adjusted for age at onset). *D*: Confirmed distal symmetric polyneuropathy (adjusted for age at onset).

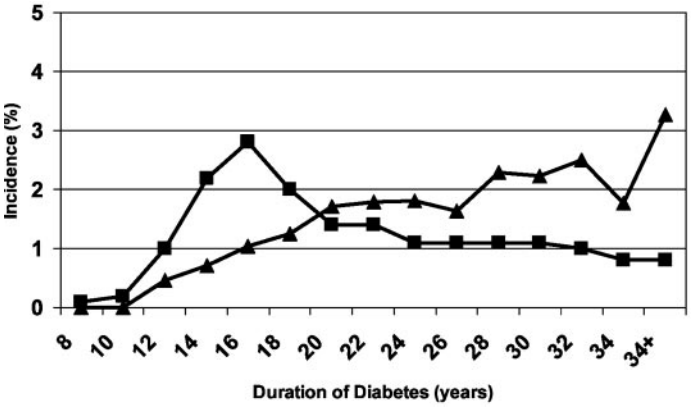

FIG. 5. Incidence of nephropathy in the Pittsburgh EDC study (▲; 1986–2000) and the Steno clinic population (■; 1933–1984).

CAD event (Table 2). As the incidence of angina and ischemia exceeds that of hard CAD in these cohorts (25), the total CAD annual risk rate is ~2% or more for individuals with 20 years' duration. Two recent reports from Steno, Denmark (1), and Linkoping, Sweden (2), show a decline in overt nephropathy and proliferative retinopathy at 20 and 25 years' duration (for those diagnosed between 1960 and 1975) but provide no data on total mortality, CAD, or neuropathy. The current report thus compliments these European data and expands both the breadth of complications studied and length of follow-up.

The dramatic decrease over time in the cumulative incidence of mortality and renal failure is consistent with two reports from our Allegheny County registry: a community-based population of childhood-onset type 1 diabetes (5,6) and an Israeli mortality study (26). The explanation for the improved mortality is likely to be multifaceted, but because our data show only a modest decrease in the underlying complications that lead to death (overt nephropathy and CAD), improved management of complications, as well as decreased incidence, are likely to contribute. Despite the declining rate, however, a major excess mortality still exists in the type 1 diabetes population compared with nondiabetic populations (27).

The true decline in renal failure may be greater than we have shown in this article, since the onset of renal failure for the predeceased rate was established at the date of death, whereas the exact onset may have appeared earlier. Because overt nephropathy demonstrated only a small decline in incidence at 20 years and no difference at 25 years, it is likely that much of the improved renal failure rates reflect better management rather than prevention of the nephropathic state. This is consistent with the Allegheny County end-stage renal disease (ESRD) survival data (5) and an increase in ACE inhibitor use, as we have documented (28). Although our overt nephropathy rates are higher than those reported from Linkoping (2,3), they are very consistent with recent Steno data (1). As shown in Fig. 5, a major shift in the incidence pattern of overt nephropathy has likely occurred compared with the earlier Steno data (24). With loss of the "16-year peak," it is important to note that incidence is only being delayed until the later years. After 20 years' duration, the incidence is in fact higher in the more recent EDC data than the earlier Steno data. The explanation for the much lower Linkoping rates is undetermined but may relate to methodological differences in follow-up, as well as reflecting a truly lower level of complications and better glycemic control (2,3).

Like Rossing et al. (9), we do not demonstrate a significant decrease in proliferative retinopathy with increasing calendar year of diagnosis, although at 20 years, a nonsignificant trend was evident ($P < 0.16$). Our rates, although slightly higher, are again comparable to the later report from Steno (1) at 20 years. Similarly, early results from Linkoping showed little change in proliferative retinopathy rates by diagnosis cohort (29), whereas a later report (2) demonstrated a marked decrease. In this report, a decline of >50% was reported for proliferative retinopathy. Again, why the more recent rates of proliferative retinopathy are much lower in Linkoping than Pittsburgh or Steno is unclear. The nonsignificant change in overt nephropathy and proliferative retinopathy at 25 years may be reflective of the sample size. However, because we do have 80% power to detect a 17% (overt nephropathy) and 20% (proliferative retinopathy) difference between the two diagnosis cohorts, we feel fairly confident declines much greater than this have not occurred.

Autonomic neuropathy showed a significant temporal decline at 20 years and a smaller (nonsignificant) reduction at 25 years. Whether this reduction in autonomic neuropathy rates relates to the reduction in renal disease is difficult to resolve at this stage (30). CDSP, on the other hand, showed a greater decline at both durations (20 and 25 years). We have previously shown hypertension to be a strong independent predictor of distal symmetric polyneuropathy (31), along with glycemic control and duration. Tesfaye et al. (32) have also found that cardiovascular disease risk factors predict neuropathy. Thus, ACE inhibitor therapy and better cardiovascular disease risk factor management in the later cohorts (1970s' cohort) may help explain this decline, in addition to better improvement of blood glucose.

Although low, CAD rates did not differ across diagnosis cohorts, even after excluding revascularization procedures. Only a suggestion of a decline at 25 years emerged, which was completely lost by 30 years. The failure to show a major decline in CAD may reflect a somewhat weaker relationship to glycemia than is seen for other complications (25,33–35), although recent data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study follow-up show a strong benefit of intensive therapy on cardiovascular disease outcomes (36). Of particular relevance is the observation of no improvement in blood pressure or lipid profiles at 25 years, according to diagno-

TABLE 3
Risk factor profiles by diagnosis cohort at the 25-year duration examination: the Pittsburgh EDC study ($n = 201$)

	1965–1969 cohort	1970–1974 cohort
n	98	103
A1C (%)*	10.9 ± 1.9	10.3 ± 1.8
HDL cholesterol (mg/dl)	50.8 ± 12.9	53.9 ± 13.9
LDL cholesterol (mg/dl)	116.3 ± 28.7	119.1 ± 40.3
Non-HDL cholesterol (mg/dl)	136.1 ± 34.7	139.3 ± 45.2
Triglycerides (mg/dl)†	97.2 ± 71.9	104.9 ± 61.9
Systolic blood pressure (mmHg)	118.5 ± 18.1	115.8 ± 12.4
Diastolic blood pressure (mmHg)	74.6 ± 10.1	73.5 ± 9.1
Smoking (%)	31	33
Hypertension (%)	29	28

Data are means ± SD unless otherwise indicated. *$P < 0.05$. †Log transformed before statistical testing.

sis cohort, despite a significant fall in A1C (Table 3). Unfortunately, as participants were not followed from diagnosis, we cannot fully compare risk factor exposure for the different year of onset cohorts. These results, however, underscore the importance of controlling blood pressure and lipids in type 1 diabetes, which we have recently shown to be particularly poor in this cohort (37). Another explanation for our failure to show a significant temporal effect for CAD may be lack of power due to the low disease rate and small sample size. However, we had 80% power to show the same proportionate decrease as demonstrated in renal failure at 25 years (1950–1959 vs. 1975–1980).

The particular strengths of these analyses are the representativeness of the original incident cohort (11), the inclusion of maximum data while minimizing survivor bias, and the careful and standard ascertainment of complications overtime. The major limitations are the small number of cases after stratification by diagnosis cohort, especially for CAD, and the lack of risk factor data from diagnosis onwards.

A further limitation is the possibility that self-reported laser therapy may have been performed for an ophthalmic complication other than proliferative retinopathy (e.g., macular edema), thus inflating our proliferative retinopathy rate. This seems unlikely to be a major limitation; of the 126 subjects with both laser history and photographs, only 2.4% had focal scars alone, suggesting macular edema is relatively rare in this cohort as the sole reason for laser therapy. Furthermore, 63% of the examination participants with laser history but no concurrent photographs had prior photographs showing advanced background changes, indicating they were close to the proliferative stage.

A potential confounder of our results is the age at diabetes onset, which increased with calendar year of diagnosis. However, even though age at onset may relate to complications (38,39), controlling for age at onset does not appear to negate the improved mortality (Fig. 1) and complication rates.

In conclusion, while these results show encouraging trends in complication rates, some of the improvements appear to be lost with longer follow-up, suggesting the major change has been delay not prevention. As recently noted (40), whereas the role of hyperglycemia in the development of complications is critical, other factors play a role. For CAD, which shows the least favorable change over time, these results suggest the need for a focus on its other risk factors, e.g., blood pressure and lipids, which are poorly controlled (37).

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