A Comparison of Renal Disease Across Two Continents

The Epidemiology of Diabetes Complications Study and the EURODIAB IDDM Complications Study

CATHY E. LLOYD, PHD
JUDITH STEPHENSON, MD
JOHN H FULLER, MRCP
TREVOR J. ORCHARD, MBBCH, MMEDSCI

OBJECTIVE — To compare prevalence rates of increased albumin excretion in the Epidemiology of Diabetes Complications Study (EDC) (in the U.S.) to similar rates in the EURODIAB study (in Europe) and determine if any differences relate to hypertension, glycemic control, or smoking status.

RESEARCH DESIGN AND METHODS — The study population is made up of two epidemiological clinic-based IDDM populations with comparable ages (x = 28 years, both studies), sex distribution (50% male, EURODIAB; 49% male, EDC), and duration characteristics. Comparison of two cross-sectional (prevalence) studies was made. Despite different laboratory assays, comparability was established for urinary albumin (r = 0.98) and GHb measures (r = 0.95). Hypertension was measured with an identical protocol. Renal status was determined by 24-h urine albumin excretion (<20 μg/min normal, 20–200 μg/min microalbuminuria, >200 μg/min macroalbuminuria) in EURODIAB. Identical cutoffs were used for EDC, though two of three samples (24-h, 4-h clinic, and/or overnight sample) had to be positive in one range. (Main findings are confirmed using only 24-h results from EDC.)

RESULTS — The prevalence of macroalbuminuria was higher in EDC (27%) than in EURODIAB (12%). Rates of microalbuminuria were similar (22 vs. 25%, respectively). These patterns were seen at all durations and ages and in both sexes. Controlling for glycemic control, hypertension, or smoking did not account for the higher rate in EDC, nor did exclusion of subjects with raised serum creatinine.

CONCLUSIONS — Advanced renal disease is more prevalent in IDDM in EDC (Pittsburgh, PA) than in Europe. This is not explained by hypertension, glycemic control, or smoking.

Renal disease is one of the most devastating of diabetes complications, being a major cause of death and an important predictor of cardiovascular disease (1,2). The prevalence of renal morbidity and mortality in IDDM has been shown to differ around the world, the reasons for which may extend beyond the availability of treatment (3,4). One aspect of renal disease that does not differ regionally is a strong association between this diabetic complication and both hypertension and glycemic control. Many researchers have demonstrated that these are the two most important risk factors for renal disease (2,5–9), including the recent Diabetes Control and Complications Trial (10). The aim of this article is to report the prevalence of renal disease in two populations of IDDM patients (one in Europe and one in the U.S.) to identify prevalence differences if they exist and to assess whether any differences are related to either of the two main risk factors for renal disease, i.e., glycemic control and hypertension.

From the Graduate School of Public Health (C.E.L., T.J.O.), University of Pittsburgh, Pittsburgh, Pennsylvania (Epidemiology of Diabetes Complications Study); and the Department of Epidemiology and Public Health (J.S., J.H.F.), University College London, London, U.K. (EURODIAB IDDM Complications Study).

Address correspondence and reprint requests to Trevor J. Orchard, MD, 5th Floor, Rangos Research Center, 3460 Fifth Ave., Pittsburgh, PA 15213.

Received for publication 23 February 1995 and accepted in revised form 26 October 1995.

BP, blood pressure; EDC, Epidemiology of Diabetes Complications Study; OR, odds ratio.

RESEARCH DESIGN AND METHODS

Study populations

The Epidemiology of Diabetes Complications Study (EDC) population has been described elsewhere previously (11). Briefly, the EDC is a prospective investigation of the development of diabetes complications in a U.S. IDDM population (Pittsburgh, PA). All subjects were originally part of a 1950–1980 registry of IDDM patients at the Children's Hospital of Pittsburgh, which included all those diagnosed with IDDM before the age of 17 and seen at the hospital within 1 year of diagnosis. When recruited into the EDC in 1986–1988, the minimum duration of diabetes (and age) was 6 years, with a maximum age of 54 years and duration of 38 years. At entry to the study, subjects were mailed questionnaires and invited to attend the research center for a full clinical examination, including assessment for the presence of each of the major diabetic complications. Subjects also collected three timed urine samples: an overnight, a 24-h, and a 4-h clinic sample. Participants continue to be followed-up every 2 years after their baseline exam.

Full details of the EURODIAB IDDM Complications Study methodology have also been published elsewhere (4). Subjects were seen between 1988 and 1990. IDDM was defined as diabetes diagnosed before age 36 with a continuous need for insulin from within 1 year after diagnosis. The EURODIAB study population consists of 31 stratified random samples of clinic IDDM patients aged between 15 and 60 years. Patients were stratified by sex, age (15–29, 30–44, and 45–60 years), and duration of disease (1–7, 8–14, and ≥15 years). Each center's investigators followed standardized procedures to assess the presence of IDDM complications. Albumin excretion rates

were calculated from a timed 24-h urine collection measured in a single laboratory.

For the purposes of this report, comparable populations were identified by including only those with IDDM diagnosed before the age of 17 and only those with durations of diabetes >6 years at the time of the study. Similarly, to achieve comparability by age, only those ≥15 years of age were included.

Definition of albuminuria

Microalbuminuria was defined as an albumin excretion rate between 20 and 200 μg/min. Macroalbuminuria was defined as an albumin excretion rate >200 μg/min. These limits were applied to the single 24-h collection in the EURODIAB study, while for the EDC, two out of three samples (24-h, overnight, and/or 4-h clinic) had to be positive. In EDC, urine collections were validated by creatinine excretion. When a classification could not be made on the basis of two valid collections, a previously validated albumin creatinine ratio from the preclinic spot urine was used. Urine collections were not validated in EURODIAB. To ensure that these classification differences did not affect the results, key findings were repeated using only the 24-h samples from EDC (n = 540). Similar or somewhat stronger results were seen. In EDC, 91% of subjects were identically identified by both the 24-h sample alone and the two-out-of-three method (Table 3).

A blinded stratified sample (n = 24) of urine (with equal proportions of urine samples taken from normoalbuminuric, microalbuminuric, and macroalbuminuric patients) was taken from the EDC center to be measured by the EURODIAB study research team. Analysis demonstrated a high correlation (r = 0.98; $P < 0.0001$) between the measurements of the samples taken by the two centers.

Possible differences in classification of albuminuria (i.e., normo-, micro-, and macroalbuminuria) were also examined using equivalent albumin concentrations. Using >19 mg/l as the cutoff for microalbuminuria and >192 mg/l for macroalbuminuria, we found 100% agreement for determining normoalbuminuria versus micro-/macroalbuminuria and 71% agreement for macroalbuminuria alone (of the seven found to be overt by EDC, five were also found to be overt by EURODIAB.)

Measurement of glycemic control

For the EDC, GHb (stable levels of total HbA_1) was originally measured with saline-incubated blood samples and microcolumn cation-exchange chromatography (Isolab, Akron, OH). In October 1987, the GHb technique was changed to high-performance liquid chromatography (Diamat, Bio-Rad, Hercules, CA), with no systematic differences observed when duplicate samples were run (r = 0.95, with an absolute difference of 0.158 [% HbA_1]). The normal range for this measure of GHb is <7.4%. For EURODIAB, HbA_{1c} was measured in a central laboratory by an enzyme immunoassay using a monoclonal antibody raised against HbA_{1c} (Dako, Ely, U.K.), the normal range being <4.9%.

A consecutive series of blood samples (n = 25) was taken from the EDC and measured by the EURODIAB study group. Results showed a high correlation (r = 0.95; $P < 0.001$) between the two sets of measurements.

Measurement of hypertension

In both studies, a random zero sphygmomanometer was used to measure blood pressure (BP), with the mean of the first and second readings recorded for the purposes of this analysis. The presence of hypertension was defined as systolic BP ≥140, diastolic BP ≥90, or a condition needing medication for high BP.

Statistical analysis

Statistical comparisons were made between groups, both within and between the two study populations, using the χ^2 test. To calculate odds ratios (ORs), the Mantel-Haenszel test (adjusting for other factors where necessary) was used. When making comparisons by level of glycemic control, tertiles of GHb were calculated at the Pittsburgh center and cutoff values were transformed to give comparable tertile values for HbA_{1c} for the EURODIAB data ($y = 4.6289 + 0.82335x$) based on the regression equation derived from the 25 duplicate samples measured by both centers.

RESULTS — Table 1 shows the demographic characteristics for the two study populations. Although the EURODIAB study has approximately double the number of study participants in the appropriate age, duration, and age-at-diagnosis categories, both studies have equal proportions of men and women and have similar proportions of the two age-groups to be considered. Although the mean age of both EURODIAB and EDC was 28 years, a greater proportion of EDC participants were ≥30 years of age ($P < 0.001$). Mean duration of diabetes was 18 years for EURODIAB and 20 years for EDC (data not shown). Overall, EURODIAB subjects were more likely to have hypertension ($P < 0.05$), particularly women ($P < 0.05$). However, a similar sex-specific pattern was observed for both studies, with a greater proportion of men having hypertension in both EURODIAB

Table 1—*Characteristics of study populations for the EURODIAB and EDC studies*

	EURODIAB		EDC	
	Men	Women	Men	Women
Total n	608	607	318	309
Age				
15–29 years	424 (70)	400 (66)	191 (60)	178 (58)
≥30 years	184 (30)	207 (34)	127 (40)	131 (42)
GHb in normal range	2 (1)	5 (2)	59 (10)	90 (15)
Hypertension	151 (25)	123 (20)	67 (21)	43 (14)
On BP medications	66 (11)	50 (8)	48 (15)	28 (9)
Current/exsmoker	296 (49)	255 (42)	130 (41)	114 (37)

Data are n (%). EDC has a greater proportion of subjects ≥30 years of age ($P < 0.001$). EURODIAB has a greater proportion of hypertensive subjects (overall, $P < 0.05$; men, NS; women, $P < 0.05$). Men are more likely to be hypertensive (EURODIAB, $P = 0.06$; EDC, $P < 0.05$). There is no difference by sex or study in frequency of BP medications. EURODIAB has a greater proportion of smokers ($P < 0.01$; men, $P = 0.03$; women, $P = 0.16$).

Table 2—*Prevalence of micro-/macroalbuminuria in two populations: the EDC and EURODIAB studies*

	Total	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Overall				
EDC	627	320 (51)	137 (22)	170 (27)*
EURODIAB	215	766 (63)	308 (25)	141 (12)
Men				
EDC	318	148 (46)	75 (24)	95 (30)*
EURODIAB	608	364 (60)	172 (28)	72 (12)
Women				
EDC	309	172 (56)	62 (20)	75 (24)*
EURODIAB	607	402 (66)	136 (23)	69 (11)
Age 15–29 years				
EDC	369	224 (61)	77 (21)	68 (18)*
EURODIAB	824	531 (64)	214 (26)	79 (10)
Age ≥30 years				
EDC	258	96 (37)	60 (23)	102 (40)*
EURODIAB	391	235 (60)	94 (24)	62 (16)

Data *n* and *n* (%). *$P < 0.0001$ compared with EURODIAB subjects.

($P = 0.06$) and EDC ($P < 0.05$). In contrast, EDC participants were somewhat more likely to be on BP medications; however, this only approached significance in men ($P = 0.07$). A greater proportion of hypertensive subjects were, thus, on BP medication in EDC (69%) than in EURODIAB (43%) ($P < 0.001$). Again, a similar sex-specific distribution was observed within both populations, with somewhat more men than women being on BP medications in both studies (EURODIAB, $P = 0.14$; EDC, $P = 0.03$). Among treated hypertensive subjects, a greater proportion was controlled (<140/90) in EDC (55%) than in EURODIAB (43%), though this was not significant ($P = 0.14$). Finally, EURODIAB participants were more likely to be smokers than EDC subjects ($P < 0.01$), a difference stronger in men ($P = 0.03$) than in women ($P = 0.16$). EURODIAB men were significantly more likely to smoke than EURODIAB women ($P = 0.02$), while this sex difference was not significant within the EDC population ($P = 0.35$).

Table 2 shows the prevalence of micro- and macroalbuminuria for both EURODIAB and EDC participants. Overall, a significantly greater proportion of EDC subjects were macroalbuminuric compared with those in the EURODIAB study (27 vs. 12%; $P < 0.0001$). This was also the case in sex-specific analyses and in both age-groups (15–29 and ≥30 years), although the difference was more striking in the older group. Although approximately equal proportions of EDC and EURODIAB participants had microalbuminuria overall (22 and 25%), the EURODIAB data indicated a somewhat greater prevalence of microalbuminuria in the younger age-group (26 vs. 21%), with no difference in those >30 years of age (24 vs. 23%).

The prevalence of albuminuria was calculated across five duration groups, as shown in Fig. 1. Unlike that of microalbuminuria, the prevalence of macroalbuminuria increased significantly by duration for EDC ($P = 0.000$, Mantel-Haenszel test for linear trend) and EURODIAB ($P = 0.000$). With the exception of the duration group of 20–24 years, the prevalence rates for microalbuminuria, although remaining more constant over time, were slightly lower in the EDC population compared with those for the EURODIAB study. A much greater difference in between-center rates is shown for macroalbuminuria (Fig. 1), where the EDC rates were consistently higher than those of EURODIAB across duration groups 10–14 years and above. Indeed, by a duration of 20–24 years, there was a twofold difference, and by durations of ≥25 years, there was almost a threefold difference in prevalence rates of macroalbuminuria between the two studies. Similar patterns were observed for men and women when considered separately, with greater differences in the prevalence of macroalbuminuria compared with microalbuminuria. When these trends were examined in the younger age-group, i.e., 15–29 years old (Fig. 2), once again little difference in the prevalence of microalbuminuria was observed across the duration groups. However, it was possible to see a gradual increase in the prevalence rates of macroalbuminuria as duration of diabetes increased, with very low rates at the earliest durations and rates of ~20% for EDC and 10% for EURODIAB by the later durations of IDDM. For subjects ≥30 years of age (Fig. 3), little difference in the prev-

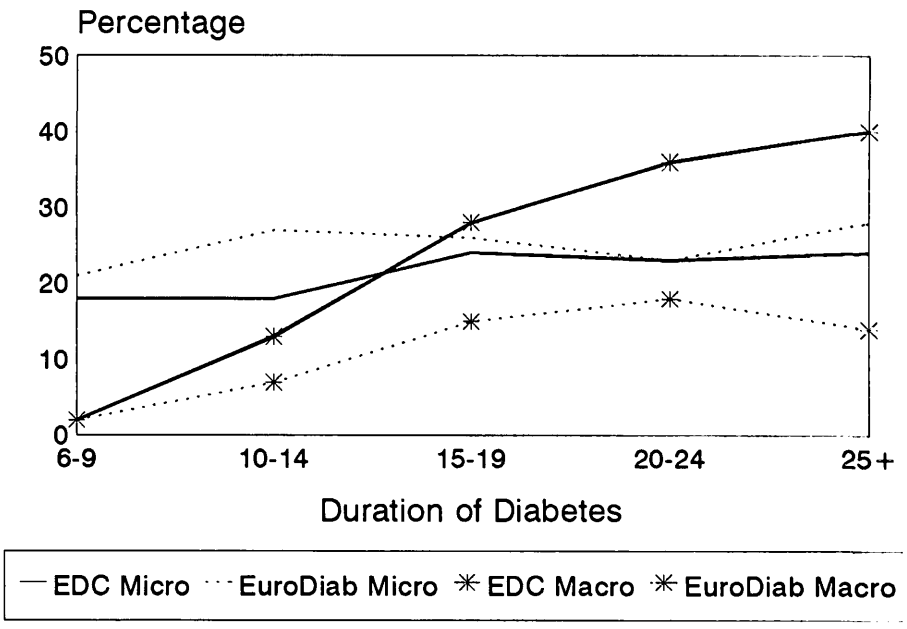

Figure 1—*Prevalence of albuminuria by duration of diabetes and study group.*

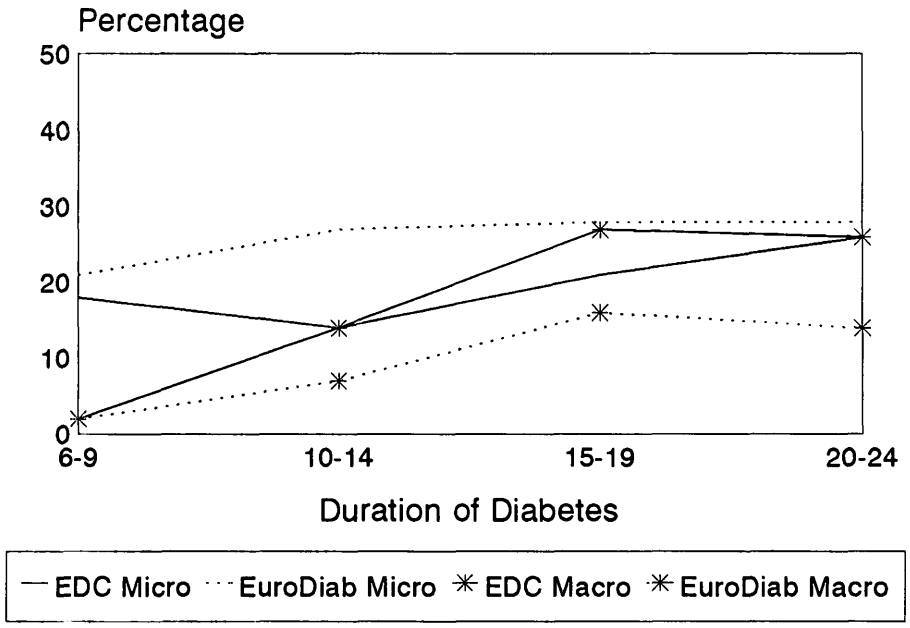

Figure 2—*Prevalence of albuminuria by duration of diabetes and study group: subjects aged 15–29 years.*

alence of microalbuminuria but a consistently higher prevalence of macroalbuminuria in EDC participants compared with EURODIAB subjects can be observed.

To examine whether the differences in the prevalence of albuminuria were associated with particular risk factors for renal disease, we compared the prevalence rates of albuminuria (micro- and macroalbuminuria) in each study by hypertension and smoking status and in those with different levels of glycemic control. Using a standard definition of hypertension (having a BP >140/90 or needing antihypertensive medication), history of cigarette use, and tertiles of GHb calculated from the EDC distribution of this variable (see METHODS), we report ORs for increased albumin excretion in Table 3. Again, adjustment for glycemic control did not reduce the OR, unadjusted, followed by a Mantel-Haenszel adjustment for each risk factor for EDC versus EURODIAB participants for developing micro-/macroalbuminuria. The unadjusted OR was 1.5 (CI 1.2–1.8) for EDC versus EURODIAB, demonstrating a greater risk for increased albuminuria for EDC participants compared with EURODIAB subjects. Adjustment for duration had no effect. When adjusted for hypertension, the OR increased slightly, showing an even greater risk of developing renal disease in the EDC participants versus the EURODIAB group (OR 1.9, CI 1.5–2.3). When this OR was adjusted for glycemic control, the OR remained similar to the unadjusted value (1.6, CI 1.3–2.0). Finally, when adjusted for smoking status, the OR also increased. These results suggest that even when accounting for these four important risk factors, there is still an excess risk of developing renal disease (micro- or macroalbuminuria) for EDC participants compared with EURODIAB subjects. When the ORs were recalculated after stratification by duration, it was clear that the major effect is in the longer-duration group, which contains the majority of cases of macroalbuminuria.

The same analysis was performed, but this time it compared normoalbuminuric and microalbuminuric subjects with macroalbuminuric subjects. A similar pattern to that described above was observed; however, even greater relative risks for developing macroalbuminuria alone were observed. The unadjusted relative risk was 2.8, which increased to 4.4 when adjusted for hypertension, and remained almost the same as when unadjusted at 2.7 when adjusted for glycemic control. These data suggest that most of the excess risk lies in macroalbuminuria rather than in microalbuminuria. These patterns were, if anything, stronger if the EDC data set were limited to 24-h urine samples.

CONCLUSIONS— This report has demonstrated a significant difference in the prevalence of albuminuria, particu-

Table 3—*ORs for increased albumin urinary excretion (>20 μg/min) in EDC compared with EURODIAB, unadjusted and adjusted for duration, hypertension, glycemic control, and smoking status*

	OR	95% CI	*P* value
Overall analysis			
Unadjusted	1.5	1.2–1.8	<0.0001
Duration adjusted	1.5	1.2–1.9	<0.0001
Hypertension adjusted	1.9	1.5–2.3	<0.0001
Glycemic control adjusted	1.6	1.3–2.0	<0.0001
Smoking adjusted	1.7	1.4–2.1	<0.0001
<20 years' duration			
Unadjusted	1.1	0.8–1.5	0.46
Hypertension adjusted	1.4	1.0–1.8	0.03
Glycemic control adjusted	1.2	0.9–1.5	0.29
Smoking adjusted	1.2	0.9–1.6	0.20
>20 years' duration			
Unadjusted	2.2	1.6–3.0	<0.0001
Hypertension adjusted	2.2	2.0–4.1	<0.0001
Glycemic control adjusted	2.0	1.4–2.8	<0.0001
Smoking adjusted	2.4	1.7–3.4	<0.0001

In the overall analysis, if a subset of 540 subjects in the EDC classified by only a 24-h urine was used, virtually identical or higher ORs were obtained, i.e., unadjusted 1.7 (1.4–2.1); duration adjusted 1.8 (1.4–2.2); hypertension adjusted 2.2 (1.7–2.7); glycemic control adjusted 1.9 (1.5–2.3); and smoking adjusted 2.0 (1.7–2.6). For duration, categories are <20, ≥20 years duration. For hypertension, categories are hypertensive (having a BP >140/90 or on BP medications): yes/no. For glycemic control, categories are tertile of GHb. For smoking, categories are non-, ex-, current smoker.

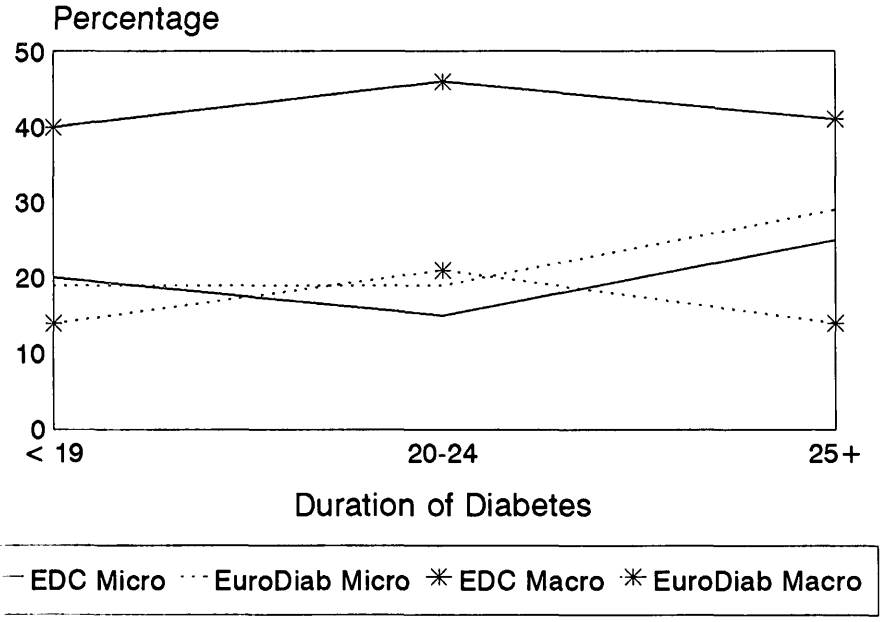

Figure 3—*Prevalence of albuminuria by duration of diabetes and study group: subjects aged ≥30 years.*

larly macroalbuminuria, between two study populations, one in Europe and one in the U.S. The difference in rates of macroalbuminuria has been shown to remain constant across several duration groups, within two age-groups, and between the sexes. We have shown that these are two comparable study populations; their age ranges and mean ages are similar, as are their durations of diabetes. Although the EDC is based on a hospital registry and is thought to be representative of the local IDDM population (12) and EURODIAB is a clinic-based study, we feel that the different rates of renal disease are not explained by this fact. Indeed, when the EDC population was redefined so as to include only those who had seen a doctor in the past year (to approximate a clinic-based group), little difference in the results was observed. The frequency of macroalbuminuric subjects in the EDC increased minimally, by 2%, with a comparable decrease in the rate of microalbuminuria. All other results remained the same. The different number of urine samples used to determine nephropathy status (one 24-h urine in EURODIAB; 24-h, 4-h, and overnight urine in EDC) is also not relevant, because agreement between the two methods was high (91%). When analysis was limited to 24-h collections only, even higher rates of increased albumin excretion were seen in EDC (i.e., 52 vs. 50%) and the ORs were higher (Table 3).

A second aim of this report was to examine whether any differences in albuminuria rates in two study populations could be explained by parallel differences in risk factors for renal disease. The main difference in the prevalence rates of renal disease lay in the rates of macroalbuminuria. These higher rates were observed in both duration groups, age-groups, and sexes and therefore could not be explained by these factors. The relationship between albuminuria and hypertension was examined next because a strong association with this factor has been reported previously (13,14). Although rates of hypertension were somewhat lower in EDC compared with EURODIAB, rates of macroalbuminuria were significantly higher in the EDC compared with the EURODIAB study. As Table 3 demonstrates, even in the nonhypertensive subjects, EDC rates of micro- and macroalbuminuria were higher than those of EURODIAB. This was also the case when normoalbuminuric and microalbuminuric subjects were compared with macroalbuminuric subjects, with an even greater OR observed for EDC. Neither more frequent use of BP medication nor better control of BP appears to account for these results because both of these factors favored EDC, which had a higher rate of macroalbuminuria. An alternative approach, using tertiles of BP rather than hypertensive/nonhypertensive, has shown that it is unlikely that these findings are due to classification differences. When tertiles of BP were examined for both studies, an excess of albuminuria was still observed for EDC participants, even for those with the lowest BPs. These results suggest that the presence of hypertension may not explain the difference in prevalence rates of albuminuria. However, it should be recognized that because these are cross-sectional data and renal disease is known to raise BP, these results may merely reflect a similar effect of albuminuria in causing hypertension rather than the reverse. Similarly, it is difficult to interpret the role of specific antihypertensive agents because the choice of agent may have been based on the presence of proteinuria rather than causing it. It is interesting to note, however, that more treated hypertensive subjects were using ACE inhibitors in EURODIAB (62%) than in EDC (42%, $P = 0.04$), while diuretics were more common in EDC (85%) than in EURODIAB (16%, $P < 0.001$). Clearly, however, ACE inhibitors cannot explain all of the excess of proteinuria seen in EDC, because even in nonhypertensive subjects (i.e., on no medication), the excess is seen (Table 3). A history of parental hypertension related neither to the prevalence of raised albumin excretion in either study population nor to the population differences (data not shown).

A second major determinant of nephropathy has been shown to be glycemic control (10,15,16). Therefore, we also assessed differences in glycemic control as one possible explanation for the study differences in albuminuria. Although overall a greater proportion of EURODIAB subjects are in good glycemic control (defined as within the normal range of control), by using tertiles of GHb defined by the EDC, we have been able to make useful comparisons between the two study populations. Using EDC cutoffs for these tertiles, it can be shown that 30% of the subjects in both studies are in the bottom tertile of control. However, even in the bottom tertile of GHb, EDC participants are more likely to have albuminuria compared with EURODIAB participants.

The EDC distribution of albuminuria versus GHb is somewhat different from that of EURODIAB in that similar proportions of EDC subjects in the first and second tertiles of GHb have albuminuria, with a substantially greater proportion having albuminuria in the top tertile

of GHb. In contrast, the EURODIAB data follows a smoother pattern, with a more gradual increase in the proportion of subjects with albuminuria in each tertile of GHb. Although this may indicate a somewhat different relationship between glycemic control and albuminuria within each study, our results show that even when adjusting for GHb, the EDC subjects still have a greater risk of developing renal disease. While it is accepted that a single GHb measurement may not adequately reflect glycemic control since diagnosis, it is a fair proxy, correlating strongly (r = 0.74, $P < 0.001$) with the mean of four samples per year over the prior 5 years (17).

Smoking, a third factor that potentially may have accounted for the difference, clearly does not because this is more frequent (both current and past) in the lower-risk EURODIAB population. Controlling for smoking status does not reduce the OR (Table 3).

In summary, we have shown that in spite of similar durations of diabetes, similar sex distribution, lower rates of hypertension, and use of the same cutoffs for glycemic control, EDC participants are significantly more likely to experience renal disease than EURODIAB participants. Although there are some differences in the distribution of GHb, we do not feel that these adequately explain the greater risk of macroalbuminuria in EDC. Even though the EURODIAB population is clinic based, we have been able to define a similar EDC population of those under current care to make the same comparisons reported here. We find that excluding those individuals not treated recently does not alter our results. Similarly, if we exclude subjects with a raised serum creatinine (>2 mg/dl) from the EDC population (because it is possible that such subjects in Europe may be referred to a renal clinic), an excess of macroalbuminuria still exists (22.5% EDC vs. 12% EURODIAB). In an earlier comparison with other U.S. studies, we also reported an apparent prevalence rate of both micro- and macroalbuminuria in EDC (18).

When ORs were calculated for EDC versus EURODIAB, it was shown clearly that EDC subjects have an increased prevalence of the later stage of renal disease, i.e., macroalbuminuria, compared with EURODIAB subjects. Furthermore, the risk of macroalbuminuria remains or even increases when adjusted for the four main determinants of renal disease: duration, glycemic control, hypertension, and smoking. Even in those with fair glycemic control and those without hypertension, EDC participants were more likely to have albuminuria, especially macroalbuminuria. Future analysis will focus further on additional possible determinants for these prevalence differences. Follow-up (incidence) data will be most helpful in explaining these differences.

Acknowledgments— This work was supported by the National Institutes of Health Grant DK-34818. The study was part of the EURODIAB Concerted Action Programme financially supported by the Commission of the European Communities. Additional financial support was received from ICI UK, Fidia, Bayer, Miles-Ames, Novo Nordisk, and Pfizer.

We would like to thank Robb Wilson and Lynda Stevens for statistical expertise; we also thank the collaborators, co-investigators, and participants in both the EURODIAB and EDC studies.

APPENDIX

EURODIAB investigators

B. Karamanos, C. Tountas, A. Kofinis, K. Petrou, and N. Katsilambros of Hippokration Hospital, Athens, Greece. R. Giorgino, M. Cignarelli, M.L. DeCicco, and I. Ramunni of Istituto di Clinica Medica, Endocrinologia e Malattie Metaboliche, Univesita di Bari, Bari, Italy. C. Ionescu-Tirgoviste, C.M. Iosif, D. Pitei, and S. Buligescu of the Clinic of Diabetes, Nutrition & Metabolic Diseases, Bucharest, Romania. G. Tamas, Z. Zerenyi, A.M. Ahmed, J. Toth, and P. Kempler of Tetenyi Teaching Hospital and Semmelweis University, Budapest, Hungary. S. Muntoni, M. Songini, M. Stabilini, M. Fossarello, and S. Pintus of Ospedale San Michele, Cagliari, Italy. J.B. Ferriss, C.C. Cronin, A.E. Whyte, and P.E. Cleary of Cork Regional Hospital, Cork, Ireland. M.Toeller, A. Klischan, T. Forst, and F.A. Gries of Diabetes Forschungsinstitut and W. Wagener of Medizinische Klinik E, Universitat Dusseldorf, Germany. R. Rottiers and H. Priem of University Hospital of Gent, Belgium. P. Ebeling, M. Sinisalo, and V.A. Koivisto of University Hospital of Helsin ki, Finland. B. Idzior-Walus, B. Solnica, L. Szopinska-Ciba, and K. Solnica of University School of Medicine, Krakow, Poland. H.M.J. Krans, H.H.P.J. Lemkes, J.J. Jansen, and J.Brachter of University Hospital of Leiden, The Netherlands. J. Nunes-Correa and J. Boavida of the Portuguese Diabetic Association, Lisbon, Portugal. G. Michel and R. Wirion of Centre Hospitalier, Luxembourg. A.J.M. Boulton, H. Ashe, and D.J.S. Fernando of Manchester Royal Infirmary, U.K. G. Pozza, G. Slaviero, G. Comi, B. Fattor, and F. Bandello of Ospedale San Raffaele, Milan, Italy. H. Mehnert, A. Nuber, and H. Janka of City Hospital Schwabing, Munich, Germany. D. Ben Soussan, M.-C. Fallas, and P. Fallas of Centre Hospitalier de Valenciennes, France. E. Jepson and S. McHardy-Young of Central Middlesex Hospital, and J.H. Fuller, D.J. Betteridge, and M. Milne of University College Hospital, NW London, U.K. G. Crepaldi and R. Nosadini of Instituto di Medicina Interna, Padua, Italy. G. Cathelineau, B. Villatte Cathelineau, M. Jellal, N. Grodner, and P. Gervais Feiss of Hospital Saint-Louis, Paris, France. F. Santeusanio, G. Rosi, M.R.M. Ventura, C. Cagini, and C. Marino of Instituto di Patologia Medica, Policlinico, Perugia, Italy. R. Navalesi, G. Penno, R. Miccoli, M. Nannipieri, S. Manfredi, Instituto di Clinica Medica II, Pisa, Italy. G. Ghirlanda, P. Cotroneo, A. Manto, C. Teodonio, and A. Minnella of Universita Cattolica del Sacro Cuore, Rome, Italy. J.D. Ward, S. Tesfaye, C. Mody, and C. Rudd of Royal Hallamshire Hospital, Sheffield, U.K. G.M. Molinatti, F. Vitelli, M. Porta, G.F. Pagano, C. Cavallo Perin, P. Estivi, R. Sivieri, Q. Carta, and G. Petraroli of Clinica Medica B, Patologia Medica, Ospedale Molinette and Ospedale "Agnelli," Turin, Italy. N. Papazoglou, G. Manes, G. Triantphyllou, A. Ioannides, G. Skazagar, and I. Kontogiannis of General Hospital of Thessaloniki, Greece. M. Muggeo, V. Cacciatori, F. Bellavere, P. Galante, and M.L. Gemma of Cattedra di Malatties del Metabolismo, Verona, Italy. K. Irsigler, H. Abrahamian, C. Gurdet, B. Hornlein, and C. Willinger of Hospital Vienna Lainz, Austria. S. Walford, E.V. Wardle, and S. Hughes of New Cross Hospital, Wolverhampton, U.K. G. Roglic, Z. Resman, Z. Metelko, and Z. Skrabalo of Vuk Vrhovac Institute for Diabetes, Zagreb, Croatia.

Steering committee members

J.H. Fuller (London), H. Keen, chairman (London), H.M.J. Krans (Leiden), R. Navelesi (Pisa), A.-K. Sjolie (Aarhus), J.M. Stephenson (London), M. Toeller (Dus-

seldorf), G.-C. Viberti (London), J. Ward (Sheffield).

Coordinating centre
J.H. Fuller, J. Stephenson, T. Partridge, and M. Milne of UCL Medical School, U.K.

Central laboratories
G. John of The Royal London Hospital and G.-C. Viberti, M. Mattock, A. Collins, A. Dredge, and R. Sharp of Guy's Hospital, London, U.K.

Retinopathy coordination
A.-K. Sjolie of Aarhus University Hospital, Denmark.

Retinopathy grading centre
E. Kohner, S. Aldington, and S. Cockley of Hammersmith Hospital, London, U.K.

References

1. Geiss LS, Herman WH, Teutsch SM: Diabetes and renal mortality in the United States. *Am J Publ Health* 75:1325–1326, 1985
2. Torffvit O, Agardh CD: The predictive value of albuminuria for cardiovascular and renal disease: a 5 year follow-up study of 476 patients with type 1 diabetes mellitus. *J Diabetic Complications* 7:49–56, 1993
3. DERI Mortality Study Group: International evaluation of cause-specific mortality and IDDM. *Diabetes Care* 14:55–60, 1990
4. Stephenson J, Fuller JH, the Eurodiab IDDM Complications Study Group: Microvascular and acute complications in IDDM patients: the Eurodiab IDDM Complications Study. *Diabetologia* 37:278–285, 1994
5. Coonrod B, Ellis D, Becker DJ, Bunker CH, Kelsey SF, Lloyd CE, Drash AL, Kuller LH, Orchard TJ: Predictors of microalbuminuria in individuals with IDDM: Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 16:1376–1383, 1993
6. Wang PH, Law J, Chalmus TC: Meta-analysis of effects of intensive blood-glucose control on late complications of type 1 diabetes. *Lancet* 341:1306–1309, 1993
7. Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 329:304–309, 1993
8. Christlieb AR, Warram JH, Krolewski AS, Busick EJ, Ganda OP, Asmal AC, Soeldner JS, Bradley RF: Hypertension: the major risk factor in juvenile-onset insulin-dependent diabetics. *Diabetes* 30 (Suppl. 2):90–96, 1981
9. Mathiesen ER, Ronn B, Jensen T, Storm B, Deckert T: Relationship between blood pressure and urinary albumin excretion in development of microalbuminuria. *Diabetes* 39:245–249, 1990
10. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
11. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH: Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 39:1116–1124, 1990
12. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Ellis D, LaPorte RE, Kuller LH, Wolfson SK, Drash AL: Factors associated with avoidance of severe complications after 25 yr of IDDM: Pittsburgh Epidemiology of Diabetes Complications I. *Diabetes Care* 13:741–747, 1990
13. Klein R, Klein BEK, Linton KLP, Moss SE: Microalbuminuria in a population-based study of diabetes. *Arch Intern Med* 152: 153–158, 1992
14. Parving HH, Hommel E: Prognosis in diabetic nephropathy. *Br Med J* 299:230–233, 1989
15. Kullberg CE, Arnqvist HJ: Elevated long-term glycated haemoglobin precedes proliferative retinopathy and nephropathy in type 1 (insulin-dependent) diabetic patients. *Diabetologia* 36:961–965, 1993
16. Dahl-Jorgensen K, Bjoro T, Kierulf P, Sandvik L, Bangstad HJ, Hanssen KF: Long-term glycemic control and kidney function in insulin-dependent diabetes mellitus. *Kidney Int* 41:920–923, 1992
17. D'Antonio JA, Ellis D, Doft BH, Becker DJ, Drash AL, Kuller LH, Orchard TJ: Diabetes complications and glycemic control: the Pittsburgh Prospective Insulin-Dependent Diabetes Cohort Study status report after 5 years of IDDM. *Diabetes Care* 12:694–700, 1989
18. Orchard TJ: From diagnosis and classification to complications and therapy: DCCT part II? *Diabetes Care* 17:326–338, 1994