Trends in Persistent Proteinuria in Adult-Onset Diabetes

A population-based study

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OBJECTIVE — This study investigates temporal trends in the prevalence and incidence of persistent proteinuria among people with adult-onset diabetes (age ≥40 years).

RESEARCH DESIGN AND METHODS — The complete community-based medical records of all Rochester, Minnesota, residents with a diagnosis of diabetes or diabetes-like condition from 1945 through 1989 were reviewed to determine whether they met National Diabetes Data Group (NDDG) criteria. All confirmed diabetes cases residing in Rochester on 1 January 1970 (n = 446), 1980 (n = 647), and/or 1990 (n = 940) were identified. The medical records of these prevalence cases were reviewed from the time of the first laboratory urinalysis value to the last visit, death, or 1 April 1992 (whichever came first) for evidence of persistent proteinuria (two consecutive urinalyses positive for protein, with no subsequent negative values). Similarly, the medical records of all 1970–1989 diabetes incidence cases (n = 1,252) were reviewed to investigate temporal changes in *1*) the likelihood of having persistent proteinuria before the date NDDG criteria was met, i.e., baseline; *2*) the risk of persistent proteinuria after baseline; and *3*) the relative risk of mortality associated with persistent proteinuria.

RESULTS — The proportion of diabetes prevalence cases with persistent proteinuria on or before the prevalence date declined from 20% in 1970 to 11% in 1980 and 8% in 1990. Among the 1970–1989 diabetes incidence cases, 77 (6%) had persistent proteinuria on or before baseline; the adjusted odds declined by 50% with each 10-year increase in baseline calendar year ($P < 0.001$). Among individuals free of persistent proteinuria at baseline, 136 subsequently developed persistent proteinuria; the estimated 20-year cumulative incidence was 41% (95% CI 31–59); the adjusted risk did not differ as a function of baseline calendar year. Survival of individuals with persistent proteinuria relative to those without was reduced but did not differ by baseline calendar year.

CONCLUSIONS — The prevalence of persistent proteinuria among people with adult-onset diabetes in Rochester, Minnesota, declined 60% between 1970 and 1990. The decline appears because of a decrease in the proportion of diabetes incidence cases with persistent proteinuria before baseline rather than secular declines in the risk of persistent proteinuria after baseline or secular increases in the risk of mortality associated with persistent proteinuria. Similarity over time in age and fasting glucose at baseline, and at prevalence dates, is evidence that earlier detection of diabetes is not the sole explanation for the decline.

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Abbreviations: ESRD, end-stage renal disease; NDDG, National Diabetes Data Group.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetes is the largest single cause of end-stage renal disease (ESRD) in the U.S., and the majority of ESRD cases are individuals with adult-onset diabetes (1). There has also been a progressive and dramatic increase in the incidence of ESRD attributed to diabetes, particularly among elderly patients (1), but the explanation(s) for this is not entirely known. Possible explanations include increased acceptance and prescription of dialysis for ESRD, increased longevity, and increased prevalence and/or incidence of renal disease in this group. There have been few population-based investigations of secular trends in renal disease among individuals with adult-onset diabetes. A study of Pima Indians with type 2 diabetes found the incidence of proteinuria, a marker for the presence of renal disease, increased nearly twofold between 1965 and 1974 and between 1985 and 1994 (2). The aim of the present study was to determine whether there have been changes in the prevalence and/or incidence of persistent proteinuria in a mostly Caucasian population of individuals with adult-onset diabetes.

RESEARCH DESIGN AND METHODS

— The opportunity for population-based studies in Rochester, Minnesota, is the result of an unusual set of circumstances. Rochester is relatively isolated from other population centers and is home to one of the world's largest tertiary care medical centers, the Mayo Clinic. A majority of the medical care received by local residents is provided either by the Mayo Clinic, together with its two affiliated hospitals, or a second group practice, Olmsted Medical Center, with its affiliated hospital. Since 1907, every Mayo Clinic patient has been assigned a unique identifier, and all information from every Mayo Clinic contact (including hospital inpatient or outpatient care, office visits, emergency room and nursing home care, as well as death certificate and autopsy information) is contained within a single dossier for each patient. The diagnoses assigned and surgical procedures per-

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Table 1—*Clinical characteristics of members of the 1970, 1980, and 1990 Rochester, Minnesota, adult-onset diabetes prevalence groups*

	1970	1980	1990
n	446	647	940
Sex (% male)	41	47	49
Age when NDDG criteria were met (years)			
Men	58.8 ± 9.9	57.8 ± 9.8	58.1 ± 10.4
Women	61.6 ± 10.4	62.6 ± 11.7	61.57 ± 12.0
Age at prevalence (years)			
Men	66.4 ± 9.6	66.8 ± 10.2	67.3 ± 10.1
Women	70.7 ± 10.0	71.9 ± 11.6	71.0 ± 11.9
Duration of diabetes (years)			
Men	6.7 ± 5.9	8.0 ± 6.9	8.1 ± 7.0
Women	8.2 ± 6.6	8.8 ± 6.5	8.7 ± 7.1
Fasting glucose when NDDG criteria were met (mg/dl)	213 ± 86	208 ± 93	212 ± 84
Fasting glucose at prevalence (mg/dl)	171 ± 77	176 ± 70	178 ± 74

Data are means ± SD.

formed at each visit are coded and entered into continuously updated computer files. With funding from the National Institutes of Health (grant number AR30582), the Mayo Clinic's indexing system was expanded to include the small number of other providers of care to local residents—primarily the Olmsted Medical Center (3).

Identification of diabetes incidence and prevalence cohorts

The Rochester Epidemiology Project was used to identify all Rochester residents with a diagnosis of diabetes or a diabetes-like condition from 1 January 1945 through 31 December 1989. Complete community medical records for each potential case, including all laboratory results, were retrieved and reviewed by trained nurse abstractors under the direction of an endocrinologist. Diagnostic criteria approximated National Diabetes Data Group (NDDG) recommendations (4), i.e., two consecutive fasting glucose levels ≥140 mg/dl or 1- and 2-h levels ≥200 mg/dl obtained during a standard oral glucose tolerance test. Using the method of West (5), adjustments were made for temporal changes in laboratory methods. Individuals who failed to meet the above criteria but for whom oral agents or insulin were used for at least 2 weeks or until death also qualified as cases.

The present study took advantage of the previous identification of *1*) three prevalence groups, i.e., people who were residents of Rochester as of 1 January 1970, 1980, or 1990, and who had met NDDG criteria before the prevalence date, and *2*) the 1970–1989 diabetes incidence cohort, consisting of all Rochester residents who first met NDDG criteria during that time period (6). The present study was limited to individuals who were age ≥40 years at the time they met criteria.

Identification of persistent proteinuria

The complete (inpatient and outpatient) medical records of the above individuals were reviewed for evidence of persistent proteinuria, defined as two or more consecutive urinalyses with grade 1 or greater protein and no subsequent negative values; exceptions were made for patients who had a single negative in a string of positive values and for those who underwent dialysis or transplant. Individuals were followed from their first laboratory urinalysis value in the record until the last visit, death, or 1 April 1992 (whichever came first). The date 1 April 1992 was selected because a change in reporting of routine urinalysis protein levels from "trace or grades 1–4" (based on the sulfosalicylic acid method and in use since 1945) to the protein/osmolality ratio went into effect 20 April 1992. Vital status and date of death was obtained from medical records and, if necessary, active telephone and mail follow-up.

Data analysis

The prevalence of persistent proteinuria among the 1970, 1980, and 1990 diabetes prevalence groups was estimated as the proportion of people with onset of persistent proteinuria on or before 1 January of the prevalence year. The 95% CIs were estimated, assuming a Poisson distribution. Additional characteristics of the three prevalence groups (e.g., sex, age, and fasting glucose values at diagnosis and at prevalence) were summarized using descriptive statistics. Because 32% of individuals belonged to more than one prevalence group, statistical tests of differences among the three groups were problematic. Therefore, we conducted an additional analysis limited to individuals who met NDDG criteria <10 years before the prevalence date, thus excluding individuals from each prevalence group who belonged to more than one group. Then, the asymptotic Wilcoxon's test was used to test for a significant trend among the 1970, 1980, and 1990 prevalence groups in the proportion with persistent proteinuria at prevalence.

The 1970–1989 Rochester diabetes incidence cohort (n = 1,251) was used to estimate the probability that a person had persistent proteinuria before the date they met NDDG criteria, i.e., baseline. To identify secular trends in this probability, the significance of baseline calendar year on the likelihood of persistent proteinuria was tested using logistic regression, adjusting for age at baseline and sex in the model. The significance of two-way interaction terms and higher order polynomials was examined.

Among diabetes incidence cases free of persistent proteinuria at baseline, the subsequent cumulative incidence of persistent proteinuria was estimated using Kaplan-Meier life-table methods (7). To identify secular trends in the incidence of persistent proteinuria, the significance of baseline calendar year was tested using Cox proportional hazards (8), with age at baseline and sex in the model. Again, the significance of two-way interaction terms and higher order polynomials was examined. Tests for nonproportionality of hazards were performed (9).

Survival free of death among members of the 1970–1989 diabetes incidence cohort was assessed using Cox regression (8). The model included sex, baseline calendar year, age and presence of persistent proteinuria at baseline, and incidence of persistent proteinuria after baseline, entered as a time-dependent covariate. To identify secular trends in the relative risk of mortality associated with persistent pro-

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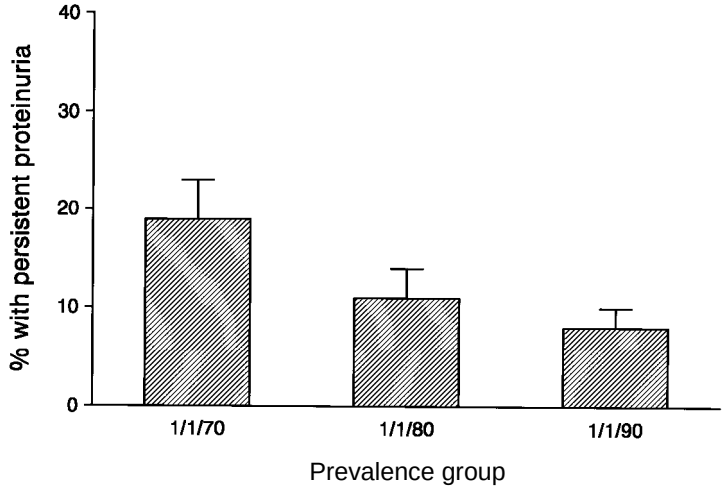

Figure 1—*Proportion of members of the 1970, 1980, and 1990 Rochester, Minnesota, adult-onset diabetes prevalence groups with persistent proteinuria on or before January 1st of the prevalence date.*

teinuria, the analysis tested for significant interactions between *1*) baseline calendar year and prevalence of persistent proteinuria at baseline and *2*) baseline calendar year and subsequent incidence of persistent proteinuria.

RESULTS — Characteristics of the 1970 (n = 446), 1980 (n = 647), and 1990 (n = 940) Rochester diabetes prevalence cases are summarized in Table 1. The three groups were similar with respect to fasting glucose at the time they met NDDG criteria and at prevalence. The proportion of men rose from 41% in 1970 to 49% in 1990; however, in each sex, age at the time they met NDDG criteria and age at prevalence were similar among the three groups. The number of individuals with persistent proteinuria on or before the prevalence dates was 89 in 1970, 72 in 1980, and 73 in 1990. The proportion decreased from 20% (95% CI 16–24) in 1970 to 11% (8.7–13.6) in 1980 to 8% (6.0–9.5) in 1990 (Fig. 1). When the analysis was limited to unique observations, i.e., people who met NDDG criteria in the 10 years before the prevalence date and therefore belonged to only one prevalence group, the proportions with prevalent persistent proteinuria were 17, 10, and 5% for 1970, 1980, and 1990, respectively ($P < 0.001$).

The Rochester diabetes 1970–1989 incidence cohort consisted of 1,251 individuals aged ≥40 years at the time they met NDDG criteria, i.e., baseline. Characteristics of incidence cases at baseline are compared for the two time periods 1970–1979 and 1980–1989 in Table 2. The two incidence cohorts were similar with respect to the proportion of men, and age and fasting glucose level at baseline. Urinalysis values were unavailable for <1% (n = 11) of individuals. These individuals were excluded from the remainder of the analyses. Of the 1,240 individuals, 6% (n = 77) had evidence of persistent proteinuria on (n = 6) or before (n = 71) baseline. There was a marked decline in this proportion with increasing baseline calendar year (Fig. 2). The probability of persistent proteinuria on or before baseline was modeled as a function of age at baseline, sex, and baseline calendar year. The final model is provided in Table 3. The odds were similar for men and women and increased significantly with age at baseline. After adjusting for age, the odds of having persistent proteinuria on or before baseline decreased by ~50% for each 10-year increase in baseline calendar year. The absence of an interaction between age and calendar year suggests that the effect of calendar year on the odds of persistent proteinuria at baseline was similar for each age.

The 1,163 diabetes incidence cases with no evidence of persistent proteinuria at baseline were followed for 8,777 person-years, during which time 136 individuals subsequently developed persistent proteinuria. The estimated 20-year cumulative incidence was 41% (95% CI 31–59). In Fig. 3, the cumulative risk of persistent proteinuria for diabetes cases who met NDDG criteria during 1970–1979 is compared with those who met criteria during 1980–1989. Cox proportional hazards was used to model the risk of developing persistent proteinuria as a function of age at baseline, sex, and baseline calendar year. Age (per 10-year increment) at baseline was significantly associated with subsequent risk of persistent proteinuria (odds ratio 1.52, 95% CI 1.30–1.77, $P <$ 0.001); but neither sex nor baseline calendar year was predictive.

Survival free of death was modeled using Cox proportional hazards. The final model (Table 4) reveals that increasing age, male sex, prevalence of persistent proteinuria at baseline, and incidence of persistent proteinuria after baseline were all significantly associated with increased risk of death. Mortality risk decreased with increasing baseline year. The contribution of persistent proteinuria at baseline to mortality decreased with increasing age and was greater for women than men. For example, the relative hazard for a 55-year-old woman was 5.6 (95% CI 3.2–9.8) and that for a 55-year-old man was 3.2 (2.0–5.3); that for an 85-year-old woman was 2.4 (1.0–3.5) and that for an 85-year-old man was 1.4 (0.8–2.4). There was no

Table 2—*Clinical characteristics of members of the 1970–1979 and 1980–1989 Rochester, Minnesota, adult-onset diabetes incidence cohorts*

	1970–1979	1980–1989
n	536	715
Sex (% male)	49	51
Age at baseline* (years)		
Men	61.7 ± 11.2	62.4 ± 11.0
Women	65.8 ± 12.5	65.1 ± 12.8
Fasting glucose at baseline* (mg/dl)	217 ± 94	218 ± 87

Data are means ± SD. *Baseline is the date NDDG criteria were met.

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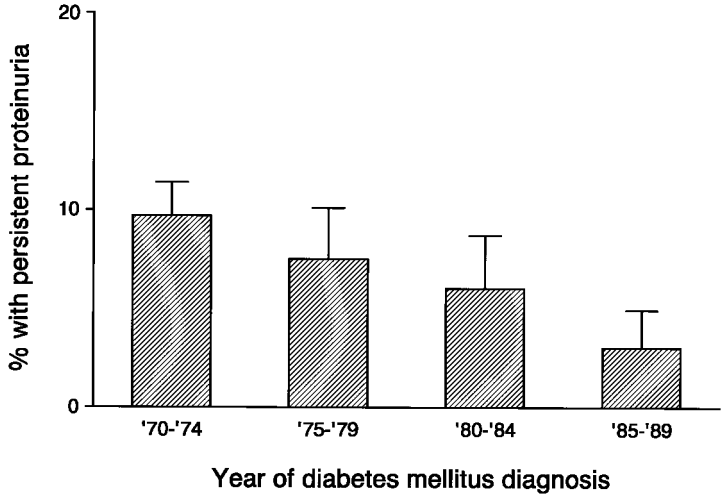

Figure 2—*Proportion of members of the 1970–1974, 1975–1979, 1980–1984, and 1985–1989 Rochester, Minnesota, adult-onset diabetes incidence cohorts with persistent proteinuria on or before the date they met NDDG criteria.*

significant interaction between baseline calendar year and either *1*) the prevalence of persistent proteinuria at baseline or *2*) the incidence of persistent proteinuria after baseline, suggesting that there was no secular trend in the relative risk of mortality associated with persistent proteinuria.

CONCLUSIONS — This study revealed that the proportion of adult-onset diabetes prevalence cases with persistent proteinuria on or before the prevalence date decreased from 20% in 1970 to 11% in 1980 and 8% in 1990 in the Rochester, Minnesota, population. The decline was accompanied by a secular decline in the proportion of adult-onset diabetes incidence cases who had persistent proteinuria on or before the date they met NDDG criteria (i.e., baseline) over the time period of 1970–1989. There was no secular trend in either the incidence of proteinuria after baseline or the effect of persistent proteinuria on mortality.

The absence of a secular trend in the risk of persistent proteinuria after baseline is similar to a previous report from Rochester in which Ballard et al. (10) found no secular trend in the incidence of persistent proteinuria among individuals who met criteria for type 2 diabetes between 1945 and 1968. The temporal decline in the prevalence of persistent proteinuria at or before baseline among diabetes incidence cases in the present study is also consistent with combined observations from two previous Rochester studies (10,11). Ballard et al. (10) found that 8.2% of the 1945–1969 type 2 diabetes incidence cohort had persistent proteinuria at or before they met criteria for diabetes. This compares with 7.2% found by Humphrey et al. (11) in their review of the Rochester cohort updated through 1979. The overall prevalence of persistent proteinuria at baseline among members of the 1970–1989 adult-onset diabetes incidence cohort in the present study was 6%. Direct comparisons of our study findings with those of Ballard et al. and Humphrey et al. is difficult, however, because of differences in diabetes case criteria. The two previous studies focused on type 2 diabetes, including all ages, rather than on individuals aged ≥40 years, and the threshold for fasting glucose in those studies was 120 mg/dl rather than the 140 mg/dl threshold used in this study.

Comparison of the present study with non-Rochester studies is even more problematic. Among nondiabetic populations, the overall prevalence of proteinuria has been reported to vary between 2 and 15% (12,13). This wide range is likely related to differences in the risk of nephropathy among different populations as well as methodological differences in the determination and definition of proteinuria. In studies that focus on people with adult-onset diabetes, differences in the definition of diabetes and in the time in the course of disease at which protein is measured contribute to even greater discrepancies in the prevalence of persistent proteinuria, with estimates ranging from 2 to 46% (13–19).

The estimated cumulative incidence of persistent proteinuria in the present study was 12% at 10 years and 41% at 20 years. This incidence compares with a cumulative incidence at 20 years of 25% reported by Ballard et al. (10) in the earlier Rochester study. The lower estimate by Ballard et al. is again due in part to the inclusion of younger subjects with milder diabetes in their study. Klein et al. (20) found a 10-year cumulative incidence of proteinuria (defined as urine protein concentration ≥0.3 g/l, as measured by a reagent strip) among Wisconsin residents with older-onset diabetes of 33–40%, depending on treatment type. The higher incidence in the study by Klein et al. is partly because Klein et al. enrolled prevalence cases (with diabetes duration ranging from 0 to 30 years), and follow-up began at enrollment.

To our knowledge, the only other population-based investigation of recent secular trends in persistent proteinuria among individuals with adult-onset diabetes is the study among Pima Indians by Nelson et al. (2), which revealed a marked increase in the cumulative incidence of proteinuria between people diagnosed with type 2 diabetes during 1965–1974 and those diagnosed during 1985–1994. The marked contrast between the findings of Nelson et al. and those reported here may be due in part to differences in methodology (diabetes in the Pima Indian study was defined based on systematic oral glucose tolerance tests; proteinuria was defined based on systematic protein/creatinine ratios) but is also likely

Table 3—*Adjusted probability of persistent proteinuria on or before baseline among members of the 1970–1989 Rochester, Minnesota, adult-onset diabetes incidence cohort*

	β	SEM	Odds ratio (95% CI)	*P* value
Age at baseline (per 10-year increment)	0.028	0.010	1.32 (1.09–1.61)	<0.01
Baseline year (per 10 years)	−0.729	0.203	0.48 (0.32–0.72)	<0.001

Baseline is the date NDDG criteria were met.

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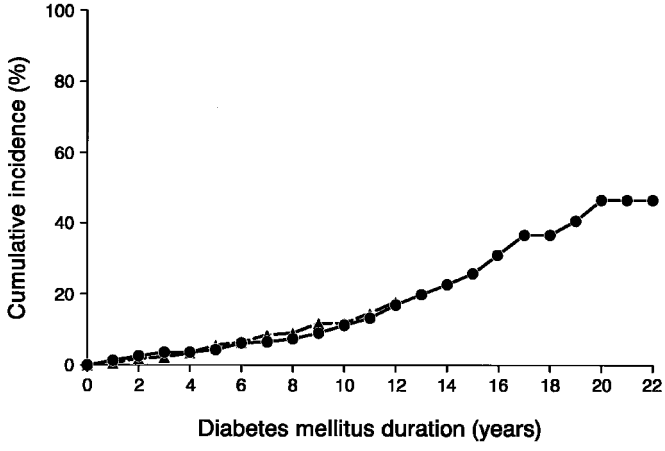

Figure 3—*Kaplan-Meier estimated cumulative incidence of persistent proteinuria among members of the 1970–1989 Rochester, Minnesota, adult-onset diabetes incidence cohort who were free of persistent proteinuria at the time they met NDDG criteria.* ●, *Individuals who met criteria in 1970–1979 (*n = *483);* ▲, *individuals who met criteria in 1980–1989 (*n = *680).*

due to major differences between study populations (Rochester is >95% white). Compared with primarily Caucasian populations, Pima Indians are characterized by earlier age of onset of diabetes, a much higher rate of renal disease, and a higher proportion of renal disease that is attributable to diabetes (2,19,21,22). Caucasian populations also differ from both diabetic and nondiabetic Pima Indians with respect to recent secular trends in cause-specific mortality (23).

One potential explanation for the secular decline in the prevalence of persistent proteinuria in the present study is that diabetes was detected earlier in more recent time periods. We cannot completely exclude this possibility, but the absence of any secular trend in either mean age or fasting glucose concentration provides indirect evidence that the decline in the prevalence of persistent proteinuria was not due to earlier detection of diabetes in more recent years. Also, if the decline in prevalence of persistent proteinuria at baseline among diabetes incidence cases was an artifact of earlier detection of diabetes, one might expect to see a temporal increase in the incidence of proteinuria after baseline or evidence of nonproportional hazards in the survival analysis. Neither was found.

Another possible explanation for the decline in the proportion of people with adult-onset diabetes who have persistent proteinuria on or before baseline is a change in the prevalence of proteinuria among the general population—diabetic and nondiabetic alike; we are presently unable to address this issue. Finally, a recent pilot study of temporal trends in hypertension and treatment for hypertension among members of the 1970–1989 Rochester diabetes incidence cohort suggests that the decline in the prevalence of persistent proteinuria was not accompanied by improved control of hypertension. Preliminary results from a random sample of 400 cases showed that the proportion of people with two outpatient blood pressure readings ≥140/90 mmHg at baseline (± 2 years) was unchanged, despite a slight but insignificant increase in the proportion of cases treated for hypertension between 1970 and 1989 (24). This latter finding is intriguing in light of clinical trial results showing certain antihypertensive medications introduced over this time period afford intrarenal arteriolar effects beyond just control of systemic hypertension for diabetic renal disease (25). Therefore, it will be important to determine whether declines in the prevalence of persistent proteinuria were accompanied by increasing use of ACE inhibitors.

There are several limits to the present study. The Rochester population is comprised largely of middle-class Caucasians of northern European ancestry, so these results cannot necessarily be extrapolated to the general population of the U.S. Another limitation is that, although the method of measuring proteinuria was consistent, the frequency and timing of urinalysis was not. The presence of persistent proteinuria was based on urinalysis samples obtained during routine medical care and not on 24-h urine total protein measurements. Proteinuria based on random samples is semiquantitative, and a positive result may not always represent clinically significant proteinuria. Cases of transiently increased proteinuria were excluded, however, because the present study defined persistent proteinuria as two or more consecutive urinalyses with grade 1 or greater protein and no subsequent negative values. Among individuals who had two consecutive values, those who emigrated or died were considered a case, whereas those who survived and acquired additional negative values were not considered a case. This distinction could account for the observed secular decline in the prevalence of persistent proteinuria on or before baseline if the opportunity to acquire subsequent negative values was greater for people who met NDDG criteria in recent years relative to those who met it earlier.

Table 4—*Adjusted risk of death among members of the 1970–1989 Rochester, Minnesota, adult-onset diabetes incidence cohort*

	β	SEM	Relative risk (95% CI)	*P* value
Male sex	0.318	0.098	—	0.001
Baseline year (per 10 years)	−0.222	0.094	0.80 (0.67–0.96)	<0.05
Age at baseline (per 10-year increments)	0.730	0.046	—	<0.001
Persistent proteinuria on or before baseline	3.246	0.857	—	<0.001
Persistent proteinuria after baseline	1.239	0.132	3.45 (2.66–4.47)	<0.001
Persistent proteinuria on or before baseline and age at baseline	−0.028	0.011	—	<0.05
Persistent proteinuria on or before baseline and male sex	−0.546	0.276	—	0.05

Baseline is the date NDDG criteria were met.

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This was not the case, however; follow-up for all individuals was censored as of April 1992. Therefore, the average follow-up for recent diabetes cases was less than that for earlier diabetes cases.

The implications of this study include the potential impact of proteinuria on the risk for end-stage renal disease and increased mortality and morbidity. The prevalence of end-stage renal disease among older patients with diabetes appears to be increasing in the U.S. on the basis of reports of a significant increase in the number of patients with type 2 diabetes receiving renal replacement therapy (1,26). Among Rochester residents with prevalent diabetes, the number of individuals who had a functioning renal allograft or were receiving dialysis in the first week of January of 1970, 1980, and 1990 was zero, one, and six, respectively. Among all Rochester residents aged ≥40 years, the proportion with adult-onset diabetes and persistent proteinuria on 1 January 1970, 1980, and 1990 decreased from 539 to 391 to 307 per 100,000 individuals, respectively. Because it takes years for most patients with persistent proteinuria to progress to end-stage renal disease, these changes in persistent proteinuria over the past 2 decades may not yet be reflected by current trends in end-stage renal disease. However, if the results of this and previous Rochester studies (10,11) are generalizable to the U.S. white population, it appears that the increase in number of patients receiving renal replacement therapy cannot be explained by an increase in the prevalence or incidence of renal disease among individuals with adult-onset diabetes, at least as defined by the presence of persistent proteinuria.

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